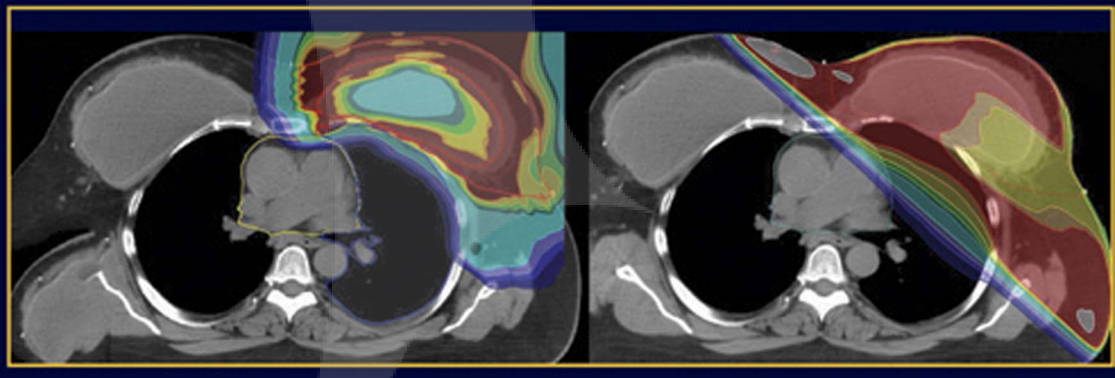
RADIATION MEDICINE ROUNDS
Series Editor: Charles R. Thomas, Jr.

BREAST CANCER



Alphonse G. Taghian • Michele Y. Halyard
Guest Editors

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BREAST CANCER
Taghian • Halyard

Radiation Medicine Rounds

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Breast Cancer

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Foreword

■ FROM THE EDITOR-IN-CHIEF

Radiation Medicine Rounds is a hardcover series published three times a year that is designed to provide an up-to-date review of dedicated radiation medicine topics of interest to clinicians and scientists who are involved in the care of patients receiving radiotherapy. It is intended to serve as both a reference and instructional tool by students, house staff, fellows, practicing clinicians, medical physicists, cancer biologists, radiobiologists, and interdisciplinary colleagues throughout the oncology spectrum.

For the current issue, *Breast Cancer*, Guest Editors Drs. Alphonse G. Taghian and Michele Halyard have gathered an ensemble of leading-edge thought leaders in the field of breast radiation oncology. They are to be congratulated for delivering an educational, research, and clinically applicable product that covers the state of the art for mammary gland cancers. On behalf of the editorial board, I congratulate Drs. Taghian and Halyard for putting together an outstanding volume that will be useful to colleagues who are involved in the delivery of clinical care to patients requiring radiotherapy for breast neoplasms.

Dr. Charles R. Thomas, Jr.
Series Editor-in-Chief
Radiation Medicine Rounds
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Preface

Well over 200,000 women are diagnosed with breast cancer in the United States each year. While systemic chemotherapy and hormonal therapy play vital roles in the management of breast cancer, radiation therapy (RT) too plays a critical role in improvement in both local control and survival. In this issue of *Radiation Medicine Rounds,* we selected topics that discuss the more salient issues regarding the role of RT in breast cancer treatment.

The field of RT has increased in complexity over recent decades as illustrated by the article by Drs. McBride and Taghian, who discuss the history of RT and breast cancer. Drs. Elkhuizen and Bartelink provide an overview of the present and future roles of RT in breast cancer treatment. Continual reassessment is occurring in breast RT related to optimal dose, fraction, and volume. Decreases in duration of therapy and treatment field size are both discussed as Drs. Somaiah and Yarnold review the rationale and outcomes with the use of hypofractionated RT and Drs. Wilkinson, Cuttino, and Vicini discuss the state of accelerated partial breast RT. The evolution of indications for RT in the postmastectomy and neoadjuvant therapy settings is discussed by Drs. Recht and Fowble, respectively. With over 40,000 women diagnosed annually with preinvasive breast cancer, many issues faced with invasive breast cancer are also addressed in patients with intraductal cancer. Drs. Daroui and Haffty provide an overview of the use of RT in ductal carcinoma in situ.

With the advent of improvement in technologies, the goal of improving outcomes while decreasing toxicity has remained at the forefront. In this issue, Drs. Pignol, Olivotto, and Sattler review the role of intensity-modulated RT, while Dr. MacDonald reviews the available data on proton therapy, both therapies designed to reduce treatment sequelae. However, despite our best attempts at minimizing side effects, toxicities do occur. Drs. Taunk and Prosnitz provide an overview of the cardiotoxicity data related to RT and how attempts at cardiac sparing have had an impact on morbidity. Drs. Ohri, McCormick, and Ho review the effect of RT on breast reconstruction, which is pertinent in decision making in the postmastectomy setting.

As the genomic revolution continues to have an impact on treatment decisions, the role of local failure related to biologic subtypes becomes increasingly important as discussed by Drs. Arvold and Taghian. Individualized medicine is the future in health care, and Drs. Mamounas and Patel describe the risk of local-regional recurrence related to molecular and genomic classifications.

With all the advances in breast cancer over the decades, we must always remember that none of these would have been possible without the knowledge we have learned by treating millions of patients with breast cancer. It is to them as well as to their families that we dedicate this issue.

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RADIATION MEDICINE ROUNDS

The History of Local Treatment for Breast Cancer

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■ ABSTRACT

The historical tale of how the current standard of care for breast cancer local therapy evolved involves the rise and fall of prominent physicians and theories. From Halsted to Fisher, the pitched battles over the role and importance of the radical mastectomy and the theories on how cancer spread that were used to justify the varieties of treatment consumed generations of oncologists. In this chapter, we attempt to summarize this history, providing insight into the key personalities and the crucial theoretical breakthroughs that brought us into the modern era.

Keywords: breast cancer, local, history

■ INTRODUCTION

Fundamental shifts in the recognized standard of care for localized breast cancer have occurred over the course of the last century. These changes, dictated by theory, brought about by the herculean efforts of lone physicians in the face of stiff, ego-driven opposition have had a dramatic impact on the lives of the millions of women who undergo yearly the intense treatments necessary to achieve cure. To tell the story of how this shift came about, one needs to reckon with both the science and the surgeons whose fierce advocacy of competing visions led to what one author has provocatively called "The Breast Cancer Wars."

To make sense of the story of breast cancer local therapy, it helps to divide it into three predominant eras wherein the standards of care were driven largely by reigning theory. It is tempting to presuppose that popular treatments were applied haphazardly with little regard for the understood biology of the breast cancer itself. However, as one delves into the primary literature and explores the reasons and rationales provided by the practitioners at the time to justify specific interventions, one finds these justifications relied heavily on the state of the science as it was.

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One man, more than any other oncologist, defined the terms and terrain of the incipient battle over local therapy. Because of this, the titles we use for the historical divisions reflect his influence. William Stewart Halsted (1852–1922) was a surgical phenom, a man of intense dedication, focused intelligence, and significant flaws. As one of the founding physicians of the Johns Hopkins Hospital, it is his publications on and popularization of the radical mastectomy that marked the beginning of the modern treatment era. In order to understand his significance, however, we must look at what came before.

■ THE PRE-HALSTEDIAN ERA

Marked mainly by the scientific confusion over what exactly constituted cancer—its etiology and its method of spread—the Pre-Halsted era was a period of intense debate between leading European surgeons and biologists. As a consequence of this confusion, the belief in the importance of local therapy waxed and waned.

One of the earliest proponents of aggressive local intervention was the French surgeon Louis Petit (1674–1750). Esteemed within Parisian intellectual circles and founder of the French Academy of Surgery, Petit was a strong and vocal advocate for the en bloc resection of the breast, underlying pectoralis muscle, and any palpable lymph nodes (1). He, along with another well-reputed French physician Henri LeDran advanced the idea that breast cancer began in its earliest stages as a local disease, spreading first to the lymph nodes before moving on to distant sites.

Although convinced of the truth of their theory and the importance of local control, continental surgeons were fundamentally limited in their ability to act on their ideas by the primitive state of surgery. Before the widespread application of anesthesia and antisepsis, the surgery itself would result in indescribable pain and horrific infection. An infamous description was penned by the English diarist Fanny Burney who, in 1811, underwent a mastectomy in Paris for a palpable breast mass (1):

> The instrument this second time withdrawn, I concluded the operation over—Oh no! Presently the terrible cutting was renewed and worse than ever, to separate the bottom, the foundation of this dreadful gland from the parts to which it adhered. Again, all description would be baffled—yet again all was not over. Dr. Larry rested but his own and… then I felt the knife tackling against the breast bone—scraping it!

As the nineteenth century progressed, in part due to the barbarity of the procedure and in part due to a shift in biological theories of cancer and its cause, aggressive surgical intervention fell out of favor. By the 1850s, most physicians fell in line with surgical giant Dr. James Paget who thought cancer a result of bad humors (morbid material, blastema, etc.) and thus believed it to be systemic from inception (2). Paget, in 1853, thusly concluded, "that which evidently makes some part of the body appropriate for the growth of a cancer tumor is a so-called 'exciting cause of cancer'; but it is a cause of cancer only insofar as it fits some part of the local manifestation of a disease which already, in its essential material, exists in the blood" (3). Driven by his theoretical vision, Paget and his compatriots dismissed local therapy as punitive rather than curative.

However, what passed for theory in the middle half of the nineteenth century was largely speculative, based upon surgical anecdote, and without any firm grounding in biological first principles. In Germany, however, three biologists, steeped in the emerging science of microscopy, began to provide convincing counters to the idea that cancer arose from dysfunction in the humors instead focusing their attention on the newly discovered cell. Chief among these mavericks of microscopy was Rudolph Virchow (4).

Virchow was a convert. Initially an advocate for the humoral theory of carcinogenesis, he eventually bought wholeheartedly into the new cellular theory of biology. More importantly, he was the first to advance the idea that cells were derived from other cells, not from the spontaneous organization of free-floating "protoplasm." Virchow thusly concluded that cancerous tumors were composed of cells, themselves the offspring of prior cell divisions. What initiated these growths? Virchow was convinced of the importance of local irritation and inflammation. He believed that these "irritative factors" led to the overgrowth of local epithelial cells.

Joining Virchow in advocating for this new theory were Karl Thiersch and Heinrich Waldeyer, who independently came to similar conclusions about the biological basis of tumors and the probable local causes of their initiation (4). The ideas of the microscopists meshed well with the clinical evidence that was beginning to emerge in favor of a local etiology for breast cancer. Chief among the clinical advocates of local origins was Dr. Charles Moore (1821–1870). A contemporary of Dr. Paget's, Moore was chief surgeon at the Middlesex and St. Luke's Hospital in what is now the United Kingdom. In 1867, he published his seminal work *On the Influence*

of Inadequate Operations on the Theory of Cancer (5). His purpose was clear and laid out explicitly in the paper's introduction: "to discover if cancer be orderly in the return, conforming to the rule of local functions, or if its morbid material be shed forth into an organ, or a region, or into the body as a whole, under an influence which is superior to local conditions." Put simply, Moore wanted to study the patterns of recurrence; he reasoned that if cancer were truly a systemic disease, its pattern of recurrence would be primarily distant. Conversely, largely local failures argued for a local, within breast, etiology.

Moore published an exhaustive descriptive analysis of 14 patients whom he had operated upon for carcinoma of the breast. In the article, he sketched, with meticulous detail, the patterns of recurrent disease relative to the initial surgical incision. He found that the vast majority of his documented failures occurred immediately adjacent to the surgical incision. Moreover, he noted that far from displaying any constitutional symptoms indicative of systemic illness, between the first surgery and subsequent recurrence, his patients remained quite healthy.

Based upon his observations, Moore argued that (a) cancer was predominantly a local disease and the recurrence was owing to incomplete removal of elements of the tumor, (b) recurrence abided by the laws of centrifugal dispersion, meaning that cancer spread slowly and continuously from the site of the primary lesion outward, and (c) in order to affect cure, the entire breast had to be removed.

While both the biologists and clinicians converged upon the idea that cancer was a local disease, derived from epithelial cells within the affected organ, and requiring extensive extirpations for cure, the still rudimentary nature of surgical science deterred physicians from large-scale resections—that is until the arrival of Joseph Lister (1827–1912). Lister, a Scottish surgeon, was one of the first individuals to use antisepsis to reduce postoperative infection (6). First tried on an 11-year-old boy who suffered a compound humeral fracture, Lister sprayed carbolic acid over the entire surgical field prior to and during open reduction and fixation. The boy failed to develop what, in the preantiseptic era, would have been the inevitable osteomyelitis. Lister thusly concluded that "decomposition of the injured part may be avoided by applying as a dressing some material capable of destroying the life of the floating particles (germs)." Although antisepsis and the concurrent development of effective anesthesia at the Massachusetts General Hospital in 1846 made en bloc resection clinically feasible, the widespread adoption of Lister's methods were hampered by the cool reception his ideas received from leading mid-nineteenth-century American surgeons. Undeterred by the disbelief of the American surgical hierarchy, William Stewart Halsted was an early adopter of the antiseptic technique. It is toward him that we now turn our attention.

THE ERA OF HALSTED

William Halsted was born into money in New York City and educated at Yale College and the Columbia College of Physicians and Surgeons. At the time, American medical education had significant deficiencies. As a result, and like most of his peers, Halsted sought the help of local tutors and took time abroad to learn from the established, accomplished European surgeons such as Theodor Billroth, who convinced him of the importance of antisepsis. Once back in the United States, Halsted pioneered the use of cocaine as a local anesthetic, and in the process, developed a significant and debilitating addiction to the drug. Marginalized by New York surgical society because of his addiction, Halsted was eventually brought to the newly constructed Johns Hopkins Hospital by William Welch to function as its first Surgeon-in-Chief. Unconstrained by the conservative strictures of his prior home, at Hopkins Halsted began to experiment with increasingly radical operations for the removal of breast tumors.

Precedence did exist for the operation that Halsted would later coin "the radical mastectomy." Several German surgeons to whom Halsted was exposed, namely Ernst Kuster and Richard Volkmann, had advocated for the resection of clinically positive axillary nodes and removal of the pectoralis muscle (2). Halsted's tremendous influence is owing mainly to the extent of his operation, his fierce advocacy of en-bloc removal, the extraordinarily low recurrence risk he reported, and the numerous leading twentieth century surgical lights he managed to train.

In mid-June of 1889, Halsted performed his first radical mastectomy at the Johns Hopkins Hospital (Figure 1). The operation entailed the en bloc removal of the breast, axillary lymph nodes up to and including Level III, and the pectoralis major muscle. In 1894, he published a case series of his first 50 operative successes (7). The women all presented with gross axillary disease and all were treated with the radical mastectomy. In his report in the *Annals of Surgery*, he boasted that 34 of these patients were

free of local or regional recurrence, with 24 alive at last follow-up. In reality, of the group of patients who had greater than 3 years of follow-up, only two were alive without evidence of locoregional recurrence. However, because of the focus on locoregional recurrence, dictated by the relative inability to diagnose visceral metastases, and Halsted's decision to use 3 years as a cutoff beyond which the patient was considered cured, he considered the radical mastectomy a "success." Certainly, compared with his European colleagues, he was reporting local failures at far less frequent rates.

Halsted had clearly bought into Virchow's and Moore's thesis on the local origins of cancer. But a question of equal importance to the surgical community focused on the mechanism of cancer metastasis. Here Halsted, in formulating his own ideas about distant dissemination, borrowed heavily from the English surgeon W. Sampson Handley (8).

For those who bought into the local origin theory, there were two primary putative mechanisms of spread: the first—the "embolic theory"—posited that tumor emboli were shed by the primary lesion into the blood stream; the second, advanced by Halsted and Handley, the latter of whom based his conclusions on autopsy examinations, saw distant spread as a result of centrifugal movement of tumor cells away from the primary tumor via deep fascial lymphatics. For instance, Halsted believed that liver metastases resulted not from hematogenous spread, but rather from invasion into the viscera by way of the lymphatics along the linea alba. He thought the presence of subcutaneous lesions distant from the primary and the "fact" that bone metastases occurred only in areas "nearest the surface" and thus "closest to the deep lymphatics" as confirmation of his theory. His absolute certainty in the truth of his own ideas led him to affirm that he was "not sure he [had] observed metastasis which [was] conveyed by way of blood vessels."

Halsted's confidence in the "centrifugal theory" was total. His absolutism led him to two practical conclusions, one much more pernicious than the other: Firstly, it affirmed his belief in the need for en-bloc resection; failure to remove intervening tissue between two areas of gross disease would inevitably leave behind tumor cells in the connecting deep lymphatics. Secondly, he thought that once the deep lymphatic routes "travelled in the metastases to bone, particularly to the humerus" were uncovered, one might "in case of involvement of this bone [amputate] the shoulder joint plus a proper removal of the soft parts" in order to "eradicate the disease."

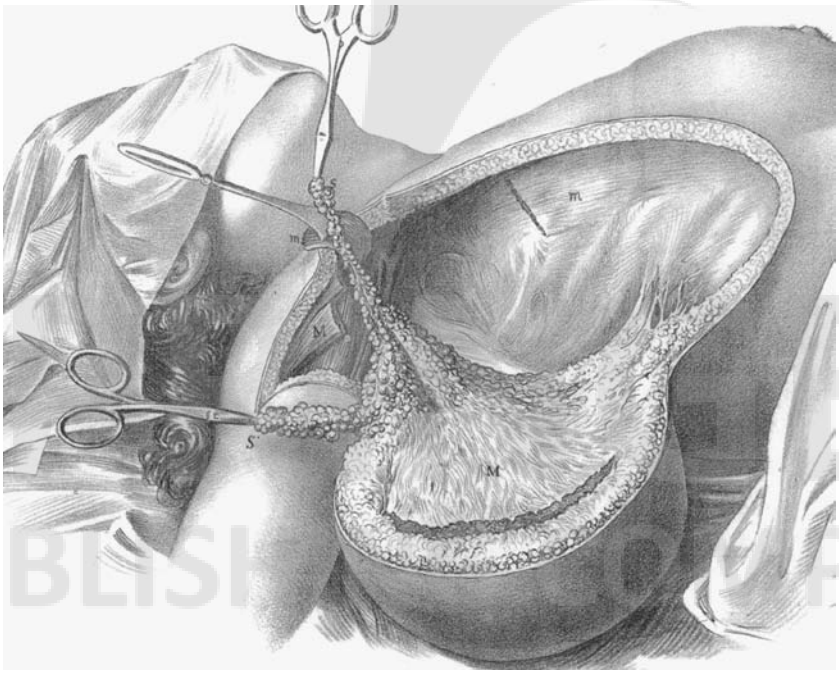

FIGURE 1 Sketch of Halsted radical mastectomy.
Source: Adapted from Ref. (7).

In the 1907 update of his case series, he took his own advice to heart (9). In 122 of the 232 patients on whom he reported, he performed a supraclavicular nodal dissection, taking cervical nodes up to the bifurcation of the carotid artery. The radicalism of this operation was unprecedented. Any outcry from patients was limited by a variety of factors, not the least of which was their sincere belief that what Halsted was doing was necessary for cure; but the reality of the results were far less impressive. Only 24.5% and 7.5% of his patients with axillary disease and supraclavicular disease, respectively, were free of disease after 3 years. More strikingly, there was no obvious significant increase in freedom from failure when looking at those patients who received the more radical of the mastectomies. Rather than call into question the veracity of the theory, however, these limitations only prodded Halsted's followers toward increasingly more radical surgical solutions.

■ THE FOLLOWERS OF HALSTED: BIGGER IS BETTER

Part of the ubiquity of Halsted's influence was his importance to the training of young American surgeons and the awe in which they held him. His ideas now widely disseminated and largely unquestioned, three mid-twentieth-century surgical titans took those ideas to their logical extremes.

Owen H. Wangensteen (1898–1981) was born in Lakeland, Minnesota, and educated at the University of Minnesota School of Medicine, graduating at the top of his class of 81 (Figure 2). After completing postdoctoral research at the Mayo Clinic and a surgical residency in Switzerland, he, at 31, was appointed chief of the Department of Surgery at Minnesota in 1930. Still reckoning with the disappointing outcomes for patients with locally advanced breast cancer, Wangensteen, at the 1950 American Surgical Society meeting, strode to the podium and threw down the gauntlet: "Today, it should be said, I believe, the Halsted operation for cancer of the breast is outmoded: it is not radical enough."

As the saying goes, with readily available hammers, every trouble turns into a willing nail. For Wangensteen, the surgical hammer was expanding in size and becoming something more akin to a wrecking ball. In 1957, he reported on his supraradical mastectomy (10): this was a two-stage operation that was, in part, dependent on the extent of evident disease. The first stage involved the standard Halsted radical mastectomy. If the axillary lymph nodes were positive,

FIGURE 2 Owen H. Wangensteen (Courtesy of Department of Surgery, University of Minnesota).

Wangensteen undertook a second operation 4 to 6 weeks after the initial operation. The second procedure involved a long longitudinal incision from the thyroid cartilage down to the sternum. The sternum was then divided and retracted. Wangensteen would then proceed to dissect the internal mammary, supraclavicular from the omohyoid inferiorly, the internal jugular, and subclavian nodes (Figure 3). Postoperative mortality was 12.5%. Of those who underwent the second stage of the operation, only three patients were alive without evidence of disease at 5 years.

Wangensteen's contemporary, practicing at the Memorial Hospital for Cancer and Allied Disease was Dr. Jerome A. Urban. Born in Brooklyn, NY, schooled at Columbia, and trained at Lennox Hill Hospital, Urban was as evangelical a worshiper of Halsted as his peers. Provoked by his own anecdotal experience that 70% of his chest wall recurrences were in the parasternal area, Urban advocated for his own extended-radical mastectomy. This procedure involved en-bloc resection of the breast, pectoralis major, and portion of the chest wall containing the mammary chain, essentially the first through fifth interspaces. He would then proceed to clear the Level I–III axillary nodes with removal of the pectoralis minor and anterior serratus sheath. Urban published his first results in *Cancer* in 1952 (11). While achieving acceptably low postoperative

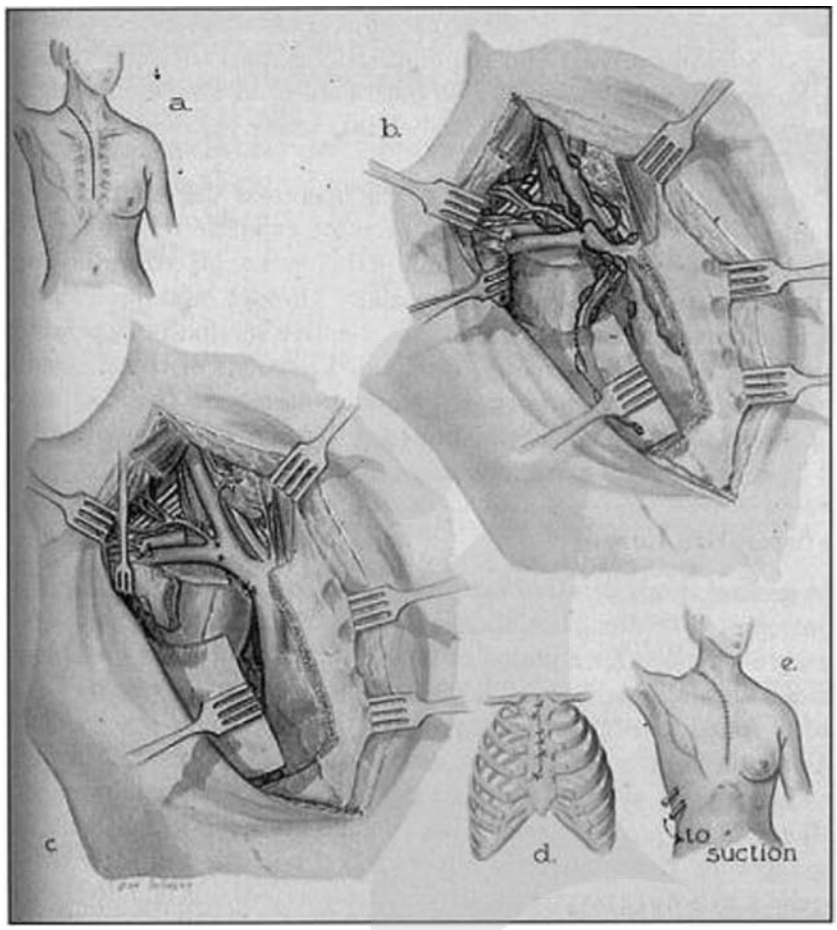

FIGURE 3 Wangensteen's supraradical mastectomy. *Source:* Adapted from Ref. (10)

mortality, Urban reported that only 52% of his axillary positive patients were free of disease at 5 years. Perhaps more disheartening was his insistence that his radical resection was best suited for those patients with early-stage, node negative disease. This conclusion was driven by his impressive results with this subgroup. He failed, however, to ask the troubling—troubling from the standpoint of prevailing dogma—question that perhaps the extent of resection was incidental to the success of the treatment. Perhaps these patients would do just as well with more conservative interventions. Unfortunately these questions were being asked, if at all, on the margins of American surgical society. By 1978, surgeons at what became Memorial Sloan Kettering Cancer Center had performed over 900 extended-radical mastectomies.

The most successful proselytizer of Halsted's canon was also centered in New York. Cushman D. Haagensen (1900–1991) fancied himself the first true breast cancer specialist. Trained at the Boston City Hospital after medical school at Harvard, Haagensen, unlike Wangensteen and Urban, made few alterations to the Halsted radical mastectomy. Lording over the surgery department at Columbia, he prided himself on exquisitely meticulous mastectomies, taking on average 5 hours to complete the procedure.

Haagensen was the most successful advocate for the radical mastectomy in part because he was one of the first to systematize staging of the disease and because he was intellectually nimble enough to recognize that not everyone required such extensive resections. By his own estimation, the 93% of the breast cancer patients in New York City receiving radical procedures were far in excess of what was clinically indicated.

Haagensen implemented regional lymph node biopsies and refused to perform radical mastectomies on patients with internal mammary metastases or

disease in the supraclavicular region. However, in the patients who he believed would benefit, namely those without clinically negative or clinically positive, but movable axillary nodes, he was as dogmatic as any of his peers. In addition, the success of his advocacy was driven by the relative quality of his evidence: the number of patients on whom he reported outcomes dwarfed all other case reports; additionally, he reported comparisons of his own similarly staged patients who received radical mastectomy to those who received radiation alone (12–14).

These three men were noble in their motivations but mistaken in their science. However, the truth as they saw it was something in which they were firmly convinced. They, along with surgical colleagues such as J. L. Ehrenhaft at the University of Iowa, who advocated pneumonectomy with hilar dissection for pulmonary metastases (15), became an old guard opposition to the antithesis to Halsted that slowly began to develop.

■ THE ERA OF HALSTED: THE CONSERVATIVE CANARIES IN THE COAL MINE

"None of us have been burnt at the stake, but feelings run pretty high," said Geoffrey Keynes (1889–1982), brother of John Maynard, in reflecting on the reaction of his surgical colleagues to his advocacy of conservative treatment measures. Born in Cambridge, England, and trained at St. Bartholomew's in London, Geoffrey was a polymath of tremendous intelligence. A pillar of the London establishment, a veteran of World War I and II, and the one unconcerned with class and reputation, Geoffrey was perfectly positioned to prod established wisdom in the realm of breast cancer local therapy.

Although Geoffrey did not posit a replacement theory of his own, he did have fundamental and nagging questions that undermined his faith in the "centrifugal theory of spread" as advocated by Halsted. He thought it unlikely that deep facial lymphatics contained in-transit cancer cells that required en-bloc resection. In fact, he doubted the very existence of these deep lymphatic vessels. These doubts led him to pursue a novel local treatment for breast cancer, which he published in the *British Medical Journal* in 1937 (16).

Like Haagensen after him, Keynes did for statistical purposes divide his patients into three simple stages: those without axillary involvement, those with axillary involvement, and those with distant disease. His treatment involved the liberal use of radium-containing needles placed in parallel throughout the breast, axilla, supraclavicular fossa, and first four intercostal spaces (Figure 4). If the tumor was large or bulky, he recommended a lumpectomy-like surgery. When he compared his same stage radium +/– lumpectomy patients to those who underwent radical mastectomy, he found no discernible differences in survival. He however reported forthrightly on the postradiation fibrosis that frequently developed and on the "neuralgia and rheumatic pains" that he saw in the breast and axilla of his patients.

Keynes was one of the first to recognize that sparing the breast provided a significant psychological comfort to woman. "Why," he asked, "subject women to the morbidity of the radical mastectomy if less invasive alternatives were available?" As his prior quotation suggests, his surgical colleagues were simply not prepared to reckon with the answers.

However, the question kept coming up. Robert McWhirter (1904–1995), professor of medical radiology at the University of Edinburgh, rose quickly, like Wangensteen, through the medical ranks, taking over the Department of Radiology at Edinburgh in 1933 at the age of 31. He was a firm believer in the clinical possibilities of radiation in the treatment of cancer, having trained at the Holt Radium Institute at the Christie Hospital in Manchester.

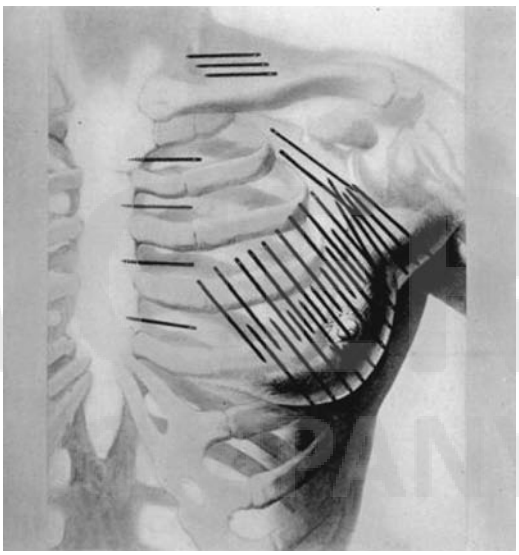

FIGURE 4 Keynes' method of breast brachytherapy. *Source:* Adapted from Ref. (16).

In 1948, McWhirter was invited to speak at the Royal Society of Medicine in front of a packed house of hostile surgeons regarding a novel treatment plan he had been pursuing at Edinburgh (17). McWhirter began his presentation with a tirade against what he perceived as the dramatic selection bias involved in the surgical series that had been reported to date. He went on to advocate for intention-to-treat analyses and the need for stricter definitions of clinically relevant end points, preferring overall survival (OS) and freedom from disease. Finally, he got to the heart of the argument:

Since 1941, Edinburgh had been treating the vast majority of its operable breast cancer patients with simple mastectomy followed by adjuvant radiation therapy using a four-field approach that included the entirety of the axilla and whole breast. Cumulative dose reached 3750 rads given over the course of 3 weeks.

Using strict staging definitions and after histologically confirming the diagnosis in over 85% of 1334 patients, McWhirter also benefited from a relatively robust control group of patients: he had collected data on 790 patients treated with radical mastectomy +/- post-mastectomy radiation at Edinburgh between 1935 and 1940. His conclusions were clear: in a stage-stratified analysis, there was no benefit in radical mastectomy compared with simple mastectomy with adjuvant radiation. In the final portion of his remarks, he emphasized the need for quality radiotherapy and argued that his method represented "an attempt at a more radical treatment of breast cancer." In essence, although he argued for the abandonment of Halstedian surgical techniques, he refused to lay aside the Halstedian theory of centrifugal spread.

Because of Halsted's influence, this British conservative streak in the treatment of localized breast cancer had a hard time finding a foothold in the United States. A prominent review published in the *Annals of Surgery* by Sprong and Pollock bluntly concluded, after tearing into McWhirter, that "radical mastectomy is superior to simple mastectomy in the treatment of breast cancer" (18). A young Bernard Fisher surveyed 25 leading American breast surgeons in 1954 on the need for super-radical mastectomy, finding that 40% of his respondents "indicated that there might be some merit in IMN dissection" (19). Keynes and McWhirter were having little luck on the opposite side of the Atlantic, that is, until the arrival of a young up-start surgeon, Dr. George Crile, Jr.

Crile (1907–1992), who was born into an esteemed medical family, whose father was a founding partner of the Cleveland Clinic, was educated at Yale College and Harvard Medical School (Figure 5). He completed his surgical training at the Cleveland Clinic before serving in the medical corp during World War II. His experiences in combat medicine deeply influenced him, and he came home from the war "convinced that operations in many fields of surgery were either too radical, or not even necessary."

Primed to receive the conservative British teachings, Crile was deeply influenced by Scottish surgeon Reginald Murley, himself a resident of Geoffrey Keynes and who was in the audience during McWhirter's whirlwind presentation. Helped along by his deep concern for his female patients' psychological well-being and convinced by British evidence and his own intuition, Crile performed his last radical mastectomy in 1955.

He published his own experience using simple mastectomy alone in 1960, comparing his results with his surgical colleagues at the Cleveland Clinic who continued using the radical mastectomy (20). Limiting the bulk of his analysis to Stage I (breast only) and Stage II (palpable, moveable axillary nodes), he found nearly equivalent 3-year overall and disease-free survival. More convincing still is far fewer Stage I patients in the simple mastectomy arm received cobalt irradiation than those Stage I patients in the radical mastectomy group. The fact that, despite this treatment imbalance, results were still equivalent was further argument against the continued use of the radical mastectomy in the early-stage subpopulation. Although he did not venture a guess as to the theoretical implications of his work concerning the theory of breast cancer spread, in his discussion, Crile made a clarion call for "blinded studies" wherein "all variables save surgery are the same."

Not content to allow the debate to play out in the professional press alone, Crile published for the lay audience *Cancer and Common Sense*, a short book in which he attacked the proponents of more radical surgeries, explicitly needling both Wangensteen and Urban. An excerpt of Crile's polemic published in *Life* magazine caused an uproar and prompted the president of the American Medical Association and directors of the National Cancer Institute and American Cancer Society to issue strongly worded condemnations of his methods. Dr. Englebert Dunphy, a surgeon at Boston Public Hospital and president of the American College of Surgeons, stated that he didn't "feel at the moment there is any justification for the adoption of Crile's methods for Stage I breast cancer because there is a 25% error in making the diagnosis."

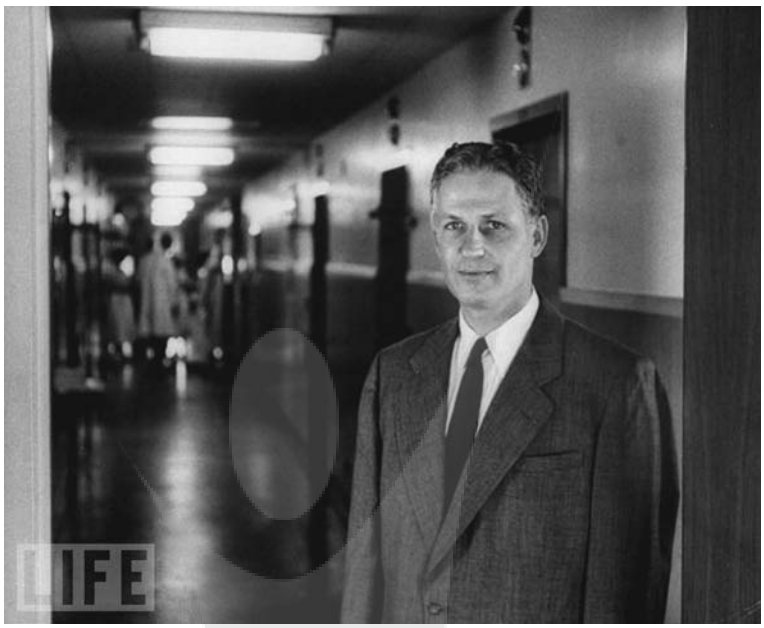

FIGURE 5 George Crile, Jr. (Courtesy of *Life* Magazine).

■ POST-HALSTED ERA: THE RISE OF BERNARD FISHER

As the conservative backlash gained both in proponents and in credibility, it still lacked a firm theoretical foundation to justify its less invasive methods. Yes, Keynes had called into question the centrifugal theory of spread, but he had proffered no convincing alternative. What drove these early clinical rebels more than anything was an understandable revulsion at the extent of the surgeries without clear benefit and the impact such morbidity had on the women.

However, arguments against the centrifugal theory began to surface slowly. One of the first to call into question the now half-century-old idea was Willis D. Gatch, dean of the Indiana University School of Medicine and one of Halsted's first trainees—a much admired diaspora that had now spread itself out across the country.

In a 1952 paper, Gatch, along with his young protégé Clyde G. Culbertson, chair of the Department of Pathology at Indiana, noted two facts that failed to fit with the reigning lymphatic paradigm (21): (a) radiologists would frequently note pulmonary parenchymal metastases without apparent involvement of the hilar nodes or pleura; if metastases reached the lung via the deep fascial lymphatics, one would think that the pleura and hilum, two areas proximal to the lung on this pathway, would be affected prior to the lung itself and (b) Gatch's observation of several patients with choroidal metastases, a location in the body relatively inaccessible to the lymphatics. With these two observations in hand, Gatch and Culbertson concluded that hematogenous spread was primarily responsible for the distant dissemination of breast cancer. Furthermore, they reasoned that extended survival had more to do with the host's ability to keep dormant tumor cells in check rather than any extent of surgical resection. However, despite the above, their closing line was strikingly timid: "The theories on which the Halsted operation is based are no longer tenable" they stated, "not withstanding this, we believe it is still the best treatment."

Perhaps a more convincing, but still largely circumstantial, argument was made by N. E. McKinnon (b. 1894), professor of epidemiology at the University of Toronto. In his book *Limitations on the Diagnosis and Treatment of Breast Cancer,* McKinnon noted that, despite the increasing use of radical mastectomy and a very robust early detection campaign in eight Canadian provinces, breast cancer mortality had not budged (22). He also aggregated a good deal of data on timing of symptom onset and presentation to a physician. Here he discovered that those who presented early to a surgeon still, in 50–60% of the cases, had distant disease at presentation. Conversely, despite quite protracted periods of neglected symptoms,

a small but distinct minority of patients still had disease limited to the breast.

McKinnon then made a significant leap arguing that "the difference between Stage I disease and cancer of other stages is largely one of type of lesion rather than time." From this biological predeterminism naturally flowed McKinnon's deduction that "in most, if not all, lethal breast cancer, the remote metastases that are the eventual cause of death are spread from the primary lesion via the blood stream before [detection]." In his final, damning statement, he sarcastically intoned that "curing nonlethal cancers does not reduce mortality." In essence, given what he believed about the natural history of breast cancer, if the disease was to spread, it would have done so long before the surgeon's knife touched the patient. If this was true, the radical mastectomy simply made no sense.

By the early 1960s, the theoretical and clinical armor of Halsted's scientific and treatment paradigm had been chinked, but the American surgical establishment still wore it proudly. However, the arguments marshaled against the Halstedian hierarchy's "centrifugal spread" theory were largely circumstantial, and the clinical evidence against radical mastectomy was retrospective. What remained to be done was to formulate a robust in vivo model showing that distant spread occurred via the bloodstream mainly prior to presentation and that, because of this biological reality, the extent of surgical resection was less important. It was Bernard Fisher (b. 1927), who stepped into this evidentiary void (Figure 6).

To be a scientific renegade—a true shifter of paradigms—one needs to be exhaustive in the marketing of an idea, unflappable in the face of withering criticism, and utterly convinced of the truth of the clinical reality that one propounds. However, above all else, one has to have a significant appetite for risk. Bernard Fisher possessed all of these attributes in abundance. Born in Pittsburgh, Pennsylvania, educated and trained at the city's School of Medicine, Fisher returned to Pittsburgh in 1953 after a fellowship at Penn to start up the university's surgical research laboratory with his brother, Edwin, a pathologist.

His storied career in breast cancer research really began in 1957, when his mentor from Penn, Isadore Ravdin, invited him to a retreat at National Institutes of Health where he became a founding member of the Surgical Adjuvant Chemotherapy Breast Project, now the world renowned NSABP. The NSABP was an early adopter of what has since become the gold standard in clinical research: the randomized controlled trial. The randomized

FIGURE 6 Bernard Fisher (Courtesy of Department of Surgery, University of Pittsburgh).

controlled trial, first popularized as a method for testing the efficacy of streptomycin in tuberculosis, was the only statistically air-tight mechanism to determine the influence of a single variable on disease outcome. From 1958 to 1961, the NSABP was the first to utilize the randomized controlled trial in breast cancer to test the efficacy of the chemotherapeutic thiotepa in 826 locally advanced patients.

However, before he wielded this formidable statistical weapon to slay the radical mastectomy, Fisher spent the better part of the 1960s devoted to laboratory research designed to test the various theories of distant spread. What he termed the *alternative hypothesis* was first presented in a publication in *Cancer* in 1969, in effect summarizing his data from a decade of research (23–27). In it, Fisher attacked the idea that clinically positive lymph nodes were a source of distant disease, arguing that they were largely a surrogate marker for inherent biological aggressiveness, thus diminishing the argument for aggressive attempts to remove them. He agreed with McKinnon's argument that time, as measured by tumor size, was of relative unimportance to curability, finding that 22% of lesions less than 1 cm had axillary metastases at presentation.

For Fisher, hematogenous spread was difficult to disentangle from lymphatic dissemination, but he was certain that the bloodstream was of critical

importance in conveying tumor cell emboli to distant sites. Finally, and perhaps most critically, Fisher believed that breast cancer was a "systemic disease" from inception and came to conclusions similar to McKinnon's that micrometastatic deposits were present early on in cancer's evolution. This led him to conclude that the extent of locoregional therapy would be of relative unimportance when it came to clinical outcomes.

Ultimately, it was no so much the novelty of Fisher's alternative hypothesis that brought him such surgical acclaim, but it was his pioneering work using the randomized controlled trial to test elements of his hypothesis that made his reputation. This all began in 1971 with the opening of NSABP Protocol 04 to enrollment. This was the first trial ever to test directly the merits of the radical mastectomy. The hurdles to recruitment were significant; the vitriol spewed at Fisher at conferences was endless, but his dedication to the project was unwavering. By 1974, he had met his enrollment goals, randomizing over 1600 women. The node positive patients were randomized to Halsted radical mastectomy versus total mastectomy and radiation; the node-negative patients fell into one of three bins: (a) radical mastectomy, (b) total mastectomy, or (c) total mastectomy with adjuvant radiotherapy. Importantly, node-negative patients in the total mastectomy group were permitted axillary lymph node dissection only if palpable nodes developed.

Upon publication, the finding of most significant clinical and theoretical relevance was that, in the clinically node-negative patients, those that underwent total mastectomy alone, without any treatment of the axilla, had rates of overall and distant metastasis-free survival that were similar to the radical mastectomy and adjuvantly irradiated patients (28–30). Given the rate of subclinical nodal positivity in the radical mastectomy arm, it was likely that the vast majority of the approximately 40% of the women who received total mastectomy alone had positive nodes that were unremoved and untreated. Based on the Halstedian hypothesis, these positive nodes would've been thought to have been a source of distant metastatic spread.

For Fisher, these findings supplied "credibility to the alternative hypothesis by indicating that variations in locoregional therapy" do not impact the risk of distant disease and survival. Despite the fact that these results were published in November of 1977, Jerome Urban, in an October 1978 piece in *Cancer*, continued to argue not only for the value of the Halsted radical mastectomy, but explicitly defended his idea of the extended radical mastectomy, all of this without even mentioning Protocol 04.

However, the triumph for Fisher was incomplete. While it was clear that there was no variation in the risk of locoregional recurrence in the node-negative patients when comparing the total mastectomy arm with the two other arms, a discerning critic could claim that perhaps a more aggressive local treatment that did reduce locoregional failure might impact OS. In order to demonstrate more definitively his idea that variations in locoregional recurrence do not impact distant disease, he needed to show that, despite variations in locoregional failure rate, distant and overall survivals were identical. This would come with the publication of the results of NSABP Protocol 06.

Enrollment in B-06 started in April 1976 and ended in January 1984. Over 1800 women with Stage I and II disease with tumors less than 4 cm were randomized to three arms: (a) total mastectomy alone, (b) lumpectomy with axillary lymph node dissection, and (c) lumpectomy with axillary lymph node dissection and radiation. The radiation used involved opposed tangents to treat the whole breast to a total dose of 50 Gy. Supplemental boosts to the operative area and regional nodes were not employed. Fisher again evaluated disease-free survival, distant disease–free survival (DDFS), and OS.

The initial results were striking and apparently confirmatory (31); despite dramatic differences in locoregional failure favoring the lumpectomy with radiation patients compared with those that received lumpectomy alone, the rates of distant disease-free and overall survival in the two arms were identical—statistically insignificant. In his 1991 Karnofsky Memorial Lecture (32), Fisher basked in the warm glow of his evident victory, concluding that

> The findings from B-06, just as those from B-04, repudiate the Halstedian principles of breast cancer management and provide support for our alternative hypothesis. How else can one interpret the findings from B-04 and B-06, which demonstrated that DDFS and OS remained unaffected in both the 40% of the patients with unremoved tumor positive axillary nodes (B-06) and the 40% of the lumpectomy patients with unremoved tumor cells who eventually experienced breast tumor recurrence.

By the mid-1990s, Fisher's alternative hypothesis had all but replaced the outmoded Halstedian notions. However, absolutism as pernicious as that present in the 1950s began to creep into the discourse on breast cancer local therapy. On questioning the alternative hypothesis, one earned sometimes

impertinent but always impatient responses from the disciples of the new consensus. However, nagging doubts persisted: could it truly be the case that differences in locoregional recurrence were utterly unimportant when it came to survival?

■ BEYOND HALSTED AND FISHER: A NEW SYNTHESIS

Samuel Hellman (b. 1932) had never been the one to tolerate absolutist dicta (Figure 7). Another precocious clinician-scientist, who was trained in radiology at Yale, and who became the first director of Harvard's Joint Center for Radiation Therapy in his 30s, Hellman, in what looked like dueling Karnofsky Lectures, laid out his own spectrum hypothesis in 1994 to counter the increasing dogmatism of the defenders of Fisher's Alternative (33).

Where Fisher and Halsted were monochromatic in their visions, Hellman saw various shades of grey in the evidence thus far accrued. He had come to believe that breast cancers represented "a spectrum of proclivities extending from a disease that remains local throughout its course to one that is systemic when first detectable." Unlike Fisher, who saw lymph node positivity as simply a surrogate for metastatic potential, Hellman asserted that positive nodes were important "not only because [they] indicate a more malignant tumor biology, but also because persistent disease in the lymph nodes can be the source of distant disease." Contra Fisher, Hellman also thought that persistent locoregional disease "may give rise to distant metastases and, therefore, in contrast to the systemic theory, locoregional therapy is important."

FIGURE 7 Samuel Hellman.
Source: Adapted from Ref. (33).

The evidentiary linchpin of Hellman's assertion was the publication of several trials of screening mammography that consistently showed a 30% decrease in breast cancer–specific mortality (34, 35); to Hellman, the decrease in mortality that resulted from screening argued for the existence of a period between mammographic detection and clinical appearance wherein metastasis had not yet occurred. This was in direct contradiction to Fisher's assertion that breast cancer was systemic from inception.

A more troubling finding for Fisher and his acolytes was the publication in 1997 of two studies, both in the *New England Journal of Medicine*, looking at the role of postmastectomy radiation (36, 37). As in B-06, both studies demonstrated an approximately 20% absolute decrease in locoregional failure in the patients who had received radiation after modified radical mastectomy and chemotherapy. However, this time, most notably in the higher-risk, node-positive patients, the addition of comprehensive chest wall and regional nodal RT led to dramatic 10% absolute improvements in overall survival. Hellman wrote a laudatory editorial to accompany the papers provocatively entitled, "Stopping Metastases at Their Source" (38).

But perhaps the most damning finding for the alternative hypothesis was the publication, in 2005, of the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analysis looking at over 42,000 women enrolled in 78 randomized trials, evaluating the effect of variations on local therapy, including radiation versus no radiation, on both locoregional recurrence and breast cancer–specific survival (39). Confirming the postmastectomy trial results, the EBCTCG study found that a 20% reduction in local failure at 5 years resulted in a 5% decrease in breast cancer mortality at 15 years. These findings again supported Hellman's assertion that at least some breast cancer patients who went without local radiation would experience a local recurrence that would ultimately contribute to metastatic outgrowths.

In fact, Fisher's 2002 update of the B-06 results showed a nearly statistically significant improvement

in breast cancer–specific mortality favoring those patients who received lumpectomy with radiation compared to those who underwent lumpectomy alone ($P = .06$) (40). The benefit would probably have translated into an improvement in overall survival had it not been offset by a late surge in nonbreast cancer mortality likely related to outmoded radiotherapy techniques.

This flood of data over a 10-year period from the mid-1990s to the mid-2000s led prominent breast cancer oncologists at Dana-Farber and Memorial Sloan-Kettering to conclude, "the findings from the mammographic screening trials and the EBCTCG meta-analysis of local therapy should end the debate about the theories of breast cancer spread. The fact that both earlier diagnosis and improved local control improve overall survival refutes the systemic hypothesis" (41).

Fisher, obviously troubled by this sweeping conclusion, offered a rejoinder. In his 2010 response in the *Journal of Clinical Oncology* to the prior decade's events, Fisher attempted to redefine, ever so subtly, the terms of the debate, stating that it had always been his position that reductions in locoregional recurrence would not "substantially" effect overall survival (42). Of course, this subtle redefinition begged the question of the statistical meaning of the word "substantial. In the EBCTCG's evaluation of the beneficial effect of chemotherapy on breast cancer–specific survival, they reported improvements in the range of 5% to 15%, which is similar to the improvements in overall survival seen in the postmastectomy trials. What absolute improvements in survival would Fisher consider insubstantial such that his alternative hypothesis could be retained?

Regardless, the dethroning of the alternative hypothesis does not take away from the tremendous statistical rigor that Fisher brought to the field of breast cancer research. More than any one individual, Bernard Fisher is responsible for the ubiquity of the randomized controlled trial, a design that has saved thousands of lives and prevented significant, untold morbidity.

CONCLUSION

Ultimately, as we move through the fourth century of this debate, Hellman's hypothesis now holds the best claim to biological truth. In a nod to the importance of gray shades and to a synthesis of both the Halstedian and Fisherian theories, three populations of breast-cancer patients likely exist: (a) patients whose disease was systemic from the very early, subclinical point of their tumor's evolution, (b) patients who present with local disease and who would likely never develop distant disease, and (c) patients whose tumors have metastatic potential but who do not yet have widespread dissemination; it is the latter group who would derive the most benefit from aggressive local therapy.

The pathway to the discovery of this underlying truth about the biology of breast cancer, the theoretical and clinical back and forth that has so dominated breast cancer oncology over these many hundreds of years, is, in the end, in service of the deep truth that all physicians continually seek and whose discovery will always benefit the patients that they treat.

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RADIATION MEDICINE ROUNDS

The Role of Radiation Therapy in Ductal Carcinoma In Situ

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ABSTRACT

Ductal carcinoma in situ (DCIS) of the breast is a noninvasive disease that has substantially risen in incidence in recent years. Several large randomized controlled trials have demonstrated that the addition of radiation therapy (RT) after breast-conserving surgery (BCS) for DCIS reduces ipsilateral breast tumor recurrences by 50% to 60%, highlighting an essential role for RT in the management of DCIS. Nevertheless, there is a persistent effort to identify certain low-risk subsets of patients with DCIS that may forgo adjuvant RT in an effort to maximize the risk–benefit ratio. In addition, the utilization of RT after BCS continues to be much lower than expected. Accelerated partial breast irradiation techniques may allow an increased utilization of RT for many patients with DCIS due to enhanced convenience of treatment, but require additional long-term prospective data.

Keywords: DCIS, radiation therapy, breast-conserving treatment, in situ breast cancer

INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast includes a heterogeneous group of noninvasive premalignant lesions that are confined to the breast ducts and lobules. Due to the widespread increase in the utilization of mammography and breast-screening programs, the incidence of DCIS has substantially risen in recent years. The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) age-adjusted database reported an increased incidence of 36.62 per 100,000 women in 2008 from 19.14 in 1990 (1). Although the prognosis of DCIS remains excellent, the main goal in the early diagnosis and treatment of DCIS is the prevention of the development of subsequent invasive disease, which may occur in up to 30% of patients at 10 years if left untreated (2). Treatment options for DCIS include (a) Mastectomy, (b) Breast-conserving treatment (BCT), consisting of breast-conserving surgery (BCS) followed by adjuvant radiation therapy (RT), or (c) BCS alone utilized

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more frequently in patients that are believed to be at a lower risk for disease recurrence.

Mastectomy has historically been the standard treatment for DCIS with an excellent local recurrence-free survival of 98 % to 99% at 10 years (3,4). However, in effort to spare patients from possible overtreatment and the morbidity of radical surgery, the treatment paradigm in recent years has shifted to an increased use of BCS. Although the local recurrence rates with BCT are higher than those with mastectomy, there are currently no randomized trials comparing mastectomy to BCT for in situ disease, and results of retrospective studies have been inconclusive in demonstrating any significant difference in long-term survival among the two treatment modalities. (5,6). However, the difference in local recurrence rates between mastectomy and BCS alone can be reduced by the addition of RT to BCS. Several large randomized controlled trials have demonstrated that the addition of RT reduces ipsilateral breast tumor recurrences (IBTR) by 50% to 60% (7–13). Although the role of RT in DCIS is strongly supported by these randomized data, there are also data that support the possible omission of adjuvant RT in certain low risk subgroups, in attempts to further optimize the risk–benefit ratio in patients with in situ disease (14).

Additionally, despite the fact that adjuvant radiation is an integral component of breast conservation treatment according to the randomized data mentioned above, the utilization of RT after BCS for patients with DCIS has been much lower than expected (15). Several factors including disease characteristics, patient preference, and access to RT facilities may contribute to the low utilization rates of RT after BCS. It is likely that decreasing the duration of RT with the implementation of accelerated partial breast irradiation (APBI) techniques could assist in increasing the rates of utilization of RT as part of BCT.

■ EVIDENCE SUPPORTING THE BENEFIT OF RT IN DCIS

Randomized Controlled Trials

In the past 25 years, overall, four large randomized controlled trials have been conducted in an effort to study the efficacy of BCS with or without radiation in the local control of DCIS (Table 1) (7–13). The design of the first large multicentered trial for DCIS patients was preceded by an observation made from a subset of patients enrolled in the National Surgical Adjuvant Breast and Bowel (NSABP) B-06 clinical trial that investigated the equivalence of mastectomy to BCT, consisting of BCS + RT, for invasive breast cancer (16). Included in the NSABP B-06 trial were 76 patients who were found to have DCIS on further review of their biopsy specimens but were nevertheless included in long-term follow-up (17). Of these patients, 28 underwent mastectomy and 48 received BCS. It was observed that among the patients receiving BCS, the local recurrence rate was 7% in the 27 patients receiving adjuvant RT and 43% in the 21 patients treated with BCS alone. These findings contributed to the establishment of a dedicated trial investigating the role of RT as part of BCT for DCIS.

The NSABP B-17 trial randomized 818 patients with DCIS to BCS alone or with adjuvant RT (7). After a margin negative resection, defined as no cells at the inked margin, patients were randomized to receive postoperative whole breast radiation or no irradiation. For randomization purposes, patients were stratified by age (lesser or greater than 49 years), tumor type (DCIS or DCIS plus LCIS) and method of disease detection (clinical or mammographic), and whether an axillary dissection was performed. The radiation technique consisted of whole breast opposed tangential fields treated to 50 Gy without any additional surgical bed boost. The results of the B-17 trial after a 12-year follow-up demonstrated that the local recurrence rate with BCS alone was 31.7%, which was significantly reduced to 15.7% ($p < 0.000005$) with the addition of adjuvant RT (8). On subset analysis for predictors of local recurrence, the presence of comedo necrosis was the single pathological feature associated with increased recurrence, and there was no difference in the survival rates among the two arms at 12 years, with 86% in the BCS group and 87% for the BCS + RT group ($P = .08$). In the most recent follow up of the trial after a median of 17.2 years, IBTR in the surgery alone arm was 35%, which was significantly reduced to 19.8% with adjuvant RT. Additionally, there was no difference in overall survival or breast cancer–specific survival in the two arms on 17.2-year follow up (9).

The European Organization for Research and Treatment of Cancer (EORTC) 10853 prospective randomized trial was conducted with a design similar to the NSABP B-17 study. The EORTC 10853 randomized 1010 patients to BCS or BCS + RT, and after 10.5 years of median follow-up, the rate of local recurrence was 26% in the BCS-alone arm and 15% in the BCS with RT arm ($P < .0001$), with 52% of the recurrences occurring as invasive cancer (10). There

TABLE 1 Randomized clinical trials comparing breast-conserving surgery alone or with radiation therapy for DCIS

	Enrollment	Number of Patients	Follow-Up (years)	Detected by Screening	Negative Margins Required	Central Pathology Review	RT Dose	BCS Alone Recurrence (%)	BCS + RT Recurrence (%)
NSABP—B-17[a]	1985–1990	818	17.2	80%	Yes (13% unknown)	76%	50 Gy/25 fractions (9% with boost)	35	19.8
EORTC 10853[b]	1986–1996	1010	10.5	71%	Yes (16% unknown)	85%	50 Gy/25 fractions (5% with boost)	26	15
SweDCIS[c]	1987–1999	1046	8.5	79%	No (11% positive, 9% unknown)	20%	50 /25 fractions or 48 Gy/20 fractions or 54 Gy/27 fractions split course (no boost)	27	12
UKCCCR[d]	1990–1998	1030	12.7	>90%	Yes	79%	50 Gy/25 fractions (no boost)	19.4	7.1

[a] Wapnir IL, et al. (9).
[b] Bijker N, et al. (10).
[c] Holmberg L, et al. (11).
[d] Cuzick J, et al. (13).

were requirements identical to that in the NSABP B-17 trial regarding no tumor cells at the inked margin, and the RT similarly consisted of tangential whole breast fields treated to 50 Gy in 25 fractions, with no boost advised. The survival rate was 95% in both arms and on multivariate analysis, factors that were significantly associated with an increased risk of local recurrence included young age (≤ 40 years; HR = 1.89), intermediately or poorly differentiated DCIS (as opposed to well-differentiated DCIS; HR = 1.85 and 1.61, respectively), cribriform or solid growth pattern (versus clinging/micropapillary subtypes; HR = 2.39 and 2.25, respectively), questionable margins (HR = 1.84), clinically detected lesions (HR = 1.55), and treatment by BCS alone (HR = 1.82).

The Swedish Breast group similarly published their results on the randomized SweDCIS trial, which consisted of 1046 evaluable patients with DCIS limited to one breast quadrant, receiving BCS consisting of a sector resection, which included excision of the underlying pectoralis fascia along with the tumor (11). The patients were randomized to observation or whole breast RT after BCS. After a median follow-up of 8.5 years, there was a 15% absolute reduction in the risk of recurrence with the addition of RT after BCS with a local recurrence rate of 27% in the observation arm versus 12% with the addition of radiation treatment after BCS. Of note, in contrast to the NSABP and EORTC trials discussed above, 11% of patients had positive margins, and RT dose ranged from 50 Gy in 25 fractions to 54 Gy in a split course regimen corresponding to a biologically equivalent dose of 46 Gy. Consistent with earlier randomized trials, the overall survival rate in this study was similar at 91% at 8.5 years for both arms (11).

The United Kingdom Coordinating Committee on Cancer research (UKCCCR) DCIS working party was conducted in a joint effort among the United Kingdom, New Zealand, and Australia to investigate the role of adjuvant radiation in DCIS (12). This trial used a 2-by-2 factorial design to randomize 1701 patients with DCIS after BCS to adjuvant RT or observation, with an additional randomization with adjuvant Tamoxifen (TAM) hormone therapy, or no additional hormonal therapy. The trial requirements included negative surgical margins, and RT consisted of tangential whole breast fields treated to 50 Gy in 25 fractions, with no boost advised. In addition, in the arms randomized to hormonal therapy, TAM was prescribed at 20 mg/day for a period of 5 years. A total of 1030 patients were included in the analysis of the effect of RT, and after a 4.4-year follow-up, RT was shown to reduce the number of IBTR from 16% in the observation group to 7% with the addition of adjuvant RT ($P < .0001$). However, TAM did not reduce the risk of overall ipsilateral tumor recurrence with 13% IBTR with TAM as compared to 15% with no hormonal treatment ($P = .42$). However, TAM did result in a significant reduction in all combined ipsilateral and contralateral DCIS events (HR = 0.68, $P = .03$) (12). More recently, long-term follow-up of the UKCCCR trial reports that after a median 12·7-year follow-up, RT reduced the incidence of all new IBTR by 59% (HR= 0.41, $P < ·0001$), with a 12 % absolute risk reduction in both invasive and in situ disease from 19.4% to 7.1% (13). Overall, there was no significant difference in overall survival across the treatment arms, but there was a small significant increase in cardiovascular deaths in those randomized to RT, with or without TAM ($P = ·008$). Furthermore, results of the 12.7-year median follow-up on the effect of hormonal treatment demonstrated that TAM significantly reduced the rate of recurrent ipsilateral DCIS (12.1% without TAM vs. 8.6% with TAM, $P = .03$), but not that of ipsilateral invasive disease (6.9% without TAM vs. 6.8 % with TAM, $P = .79$). The benefit of TAM was small but significant in reducing both invasive and in situ contralateral breast recurrences with an overall reduction of 4.2% to 2.9% with TAM ($P = .005$). Overall, there was an absolute 10-year reduction of 3.9% for all ipsilateral events and 2.3% for contralateral events, with a combined 6.5% reduction in new breast events with TAM use (13).

More recently, the Radiation Therapy and Oncology Group (RTOG) completed enrollment of 636 women with DCIS on the RTOG 9804 trial investigating the role of adjuvant RT after BCS in a 2-by-2 factorial design with and without TAM. This study also required negative surgical margins, and the RT allowed several possible fractionation schemes including 42.5 Gy in 2.7 Gy fractions, 50 Gy in 2.0 Gy fractions or 50.4 Gy in 1.8 Gy fractions, with no boost recommended. Although the study did not reach target enrollment, the results of the trial are currently pending.

Systematic Reviews and Meta-Analyses

A meta-analysis of the four randomized controlled trials comparing RT to observation after BCS in 3665 women with DCIS was reported by Viani et al. (18). The results of the meta-analysis indicated that the addition of RT to BCS conferred a 60% reduction in both invasive and in situ breast cancer

recurrence ($P < .00001$). There was also a 1.5-fold increase in the rate of contralateral breast cancer in patients who received adjuvant RT compared with those who received BCS alone ($P = .03$). However, there was no significant benefit in overall survival (98% for both groups, $P = 0.77$) or distant metastases (1.5% for both groups, $P = 0.89$) with the addition of RT as compared to that in BCS alone.

The Early Breast Cancer Trialists Collaborative Group (EBCTCG) recently completed a meta-analysis of the four previously mentioned randomized controlled trials of RT for DCIS after BCS (19). The meta-analysis included 3729 women with DCIS who were treated in these four trials, and after 10 years the addition of RT reduced the risk of IBTR by 15.2% ($P < .00001$) from 28.1% to 12.9%, for both recurrent DCIS and invasive recurrences. The benefit of adjuvant RT was independent of age at diagnosis, extent of BCS, use of TAM, method of DCIS detection, margin status, lesion focality, grade, comedonecrosis, architecture, or tumor size. However, there was a greater reduction in IBTR with adjuvant RT in older women, as compared to younger women, with an absolute difference in IBTR of 18.5% versus 29.1% in women aged more than 50 years as compared to 10.8% versus 27.8% for women ≥50 years. (19). Of note, the effect of adjuvant RT was seen even in women with small, low-grade tumors and negative margins, with an absolute reduction of 18% in the 10 year IBTR in this subgroup. However, there was no significant effect seen on 10-year breast cancer recurrence free survival (approximately 94% for both arms) or overall survival (approximately 98.5% for both arms) with the addition of RT.

In addition, a Cochrane systematic review of the four large randomized trials was performed by Goodwin et al. (20). This review confirmed a statistically significant benefit with the addition of adjuvant RT on all IBTR (HR = 0.49, $P < .00001$), with all subgroups benefiting from the addition of radiotherapy, regardless of margin status, patient age, and tumor grade. It was also concluded that nine women require treatment with radiotherapy to prevent one ipsilateral breast recurrence (NNT = 9). In addition, there was no significantly higher number of deaths due to vascular disease and pulmonary toxicity for women who received adjuvant RT.

Population-Based Observational Studies

Several studies have reviewed the role of RT in DCIS in large population-based cohorts. Among these, Smith et al. (21) published results on a SEER analysis of 3409 women with DCIS, older than 66 years treated with BCS, with approximately half of this group also receiving RT as part of their treatment. The definition of IBTR in this study included the documentation of a salvage mastectomy used as a surrogate for recurrence, or any second ipsilateral breast event. The 5-year recurrence risk was determined for patients with and without certain high-risk features, which were defined as one of the following; age 66–69 years, tumor larger than 2.5 cm, comedo histology, or any high-grade lesion. It was observed that for patients without any high-risk features, the 5-year IBTR risk was 8% with BCS alone as compared to 1% with the addition of RT after BCS ($P < .001$). Similarly, for patients who had any single high-risk feature, the 5-year IBTR risk was 14% for BCS alone as compared to 4% with BCS + RT ($P < .001$). Therefore, it was suggested that the addition of RT after BCS was able to confer a benefit to both low- and high-risk patients with DCIS. Furthermore, it was concluded that for this patient population, the number needed to treat with adjuvant RT to prevent one breast cancer event in 5 years was 11 for high-risk patients and 15 for low-risk patients (21).

Another study of DCIS patients treated in the East Netherlands also supports the benefit of RT in reducing IBTR after BCS in a population-based cohort. In this study, data from 798 patients treated with BCS with or without adjuvant RT were analyzed. The beneficial effect of RT in preventing IBTR was confirmed, with the 5-year recurrence rate of 25% for BCS alone as compared to 9% for patients treated with BCS +RT. ($P < .01$) (22). In addition, patients with close or involved margins had an increased IBTR rate of 17% compared with 9% IBTR in patients with negative margins ($P < .01$). In univariate analysis, the only pathologic variable significantly related to IBTR was the presence of comedo necrosis with a 5-year IBTR of 14% seen in the presence of necrosis as compared to 1% IBTR without necrosis ($P < .01$).

The role of RT in decreasing the risk of IBTR is further supported by another population-based study by Warren et al. on 1103 women with DCIS in the SEER registry with a 91-month follow-up (23). This analysis demonstrated the IBTR for BCS alone to be 15% as compared to 10.7% with the addition of RT to BCS. This study also found the risk of breast cancer–associated mortality to be 2.8% versus 0.8% (p=0.02) in the BCS alone and BCS+RT groups.

More recently, a population-based study on a cohort of 994 women with DCIS in Monroe County

in New York and The Henry Ford Health System in Michigan was published by Dick et al. in order to characterize the comparative effectiveness of different treatment strategies in the management of DCIS, the role of the treating surgeon in the margin status, and the treatment outcomes (24). The results of this study indicated that the treatment received was independently associated with the risk of IBTR. It was found that in women who had mastectomy and achieved negative margins, the relative risk of recurrence was 0.03 ($P < .001$) compared with that in women who had BCS and negative margins. Patients who underwent BCS with a positive margin had a relative risk of recurrence of 3.38 ($P = .02$). However, the addition of RT was independently associated with a reduced relative risk of recurrence (RR = 0.25, $P < .001$). The results confirmed that BCS in the absence of RT resulted in substantially higher IBTR compared with BCS followed by either RT or mastectomy, confirming the role of RT in the treatment of DCIS. However, surprisingly, a unique finding in this study was the detection of a significant difference in the 5-year disease-free survival rates among the treatment modalities, with a 99.3% 5-year survival with mastectomy compared with 94.5% with BCS + RT and 82.4% with BCS alone ($P_{diff} < .001$ for each of the differences) (24).

■ RISK STRATIFICATION AND PATIENT SELECTION FOR ADJUVANT RT

As mentioned previously, the large randomized trials for DCIS established the essential role of RT in conferring an approximate 50% to 60% reduction in IBTR in patients after local excision, and the standard of care has been to include adjuvant RT as a component of treatment for the majority of these patients. However, these large trials were not able to provide specific criteria that could be used to identify subgroups of patients in which RT could be omitted.

Nevertheless, in-depth analysis of these trials suggest that, tumor size, histological grade, margin status, and patient age may be prognostic factors associated with local recurrence after BCS alone (25–28). The National Institutes of Health consensus statement for DCIS recently highlighted the need to accurately risk-stratify patients with DCIS to identify subsets of women that could be managed with more conservative treatment (29). Based on these data, several groups have attempted to examine outcomes in patients treated with BCS alone and to identify certain low-risk subsets of patients with DCIS that may forgo adjuvant RT in an effort to maximize the risk–benefit ratio. In 1995, Silverstein et al. conducted a retrospective analysis of 333 patients with DCIS treated with BCS alone or with BCS and RT to correlate IBTR with clinical and pathological disease characteristics in an attempt to identify risk groups for disease recurrence (30,31). The analysis generated a classification system known as the Van Nuys Prognostic Index (VNPI), which consists of risk stratification based on three factors: tumor size, tumor grade and/or comedo-necrosis, and margin status. Recently, an additional variable has been incorporated in the newest classification, which now includes patient age, in addition to the three factors mentioned above (32). Each variable is assigned a point ranging from 1 for the lesions with the best prognosis to 3 with the lesions with worst prognosis to generate a score to classify patients into low-risk (4–6 points), intermediate–risk (7–9 points), or high-risk (10–12 points) subgroups. In the most recent update of the VNPI data, the retrospective analysis included 939 women with DCIS treated with BCS alone or with adjuvant RT (33). Overall, the authors concluded that for patients with a VNPI of 4, 5, or 6, the risk of local recurrence with BCS alone was very low with 6% IBTR at 12 years, which was further reduced to 3.5% with adjuvant radiation. In contrast, patients with a VPNI of 10, 11, or 12 had a very high IBTR rate of over 40% at 12 years, even with the addition of adjuvant RT. In patients with intermediate VNPI scores of 7, 8, or 9, the IBTR rate was above 20% at 12 years with BCS alone, but was dependent on the width of the resection margin. In these patients, adjuvant RT decreased the IBTR to below 20% at 12 years for patients with a score of 7 and margins < 3 mm, a score of 8 and margins ≥3 mm, and for patients with a score of 9 and margins ≥5 mm. In addition, patients with a score of 7 and with margin widths ≥3 mm had a low IBTR of less than 20% at 12 years and could be managed with BCS alone, which is similar to patients with a score of 4, 5, or 6. The group also recommended mastectomy for all patients with a score of 10, 11, or 12, for patients with a score of 8 and margins < 3 mm, and for those with a score 9 and margins <5 mm in order to maintain IBTR rate below 20% at 12 years. However, it should be noted that the VNPI classification is based on data that are limited due to their retrospective nature and need to be validated in a randomized setting with a larger sample size.

More recently, Wong et al. performed a prospective single arm study analyzing the risk of IBTR

in patients with low or intermediate grade DCIS excised with greater than 1 cm margins. In their initial analysis of 158 patients with 40 month follow-up, there was a 5 year IBTR rate of 12% with BCS alone (34). The results of this study were recently updated in abstract form demonstrating that on 8 year follow-up of 132 of these patients, there was an IBTR rate of 14.5% with BCS alone (35). The authors concluded that even in a highly selected subgroup of patients with small low and intermediate grade DCIS with wide excision margins there seems to be a substantial ongoing risk of IBTR.

Similarly, the Eastern Cooperative Oncology Group (ECOG) conducted a single arm, multi-institutional prospective trial E5194 for patients with DCIS managed with BCS alone (14). The eligibility criteria for patients enrolled in this trial included low- or intermediate-grade DCIS measuring 0.3 to 2.5 cm in size with margin widths ≥3 mm, or high-grade DCIS measuring 0.3 to 1.0 cm in size with margin widths ≥3 mm. After a median follow-up of 6 years, the study reported a 5-year and 7-year IBTR rate of 6.1% and 10.5% in the low-grade group and 15.3% and 18% in the high-grade group, respectively. The authors concluded that although the low 5-year IBTR rates with surgery alone in the low-grade cohort were acceptable, patients with high-grade disease had high IBTR at 5 and 7 years, highlighting an essential role of adjuvant RT in these higher-risk patients.

As mentioned previously, RTOG 9804 enrolled 636 women on a trial similar to the E5194 investigating the role of adjuvant RT after BCS with negative surgical margins for patients with low- to intermediate-grade DCIS. The study did not reach target enrollment, and results of the trial are currently pending.

■ UTILIZATION OF RT AS PART OF BREAST-CONSERVING TREATMENT FOR DCIS

In recent years, the use of BCS for focal DCIS has largely replaced mastectomy as an acceptable alternative because radical surgery has been generally considered overtreatment for a localized noninvasive disease with a high survival rate and a low absolute risk of recurrence (15). However, the large prospective randomized data that support the use of BCS also emphasize the need for RT as part of BCT to ensure adequate local control after local excision. Although BCT for DCIS has increased since the publication of these large studies, the utilization of radiation as part of BCT for these patients has been much lower than expected. In a SEER analysis of patients with DCIS treated in the period from 1992 to 1999, it was demonstrated that only 52% of patients received RT after BCS (15).

Several factors are thought to contribute to the omission of RT after BCS in the management of DCIS. One of the main arguments to forgo RT for patients after local excision is the lack of prospective randomized data demonstrating a survival benefit with the addition of RT to BCS. This is probably because most patients who develop IBTR can be salvaged by surgery. In addition, the absolute difference in survival that can be attributed to RT is too small to be demonstrable without larger sample sizes than our current available data and will only be evident with longer follow-up of the large cohort. However, a hypothetical survival benefit for RT in the management of DCIS may be revealed if we are able to employ the algorithm from the Early Breast Cancer Trialists Collaborative Group (EBCTCG)-published meta-analysis for invasive breast disease that states that for every four invasive recurrences that are prevented by the addition of RT, one disease-related death can be potentially avoided (36). Considering that the pooled data from the four large randomized trials demonstrated a 15% reduction in IBTR at 10 years with the addition of RT to BCS, and since half of these recurrences are invasive disease, this local recurrence benefit could theoretically translate in to a 2% benefit in long-term survival (37,38).

Another important aspect that may influence the use of RT after BCS in DCIS is that most of the randomized data demonstrate a 50% to 60% relative benefit in IBTR with the addition of RT after BCS. However, this relative reduction in recurrence risk is therefore highly dependent on whether the patient has high-risk features that would translate into a large absolute benefit in IBTR with the addition of RT. This fact ultimately results in the omission of RT for patients with smaller, low-grade tumors, excised with wide margins that seem to have a low absolute benefit in IBTR rate with RT. However, as discussed previously, prospective studies (14,34) have not been able to definitively determine whether it is safe to omit RT even in these highly selected low-risk groups. These single arm prospective trials have demonstrated a 10% to 15% IBTR rate on longer follow-up for low- to intermediate-grade lesions treated with surgery alone, which warrants the use of RT even in these low risk subgroups.

Finally, among other factors that influence the decision to offer or omit RT after BCS for DCIS are patient demographics, including older age and

comorbidities, in addition to geographical location and the availability of local RT facilities (39,40).

In the SEER analysis of patterns of care in DCIS mentioned earlier, only 52% of patients received RT after BCS, and the utilization of RT varied markedly from 39% to 74% with geographical location across the United States (15). In another study, Rakovitch et al. analyzed the utilization of RT in a population-based cohort of 727 women with DCIS in Ontario, Canada. In this cohort, 530 women underwent BCS, and of these, 49% received adjuvant RT. On multivariate analysis, RT use was associated with age younger than 70 years, in addition to other high-risk factors (41).

■ THE ROLE OF ACCELERATED PARTIAL BREAST IRRADIATION IN DCIS

Considering that the use of RT as part of BCT is dependent on the geographic availability of radiation facilities and ease of radiation access, APBI techniques may offer the opportunity to increase the proportion of patients with DCIS who receive RT as part of BCT due to the flexibility and convenience of a shorter course of treatment. In such a scenario, the protracted 5- to 6-week course of RT can be abbreviated to 1 week, possibly allowing for enhanced ease of access to radiation resources. However, the lack of sufficient prospective data for the use of APBI in DCIS limits the widespread clinical use of these techniques.

The American Society for Radiation Oncology (ASTRO) recently released a consensus statement regarding guidelines for patient selection and appropriate use of APBI techniques (42). The task force proposed three patient groups: a "suitable" group, for whom the use of APBI techniques outside of a clinical trial is acceptable, a "cautionary" group, for whom caution should be applied when considering APBI techniques outside of a clinical trial, and an "unsuitable" group, for whom APBI should only be considered in context of a clinical trial. As per the recommendations of the task force, patients with small (≤ 3 cm) pure DCIS are "cautionary" largely due to the fact that most of the single-arm prospective trials of APBI with long-term follow-up that demonstrate an acceptably low IBTR, excluded patients with DCIS (42). In addition, the consensus statement also recommended that patients with more extensive DCIS be placed in the "unsuitable" group, mainly due to the higher IBTR rates attributable to the discontinuous growth pattern seen in DCIS (43).

In a study by Shaitelman et al., the ASTRO consensus guideline was applied to 1449 patients treated with APBI on the American Society of Breast Surgeons Mammosite Registry Trial, to determine potential differences in clinical outcome based on the task force classification (44). Of the 34 total DCIS patients with sufficient information to be classified per the task force guidelines, there were only 8 patients in the cohort of 430 cautionary patients, with the majority allocated to the unsuitable group. On 5-year follow-up, there was a 5.4% IBTR rate in the 430 cautionary patients. Since only 34 patients with DCIS could be categorized by task force grouping, a univariate analysis was performed on data from 194 patients in the registry with DCIS that were not analyzed in a task force classification group due to missing information. Univariate analysis of the 194 patients demonstrated that only age < 50 years and close-positive margins were associated with a higher IBTR rate with odds ratio of 1.12 ($P = .007$) and 7.81 ($P = .01$), respectively. Goyal et al. recently reported on an updated analysis of the 194 DCIS patients in the Mammosite registry trial, with a comparison of the IBTR outcomes to the Intergroup E5194 trial (45). This study found that 70 of the total 194 patients in the registry who that met the criteria of E5194 and were treated with APBI had very low rates of recurrence. The 5-year IBTR rate in the low- to intermediate-grade cohort of this group of patients was 0% with APBI versus 6.1% with observation as per E5194. Similarly, in the high-grade cohort, 5-year IBTR was 5.3% with APBI versus 15.3% with observation as per E5194 results. The authors suggested that based on their analysis APBI reduced the risk of IBTR in the low-, intermediate-, and high-grade cohorts of DCIS patients treated by observation alone who met the eligibility criteria of E5194.

Recently a single institution retrospective review was performed by Stull et al. to determine the patterns of IBTR after APBI in patients classified as cautionary by the ASTRO consensus statement (46). Overall the study involved 109 cautionary patients, 46 of whom had DCIS. After a median follow-up of three years, the study found no instances of IBTR in the DCIS group. Similarly, McHaffie and al. reported outcomes on 136 cautionary patients, including 32 patients with DCIS treated with APBI at the University of Wisconsin (47). After a five year follow-up period, there were no IBTR's in the DCIS patients, as compared to a 4.8% IBTR rate in the entire cautionary cohort.

Although as seen above, the current retrospective data support the selective use of APBI for DCIS,

there is clearly a requirement for larger prospective studies that could further support the use of APBI in this patient population. The current NSABP-39/RTOG 0413 trial randomizing patients to APBI or whole breast irradiation includes patients with DCIS and will help to further define the appropriate use of APBI in patients with DCIS.

CONCLUDING REMARKS

The role of adjuvant RT for DCIS is largely based on four large randomized trials that demonstrate a significant improvement in local control for patients with DCIS treated with BCS and RT, as compared to BCS alone (7–13) (Table 1). These trials collectively demonstrated a 10% to 15% absolute reduction in IBTR with 8–17 year follow-up but were unable to show a significant survival benefit with adjuvant RT after BCS. However, since half of the IBTR events prevented by RT are invasive disease recurrences, thus this local recurrence benefit could theoretically translate into a small benefit in long-term survival, utilizing the example of the EBCTCG algorithm for invasive breast disease that states that for every four invasive recurrences that are prevented by the addition of RT, one disease-related death can be potentially avoided (36). Several large systematic reviews and population-based studies have confirmed that the beneficial effect of RT in reducing IBTR is largely present regardless of disease characteristics (18–24). However since certain favorable prognostic features may be associated with only a small absolute local recurrence benefit with RT, efforts are underway to identify certain low-risk subsets of patients with DCIS that may forgo adjuvant RT in an effort to maximize the risk–benefit ratio. The recent publication of the results of the Intergroup E5194 prospective trial of observation alone in selected patients with low-intermediate grade DCIS and high grade DCIS demonstrated a low 5 year IBTR rate with surgery alone in the low grade cohort, but a relatively higher IBTR for high grade disease, highlighting the role of adjuvant RT in these higher risk patients (14). Nevertheless, optimization of patient selection for tailored treatment requires additional long-term prospective data, including results of the RTOG 9804 trial, which is currently pending.

Although the prospective randomized data that support the use of BCS also emphasize the need for RT as part of BCT to ensure adequate local control after local excision, the utilization of radiation for these patients has been much lower than expected (15,41). Since the utilization of RT after BCS is dependent on the geographic availability of radiation facilities and ease of radiation access (39,40), APBI techniques may offer the opportunity to increase the proportion of patients with DCIS who receive RT due to increased convenience. Although the use of APBI techniques is considered cautionary as per the recent ASTRO APBI consensus guidelines due to insufficient supportive data, several retrospective studies demonstrate a low IBTR rate with APBI for select DCIS patients. (45–47). However, larger prospective trials of APBI in DCIS are needed to support the safe use of APBI in this patient population.

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Advances in Accelerated Partial Breast Irradiation

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■ ABSTRACT

Accelerated partial breast irradiation (APBI) is a method of adjuvant radiation therapy available for select women diagnosed with low-risk, early-stage breast cancer following breast-conserving surgery. This technique is based upon pathologic data demonstrating that the highest probability for recurrence exists within a close proximity to the lumpectomy cavity, as opposed to elsewhere in the breast. Several specialty societies have provided guidelines to assist in patient selection, and multiple APBI techniques are available, including interstitial brachytherapy, applicator-based brachytherapy, and 3D-CRT. Clinical outcome data is primarily limited to 5 years or less and is usually retrospective in nature, although some single-institution data extends up to 12 years of follow-up. Multiple Phase III trials are currently accruing patients, including the NSABP B-39/RTOG 0413 trial, which will evaluate APBI versus whole-breast irradiation and provide important guidance on the safety and efficacy of this growing segment of radiation oncology.

Keywords: breast cancer, accelerated partial breast irradiation, APBI, breast-conserving surgery, radiation therapy, hypofractionation

■ INTRODUCTION

The evolution of breast cancer treatment over the past 30 years demonstrates the value of multidisciplinary, personalized approach to oncologic care. In the early 1980s, the importance of radical surgery was brought into question with the initial publication of the National Surgical Bowel and Breast Project (NSABP) B-06 and National Cancer Institute in Milan trials demonstrating equivalence between radical mastectomy and breast-conserving surgery combined with whole-breast radiotherapy. These results have been updated by the original authors (1,2) and verified in other trials, including studies from the Institut Gustave-Roussy Breast Cancer Group and the Danish Breast Cancer Cooperative Group (3,4). Other randomized trials from the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute have

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shown equal rates of overall survival and distant metastases between mastectomy and breast conservation for invasive carcinoma of the breast (5,6).

Over time, data have emerged demonstrating that the highest risk for local recurrence following lumpectomy lies near the original tumor bed. For selected patients, this concept has led to the development of tailored options for adjuvant radiation therapy delivering the prescription dose to the peri-lumpectomy tissues alone, as opposed to the whole breast and first level of regional lymphatics. Although current outcome data is primarily in the form of retrospective analyses, ongoing Phase III clinical trials including the NSABP B-39/Radiation Therapy Oncology Group (RTOG) 0413 study will assist in answering the effectiveness and safety of limited radiotherapy to the lumpectomy cavity alone.

■ IMPACT OF ADJUVANT RADIOTHERAPY

Updates to the original NSABP B-06 and Milan III trials have shown the importance of including adjuvant radiotherapy to breast-conserving surgery. In a variety of series, omission of the second component of breast-conserving therapy yields an approximately double-digit increase in the absolute rate of local failures. In the B-06 trial, for example, patients who received surgery plus radiation had a local control rate of 86% at 20 years versus 61% for women who received surgery alone (1). The relationship between delivery of radiotherapy and local control has also been further emphasized with the randomized trials testing the impact of adding a radiotherapy boost to the lumpectomy bed. Both the EORTC and Lyon trials have firmly shown the impact of additional dose to the peri-lumpectomy tissues with decreases in absolute rates of local failure following traditional breast-conserving therapy (7,8). Additionally, a positive impact on overall survival has now been established through a meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) showing improved survival at 15 years when local recurrences are prevented by adjuvant radiotherapy 10 years earlier (9).

Although adjuvant radiation therapy has proven to be an important part of breast-conserving therapy, many women eligible for conservation of their breast receive either a mastectomy or lumpectomy alone. These decisions are likely related, in part, to the extended time course of whole-breast radiotherapy. For at least some women, the proximity of a radiation oncology facility influences whether they receive complete breast-conserving therapy or breast-conserving surgery alone. A study by Athas et al. confirmed this by showing an increased rate of complete breast conservation for patients who live close to a radiation center (10). Approximately 20% of patients with early-stage breast cancer who receive breast-conserving surgery forgo radiation treatments (10–12), which places them at a threefold increased risk of local recurrence when compared to patients who receive proper adjuvant therapy (1,2).

■ HISTORY OF ACCELERATED PARTIAL BREAST IRRADIATION

The first known application of radiation to treat breast cancer came 2 years after Marie and Pierre Curie's discovery of radium in 1898. In this initial application, a vial of radium salt was placed on the skin surface of a woman with breast cancer and the tumor was observed to decrease in size (13). Delivery of radiation therapy to a portion of the breast continued in the early 1900s with implantation of radium needles into clinically evident breast tumors. Although the current technique has been significantly refined and the pathological basis for accelerated partial breast irradiation (APBI) is different, credit for initial percutaneous implantation of radiation within a limited segment of the breast belongs to some of the earliest radiotherapists, including Geoffrey Keynes.

As technology for teletherapy was introduced and improved, interest in radiation treatment using radium needles decreased over time. The risk-adjusted rationale of partial breast irradiation did not reemerge until after the breast conservation movement, which took place beginning in the 1970s. In the United States, modern APBI was initially investigated in 1991 at the Oschner Clinic in New Orleans in Louisiana, and William Beaumont Hospital in Royal Oak in Michigan. In both locations, accelerated radiation treatment to a limited portion of the breast was designed for women who could, for family or logistical reasons, not stay at the respective clinics for the traditional 5-week whole-breast radiation therapy. Because the entire breast was not being treated with prescription doses of radiation, it was felt that the dose could be hypofractionated and accelerated to achieve excellent local control while maintaining minimal normal tissue toxicity.

■ PATHOLOGIC BASIS FOR APBI

Aside from the logistical benefits of shortening the length of treatment for patient convenience and decreased health care expenditure, there is pathologic support for decreasing the amount of breast tissue treated with adjuvant radiotherapy. Vicini et al. showed that for tumors that initially met NSABP criteria for negative microscopic margins (no tumor on ink), residual carcinoma (if present) was primarily limited to the first one centimeter beyond a lumpectomy margin in over 90% of cases (14). In a separate study of 1,598 patients treated with BCT by Kurtz et al., 179 had a recurrence of which 79% occurred within close proximity to the lumpectomy bed (15). Other reports support these findings showing recurrences after BCT typically occur within the same quadrant of the treated breast and that ipsilateral breast tumor recurrences in different quadrants occur at a rate of less than 4% (16–18). If a vast majority of recurrences occur within a close proximity of the initial surgical margin, it has been rationalized that radiotherapy could be applied only to this high-risk region, which is the pathologic premise of partial breast irradiation.

■ PATIENT SELECTION

Appropriate patient selection for APBI begins with proper identification of a patient for breast conservation. Nearly all absolute contraindications to BCT also apply to APBI. These include persistently positive margins, multicentricity, and diffuse microcalcifications. Relative contraindications to BCT should also be considered when counseling women regarding APBI, which primarily include a first or second trimester pregnancy, connective tissue disorders, and prior breast or chest wall radiotherapy. Additional constraints for partial breast irradiation include an inadequate device to skin distance (typically < 7 mm for single-lumen devices or < 3 mm for multilumen applicators) and close proximity of the lumpectomy cavity to a rib or the musculature of the chest wall. Since distance is only a surrogate for dose, many institutions have now moved away from distance-based constraints. Toxicity can be minimized if the doses to the skin and chest wall are kept below 120% and 145%, respectively (19).

Several specialty societies have issued criteria for the appropriate use of APBI. These include guidelines developed by the American Society of Breast Surgeons (ASBrS) (20), the American Brachytherapy Society (ABS) (21), and the eligibility criteria for enrollment on current NSABP/RTOG trial (22) (Table 1). Additional off-protocol guidelines include those issued by the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) (23) (Table 2). In contrast to the ASBrS and ABS guidelines, GEC-ESTRO stratifies women into three categories, recommending APBI only for women in their low-risk category. Patients in the intermediate risk category are advised not to undergo APBI outside the setting of a clinical trial and APBI is not recommended for women with any high-risk features.

In 2009, the American Society of Radiation Oncology (ASTRO) issued consensus panel (CP) recommendations, which identified the amount of prospective data for various groups of patients based on clinical and pathologic factors (24). Patients were grouped in suitable, cautionary, and unsuitable categories, which are listed in Table 3. It is important to note that although the word unsuitable is used in the ASTRO guidelines, this only refers to the amount of prospective data that is presently available for patients with these pathologic features. This designation does not indicate that it is entirely inappropriate to treat patients with these features as part of a clinical trial and, perhaps, a more appropriate term

TABLE 1 ASBrS, ABS, and NSABP/RTOG appropriateness criteria for APBI

ASBrS (20)	ABS (21)	NSABP/RTOG (22)
Age ≥ 45 (IDC), ≥ 50 (DCIS)	Age ≥ 45	Age ≥ 18
IDC, DCIS	Unifocal IDC	DCIS or invasive adenocarcinoma of the breast
Size ≤ 3 cm	Size ≤ 3 cm	Size ≤ 3 cm
Negative microscopic margins	No tumor on ink	No tumor on ink
LN negative	LN negative	Up to 3 LNs positive[a]

[a]When enrolled on a clinical trial.

TABLE 2 GEC-ESTRO APBI guidelines

Low Risk	Intermediate Risk	High Risk
Age ≥ 50	Age 41–49	Age ≤ 40
Margins ≥ 2 mm	Margins < 2 mm	Positive margins
Unicentric, unifocal disease	≤ 3 LNs positive	Multicentric disease
Tumor ≤ 3 cm		Tumor > 3 cm
No EIC, invasive lobular histology, or LVSI[a]		LVSI or EIC present
pN0		≥ 4 LNs positive or unknown axillary LN status

[a]Lymphovascular space invasion.
Source: Adapted from Ref. (22).

for this group of women would be "investigational." In addition, the "cautionary" designation only refers to the fact that limited data existed at the time the guidelines were published for the use of APBI in this subgroup of patients. Since that time, additional data have emerged (see below) challenging the use of these guidelines to select for the most optimal application of APBI.

For example, several authors have demonstrated similar clinical outcomes following partial breast irradiation without regard to which category they belong. These retrospective reviews quote similar rates of local recurrence, axillary failure, and distant metastasis for patients with pure ductal carcinoma in situ, invasive lobular carcinoma, triple negative histology, and node-positive disease (25–28). In a review of the ASBrS MammoSite® Registry Trial, the only factor on multivariate analysis that showed an increased propensity for local recurrence was estrogen receptor negative status ($P = .002$) (29). Although there has been recent discussion regarding revision of these groups, no definitive plans have yet been made to change the current ASTRO CP guidelines for APBI. Initial results of NSABP B-39/RTOG 0413 Phase III trial are not expected until at least 2015; and until that time, appropriate patient selection will continue to be performed using the specialty society references listed above.

■ TECHNIQUES FOR PARTIAL BREAST IRRADIATION

The method of partial breast irradiation that has been in use the longest and has the most extensive follow-up is the multicatheter interstitial technique (Figure 1). At William Beaumont Hospital, this technique was originally developed as a method to boost the lumpectomy cavity with low dose rate (LDR) radiotherapy (30). This approach was then applied to the treatment of the peri-lumpectomy tissues alone, first with LDR radiotherapy and now high dose rate (HDR) radiotherapy (31–33). Most interstitial implants require 15 to 20 catheters, which are typically arranged in two to three planes. Arguably, the most versatile form of APBI, the interstitial technique, is planned three dimensionally, which allows optimal shaping of the prescription dose and avoidance of critical structures such as the skin and chest wall. The most common dose and fractionation scheme for interstitial HDR brachytherapy is 3.4 Gy for ten fractions delivered in a BID fashion with an interfraction time of at least 6 hours.

Initially cleared by the U.S. Food and Drug Administration (US FDA) in 2002, applicator-based APBI has dramatically changed the landscape and interest in partial breast irradiation in the United States. Since 2002, the MammoSite® radiation therapy system (RTS) (Hologic, Inc., Bedford, MA) has been used to treat over 60,000 women with early-stage breast cancer (Figure 2). A patterns-of-care analysis of the Surveillance, Epidemiology, and End Results (SEER) database by Husain et al. has shown a tenfold increase in the use of partial breast irradiation in 2007 as compared to that in 2002 (34). One of the primary reasons for increased use of applicator-based brachytherapy as compared to traditional interstitial techniques is that interstitial implants require significant technical expertise while the initial single-lumen, single-entry device was more straightforward about implantation and dosimetric planning.

With the success of applicator-based brachytherapy, additional devices have been introduced.

TABLE 3 ASTRO Consensus Panel Groups for APBI

Factor	Suitable	Cautionary	Unsuitable
Age (years)	60	50–59	< 50
BRCA 1 or 2 mutation	Not present	—	Present
Tumor size	≤ 2 cm	> 2 cm, ≤ 3 cm	> 3 cm
T stage	T1	T0 or T2	T3 or T4
Margin status	Negative by ≥ 2 mm	Close (< 2 mm)	Positive
Grade	Any	—	—
LVSI	No	Limited/focal	Yes
ER status	Positive	Negative	—
Multicentricity	Unicentric only	—	Present
Multifocality	Clinically unifocal with total size ≤ 2 cm	Clinically unifocal with total size 2.1 to 3.0 cm	Multiple foci > 3 cm apart
Histology	Invasive ductal or other favorable subtype	Invasive lobular	
Pure DCIS	Not allowed	≤ 3 cm	If > 3 cm
EIC	Not allowed	≤ 3 cm	If > 3 cm
Associated LCIS	Allowed	—	—
N Stage	pN0 (i^-,i^+)	—	pN1, pN2, pN3
Nodal surgery	SLN Bx or ALND	—	None performed
Neoadjuvant therapy	Not allowed	—	If used

Source: Adapted from Ref. (23).

(A)

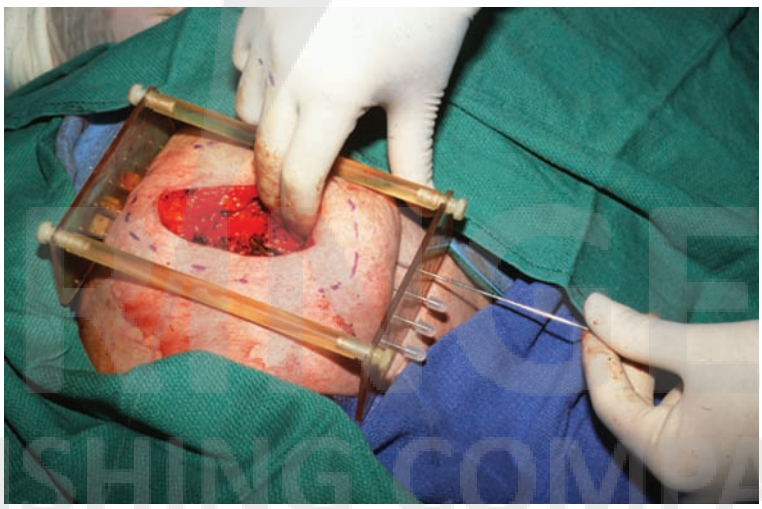
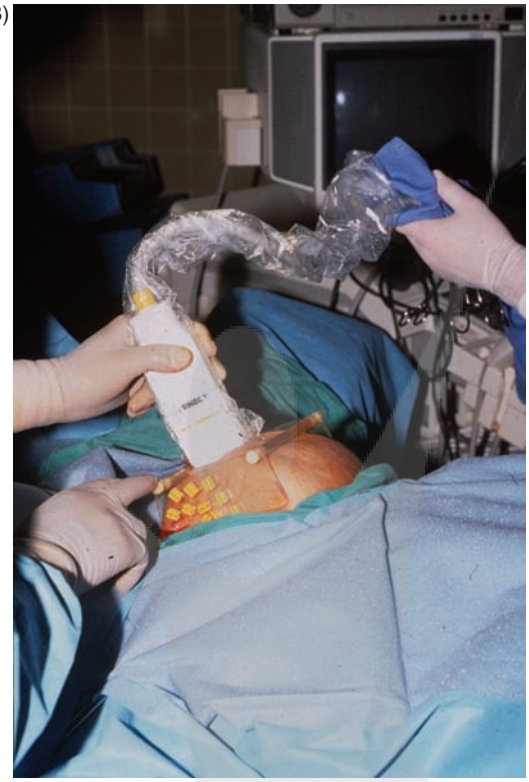


FIGURE 1 (A) Interstitial implant for brachytherapy.

(B)



(C)

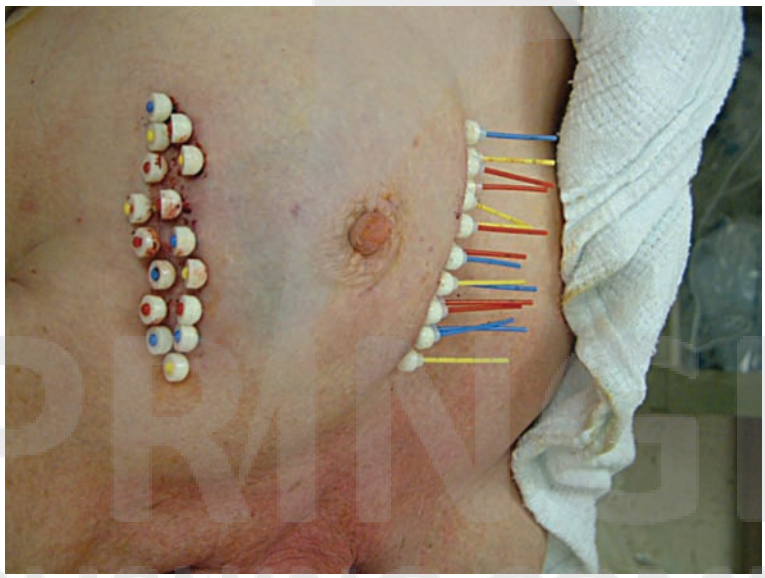


FIGURE 1 (B) Ultrasound guidance during catheter placement. (C) Completed interstitial implant.

(D)

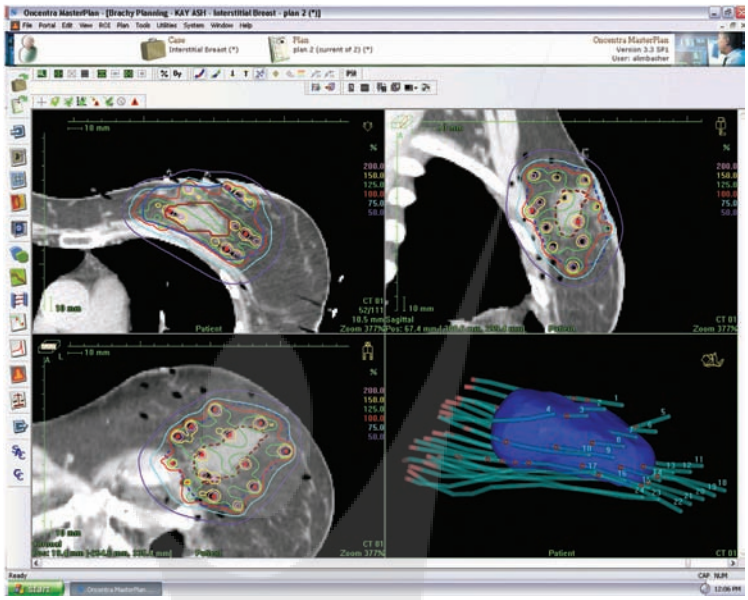


FIGURE 1 (D) Three dimensional rendering of an implant and dosimetry of an interstitial implant within the treatment planning software.
Source: Images courtesy of F. Vicini.

FIGURE 2 The original, single-lumen MammoSite® Radiation Therapy System which received FDA clearance in 2002.
Source: Photo courtesy of Hologic, Inc.

The first balloon-based multilumen device was the Contura® multilumen balloon (MLB) (Bard Biopsy Systems, Irvine, CA), which received FDA approval in May 2007 (Figure 3). The Contura MLB differs from the original MammoSite® device in that four additional catheters are offset and flexed away from the central catheter by 0.5 cm, which allows shaping of the dose away from critical structures that may be in close proximity to the lumpectomy cavity. The Contura® device also includes vacuum ports at the distal and proximal ends of the balloon, which allows aspiration of seroma fluid or air prior to treatment planning and delivery. Seroma fluid or a trapped volume of air greater than 10% of the prescription volume, if left in place, may make some patients ineligible for balloon-based brachytherapy.

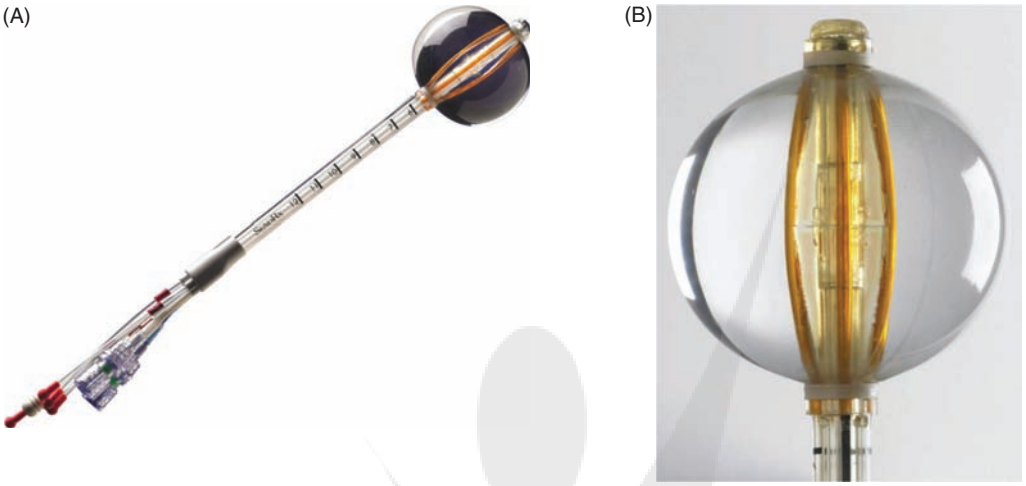


FIGURE 3 Contura® MLB with four additional lumens offset from the central channel by 5 mm (Figure 3B). *Source:* Photos courtesy of Bard Biopsy Systems, Inc.

Since the introduction of the Contura® MLB, a multilumen version of Hologic's device has been developed. The MammoSite® multilumen adds three additional lumens offset from the central lumen by 3 mm, which offers improved flexibility in treatment design. Prior to the introduction of multilumen devices, the optimal distance between the skin and balloon surface was 7 mm, which made many women ineligible for APBI. The improved dosimetric flexibility of multilumen applicators, in some cases, allows the treatment of patients with up to 3 mm or less of skin spacing, so long as dose constraints to the skin can still be met. Additional design improvements of the newer applicators include a more flexible shaft for patient comfort and the recent introduction of a keyed stylet within the center of the new MammoSite® Multilumen. The keyed stylet, shown in purple in Figure 4, is designed so that the shaft and balloon move in union when the device is rotated, eliminating the concern of balloon misalignment during a subsequent fraction as opposed to its original position at the time of treatment planning.

The first multilumen applicator that does not use a balloon is the Strut Adjusted Volumetric Implant® (SAVI®) (Cianna Medical, Aliso Viejo, CA), which received FDA approval in 2006 (Figure 5). Unlike other applicators, the SAVI® has multiple struts that project outward to create a whisk-like apparatus in which each of the exterior struts can be traversed by the HDR source. This device resembles a traditional interstitial-type technique since catheters are in direct contact with the tissue to be treated, yet it remains a single-entry device since only one percutaneous entry site is required. Potential concerns with this type of device include interfraction splaying of the struts, as they are not in fixed positions relative to one another (which tend to occur within the first 24 hours of device placement) and changes in relationship of air pockets and breast tissue to the device including the interdigitation of tissue between the struts (35). Because of the device's design, SAVI® implants are associated with a larger volume of tissue receiving 200% of the prescription dose (V_{200} > 10 cc for SAVI® vs. < 10 cc for balloon-based brachytherapy) (35–36). In addition, current treatment planning algorithms for brachytherapy do not use heterogeneity corrections. Because SAVI® has the potential for different amounts of air and/or fluid to reside within the interior of its strut system, dose calculations assuming a homogeneous or tissue-equivalent material may be inaccurate (37). Despite these technical considerations, initial early clinical outcomes appear good as Yashar et al. have published results using the SAVI® applicator to treat 100 patients. With a median follow-up of 21 months, there was one recurrence and minimal acute toxicity reported (38).

Currently, the most common method to deliver dose for brachytherapy-based APBI is via a HDR source administered using a robotic afterloader (Figure 6). Alternate methods exist including LDR seed implantation into the breast and electronic brachytherapy which inserts a miniature kilovoltage

FIGURE 4 MammoSite® ML with keyed stylet.
Source: Photo courtesy of Hologic, Inc.

(A)

FIGURE 5 (A) SAVI® applicator in four different sizes (six-strut mini, six-strut, eight-strut, and ten-strut versions of the SAVI® applicator shown from right to left).

(B)

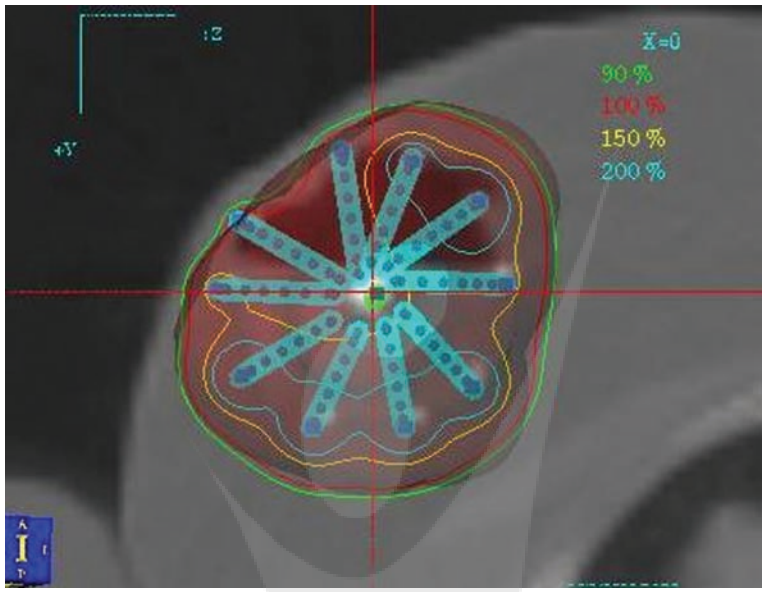


FIGURE 5 (B) Sample dosimetry using the SAVI® applicator.
Source: Photos courtesy of Cianna Medical, Inc.

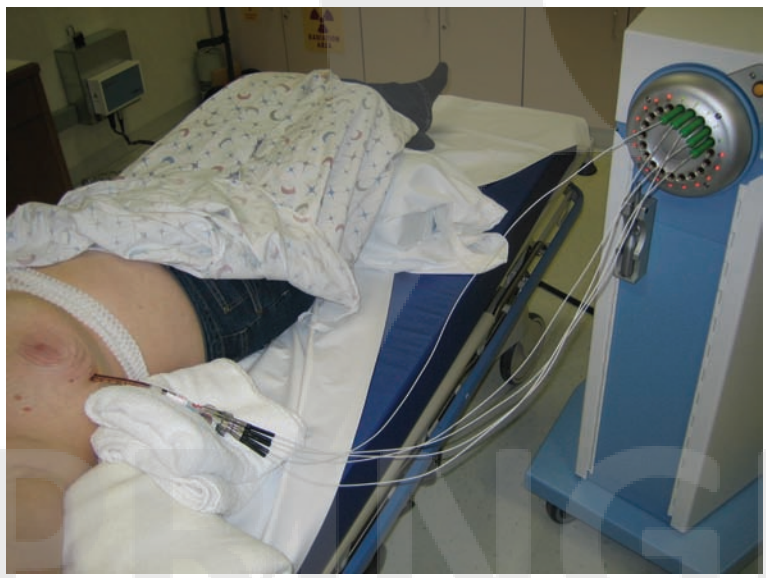


FIGURE 6 HDR afterloader connected to a multilumen applicator.
Source: Photo courtesy of L. Cuttino.

(kV) x-ray source into the Accent® brachytherapy applicator (Xoft, Inc, Sunnyvale, CA) (39) (Figure 7). Because of the relative increase in size of the electronic brachytherapy source as compared to an HDR source, conventional APBI applicators (MammoSite®, Contura®, etc.) cannot be used with the Xoft® system. Although it has not been widely adopted, an advantage of electronic brachytherapy is the reduced shielding requirements for brachytherapy treatment rooms. Concerns with this approach include a significantly higher dose at the balloon surface and the higher radiobiologic effect of kV x-rays,

both of which may lead to increased toxicity. This will need to be closely monitored as radiation centers gain experience with this system.

The third and one of the most widely used methods of APBI is three-dimensional conformal radiotherapy (3D-CRT). Initially introduced in 2003, this method uses a standard linear accelerator with a typical beam arrangement between three and five noncoplanar external radiotherapy segments to deliver the accelerated course of radiotherapy to the area surrounding the lumpectomy cavity (Figure 8) (40). Limitations of the 3D-CRT technique include increased dose to the contralateral breast, heart, and lungs. The dose is also delivered two times per day although the prescription dose is slightly higher to account for the lack of heterogeneity with 3D-CRT that exists with interstitial and applicator-based brachytherapy.

In Europe, several centers use intraoperative radiation therapy (IORT), which delivers a single dose of radiation immediately following removal of the lumpectomy specimen. The technique, which includes the ongoing Intraoperative Radiotherapy with Electrons (ELIOT) Phase III trial, was originally described by radiotherapy centers in Paris during the 1980s (41) and subsequently refined at the National Cancer Institute in Milan (42–44). Memorial Sloan-Kettering Cancer Center has also developed an

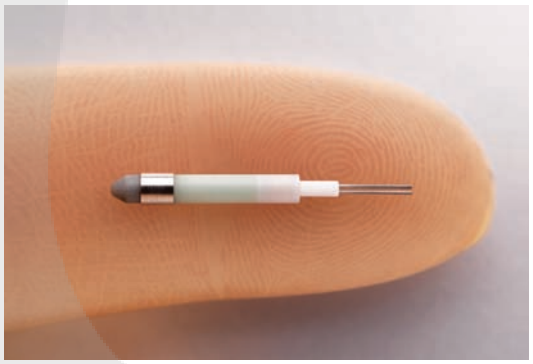


FIGURE 7 Example of applicator, X-ray source, and treatment console for electronic brachytherapy. *Source:* Photos courtesy of Xoft, Inc.

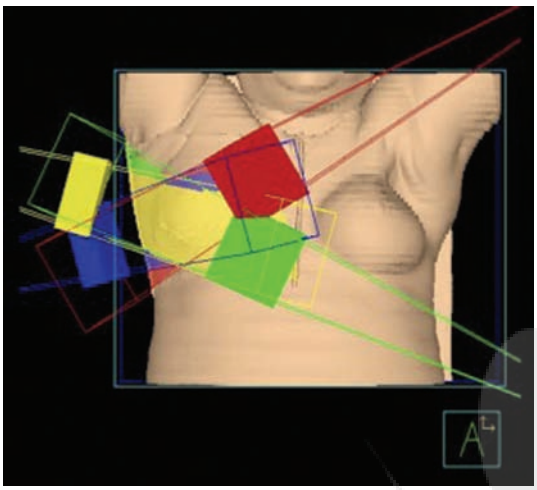


FIGURE 8 Example of four-field three-dimensional conformal radiation therapy
Source: Image courtesy of F. Vicini.

intraoperative HDR brachytherapy technique for delivery of APBI at the time of surgery (45).

Intraoperative partial breast irradiation has the distinct advantage of visualizing the tumor bed at the time of surgery; however, margin status and final details regarding tumor size and lymph node metastases are not available at the time of treatment. Advocates for IORT promote the potential benefit of treating residual tumor cells prior to the onset of hypoxia, which can occur following breast surgery. Intraoperative RT using a 50-kV photon source supplied by a mobile linear accelerator is presently being tested as part of the randomized Targeted Radiotherapy (TARGIT) for Breast Cancer Trial (INTRABEAM® System, Figure 9). Preliminary results published in 2010 showed noninferiority of the IORT arm as compared with whole-breast irradiation (46,47). Concerns regarding this technique include unknown margin status and the variant dosing used in the TARGIT trial (single fraction of 5–7 Gy at 1 cm depth as opposed to 34 Gy at 1 cm delivered in 10 fractions, BID).

Novel concepts currently being studied in partial breast irradiation include preoperative radiation therapy, stereotactic radiation therapy, and particle therapy. Feigenberg et al. at the University of Maryland reported a 17% pathologic complete response rate following preoperative APBI with a decrease in mean Ki-67 proliferation index from 17.4 to 6.1 (48). Preoperative radiotherapy is also under investigation at Duke University and the University of North Carolina (49,50). A stereotactic radiotherapy system using a cobalt-60 source delivering multiple noncoplanar arcs is currently in development by Xcision Medical Systems (GammaPod™, Columbia, MD) (Figure 10), which aims to have similar dosimetry to brachytherapy without the addition of an invasive procedure. Proton therapy for partial breast irradiation has been investigated at several centers including Massachusetts General Hospital, MD Anderson Cancer Center, and Loma Linda University (51–53). An initial publication from Massachusetts General by Kozak et al. suggested a higher-than-expected acute skin toxicity with proton-based APBI; however, a separate Phase II trial conducted at Loma Linda University did not report this same toxicity pattern. Ongoing prospective study of particle therapy for partial breast irradiation with long-term follow up is needed.

Dosing for all currently available APBI applicators used in an adjuvant setting is the same as interstitial-based brachytherapy (3.4 Gy × 10 fractions, BID). As mentioned above, 3D-CRT is typically given using the same fractionation pattern (10 fractions, BID), it but delivers a total dose of 3850 cGy, as opposed to 3400 cGy. Some centers, including New York University and sites in Europe, use different 3D-CRT dosing schedules (54). Further hypofractionated APBI (hypo-APBI) has also been tested. In a Phase II trial from William Beaumont Hospital, 45 patients were treated with adjuvant radiotherapy using the single-lumen MammoSite® RTS to deliver a total dose of 2800 cGy in four fractions. Updated results published in 2011 show excellent local and regional control with minimal acute and late toxicity (55). A previously underappreciated dose constraint to the chest wall was encountered as part of this trial which produced three rib fractures, two of which occurred in patients with a D_{max} to the chest wall > 160% of the prescription dose. An ongoing hypo-APBI clinical trial using a multilumen applicator is now accruing patients with which will deliver between two and four fractions of adjuvant radiotherapy using the Contura® MLB (Atif Khan, MD, Robert Wood Johnson University Hospital, written communication, April 2011). In this trial, the required D_{max} to a rib is less than or equal to the prescription dose.

■ TARGET DEFINITION

To determine the clinical target volume (CTV) for APBI, we rely on many of the publications that

FIGURE 9 (Left) INTRABEAM® IORT system. (Right) Placement of INTRABEAM® applicator within lumpectomy cavity following tumor removal.
Source: Photos courtesy of Carl Zeiss Meditec, Inc.

FIGURE 10 GammaPod™ stereotactic radiation therapy system.
Source: Photo courtesy of S. Feigenberg.

initially established support for treating only a limited segment of the breast. Most radiation oncologists who specialize in partial breast irradiation agree that if a lumpectomy margin is negative, it is the first 1- to 1.5-cm rim of peri-lumepctomy cavity tissue that has the highest likelihood to harbor microscopic disease. Goldstein et al. showed that patients with positive surgical margins following lumpectomy had a 29% chance of residual disease greater than 2 cm from the lumpectomy margin versus only 10% if the initial margin was negative (using NSABP criteria) (56). A report of 10-year data using 2-cm margins, classified as a large volume implant, showed excellent control rates (57), while treating just the surgical cavity with smaller implant volumes had a 16% rate of local recurrence (58). For APBI, a balance between the above data is reflected in the current lumpectomy bed to CTV expansion guidelines. Depending on which treatment modality is selected, recommended expansion to create the CTV from the edge of the lumpectomy cavity ranges between 1 and 1.5 cm. This rim of peri-lumpectomy tissue is at the highest

risk for local recurrence and should be encompassed by the highest isodose lines (IDL) of the proposed APBI treatment plan (14,59,60).

An issue that faces many radiation oncologists at the time of consultation with a candidate for APBI is whether reexcision of the lumpectomy cavity is necessary. Published rates of reexcision vary between 10% to nearly one-half of cases (61,62). Although multiple definitions of clear margins exist, the current national standard for NSABP trials is that the margins of the resected tumor must be microscopically free of cancer including DCIS (21), or "no tumor on ink." At William Beaumont Hospital, physicians advocate for surgical margins of 2 mm or greater, and reexcision of the lumpectomy bed, in general, is required prior to radiotherapy if this condition is not met (40). If a surgical margin is close (i.e., < 2 mm, but not positive), a discussion should be held with the surgeon to determine whether it is possible to remove additional tissue.

In the case of balloon-based brachytherapy devices, it has been accepted that a certain amount of compression of the tissue surrounding the lumpectomy cavity occurs when the device is inflated. Edmonson et al. and Dickler et al. both estimated that the first 1 cm of tissue surrounding an inflated MammoSite® balloon is equivalent to a 2-cm CTV surrounding a noncompressed lumpectomy cavity (63,64). This is reflected in the fact that a 1-cm CTV is required for MammoSite® treatment while a 1.5-centimeter CTV expansion is called for in 3D conformal and interstitial implants treated as part of the NSABP B-39/RTOG 0413 Phase III trial. Although this is the current convention, a volumetric analysis by Shaitelman et al. indicates that the 1-cm margin for MammoSite® may correlate with less tissue than originally had been projected (65).

Planning target volume (PTV) expansions are generally used only in 3D conformal applications of APBI. Because interstitial catheters and brachytherapy devices move together with the lumpectomy cavity, the CTV with these treatment modalities is equivalent to a PTV and no additional expansion is necessary. With IORT, the breast gland and tissue at risk is directly visualized, which also obviates the need for a PTV. For 3D-CRT, however, an additional expansion must be added to the CTV to account for organ motion (respiration, cardiac systole) and setup error. The NSABP B-39/RTOG 0413 calls for a 10-mm expansion from CTV to PTV for both whole breast and partial breast mini-tangent radiation plans.

■ TREATMENT PLANNING AND PLAN EVALUATION

Although the details of treatment planning for each APBI modality is beyond the scope of this chapter, it is important to note some of the differences in physical delivery of dose between the three main partial breast treatment options in the United States.

Interstitial brachytherapy offers the most flexible approach to APBI as the treatment planning software is not limited by a fixed geometry of catheters within a single-entry device. As such, conforming the prescription dose to an irregularly or nonspherical-shaped lumpectomy cavity is a strict advantage of this technique. Either a free-hand or template-based approach may be used, both of which can be done in an operative setting with the use of ultrasound guidance. Once the catheters are in place, a CT scan is obtained to reconstruct the relative position of each brachytherapy catheter relative to the lumpectomy cavity and target. Although coverage is deemed acceptable if 90% of the prescription dose is delivered to 90% of the target, it is common to be able to achieve much higher levels of CTV coverage through dose optimization within the treatment planning software. For multicatheter brachytherapy, the NSABP B-39/RTOG 0413 clinical trial requires the V_{150} and V_{200} to be ≤ 70 cc and ≤ 20 cc, respectively, with a corresponding dose homogeneity index ($1\text{-}V_{150}/V_{100}$) of ≥ 0.75 (66).

Treatment planning for applicator-based brachytherapy using single-entry devices has become more complex with the introduction of multi-lumen applicators. The initial single-lumen MammoSite® RTS was typically planned with between one and five source dwell positions and the resultant treatment plan was largely influenced by balloon fill, skin spacing, and chest wall distance. While these factors remain important when planning a case using a multi-lumen device, complex treatment planning algorithms can now be used to sculpt dose away from critical structures while maintaining acceptable coverage of the peri-lumpectomy tissues (Figure 11). For treatment on the NSABP B-39/RTOG 0413 protocol using either the MammoSite® or Contura® MLB, the maximum skin dose must be ≤ 145% of the prescription dose, and V_{150} and V_{200} must be ≤ 50 cc and ≤ 10 cc, respectively. With the advent of multilumen applicators, lower dose constraints can often be achieved including a maximum skin dose ≤ 125% of the prescription dose and a V_{150} and V_{200} of less than 30 cc and 10 cc, respectively. An important consideration is that, when possible, reductions

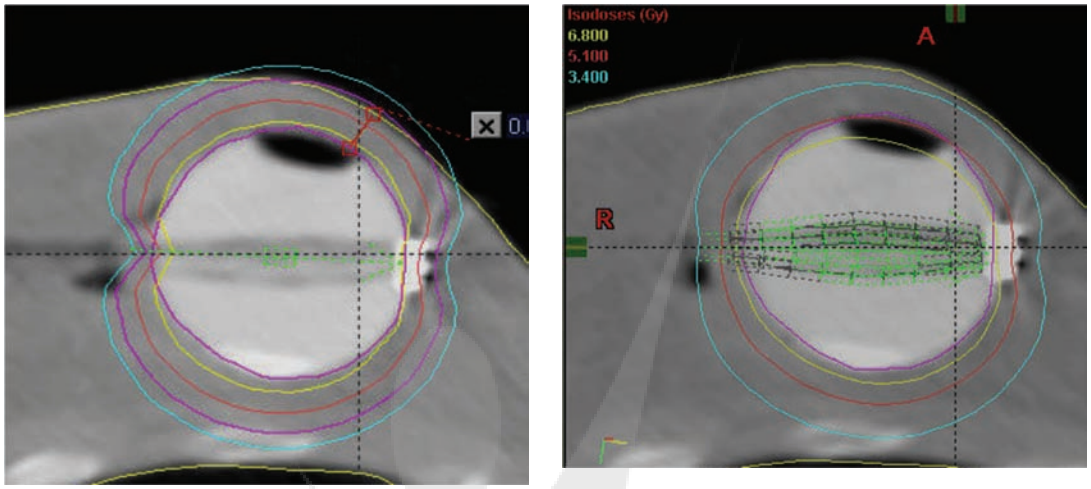


FIGURE 11 Dosimetry using the Contura® multi-lumen brachytherapy applicator before and after treatment planning software optimization to decrease dose to the skin.
Source: Images courtesy of L. Cuttino.

in these parameters will likely lead to improved outcomes regarding improved cosmesis and reduced toxicity and, thus, use of the later set of guidelines for balloon-based brachytherapy is encouraged.

Plan evaluation for cases treated with the SAVI® applicator require an understanding that because of the presence of catheters at the periphery of the device, which are in direct contact with breast tissue, higher V_{150} and V_{200} are a reality with this type of application. Nonuniform catheter spacing or clumping, especially at the ends of the device, is an important consideration that must be evaluated to ensure unwanted high-dose heterogeneity does not exist in these locations. Although some investigators have described acceptable V_{150} and V_{200} levels for the SAVI® device as less than 70 cc and 20 cc, respectively, these values were derived from the multicatheter interstitial experience. Since the SAVI® is an intra-cavitary device and not an interstitial implant, the current NSABP/RTOG trial requires SAVI® implants to adhere to intra-cavitary device constraints (V_{150} of less than 50 cc and V_{200} of less than 10 cc). Use of a V_{200} greater than 10 cc for a single-entry device, such as the SAVI®, would violate the current dose constraints of the NSABP/RTOG Phase III trial. Although heterogeneity corrections are not typically applied in APBI cases, varied levels of fluid and air within the center of the SAVI® device may lead to higher-than-planned dose delivery since a tissue-equivalent material is not in place in between the struts. Richardson et al. have estimated this increased dose at between 5% and 10% at the prescription point using Monte Carlo dose calculations as compared to a standard TG-43-based homogeneous calculation (67).

The most homogeneous dose distribution with partial breast irradiation is delivered using the three-dimensional conformal technique. Because of the lack of heterogeneity, which is inherent in implant-based APBI, 3D-CRT plans result in a lower uniform dose. To account for this, the 3D-CRT dose is slightly higher per fraction (385 cGy) as compared to interstitial and applicator-based brachytherapy. Patients are simulated supine with arms elevated in a cradle device. Radioopaque markers should be placed at the time of simulation outlining the superior, inferior, medial, and lateral aspects of the breast tissue. For left-sided lesions, breath-hold or other techniques should be attempted to minimize the amount of the anterior cardiac wall to be included in the radiation fields. To create a CTV for a 3D-CRT case, 1.5 cm is added to the edge of the lumpectomy bed followed by a CTV to PTV expansion of an additional 1 cm to account for setup uncertainty and internal motion. In some cases, a modified PTV is required depending on the skin spacing and distance of the lumpectomy cavity to the chest wall. In these cases, a PTV_EVAL is created by subtracting the first 5 mm of either the skin and/or chest wall (including the pectoralis muscles) away from the newly created PTV. An important note is that the PTV_EVAL is only used for dose volume histogram analysis, and not to determine

beam orientation or aperture. Beam arrangement is typically noncoplanar variants of standard tangential fields, which are labeled based on their trajectory (anterior, inferior, superior, oblique etc.). At William Beaumont Hospital, 3D-CRT plans are manually optimized using 60° wedges and varied beam weights to ensure the CTV is covered by the 100% IDL and the PTV is covered by the 95% IDL. Dose constraints for all of APBI modalities, including 3D-CRT, are summarized in Table 4.

■ OUTCOMES FOLLOWING APBI

Several single-institution and collaborative series on APBI have been published and updated including reports by William Beaumont Hospital, Virginia Commonwealth University, Tufts Medical Center, New York University, and others (Table 5). At this time, results for only two Phase III trials are available that compare APBI and whole breast irradiation. The National Institute of Oncology in Hungary conducted a randomized trial of 258 patients, reporting 5-year interim analysis in 2007 showing equivalent control between the study arms with a local recurrence of 4.7% in the partial breast irradiation arm and 3.4% in the WBI arm (not statistically significant) (68). Cosmesis was improved in the patients receiving HDR partial breast irradiation versus those who received standard WBI. The TARGIT A trial, as discussed above, reported in 2010 noninferiority between their single-fraction partial breast and standard whole breast treatment arms although the median follow up was less than 3 years. Other groups have attempted to compare APBI and WBI through retrospective methods. A 12-year matched pair analysis was published by Shah et al. comparing 199 patients treated with APBI with a similar cohort of 199 patients treated with WBI. This study concluded that patients who received a limited radiation field had outcomes similar to that of whole-breast irradiation including local relapse ≤ 5.0%, regional relapse ≤ 2.0%, and disease-free survival > 87% at 12 years (69). Outcomes of other published series are included in Table 5 (brachytherapy) and Table 6 (3D-CRT).

Regarding long-term toxicity, Hepel et al. and Jagasi et al. have published reports of increased skin toxicity with resultant untoward effects on cosmesis for patients treated with the 3D-CRT form of APBI (70,71). In the series from Tufts University, 8.3% of patients had Grade III skin toxicities while Jagasi et al. reported development of unacceptable cosmesis in 7 out of 32 evaluable patients, which led to early

TABLE 4 Dose constraints for APBI

Structure	10 Fraction (3D-CRT)	10 Fraction (Interstitial)	10 Fraction (Applicator-Based)
Heart	$V_2 \leq 40\%$[a] $V_2 < 5\%$[b]		$V_{1.7} < 40\%$[a] $V_{1.7} < 5\%$[b]
Lung			
Ipsilateral	$V_{11.5} < 10\%$		$V_{10} \leq 15\%$
Contralateral	$V_2 < 10\%$		
PTV coverage	$D_{90\%} \geq 90\%$ IDL	$D_{90\%} \geq 90\%$ IDL	$D_{90\%} \geq 90\%$ IDL
Thyroid	$D_{max} \leq 1.0$ Gy	$D_{max} \leq 1.0$ Gy	$D_{max} \leq 1.0$ Gy
Breast			
Uninvolved ipsilateral	$V_{19} \leq 60\%$	$V_{17} \leq 60\%$	$V_{17} \leq 60\%$
Entire ipsilateral	$V_{38.5} \leq 35\%$		
Contralateral	$D_{max} \leq 1.0$ Gy		$V_1 \leq 3\%$
Skin		$D_{max} \leq 100\%$	$D_{max} \leq 120$- 145%[c]
Rib	$D_{max} \leq 145\%$	$D_{max} \leq 145\%$	$D_{max} \leq 145\%$
High-dose regions	$D_{max} \leq 120\%$	$V_{150\%} < 70$ cm^3 $V_{200\%} < 20$ cm^3	$V_{150\%} < 30$- 50 cm^3 $V_{200\%} < 10$ cm^3

[a] If tumor is located on left side.
[b] Right-sided lesions.
[c] ≤ 145% for 4-cm sphere, ≤ 130% for 3-cm sphere, although the lowest dose while maintaining appropriate PTV coverage should be sought.

TABLE 5 Interstitial and balloon-based APBI trials

Institution	Number of Patients	Follow-Up (Years)	Local Recurrence (%)	Toxicity
National Institute of Oncology, Hungary (76)	45	12	9.3	< 3% Grade III
William Beaumont Hospital (63)	199	12	5	
Oschner Clinic (30)	71	6.25	8	Grade III (late): LDR: 3.8% HDR: 7.7%
Tufts Medical Center (77)	32	5	6	Fat necrosis, skin, and subcutaneous toxicity declined with additional follow-up
RTOG 95–17 (78)	99	5	3 (HDR) 6 (LDR)	Grade III (late): LDR 18% HDR 4%
ASBrS MammoSite® Registry (79)	1449	5	3.8	
William Beaumont Hospital—MammoSite® (80)	80	3.5	2.9	
Multi-institutional (VCU) (81)	493	2	1.2	9% infection rate (5% if closed-cavity technique used)

TABLE 6 3D-CRT APBI trials

Institution	Number of Patients	Follow-Up (mo)	Local Recurrence	Grade III Toxicity
William Beaumont Hospital (82)	96	47	1%	4%
RTOG 0319 (83)	52	42	6%	4%
NSABP B-39/RTOG 0413 (21)	1,392	42	—	≤ 3%
Tufts University (63)	64	15	—	8.3%
Rocky Mountain CC (84)	55	10	0%	3.6%

closure of their Phase II trial. Fortunately, other centers have not experienced these results. A toxicity analysis of the ongoing NSABP B-39 / RTOG 0413 Phase III trial, of which 70% of enrollees on the partial breast treatment arm receive 3D-CRT, was conducted and presented at the 2011 Annual Meeting of ASTRO. In this report, less than three percent of nearly 1,400 women treated with 3D-CRT had a Grade 3 or higher skin toxicity (72). Despite the focus on skin appearance, fibrosis, and cosmesis, other acute and chronic toxicities following APBI exist including symptomatic fat necrosis, acute and late infection, seroma formation, and extreme forms of skin toxicity (such as nonhealing fistulous tracks). In general, however, APBI is thought to be well tolerated when used to treat appropriately selected patients and rates of toxicity following APBI have been comparable to the side effects of standard whole breast irradiation.

With the publication of the ASCOSOG Z0011 trial (73) and the initial report of the MA.20 trial (74) by Whelan et al., there has been renewed interest in to what extent the regional lymphatics need to be treated for women diagnosed with early-stage breast cancer. APBI offers a unique perspective on this debate as no prescription dose is delivered to the regional lymphatics with this technique. Although tumor cells are likely in-transit for some patients with node-negative breast cancer, irradiation of the lumpectomy cavity alone without whole breast irradiation yields a rate of axillary recurrence between 1% and 2% (62,75). In a trial that allowed up to three lymph nodes positive, the 5-year rate of axillary recurrence was 5% (71). This represents a further point on the

spectrum of risk-appropriate treatment for women with early-stage breast cancer.

■ FUTURE DIRECTIONS

Over the next 10 years, we will likely see a continued paradigm shift in oncology care where adjuvant therapies are no longer given to broad groups of patients based on their anatomic stage alone, but instead will be more risk-adjusted and personalized based on a multitude of histopathologic and genetic factors. Although radiotherapy recommendations are not presently based on allelic expression, further efforts will be made to improve organ preservation and limitation of toxicities so that the type and extent of treatment is more closely tailored based on the risk and potential pattern for tumor recurrence.

Continued development of safe and effective fractionation schedules will also continue to be important. At least two of the companies that manufacture brachytherapy applicators have sponsored Phase II trials using 2-day dose fractionation schedules in the United States. As results from these trials mature, consideration of a Phase III trial to compare various fractionation patterns should be discussed.

Future challenges to this segment of breast cancer care will be defining the appropriate management for recurrences/new primaries following both whole and partial breast irradiation while maintaining appropriate guidelines for APBI as additional data become available, including the publication of the ongoing Phase III trials.

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Hypofractionation for Breast Cancer

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■ ABSTRACT

Randomized trials testing 2.67 Gy fractions of adjuvant whole-breast radiotherapy after breast-conservation surgery for early stage cancer confirm that local tumor control and late adverse effects are comparable to that of standard schedules based on daily 2.0 Gy fractions. Current 15- or 16- fraction schedules of 2.67 Gy may not represent the limits of this approach, and it is possible that fewer, larger fractions can be delivered safely, provided appropriate downward adjustments are made to the total dose. Based on current evidence, testing a 5-fraction schedule of hypofractionated whole-breast radiotherapy appears to be a realizable research objective. Therapeutic gain could be compromised if breast cancer proves to be, on average, significantly less sensitive to fraction size than the dose-limiting late reacting normal tissues, but the data argue against this at the present time. Even if there is a slight disadvantage in terms of fractionation sensitivity, shortened overall treatment times might offset this disadvantage by reducing tumor cell repopulation during radiotherapy. The encouraging initial experience with accelerated partial breast irradiation suggests a strong volume effect for late normal tissue damage. Schedules that are safe when delivered to small partial volumes cannot be assumed safe if delivered to larger partial volumes or to the whole breast.

Keywords: breast cancer, radiotherapy, hypofractionation

■ INTRODUCTION

Conventional radiotherapy schedules use fractions of 1.8 to 2.0 Gy, a choice reflecting historical observations that late-reacting normal tissues are, on average, more sensitive to fraction size compared with malignant tissues. Attempts to reduce the number of fractions in the 1970s made inadequate downward adjustments to total dose, resulting in unacceptable rates of late complications (1). These miscalculations inhibited further research in breast radiotherapy fractionation for decades, but interest in fewer larger fractions delivered over a shorter overall treatment time has been rekindled by randomized clinical trials based on a better understanding of normal tissue and tumor responses. Four large randomized trials have compared a lower total dose in fewer larger fractions against 50 Gy in 25 fractions, and all have reported favorable results in terms of local tumor control and late adverse effects (2–7). In fact, the data strongly suggest that breast cancer behaves rather like a late-reacting normal tissue in its response to fraction size, meaning that small fractions are as gentle on the cancer as on the healthy tissues (3–5). Recognition that small fractions do not always have the advantages previously attributed to them creates possibilities to

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exploit accelerated hypofractionation, a term referring to the use of fewer, but larger, fractions (>2.0 Gy) delivered over a shorter overall time than standard regimens.

■ HYPOFRACTIONATION IN RADIOTHERAPY: A BRIEF HISTORY

Early radiation therapy evolved as an empirical art rather than an exact science. Fractionation was introduced, not because of an appreciation of the nuances of radiobiology, but because the technological limitations of the early therapy machines meant that treatment had to be given using interrupted regimens (8). Clinical innovation and experience were consistently followed by attempts to explain the underlying biology. One of the important lessons that history taught us is that fractionation cannot be considered in isolation. There is a complex interdependence between total dose, dose per fraction, overall treatment time, treated volume, beam parameters, prescribing conventions, and quality control procedures (1,9–11).

Frank Ellis introduced the concept of nominal standard dose (NSD) into clinical radiotherapy (12). This was an attempt to enable clinicians to change from one fractionation regimen to another, while maintaining equivalent biological effects on both tumor and normal tissues. Unfortunately, the NSD model did not allow for the relative importance of dose per fraction in determining late effects in normal tissues, but it was adopted by clinicians without an appreciation of this important limitation (1,9,10,13). When clinically safe regimens using 30 fractions were converted, using the NSD concept, to their 'equivalent' in 10–15 fractions, the biological effects on late-reacting normal tissues were systematically underestimated.

Currently, the linear quadratic (LQ) model dominates the field of mathematical radiobiology (14–15). This model incorporates the effect of dose per fraction and can, by making additional assumptions, also incorporate the effects of repopulation during a course of fractionated radiotherapy. The distinct fractionation sensitivities of early and late responding normal tissues are well described using the LQ model in which an endpoint-specific quantity, the α/β ratio, offers a reliable way of describing these differences (14,15). Assuming a typical α/β value of 3.0 Gy for late-reacting normal tissue responses, a 15-fraction regimen reproducing the effects of 25 fractions of 2.0 Gy requires a reduction in total dose from 50 to 42.8 Gy in fractions of 2.85 Gy (16). There is, therefore, nothing intrinsically unsafe about doses >2 Gy per fraction, but the total dose must be reduced in order to maintain the same level of normal tissue effect. Demonstrating equivalence in dose-limiting adverse effects is not enough to make the schedule useful: tumor control must be maintained or improved as well.

For fraction sizes in the range of 1 to 6 Gy, the LQ model offers a reliable guide for identifying a hypofractionated schedule equivalent to a conventionally fractionated regimen in terms of late adverse effects, assuming an appropriate value of α/β ratio is used (14,15). The assumption that cancers are, on average, relatively insensitive to fraction size hold true for some squamous carcinomas (α/β >10 Gy), but α/β value estimates derived from human data suggest that breast cancer is more sensitive to fraction size than previously thought. An α/β value of 4 to 5 Gy was first estimated for locally advanced and recurrent breast cancer by Douglas in the mid-1980s based on clinical data published by Cohen in the early 1950s (17,18). The underlying cell and molecular processes that explain these differences are not clear, but a mechanistic understanding is not needed to apply the LQ model safely and effectively.

■ HYPOFRACTIONATED WHOLE BREAST IRRADIATION: THE EVIDENCE FROM TRIALS

Over the last 20 years, several randomized trials involving a combined total of around 8,000 women compared hypofractionated adjuvant radiotherapy to a standard regimen of 50 Gy in 25 fractions (Tables 1–3) (2–7,19). The UK Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) and Standardisation of Breast Radiotherapy Trial A (START A) trials tested two dose levels of a 13-fraction regimen in terms of late adverse effects and tumor control. The study design allowed direct estimates of α/β for each trial (3–5). Based on a combined total of 278 locoregional tumor relapses in the two trials, the adjusted α/β value for tumor control was 4.6 Gy (95% confidence interval [CI], 1.1–8.1), comparable to 3.4 Gy (95% CI, 2.3–4.5) for late change in photographic breast appearance. The two trials' results suggested that a 13-fraction regimen delivered over 5 weeks can be as safe and effective as 50 Gy in 25 fractions.

Results from the Canadian and START B trials are consistent with this interpretation. The Ontario trial compared 42.5 Gy in 16 fractions of 2.66 Gy

TABLE 1 Selected characteristics of randomized trials of breast hypofractionation

	RMH/GOC (3,4)	START A (5)	START B (6)	Canadian (2,7)	FAST (19)
Years accrual	1986–1998	1998–2002	1999–2001	1993–1996	2004–2007
Total number of patients	1410	2236	2215	1234	915
Standard arm (Gy/fractions/weeks)	50/25/5	50/25/5	50/25/5	50/25/5	50/25/5
Test arm A (Gy/fractions/weeks)	42.9/13/5	41.6/13/5	40.0/15/5	42.5/16/3.1	30/5/5
Test arm B (Gy/fractions/weeks)	39/13/5	39/13/5	n/a	n/a	28.5/5/5
Mean age (years)	54.5	57.2	57.4	Not reported	62.5
Node+ (%)	32.7	28.8	22.8	0	0
Mastectomy (%)	0	15	8	0	0
Tumor size ≥T2 (%)	42.5[a]	48.6	35.9	20	17.8
Boost (%)	74.5	60.6	42.6	0	0
Chemotherapy (%)	13.9	35.5	22.2	11	0
Regional radiotherapy (%)	20.6	14.2	7.3	0	0

[a]Clinical T stage.

(3.2 weeks) with 50 Gy in 25 fractions over 5 weeks (2,7). Schedules are expected to be equivalent in terms of late normal tissue and tumor responses assuming an α/β value of 3.0 Gy for each and no influence of treatment time. Rates of breast cosmesis at a median follow-up of >11 years were virtually identical in both treatment arms, consistent with this expectation. Given that tumor control might be sensitive to a 2-week difference in treatment duration, it is not possible to estimate tumor fractionation sensitivity from these two trials. The UK START B trial compared 40 Gy in 15 fractions of 2.67 Gy (3 weeks) to 50 Gy in 25 fractions and recorded a lower rate of change in breast appearance after the 15-fraction regimen (hazard ratio [HR] = 0.83; 95% CI, 0.66–1.04; $P = .06$) (6). An HR of <1 for late adverse effects is likely to be real, since 40 Gy in 15 fractions is equivalent to 45.5 Gy in 2-Gy fractions if the α/β ratio = 3 Gy. In other words, 40 Gy in 15 fractions is gentler on late-reacting normal tissues compared with 50 Gy in 25 fractions. The next important question is whether it is also gentler on breast cancer. If the α/β value for tumor control is ≥10 Gy, tumor control should be inferior after such a large reduction in total dose (from 50 to 40 Gy), unless there is a major effect of shortening overall time, but tumor control does not appear to be worse (Table 3). Although there were only 65 local-regional tumor relapses in START B at the time of reporting, the HR for this endpoint was 0.79 (95% CI, 0.48–1.29), indicating similar rates of local-regional relapse after 40 Gy in 15 fractions compared with the control arm. The residual imprecision indicated by the upper and lower 95% CI limits for the absolute difference between 40 Gy in 15 fractions and the control schedule in START B suggests that locoregional tumor relapse is unlikely to be more than 1% higher, and perhaps 1% or 2% lower, than after 50 Gy in 25 fractions.

A 15-fraction schedule is now the UK standard recommended by the National Institute for Health and Clinical Excellence, but it is unlikely to represent the useful limits of hypofractionation for whole-breast radiotherapy. There is a history of prescribing once-weekly fractions of whole breast radiotherapy for women too frail or otherwise unable to attend for conventional schedules. In a French series of 115 patients undergoing primary radiotherapy without surgery for nonmetastatic breast cancer from 1987 to 1999, the whole breast received 5 once-weekly fractions of 6.5 Gy (20). Of these patients, 101 were given additional tumor bed boost doses, 7 with 1 fraction, 69 with 2 fractions and 25 with 3 once-weekly fractions of 6.5 Gy using electrons. Kaplan-Meier estimates of late effects in the breast were 24% Grade 1, 21% Grade 2, and 6% Grade 3 at 48 months. The 5-year local progression-free rate was 78% (95% CI, 66.6–88.4). In a separate French series, 5 once-weekly fractions of 6.5 Gy to the whole breast with no boost were given to 50 women after local tumor excision (21). Grade 1 or 2 induration was reported in 33%

TABLE 2 Comparison of cosmesis and normal tissue effects of hypofractionated and standard breast radiation therapy

Trial	Total Dose (Gy/Fractions)	Excellent/Good Cosmesis or No Change (%)		Moderate/Marked Change (% or HR[a])		Moderate/Marked Induration (% or HR[a])	
		5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
RMH/GOC (3,4)	50/25	60.4	46.6	6.4	9.8	23.1	36.3
	42.9/13	54.3	42.0	11.2	15.6	35.6	51.1
	39/13	69.7	43.9	3.9	6.6	16.0	27.7
START A (5)	50/25	57.1		1.0[a]		1.0[a]	
	41.6/13	56.4		1.05[a]		1.09[a]	
	39/13	67.9		0.86[a]		0.81[a]	
START B (6)	50/25	57.8		1.0[a]		1.0[a]	
	40/15	63.5		0.83[a]		0.89[a]	
Canadian (2,7)	50/25	79.2	71.3			6.1	10.4
	42.5/16	77.9	69.8			4.7	11.9
FAST (19)	50/25	98.3[b]		7.6[c]		1.9[c]	
	30/5	90.7[b]		13.7[c]		4.0[c]	
	28.5/5	96.2[b]		7.9[c]		2.6[c]	

[a]Hazard ratio.
[b]2 years post randomization.
[c]3 years post randomization (breast shrinkage only).

TABLE 3 Rates of local recurrence in the altered fractionation trials

Trial	Total Dose (Gy/Fraction)	3-Year Local Recurrence (%)	5-Year Local Recurrence (%)	10-Year Local Recurrence (%)
RMH/GOC (3,4)	50/25		7.9	12.1
	42.9/13		7.1	9.6
	39/13		9.1	14.8
START A (5)	50/25		3.2	
	41.6/13		3.2	
	39/13		4.6	
START B (6)	50/25		3.3	
	40/15		2.0	
Canadian (2,7)	50/25		3.2	6.7
	42.5/16		2.8	6.2
FAST (19)	50/25	0.7		
	30/5	0		
	28.5/5	0		

of the patients at a median follow up of 93 months (range 9–140). The 7-year local relapse-free survival was 91%. Five fractions of 6.5 Gy are equivalent to 62 Gy in 31 fractions assuming α/β = 3.0 Gy, a significantly higher dose intensity than conventional schedules deliver.

The recently reported UK FAST Trial tested two dose levels of a 5-fraction regimen delivering 1 fraction per week against a control schedule of 50 Gy in 25 fractions, defining radiotherapy adverse effects as the primary endpoint (19). Once-weekly fractions were chosen to minimize confounding of treatment outcome measures by differences in overall treatment time. The two test dose levels delivered 5 fractions of 5.7 or 6.0 Gy (total dose 28.5 or 30 Gy), estimated to be iso-effective with the control regimen assuming α/β values of 3.0 or 4.0 Gy, respectively. Seven hundred and twenty nine patients had 2-year photographic assessments. Risk ratios for mild/marked change were 1.70 (95% CI, 1.26–2.29, $P <$ .001) for 30 Gy and 1.15 (0.82–1.60, P = .489) for 28.5 Gy versus 50 Gy. Three-year rates of physician-assessed moderate/marked adverse effects in the breast were 17.3% (13.3%–22.3%, $P <$ .001) for 30 Gy and 11.1% (7.9–15.6%, P = 0.18) for 28.5 Gy compared with 9.5% (6.5–13.7%) after 50 Gy. With a median follow-up of 37.3 months, 2 local tumor relapses and 23 deaths have occurred. Change in photographic breast appearance, the primary endpoint, gave an estimate of α/β of 2.6 Gy (95% CI, 1.4–3.7). Using this estimate, the isoeffect doses expressed in 2-Gy equivalents for 30 and 28.5 Gy in 5 fractions are 56.3 and 51.6 Gy, respectively. Therefore, at 3 years median follow-up, 28.5 Gy in 5 fractions is comparable to 50 Gy in 25 fractions, and significantly milder than 30 Gy in 5 fractions, in terms of adverse effects in the breast.

All the evidence so far suggests that the α/β value for tumor control is around 4 Gy, which is comparable to values for late-responding normal tissues (3–5). Despite a 10-Gy reduction in total dose, from 50 to 40 Gy, introduced in UK trials to compensate for the increase in fraction size from 2.0 to 2.67 Gy, no inferiority in tumor control was reported. This observation suggests that breast cancer responded strongly to this modest increase in fraction size.

Benefits of Hypofractionation

Immediate advantages of hypofractionation include increased patient convenience, lower treatment costs, and lower radiotherapy waiting times, especially important in countries where these resources are restrained (22). The lower total dose delivered in fewer, larger fractions means shorter overall treatment duration (accelerated hypofractionation), which may be more effective in subsets of patients with high proliferative indices (a hypothesis that needs testing). Shorter treatment times may also have scheduling advantages in that radiotherapy can be delivered straight after surgery when the residual tumor burden is likely to be lowest, as in current accelerated partial breast conformal radiotherapy techniques (23,24). A benefit of the lower total dose delivered using hypofractionation is a lower rate of moist desquamation, often developing in the inframammary fold of large-breasted women. This was demonstrated in the UK FAST trial, in which the rate of moist desquamation fell from 12/110 (10.9%) after 50 Gy in 25 fractions to 2/106 (1.9%) after 28.5 Gy in 5 fractions (19). One of the benefits expected from lower rates of moist desquamation are lower rates of consequential late effects, including cutaneous atrophy, telangiectasia, and subcutaneous induration, the direct consequences of severe epidermal denudation and delayed healing.

Concerns Regarding Hypofractionation

Most of the apprehension regarding accelerated hypofractionated schedules is based on the memory of severe late toxicities from schedules based on misapplication of dose algorithms in the 1960s and 1970s (1,9–11). Other factors contributing to poor historical results of hypofractionated breast radiotherapy included poor dosimetry, high skin doses delivered by low-energy beams, use of nonstandard reference points, and position errors causing overlap at field junctions (25,26).

With regards to stochastic and nontochastic adverse effects from radiotherapy, these continue to develop over the whole lifetime of a patient so that many decades are needed for a complete description. The important question for interpreting trials of hypofractionation is whether the ratio of dose-limiting adverse effects in experimental and control arms at the time of reporting predicts the ratio of relevant adverse effects at later time points. Comparisons of 5- and 10-year results for a range of late adverse effects scored in the RMH/GOC trial are consistent with this requirement for the safe adoption of hypofractionation (3). Also persuasive are the 14-year follow up data of the EORTC 22881–10882 tumor bed

boost trial, in which the relative risk of breast induration 14 years after randomization to boost versus no boost could be accurately quantified within 5 years of treatment (27).

Where the heart is concerned, even 10 years is insufficient to estimate the relative risk of heart disease. However, the issue of fractionation is irrelevant for this organ. An excess risk of ischaemic heart disease is apparent after cardiac doses <10 Gy, so the priority is to exclude the heart from the treatment volume whatever fractionation regimen is used (28,29). Fractionation issues are also irrelevant where the lung is concerned, since lung tolerance of 20 Gy in 2-Gy fractions is exceeded whatever fractionation is used. Radiation pneumonitis risk is more closely related to volume, so that an increased risk is unlikely to be seen with hypofractionation in the absence of higher volume of lung irradiated (30–32).

Another concern is the implication of 'double trouble', a term describing the clinical effects of higher total doses and higher doses per fraction in partial volumes (hotspots) receiving more than 100% prescribed dose (33). Due to the mathematical form of the linear quadratic dose effect relationship, hotspots are penalized more severely in a hypofractionated treatment, so-called "triple trouble" (34). In practice, triple trouble is of little clinical significance if hot spots are limited in volume and dose gradients are restricted to between 95% and 107% of the reference isodose (3). Despite this reassurance, full dose compensation is recommended as standard practice for patients who were prescribed breast radiotherapy regardless of fractionation regimen, since it has been shown in a randomized trial to reduce the incidence and severity of late adverse effects (35). With improved dose homogeneity, there should be no concern about treating large breast size with hypofractionation.

After irradiation of the axilla and/or supraclavicular fossa in over 400 patients within hypofractionated arms of the RMH/GOC, START A, and START B trials, there was no increase in reports of brachial plexopathy at a median follow up of ≥6 years (3–6). The 40 Gy in 15 fractions regimen is equivalent to 47 Gy in 2-Gy fractions regimen if the α/β value for brachial plexus is 2 Gy, or 49 Gy in 2-Gy fractions if α/β is 1 Gy. In other words, this hypofractionated regimen is actually gentler than 50 Gy in 25 fractions with respect to late effects in all normal tissues. If radiotherapy centers are confident that their techniques are safe when prescribing 50 Gy in 25 fractions, there is a reduced risk of late adverse effects after 40 Gy in 15 fractions using the same treatment position, field arrangement, dosimetry and reference points.

■ ACCELERATED PARTIAL BREAST HYPOFRACTIONATION

Partial breast irradiation (PBI), which is less than whole breast irradiation (WBI), refers to irradiation of a limited volume of breast tissue around the tumor bed. The rationale behind PBI is that most of the ipsilateral breast tumor recurrences occur in the same quadrant as the original tumor. Spatial patterns of ipsilateral breast tumor recurrence reported in 5 randomized trials of breast-conserving surgery with or without WBI demonstrated a 76% to 90% incidence of "same site" relapse with most recurrences occurring within 2 cm of the primary lesion (36–41). Currently there are 7 prospective randomized phase III trials comparing WBI with PBI using various techniques and dose fractionations as outlined in Table 4.

Accelerated hypofractionated regimens have found immediate acceptance for PBI based on the assumption that a reduction in treatment volume counterbalances unexpected adverse effects of increased fraction size on normal tissue reactions. Current protocols for accelerated PBI (APBI) include twice-daily fractions separated by 6 hours (42–44). Whatever the schedule is, a twice-daily schedule will have a greater biological effect due to incomplete recovery. For example, in the National Surgical Adjuvant Breast and Bowel Project B-39 trial, 38.5 Gy in 10 fractions delivered by external beam conformal radiotherapy in twice-daily fractions over 1 week is equivalent to 53 Gy in 2-Gy fractions, assuming complete repair and an α/β value of 3.4 Gy (42). If the recovery halftime for late effects is taken as the 4.4 hours estimated for subcutaneous fibrosis in the Continuous Hyperfractionated Accelerated Radiotherapy head and neck trial (45), the twice-daily schedule delivers the equivalent of 65 Gy in 2-Gy fractions. The satisfactory interim cosmetic results reported with this schedule suggest a significant volume effect in sparing late adverse effects, but mature results from all APBI trials are awaited both in terms of cosmesis and local control rates (46,47).

■ HYPOFRACTIONATION AND CONCURRENT TUMOR BED BOOST

Of the 5 prospective studies for hypofractionated WBI, two did not use a boost, two used a boost at

TABLE 4 Prospective Phase III trials APBI

Trial	*N*	Inclusion Criteria	Control Arm	Experimental Arm	Activated
TARGIT (42)	2232	≥45; T1, small T2; N0–1; ductal	WBI; As per institutional guidelines	Low-energy X-rays 50 kV; 20 Gy/1 fraction	2000 (reported at 4 years median follow-up)
ELIOT (23)	824	≥48; Invasive carcinoma; T≤2.5 cm; pN0; quadrantectomy	WBI; 50 Gy/25 fractions ± 10 Gy boost	Intraoperative electrons 21 Gy/1 fraction electrons up to 9 MeV	2000 (in press)
GEC-ESTRO (53)	1170	Age ≥40; Stages 0-II; Ductal/lobular carcinoma; DCIS; T ≤ 3 cm; pN0–pNmi; Margin ≥2 mm	WBI 50–50.4 Gy/25–28 fractions ± 10 Gy boost	Interstitial brachytherapy 32 Gy/8 fractions HDR, 30.3 Gy/7 fractions HDR, 50 Gy PDR	2004 (in follow-up)
NSAPBP-39/ RTOG 0413 (54)	4300	≥18 years; Stage 0, I or II; (T<3 cm); DCIS or invasive adenocarcinoma; ≤3 nodes positive; Lumpectomy; Margin negative; PBI judged to be technically deliverable	WBI; 50–50.4 Gy/25–28 fractions ± 10–16 Gy boost	Multicatheter bracytherapy/ MammoSite; 34 Gy/10 fractions (5–10 days) Or 3D EBCRT 38.5 Gy/10 fractions (5–10 days)	2005 (accrual closed to low-risk patients)
RAPID/ Ontario Clinical Oncology Group (43)	2128	≥40 years; DCIS or invasive carcinoma; T<3 cm; Margin negative; Node negative; Not BRCA1/BRCA2	WBI 42.5 Gy/16 fractions/ 22 days (small breast); 50 Gy/25 fractions/35 days (large breasts) ± 10 Gy/4–5 fractions boost	3D EBCRT; 38.5 Gy/ 10 fractions/5–8 days	2006 (in follow-up)
IMPORT LOW (55)	2015	≥50; Invasive adenocarcinoma (not lobular); T≤3 cm; Margin ≥2 mm; Node negative	WBI; 40 Gy/15 fractions/21 days	3D EBCRT; Arm 1: 40 Gy/15 fractions to primary tumor region + 36 Gy/15 fractions to low-risk region; Arm 2: 40 Gy/15 fractions to primary tumor region	2006 (in follow-up)
IRMA (56)	3302	≥49; Pt1–2 (<3 cm); Invasive Ca; pN0–N1; Margins ≥2 mm	WBI	3D EBCRT; 38.5 Gy/10 fractions/5 days	2007 (still recruiting)

the discretion of the treating department policy, and only one examined the boost in a prospective fashion (Table 1) (2–7). In all these cases, the boost was delivered sequentially with standard fractionation. The boost dose was 10 Gy in 5 fractions in the START trials and 14 Gy in 7 fractions in the earlier RMH/GOC trial. The use of a sequential boost extends the overall treatment time to nearly 5 weeks in some cases reducing the potential time-saving benefit to patients. None have data on a hypofractionated boost dose schedule that is biologically equivalent to the cumulative dose from a conventional tumor bed boost.

Improvements in RT techniques with intensity-modulated radiotherapy and three-dimensional conformal RT can be used to test hypofractionation with a simultaneously integrated boost. There are 3 recent Phase I/II trials showing the safety and short-term efficacy of hypofractionated radiation therapy with a concurrent boost (48–50). The integrated boost doses per fraction used were 2.8 Gy in 20 fractions, 3.17 Gy in 15 fractions, and 3 Gy in 15 fractions.

With a median follow-up ranging from 12 to 54 months across the 3 trials, there were no reports of unusual acute or late toxicity.

There are now at least two randomized Phase III trials underway comparing standard sequential boost with a simultaneous integrated boost in high-risk women after breast-conservation surgery and appropriate adjuvant systemic therapy (51,52). The RTOG-1005 trial tests standard sequential boost (12 Gy in 6 fractions or 14 Gy in 7 fractions) after 50 Gy in 25 fractions or 42.5 Gy in 16 fractions to whole breast versus the same dosed to whole breast delivered with a concurrent tumor bed boost to 48 Gy in 15 fractions of 3.2 Gy (51). This represents an equivalent tumor bed dose (assuming an α/β ratio of 4 Gy, and correcting for proliferation effects) in 2 Gy per fraction of approximately 63 to 66 Gy in 2-Gy fractions.

The UK IMPORT HIGH trial (activated in 2009) also tests advanced techniques of dose-intensity modulation to adjust fraction size across the breast as a way of matching dose to tumor relapse risk (52). The control arm delivers 40 Gy in 15 fractions to the whole breast followed by 16 Gy in 8 fractions to the tumor bed. Two test arms deliver 36 Gy in 15 fractions to whole breast, 40 Gy in 15 fractions to partial breast, and 48 Gy (test arm 1) or 53 Gy (test arm 2) in 15 fractions concomitant boost to tumor bed. Assuming an α/β ratio of 3 Gy, the total tumor bed doses in the control arm, test arm 1, and test arm 2 are equivalent to 62 Gy, 60 Gy, and 69 Gy in 2-Gy fractions, respectively. The modest dose reduction to whole breast in the test arms, equivalent to a reduction from 46 Gy in 23 fractions (control) to 40 Gy in 23 fractions (test 1 & 2) assuming α/β = 3 Gy, is intended to reduce late adverse effects and allow safe dose escalation to the tumor bed. The two dose levels of concomitant boost will enable quantification of a dose-volume effect for late adverse effects. If there is no sparing effect, the degree of moderate/marked induration at the boost site will be comparable in control group and test arm 1. If there is a lot of sparing, the equivalence will be closer to test arm 2.

TABLE 5 UK FAST-Forward trial (N = 4000), primary end point of local tumor control

	Total Dose (Gy)	Fractions	Dose per Fraction (Gy)	Time
Control arm 1	40.0	15	2.67	3 weeks
Test arm 1	27.0	5	5.4	5 days
Test arm 2	26.0	5	5.2	5 days

CONCLUSIONS

In conclusion, it is fair to say that after decades of resistance to evaluating larger radiotherapy fraction sizes in breast cancer, expert opinion is responding to an accumulating body of evidence supporting the safety and effectiveness of this approach. The standard UK schedule of 40 Gy in 15 fractions is gentler on normal tissues compared with 50 Gy in 25 fractions, without evidence of inferior local tumor control. This schedule, or 42.5 Gy in 16 fractions, can be recommended as safe and effective alternatives to 50 Gy in 25 fractions for whole-breast, postmastectomy chest wall, and lymphatic radiotherapy. Future challenges will involve testing the limits of hypofractionation for whole- and partial breast RT. Experience gained with APBI cannot be translated to the context of WBI due to a strong volume effect. A Phase-III randomized trial in the UK is currently testing a 5-fraction schedule of adjuvant whole-breast radiotherapy delivered in 1 week against a 15-fraction schedule in women with early stage breast cancer (Table 5). Finally, it is important to understand that population-based estimates of the α/β value represent averages, which are likely to vary within tumor types as well as between them. An aim of future research should therefore be to identify biomarkers of fractionation sensitivity that allow more effective stratification of our patients for this important treatment parameter.

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The Role of Postmastectomy Radiotherapy in the Treatment of Breast Cancer

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ABSTRACT

Postmastectomy radiotherapy (PMRT) is very effective at preventing locoregional failure (LRF) and thereby increases relapse-free, breast cancer–specific, and overall survival rates. Nonetheless, its role remains controversial for many patients. This chapter focuses on the role of PMRT for patients with clinical Stage I or II cancers with uninvolved (negative) axillary nodes, particularly those with large cancer, for patients with one to three positive nodes, and for those with four or more positive nodes. This chapter also discusses how specific prognostic factors affect this risk.

Keywords: breast cancer, mastectomy, radiotherapy

INTRODUCTION

Postmastectomy radiotherapy (PMRT) is very effective at preventing LRF and thereby increases relapse-free, breast cancer–specific, and overall survival rates. Nonetheless, patients may not benefit from PMRT, either because they would not have developed LRF without it, because they may develop LRF despite PMRT, or because they will develop distant metastases despite having locoregional tumor control. Also, PMRT can cause complications, some of which are potentially life threatening (1). Hence, while there has been general consensus for some time now that PMRT should be used routinely for patients with four or more involved axillary nodes, patients with tumors larger than 5 cm and with any number of positive nodes, or partients with T4 cancers (2–8), there has been considerable controversy regarding the indications for using PMRT for patients perceived to be at lesser degrees of risk.

This chapter focuses on the role of PMRT for patients with clinical Stage I or II cancers. The chapter also reviews the risks of LRF in patients with uninvolved (negative) axillary nodes, one to three positive nodes, and four or more positive nodes, and how specific prognostic factors affect their risk. I will then discuss the randomized clinical trials showing how PMRT affects breast cancer–specific and overall survival rates. I will not review the controversies

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regarding when to use PMRT in patients with clinical Stage I and II disease receiving neoadjuvant chemotherapy (9–13). Detailed discussion of treatment techniques may also be found elsewhere (14–16).

■ LOCOREGIONAL FAILURE RATES FOR PATIENTS WITH UNINVOLVED AXILLARY NODES

The risk of LRF after mastectomy for patients with pathologically uninvolved axillary nodes was reduced from 10%–20% to 5%–10% by the use of chemotherapy or hormonal therapy in several randomized trials (3,17). Several studies have identified potential adverse risk factors for LRF: age younger than 35 to 40 years at diagnosis, tumor larger than 2 to 3 cm, presence of lymphovascular invasion, high histologic grade, negative hormone receptor status, and positive margins (18–21). However, systemic therapy still seems effective when only one of these adverse factors is present. For example, the LRF rate was 5% at a median follow-up time of 65 months in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-23 trial on 8762 patients with node-negative, hormone receptor–negative tumors who received either CMF or doxorubicin-cyclophosphamide (AC) with or without tamoxifen (22). Patients who have two or more unfavorable risk factors may be at much greater risk (20,23). For example, a study from British Columbia of patients with negative nodes but positive margins found that LRF rates were low except for patients with one or more additional risk factors (e.g., 4% for patients with T1 lesions and 19% for patients with T2 lesions) (23).

There are as yet few data on how genetic profiles of tumors affect the risk of LRF after mastectomy for patients with negative nodes. Having a high-range, 21-gene recurrence ("Oncotype DX") score was found to correlate with an increased risk of LRF after mastectomy in a combined analysis of patients treated with tamoxifen in the NSABP B-14 and B-20 trials (24).

The three largest studies of the risk of LRF in patients with pathologic T3 tumors and negative nodes (currently classified as Stage IIB) (25) are from the NSABP database with 313 patients (of whom 233 patients received chemotherapy or tamoxifen or both) (26), a combined study on 70 patients treated at the Massachusetts General Hospital, Yale-New Haven Hospital, and the MDACC (27), and 56 patients treated in British Columbia, Canada (28). With median follow-up times of 15.1 years, 7.1 years, and 10 years, respectively, the 10-year risks of isolated LRF in patients receiving systemic therapy were 10%, 8%, and 9%, respectively. However, all of these included many tumors that were "exactly" 5 cm (144 patients in the NSABP study, or 46% of the study population; 24 in the combined study, or 34%; and 23 in the British Columbia study, or 41%). These are classified as T2 rather than T3. In the combined study, the LRF rate was higher for tumors larger than 5 cm than for those exactly 5 cm (none versus 12.4%, respectively) (27). This effect was not found in the NSABP study, which however contained only 39 tumors larger than 7 cm (26). More importantly perhaps, there are few analyses of subgroups defined by other potential risk factors. In the combined study, the LRF rate was 21% when lymphovascular invasion (LVI) was present, and it was 4% when LVI was not present. However, only 14 patients had LVI. Such information was not available in the NSABP database. In the British Columbia study, the crude rate of LRF among the 29 patients with Grade 3 tumors was 17%, compared with no failures among 21 patients with Grade 1–2 tumors (28). (Of note, there was only 1 failure among the 23 patients in this study who received PMRT.) Finally, some patients did not receive systemic therapy. The LRF rate was 17% (13/80) for patients in the NSABP study who did not receive systemic therapy compared with 8% (18/233) for patients who received systemic therapy (26).

■ LOCOREGIONAL FAILURE RATES FOR PATIENTS WITH ONE TO THREE POSITIVE NODES

The risk of LRF is approximately 10% to 15% for those with one to three positive axillary nodes and 20% to 30% for those with four or more positive nodes in most studies using chemotherapy (Table 1). These rates vary substantially, however, which probably reflects the impacts of additional pathologic, clinical, and patient factors, as discussed below.

Proportion of Involved Axillary Nodes and Number of Involved Nodes

Several studies suggest that the risk of LRF is substantially increased when the proportion of recovered nodes involved by cancer (or "nodal ratio") is 0.15 to 20 or greater, which parameter may be a more useful indicator of risk than the absolute number of involved nodes (29–31). However, other factors seem

TABLE 1 Locoregional failure rates in patients with positive axillary nodes treated by modified radical mastectomy (without radiotherapy) and chemotherapy with median follow-up of five years or longer

Series	Years	Median FU (mo)	1–3 LN±	4± LN±
GABG I (70)	1981–1986	?	10% [14/138]	24% [57/237]
CALGB 9344 (71)	1994–1997	67	8% [21/254]	14% [35/244]
Ludwig I–II[b] (72)	1978–1981	72	13% [63/491]	18% [60/327]
Massachusetts General Hospital[a] (47)	1990–2004	84	10-yr: 11% [165]	—
MD Anderson (54)	1997–2002	90	10-yr: 4% [176]	—
Sydney[a] (73)	1980–1991	104	16% [26/165]	31% [16/52]
Denmark 82b[a] (55)	1982–1989	114	30% [155/516]	42% [110/262]
MD Anderson[b] (38)	1975–1994	116	13% [60/466][a]	24% [63/263][a]
Southeast Group[ab] (74)	1976–1983	120	11% [32/302]	23% [47/176]
NSABP[a] (75)	1984–1994	133	13% [397/2957]	27% [754/2784]
ECOG[a] (48)	1978–1986	145	10-yr: 13% [1018]	10-yr: 29% [998]
British Columbia[a] (61, 62)	1979–1986	249	20-yr: 21% [92]	20-yr: 41% [54]

Note: Number of patients in square brackets: locoregional failure rates as first site of failure (with or without simultaneous distant failure) reported as either crude incidence or as actuarial rate at the particular times indicated.
[a] Includes patients with simultaneous distant failure.
[b] Includes some patients treated with radical mastectomy.
?: not stated or unknown.
A: average length of follow-up.
Abbreviations: CALGB = Cancer and Acute Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; FU = length of follow-up; GABG = German Adjuvant Breast Group; LN+ = number of positive axillary lymph nodes; NSABP = National Surgical Adjuvant Breast and Bowel Project.
Source: Adapted with permission of the publisher from: Recht A. Postmastectomy radiotherapy. In: Bland KI, Copeland EM, III., eds. *The Breast: Comprehensive Management of Benign and Malignant Disease*. 4th ed. Philadelphia: Saunders, 2009:1083–1090.

likely to modify this risk sufficiently so that nodal ratio alone cannot be used for decision making. For example, a combined study on patients with one to three positive axillary nodes from the MD Anderson Cancer Center (MDACC) (462 patients) and British Columbia Cancer Agency (82 patients) found that a nodal ratio of 0.20 or lower was associated with a significantly smaller risk of LRF in the combined study population (30). However, the 10-year LRF rate for "low-risk" patients treated at the MDACC was 11%, compared with 18% for the British Columbia patients; for "high-risk" patients, the respective rates were 23% and 28%.

Extracapsular Extension

The presence of extracapsular extension did not increase the risk of LRF in several series with either one to three or four or more involved nodes (32–35), although in two studies, extracapsular extension substantially increased the risk of chest-wall recurrence for patients with one to three positive axillary (Table 2) nodes (36,37). In a study from the MDACC, extranodal extension of 2 mm or greater was a significant risk factor for LRF (38). However, these studies were relatively small, and central pathology review was not usually performed. Retrospective analysis of the British Columbia trial found that there was a statistically significant improvement in overall survival rates from PMRT for patients with extensive extracapsular spread or extensive nodal involvement (defined essentially as replacement of the node by tumor), but not when this finding was absent (39).

Tumor Size

The effect of tumor stage is highly inconsistent in studies of patients with one to three positive nodes (Table 2). Of interest, in a recent study from the MDACC, the LRF rate at 10 years decreased

TABLE 2 Ten-year actuarial locoregional failure rates in patients with one to three positive axillary nodes in relation to T-stage

Study	Follow-Up (years)	T1	T2	T3
MD Anderson, 1975–1994 (38)	9.7	9% (190)	26% (214)	29% (34)
IBCSG, 1976–1993 (40)	14.5	16% (1013)	20% (1237)	24% (92)
ECOG, 1978–1987 (48)	12.1	12% (407)	12% (576)	31% (35)
NSABP, 1984–1994 (75)	11.1	11% (1045)	15% (1489)	11% (229)
MD Anderson, 1997–2002 (54)	7.5	2% (189)	10% (77)	—

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IBCSG = International Breast Cancer Study Group; NSABP = National Surgical Adjuvant Breast and Bowel Project.
Source: Adapted with permission of the publisher from: Recht A. Postmastectomy radiotherapy. In: Bland KI, Copeland EM, III., eds. *The Breast: Comprehensive Management of Benign and Malignant Disease.* 4th ed. Philadelphia, PA: Saunders, 2009:1083–1090.

substantially for patients with T1 lesions but minimally for patients with T2 lesions treated from 1997 to 2002, compared with earlier American studies from other institutions. Further, tumor size may have different impacts on different subgroups. For example, in the International Breast Cancer Study Group (IBCSG) study, T-stage was a statistically significant risk factor on multivariate analysis for postmenopausal patients, but not for premenopausal ones (40).

Few studies have looked at smaller divisions of tumor size for patients with one to three positive nodes. An older study from MDACC found crude rates of LRF of 3% (1/36) for patients with tumors 1 cm or smaller, 11% (14/154) for tumors 1.1 to 2 cm, 15% (18/120) for tumors 2.1 to 3 cm, 15% (11/69) for tumors 3.1 to 4 cm, and 16% (4/26) for patients with tumors 4.1 to 5 cm (38).

Lymphovascular Invasion

The presence of LVI substantially increases the risk of LRF in most, but not all, series examining this issue (Table 3). While I believe LVI to be a powerful risk factor, two problems make using it for treatment decisions less straightforward. First, interobserver variability between pathologists reduces the reliability of this diagnosis although the use of stringent criteria can result in concordance rates in excess of 80% (41). Second, only some of these studies examined the effect of LVI in patient subgroups defined according to other prognostic factors. In the IBCSG study, the presence of LVI was an important risk factor for premenopausal patients but not postmenopausal patients on multivariate analysis (40). In the older MDACC study, LVI was significantly associated with the risk of LRF for patients with 4 or more positive nodes, but not one to three positive nodes; however, the exact rates in these latter subgroup were not given (42).

TABLE 3 Lymphovascular invasion and the risk of locoregional failure

Series	FU (mo)	LVI Negative	LVI Positive
Taipei (pN1) (46)	40	7% (279)	17% (90)
Ankara (pN1) (31)	70	Hazard ratio 3.3 (262/64)	
Nottingham (76)	84	19% (505)	36% (505)
MD Anderson, 1997–2002 (pN1)	90	4% (?)	5% (?)
MD Anderson, 1975–1994 (42)	116	15% (364)	25% (643)
IBCSG (40)	174	16% (2200)	24% (2390)

Abbreviations: FU = median follow-up time; IBCSG = International Breast Cancer Study Group; LVI = lymphovascular invasion.
Source: Adapted with permission of the publisher from: Recht A. Postmastectomy radiotherapy. In: Bland KI, Copeland EM, III., eds. *The Breast: Comprehensive Management of Benign and Malignant Disease.* 4th ed. Philadelphia, PA: Saunders, 2009:1083–1090.

Margin Status

There are no studies examining the impact of margin status for only patients with one to three positive nodes. Several studies in patients with negative or negative and positive axillary nodes have shown a trend for increased LRF rates in patients with "close"

TABLE 4 Early breast cancer Trialists' group 2006 meeting: Actuarial results for patients treated with mastectomy and axillary clearance, with or without PMRT

# Involved Nodes	# Pts	Isolated LRF (5/15 years)		Breast Cancer Death (15 years)		Any Death (15 years)	
		No PMRT	PMRT	No PMRT	PMRT	No PMRT	PMRT
0	1354	4.4%/5.8%	1.6%/2.4%	26.0%	26.6%	37.4%	41.3%
1–3	3344	19.1%/24.7%	3.4%/5.3%	50.9%	43.3%	56.1%	50.9%
4 or more	2876	32.3%/40.6%	10.0%/12.9%	76.4%	69.5%	79.0%	72.8%

Note: All differences statistically significant except for the risk of breast cancer deaths for pN0 patients.
Abbreviations: LRF = local-regional failure; PMRT = postmastectomy radiotherapy.
Data from Ref. (66).
Source: Adapted with permission of the publisher from: Recht A. Postmastectomy radiotherapy. In: Bland KI, Copeland EM, III., eds. *The Breast: Comprehensive Management of Benign and Malignant Disease*. 4th ed. Philadelphia: Saunders, 2009:1083–1090.

or positive margins (42–45). However, it is not clear whether there was a standardized approach to assessing the deep margin status in these series. Also, margin status seems likely to have a significant impact on the risk of LRF when combined with other factors, but not by itself. A study from Fox Chase Cancer Center in Philadelphia found that close margins were a risk factor only for patients younger than 50 years old (45). As noted above, the study from British Columbia on patients with negative nodes with positive margins found that LRF rates were low except when patients with one or more additional risk factors (aged 50 or younger, T2 tumor, grade 3 histology, or the presence of LVI) (23). It seems likely this is also true for patients with involved nodes.

Tumor Grade

Most studies of the impact of tumor grade on the risk of LRF do not distinguish between patients according to the number of involved nodes or did not use systemic therapy, or both. A study of patients treated in Taipei, Taiwan, from 1991 to 2005 with a median follow-up of 40 months found LRF rates of 6% among 186 patients with Grade 1 to 2 tumors, compared with 13% among patients with Grade 3 tumors (46). Similarly, a study of patients treated at Massachusetts General Hospital, Boston, from 1990 to 2004 found respective rates in these groups of 2% (96 patients) and 14% (59 patients), with a median follow-up of 84 months (47). However, in a study of the International Breast Cancer Study Group of patients with T1–2N1 tumors treated from 1978 to 1993 with a median follow-up of 174 months, the respective LRF rates were much closer together at 17% (650 patients) and 23% (353 patients), respectively (40). None of these studies subdivided the results further in relation to hormone receptor or HER2 status, which tend to be more often adverse in high-grade tumors. Thus, tumor grade appears to have some effect on the risk of LRF, but this may diminish with time.

Biologic Factors

Estrogen receptor (ER) expression was a statistically significant predictor of LRF on multivariate analysis in the ECOG study (48), but there was no difference in rates according to ER status in an analysis of the combined Danish trials (49). However, negative progesterone receptor (PR) status was a statistically significant risk factor in the latter study.

Few studies have examined the role of the ER and PR status separately for the subgroup of patients with one to three positive nodes. It was not statistically significant on univariate analysis in the ECOG study within this subgroup, but it was in a study from Taipei, albeit with a median follow-up of only 40 months (46).

There are few data on the role of HER2 expression in determining the risk of LRF. These have not shown a substantial impact in patients receiving chemotherapy regimens that did not contain trastuzumab (46,49,50).

Combinations of these receptor markers may be of more importance than individual ones. The Danish study showed that patients with "triple-negative" tumors (negative ER and PR and normal expression of HER2) had a statistically increased risk

of LRF compared with other subgroups (49). (The effectiveness of PMRT also seemed to be reduced in this subgroup and in those patients with HER-positive tumors where both ER and PR were negative.) However, very little data is available for patients stratified by nodal status. A study from Beijing of 319 patients with T1–2N1 tumors treated from 2000 to 2004 who did not undergo PMRT found, with a median follow-up of 47 months for the entire study population, that actuarial 5-year LRF rates for patients with triple-negative receptor status was 12%, compared to 17% for patients with HER2 positive tumors but negative ER and PR, 18% for patients with positive ER or PR and positive HER2, and 9% for patients with positive ER or PR and negative HER2 (51).

There are as yet few data on how gene-expression analysis might be used to predict the risk of LRF after mastectomy for patients with involved axillary nodes. An investigation from the Sun Yat-Sen Cancer Center in Taipei, Taiwan, found that a 34-gene model divided patients into two groups: one with a 3-year LRF rate of 32% and another with no LRFs (52). However, LRF rates were unusually high in their training sample (2/17 patients with negative nodes, 10/36 patients with one to three positive nodes and 6/9 patients with 4 or more positive nodes). Hence, much more work needs to be done in this area before such an approach can be used for clinical decision making.

Patient Age

The role of PMRT in relation to young age at diagnosis (35–40 years or younger) has not been routinely analyzed in either randomized trials or retrospective series (53). Several studies suggest that patients age 40 or younger with one to three positive nodes have considerably higher LRF rates than older patients (31, 46, 54), but others have not (38). In the Danish 82b trial, there were no differences in the risks of LRF or distant failure between patients younger than age 40 years, those 40 to 49 years old, or those aged 50 or older (55). Similarly, "elderly" patients (70 years or older) appear to have LRF rates similar to other patients (56, 57).

Combinations of Prognostic Factors and the Risk of Locoregional Recurrence

Several investigators have proposed combining multiple factors into a single "prognostic index" for patients with positive nodes (31,58). For example, a study on 326 patients with one to three positive nodes treated at the Oncology Training and Research Hospital in Ankara, Turkey, identified three risk factors to be statistically significant predictors of LRF on Cox modeling: age of 35 years or younger, the presence of LVI, and a nodal ratio greater than 15% (31). With a median follow-up of 70 months, the risk of LRF in patients with zero or one risk factor was 3% compared with 23% for patients with two or three risk factors. While this approach is promising in my view, such attempts require extensive validation in order to achieve consensus on their use.

■ LOCOREGIONAL FAILURE RATES FOR PATIENTS WITH FOUR OR MORE POSITIVE NODES

There has been much less attention given to risk factors for LRF for patients with four or more positive nodes compared with that for patients with one to three positive nodes. Both tumor size and the number of involved nodes influenced LRF rates in the ECOG study. The risk of LRF (with or without distant failure) at 10 years for patients with four to seven positive nodes was 20% for 180 patients with T1 tumors, 27% for 349 patients with T2 tumors, and 45% for 33 patients with T3 lesions; the rates for patients with eight or more positive nodes were 33% (110 patients), 33% (407 patients), and 33% (29 patients), respectively (48). In the NSABP study, patients with 4–9 positive nodes with T1 tumors has a 1-year total LRF rate of 20% (512 patients), those with T2 tumors a risk of 24% (982 patients), and those with T3 lesion a risk of 31% (220 patients); the respective rates for patients with 10 or more positive nodes were 26% (187 patients), 33% (500 patients), and 34% (165 patients) (26). In the ECOG study, ER status was a significant predictor of LRF for the group of patients with T2 tumors and 4 or more positive nodes on univariate analysis, but not on multivariate analysis (48).

■ IMPACT OF PMRT ON BREAST CANCER–SPECIFIC AND OVERALL MORTALITY

Because of biases in treatment assignment, retrospective studies cannot accurately estimate the long-term effect of PMRT on breast cancer–specific and overall survival. There have been many randomized

trials comparing mastectomy to mastectomy plus PMRT, but a large proportion did not routinely employed systemic therapy and are hence irrelevant to making treatment decisions today (3). The four largest trials that did so had median follow-up times of approximately 20 years at last report and are described below.

The earliest of these four trials, conducted from 1976 to 1985, randomly assigned 483 postmenopausal women in southern Sweden to receive tamoxifen or tamoxifen plus PMRT (59). With a median follow-up time of 22.9 years, LRF rates in the two arms were 18.5% and 5% (60). The cumulative incidences of systemic disease at 20 years were in each arm 45% and 40%. These rates were 41% and 40% when analysis was confined to the 212 patients known to have positive estrogen and/or progesterone receptors. There was no difference in overall survival for the entire population, but in the hormone receptor-positive subgroup the 20-year mortality rate was lower in the tamoxifen arm than in the patients receiving combined-modality therapy (54% and 67%). This is the also only trial reporting whether PMRT reduced the ultimate risk of having uncontrollable LRF. In an earlier report, these rates were 4% and 7% in the PMRT and control arms, respectively (59).

A trial in British Columbia, Canada, conducted from 1979 to 1986, included 318 premenopausal patients, all of whom received CMF (61). With a median follow-up of 20.75 years in living patients, PMRT resulted in statistically-significant improvements in survival free of isolated LRF (74% versus 90% in the control and PMRT arms, respectively), systemic relapse-free survival (31% versus 48%), breast cancer–specific survival (38% versus 53%), and overall survival (27% versus 47%) (62). Long-term toxicities, including cardiac deaths (1.8% versus 0.6%), were minimal for both arms.

Finally, the two largest trials of PMRT were performed simultaneously in Denmark from 1982 to 1989 (55, 56). One recruited 1705 premenopausal patients, who received cyclophosphamide, 5-fluorouracil, and methotrexate (CMF); the other enrolled 1375 postmenopausal patients, who received one year of tamoxifen. With a median follow-up time of 18 years, the 18-year rates of LRF (with or without simultaneous distant metastases) were 49% and 14% in the control and PMRT arms, respectively (63). There was a statistically significant reduction in the 18-year risk of developing distant metastases (64% and 53% in the two arms). The 15-year overall survival rates for patients who had 8 or more examined axillary nodes were 29% and 39% ($P = .015$) (64).

The Early Breast Cancer Trialists' Collaborative Group has compiled all randomized trials comparing surgery alone to surgery plus PMRT for patients treated with mastectomy and axillary dissection. Their most recent fully published meta-analysis found that PMRT improved the 15-year overall survival and breast cancer–specific survival by roughly one-fifth to one-fourth of the 5-year risk of developing an isolated LRF (65). For example, PMRT would decrease breast cancer mortality by 4% to 5% for a patient with a 20% risk of LRF. However, a more subtle picture emerges from the results of their 2006 meeting in Oxford, England, which were presented at the plenary session of the annual meeting of the American Society for Radiation Oncology in Philadelphia in November 2006 (66). This showed that PMRT resulted in statistically significant reductions in the risk of breast cancer death and any death for patients with one to three positive nodes (by 7.6% and 5.3%, respectively) or four or more positive nodes (by 6.9% and 6.2%, respectively). However, there was no statistically significant benefit for patients with negative nodes with regards to breast cancer–specific survival (and in fact an increase of 0.6% was seen) and significantly higher overall mortality (by 3.9%) for irradiated patients. The "benefit ratio" of reduced mortality to LRF was 0.14 for patients with negative nodes, 0.4 for patients with one to three positive nodes, and 0.21 for patients with four or more positive nodes. There was also higher overall mortality (by 3.9%) for patients with negative nodes treated with PMRT.

Determining the implications of the Oxford overviews for current patient care is not easy. Their results were dominated by the Danish trials, which have higher failure rates than most current studies, as discussed above. Also, many of the trials employed outdated radiotherapy techniques, such as the use of orthovoltage equipment. There are limited or no information on potential prognostic factors, such as histologic grade and the presence of LVI. Most importantly, this study did not segregate results of the trials in which systemic therapy was routinely given from those in which it was not. (About one-third of patients with involved axillary nodes did not receive systemic therapy.) An earlier meta-analysis restricted to trials using systemic therapy routinely showed that PMRT reduced overall mortality by 17% (67).

Thus, these trials show that PMRT reduces breast cancer–specific mortality. However, the magnitude of this benefit is proportional to the risk of LRF, which is likely smaller now than for patients in these trials due to the use of better surgical techniques and

improved systemic therapy. These trials are therefore of limited value in determining the likely benefits of PMRT for patients treated today.

Several cooperative oncology groups have attempted to further study the role of PMRT for patients with one to three positive nodes. A trial began in North America in 2000 under the leadership of Southwest Oncology Group (trial 9927). However, this was closed in late 2003 because of severe accrual problems. A similar trial (titled "SUPREMO") began in 2006 in the United Kingdom, Europe, Australia, and Asia for patients with pathologic T1–2 tumors and one to three positive nodes or pT2N0 tumors with grade 3 histology or LVI, with an accrual goal of 3700 patients (68).

Additional randomized trials would also be helpful for delineating the role of PMRT in subgroups considered at increased risk of LRF due to biologic risk factors. A randomized trial was performed in China from 2001 to 2006 in which 681 patients with triple-negative T1–2 cancers were randomly allocated to receive chemotherapy alone (CMF of 5-fluourouracil, doxorubicin, and cyclophosphamide) or chemotherapy followed by PMRT. Eighty-two percent of patients had uninvolved axillary nodes and were irradiated to the chest wall, 16% had one to three involved nodes (some of which also received nodal irradiation), and the rest four to nine positive nodes (69). With a median follow-up of 86.5 months, 5-year relapse-free survival rates in the two arms were 75% and 88% (hazard ratio 0.77, $P = .02$); the respective 5-year overall survival rates were 79% and 90% (hazard ratio for death, 0.74, $P = .03$). The risks of LRF in the two arms were not reported.

■ CONCLUSIONS

PMRT is a powerful tool in reducing the risk of LRF. However, there is no consensus on what threshold is sufficient to recommend PMRT or how to combine patient-, tumor-, and treatment-related factors to estimate the risk of LRF. I generally recommend PMRT for patients I estimate to have a LRF rate of 15% or higher, which will result in improving the breast cancer–specific survival rate by about 3%. (Individual patients and physicians will of course differ substantially regarding this threshold.) This group in my view includes patients with negative axillary nodes receiving systemic therapy who have three or more high-risk features (aged 40 or younger, T2–3 tumor size, LVI, high histologic grade, negative hormonal receptors, and positive or close margins for invasive cancer). I recommend PMRT to all patients with one to three positive nodes when LVI is present and to some patients without LVI with combinations of these other risk factors. All patients with four or more positive axillary nodes should be irradiated.

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Radiation Therapy After Neoadjuvant Chemotherapy for Operable Breast Cancer

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■ ABSTRACT

Neoadjuvant chemotherapy once reserved for locally advanced breast cancer has now become an accepted approach for any woman for whom chemotherapy would be recommended. Unlike the adjuvant setting, decisions for locoregional therapy are based on both the initial and residual disease extent. Downstaging of the disease in the breast and/or axilla has resulted in increased rates of breast-conserving surgery. Ipsilateral breast tumor recurrence rates are low in women who achieve a pathologic complete response or have minimal residual disease. There are no established guidelines for postmastectomy radiation in the neoadjuvant setting and data to address this issue are limited. Indications for radiation include initial Stage IIIB or IIIC disease and any stage with four or more positive nodes. Indications for radiation in women with Stage II disease and one to three positive nodes include the presence of lymphovascular invasion, extracapsular extension, triple negative subtype, and young age. As additional data becomes available, recommendations may change.

Keywords: neoadjuvant chemotherapy, breast-conserving surgery, radiation, mastectomy

Neoadjuvant chemotherapy allows for the in vivo assessment of response to systemic therapy, which has been correlated with outcome and in some patients has decreased the extent of surgery from mastectomy to breast-conservation therapy and from axillary dissection to sentinel node biopsy. While it was anticipated that the earlier administration of systemic therapy would result in improved survival in operable breast cancer, the results of seven prospective randomized trials (1–7) comparing neoadjuvant to adjuvant chemotherapy in clinical Stage I to III breast cancer have demonstrated no significant difference in overall survival (Table 1). Two meta-analyses of neoadjuvant chemotherapy, one with nine randomized trials of 3,946 women (8) and the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) analysis (9) of 14 eligible randomized trials with 5,500 women, reported equivalent disease-free survival and overall survival with up to 10 years of follow-up. However, trends in favor of preoperative chemotherapy were reported in the Nationa Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial for disease-free and overall survival in women less than 50 years of age (1).

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TABLE 1 Randomized trials comparing neoadjuvant to adjuvant chemotherapy in operable breast cancer

Trial	Number of Patients	Chemotherapy	% T3 or > 4 cm	Path CR (%)	Breast Conservation (%)		Overall Survival (%)		Follow-Up (Years)
					Adjuvant	Neoadjuvant	Adjuvant	Neoadjuvant	
NSABP B-18 (1)	1523	AC	13	13	60	67	69	70	10.3 mean
EORTC (3)	698	FEC	21	4	21	37	66	64	0 act.
ECTO (2)	834	AT→CMF	20	20	34	63	85	84	6.3 median
Curie (4)	414	FAC	27	—	77	82	65	60	8.8 median
Royal Marsden (6)	309	MM(M)	5	13	79	89	70	63	9.3 median
Bordeaux (7)	272	EVM/MTV	17	—	0	45	62	59	10.3 median
ABCSG-07 (5)	398	CMF	9	6	89	79	64	68	10 act.

CR = complete response; NSABP = National Surgical Adjuvant Breast and Bowel Project; EORTC = European Organization Research and Treatment Cancer; ECTO = European Cooperative Trial in Operable Breast Cancer; ABCSG = Austrian Breast Cancer Study Group; AT= doxorubicin and paclitaxel; AC = doxorubicin and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; MM(M) = mitomycin, mitoxantrone, methotrexate; EVM/MTV = epirubicin, vincristine, methotrexate, mitomycin, thiotepa, and vindesine; CMF = cyclophosphamide, methotrexate, 5-fluorouracil.

Clinical response to neoadjuvant chemotherapy occurs in approximately 80% of operable breast cancers (10, 11). A complete clinical response is defined as no evidence of tumor by clinical exam and imaging studies; a partial response is ≥ 50% reduction in tumor size with stable or progressive disease defining the remaining two categories. Conventional imaging and clinical examination can underestimate the extent of the pre- and posttreatment disease (12, 13). Several studies report a more accurate delineation of disease extent with magnetic resonance imaging (MRI) compared with conventional imaging (13–16). However, the negative predictive value of MRI has been reported to be 65% in one series and its accuracy appears less in younger women (13). MRI evaluation of pre- and posttreatment extent of disease remains an active area of research.

Several tumor characteristics have been associated with increased clinical and pathological response rates. Smaller clinical size (T1 vs. T3), infiltrating ductal rather than lobular carcinoma, estrogen receptor negativity, high grade (high mitotic index, MiB-1) are independent predictors of response to neoadjuvant chemotherapy (2, 10, 17–20). A pathological complete response (pCR) is defined as no residual invasive cancer in the breast and/or axilla. In the NSABP neoadjuvant chemotherapy trials, pCR was defined as no residual disease in the breast regardless of the status of the axillary nodes. However, most studies now define pCR as no residual invasive cancer in the breast and axillary nodes. The finding of only residual ductal carcinoma in situ (DCIS) is considered a pCR. The range of pCR reported in the neoadjuvant chemotherapy randomized trials was 4% to 20% (Table 1). Higher pathologic complete response rates have been reported in estrogen receptor (ER) negative tumors (10, 21, 22), BRCA1 mutation carriers (21), and the basal-like molecular subtype (23–26). Pathologic complete response is infrequent in invasive lobular cancers (27). Several gene expression profiles including Oncotype Dx®, MammaPrint™, and genomic grade index have been correlated with pCR rates (25, 28, 29). The neoadjuvant chemotherapy agents selected also influences pCR rates (30). In the NSABP B-27 trial, the addition of a taxane to AC increased the pCR rate from 13% to 26.1% (10). Buzdar et al. (31) reported an unprecedented pCR of 65% compared to 26% (p = .016) with the addition of preoperative trastuzumab in HER2-positive disease. A nomogram predicting response to neoadjuvant chemotherapy can be found at: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert2. Factors included in the nomogram include type of chemotherapy, age, stage, primary tumor size, histology, grade, ER, and multicentricity. Women who achieve a pCR have a significantly improved long-term outcome (1, 6, 32). In the NSABP B-27 trial, the cohort of women who achieved a pCR demonstrated a superior disease-free and overall survival when compared to those did not (1, 10). The pCR has now become the primary endpoint for evaluating the efficacy of new systemic therapies in the neoadjuvant setting.

However, response to neoadjuvant chemotherapy is not a dichotomy of pCR vs. no pCR because residual disease may be minimal or extensive. Predicting outcome in patients who do not achieve a pCR is complex. One method for quantitating the extent of residual disease is the use of the residual cancer burden (RCB) as proposed by Symmans et al (33). This approach combines the pathologic measurements of the size and cellularity of the residual invasive cancer in the breast and the number and size of the axillary metastases. Scores from 0 to 3 are obtained and distant relapse free survival has been correlated with these scores. The RCB has been correlated with locoregional recurrence rates in women with ER negative tumors and/or lymphovascular invasion undergoing breast-conserving surgery or mastectomy with radiation (34). A calculation tool for RCB is available at www.mdanderson.org/breastcancer_RCB.

■ DECISIONS FOR LOCOREGIONAL THERAPY FOLLOWING NEOADJUVANT CHEMOTHERAPY

Downstaging of the tumor in the breast and/or axilla has complicated the decision-making process for local therapy. Questions have risen regarding the selection of suitable candidates for conversion to breast-conserving surgery after preoperative chemotherapy, determining the "at-risk" volume (pre or post treatment) for excision at lumpectomy, timing, and role of the sentinel node biopsy in assessing the status of the axillary nodes and the integration of this information in guiding decisions for regional node and postmastectomy radiation (PMRT).

The more frequent use of neoadjuvant chemotherapy in clinical node negative patients prompted a debate regarding the timing of the sentinel node biopsy: before or after chemotherapy. Conversion from initial clinical node positive disease and/or FNA positive to path node negative has been reported in 20% to 40% of patients (10, 17, 32). In the NSABP B-27

trial, 428 patients had sentinel node biopsies followed by axillary dissections (35).Sentinel nodes were identified in 85% with a false negative rate of 11%. Two meta-analyses of patients undergoing sentinel node biopsy followed by axillary dissection after chemotherapy reported a pooled identification rate of 90% and a false negative rate of 10% to 12% (36, 37). Thus the identification and false negative rates are similar to studies where sentinel node biopsy was performed before chemotherapy (38, 39). Alternatively, sentinel node biopsy can be performed before chemotherapy. If the sentinel node is positive, an axillary dissection is required. The opportunity for downstaging the axilla to pathologic node negative status with the avoidance of an axillary dissection and its morbidity is then lost. Patients with clinically positive or FNA positive axillary nodes at presentation who do not undergo surgical evaluation of the axilla before chemotherapy are advised to undergo an axillary dissection based on a false negative rate of sentinel node biopsy of 25% (40) in this clinical scenario. A nomogram was developed by investigators from MDA to predict nonsentinel node positivity in patients with positive sentinel nodes (41) This nomogram includes five factors: lymphovascular invasion, method of detection of positive sentinel node, multicentricity, initial clinical nodal status, and pathologic tumor size. An online calculator for predicting nonsentinel node positivity is available at http://www3.mdanderson.org/app/medcalc/bc_nomogram/index.cfm?pagename=nsln

■ NEOADJUVANT CHEMOTHERAPY, BREAST-CONSERVING SURGERY, AND RADIATION

The randomized trials of neoadjuvant chemotherapy demonstrated an increase in the use of breast-conserving surgery and a decrease in mastectomy rates when compared to adjuvant chemotherapy (Table 1). Mieog et al. (9) in a systematic review of 14 trials with 5,041women reported a breast conservation rate of 47% with adjuvant chemotherapy and 64% with neoadjuvant chemotherapy. In the NSABP B-18 and European Organization Research and Treatment Cancer (EORTC) trials, 9% and 23% respectively of the patients who had planned mastectomy were able to undergo breast-conservation therapy (42, 43).

Surgery for the Primary

Prior to neoadjuvant therapy, a titanium clip should be placed in the primary tumor to mark its location. The titanium clip is then used for localization in cases where a complete clinical and radiographic response is achieved (44). Clip placement has been associated with improved local control in patients receiving neoadjuvant chemotherapy and undergoing breast-conserving surgery (45). The volume of breast tissue excised after neoadjuvant chemotherapy is generally the residual nidus and not the original volume. However, all malignant appearing calcifications must be excised prior to radiation. Neoadjuvant chemotherapy has been associated with a decreased number of reexcisions and smaller total volume of breast tissue excised in women with primary tumors ≥ 2 cm undergoing breast-conserving surgery when compared to women undergoing initial surgery (46, 47). Ipsilateral breast tumor recurrence (IBTR) rates for patients who experienced a complete clinical response and treated with radiation without primary surgery have ranged from 30% to 36% (48, 49). Therefore, excision of the primary tumor should not be omitted in these patients regardless of clinical response. A nomogram predicting the probability of breast-conserving surgery based on response to neoadjuvant chemotherapy can be found at: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert2

Ipsilateral Breast Tumor Recurrence

IBTR rates following neoadjuvant chemotherapy, breast-conserving surgery, and radiation from the randomized trials (1, 3, 4, 7) and retrospective series (50–54) are presented in Table 2. In the randomized trials, IBTR rates were not significantly different when comparing patients who had neoadjuvant chemotherapy with those who had adjuvant chemotherapy. However, Mauri et al (8) reported an increase in the relative risk (1.22) of locoregional recurrence with neoadjuvant chemotherapy in a meta-analysis of nine randomized trials. This finding was attributed to the inclusion of three studies in which more than one-third of the patients did not undergo excision of the primary tumor but proceeded directly to radiation after a complete clinical response (4, 7, 55). IBTR rates were 23% to 25% in these patients. Therefore, surgery should not be omitted for them. In the meta-analysis reported by Mieog et al (9), the timing of chemotherapy and type of surgery had no effect on the locoregional recurrence rates when these three trials were excluded.

Concern was raised regarding outcome in the cohort of women who were converted to

TABLE 2 Randomized trials and retrospective series: Neoadjuvant chemotherapy, breast-conserving surgery and radiation

Trial/Study	No. of Patients	Ipsilateral Breast Tumor Recurrence (%)		Follow-Up (Years)
		Adjuvant	Neoadjuvant	
NSABP B-18 (1)	951	10	13	16 median
NSABP B-27 (1)	1478		5	6.5 median
ECTO (2)	1355	5	5	6.3 median
EORTC (3)	199	20	20	10 median
Curie trial (4)	390[a]	19	25	9
Bordeaux (7)	272[a]	12	23	10.3 median
Michelangelo Cooperative Group (50)	213		4	5 median
Institut Gustave Roussy (51)	287		12	8 act.
NCI Milan (52)	455		7	5 act.
MD Anderson (53)	340		5	5 act.
Curie nontrial (4)	308		23	10 act.
National Cancer Center Korea (54)	251		8	5 act.

NSABP = National Surgical Adjuvant Breast and Bowel Project; act = actuarial.
[a] Patients who had complete response were treated with radiation without excision of primary tumor.

breast-conserving surgery instead of mastectomy. In the NSABP B-18 trial, women who were downstaged from mastectomy and subsequently underwent breast-conserving surgery and radiation experienced a 15.9% IBTR rate compared to 9.9% in those whom breast-conserving surgery was initially planned (42). Most of these women had clinical stage T3 disease (17). After 10 years of follow-up, the EORTC reported no significant differences in locoregional recurrence or overall survival when comparing women treated with breast-conserving surgery and adjuvant therapy with women in the neoadjuvant group who were initially eligible for breast-conserving surgery and with women in the neoadjuvant group who were converted to breast-conserving surgery after downsizing of the primary tumor (3). Fitzal et al (56) reported no increase in IBTR rates in women who were initially planned for mastectomy and underwent breast-conserving surgery provided neoadjuvant chemotherapy resulted in a pathologic complete or partial response. However, 5-year locoregional recurrence free survival was significantly less when compared to mastectomy in those who had no pathologic response and underwent breast-conserving surgery.

Factors Associated With Locoregional Failure in Women Receiving Neoadjuvant Chemotherapy

Investigators at the University of Texas (MDA) using a multidisciplinary approach and careful patient selection reported 5- and 10-year locoregional recurrence rates of 5% and 10% in a retrospective analysis of 340 patients with Stage II and III non-inflammatory invasive breast (53).Seventy-two percent of patients had Stage IIB or Stage III disease. They identified four factors that were independently associated with locoregional recurrence in women undergoing breast-conserving surgery and radiation: clinical N2 or N3 disease, lymphovascular space invasion (LVI), a multifocal pattern of residual disease, and residual disease larger than 2 cm. A prognostic index score was developed, which stratified patients by their IBTR rates (57). Ten-year locoregional failure rates for patients undergoing breast-conserving surgery and radiation following neoadjuvant chemotherapy were 5% for those with no factor, 9% for those with one factor, 28% for two factors and 61% for three to four factors (58). For none or one factor, the ten-year locoregional failure rate for

patients undergoing mastectomy and radiation was 4% and 7% respectively. However, with two factors, the risk of a locoregional failure with mastectomy and radiation was 12% compared to 28% for breast-conserving surgery and radiation. For three or four factors, the 10-year locoregional failure rate was 19% for mastectomy and radiation compared to 61% for breast-conserving surgery and radiation. Evaluation of the index in a separate cohort of patients confirmed an improved 5-year LRF-free survival with mastectomy and radiation for scores of 3 to 4 but not for scores of 0 to 2 (59).

Therefore, a combination of initial disease extent and residual disease appears to predict for locoregional failure. However, the extent of residual disease may have greater implications for locoregional failure in certain subsets of patients. In an analysis by investigators at MD Anderson using RCB, a score of ≥ 2 was associated with an increased risk of locoregional failure in women with ER negative disease or lymphovascular disease (LVI) undergoing breast-conserving surgery and radiation or mastectomy and radiation (5-year LRF 20.6% score ≥ 2 compared to 4% for score < 2) (34). There was no correlation with RCB and LRF in women with ER positive disease and no LVI. Using immunohistochemical receptor status as a surrogate for molecular subtype, Yu et al (60) reported 5-year LRF rates of 3% for luminal A tumors (ER+, PR+, HER-), 2% for luminal B tumors (ER+, PR+, HER2+), 10% for basal or triple negative tumors, and 15% for HER2+ tumors in the absence of trastuzumab. Patients with luminal A and B tumors had low LRF rates regardless of response to chemotherapy while basal and HER2+ patients who did not respond had LRF rates of 16% and 17% respectively. Therefore, the presence of more extensive residual disease in patients expected to have a favorable response to chemotherapy (ER negative, triple negative) is associated with a higher locoregional failure rate.

Pathologic complete response has been associated with decreased LRF rates. In the NSABP B-18 trial, patients who experienced a pathologic complete response for invasive cancer in the breast and axilla experienced a 6.7% IBTR compared to 11.5% for those who had residual disease in the breast (61). In the MD Anderson series, patients who achieved a pathologic complete response defined as no residual invasive cancer had a 10-year actuarial IBTR rate of 3%. Locoregional failure rates were 0% to 4% for women with luminal A or B tumors or basal subtype who had a pCR but were 14% for HER2+ patients with a pCR (60). However, none of these patients received trastuzumab. The finding of residual DCIS in patients who otherwise have a complete pathologic response in the breast and axilla has not been associated with an increased risk of IBTR (62).

Young age continues to predict for locoregional failure in patients treated with breast-conserving surgery and radiation following neoadjuvant chemotherapy. In the NSABP B-18 randomized trial, women < 50 years of age experienced a 13% IBTR rate with neoadjuvant chemotherapy and breast-conserving surgery and radiation compared to 5% for those ≥ 50 years of age with a mean follow-up of 9.5 years (42). In the Institut Gustave Roussy series (63), the IBTR rate for women ≤ 40 years of age with neoadjuvant chemotherapy, breast-conserving surgery, and radiation was 40% compared to 15% for women > 40 years of age at 10 years. The 10-year locoregional recurrence rate in women < 35 years of age treated with neoadjuvant chemotherapy, breast-conserving surgery, and radiation was 26% compared to 11% for women 35 to 40 years of age in a series from MD Anderson (64). Therefore, young age variously defined as < 35 to 40 years is associated with an increased risk of IBTR. Arvold et al (65) reported young age as an independent prognostic factor for IBTR in a multivariate analysis that included breast cancer subtype approximated to receptor status in women undergoing breast-conserving surgery and radiation. These women did not receive neoadjuvant chemotherapy. The paradox of young women is that their tumors are more often high grade and estrogen-receptor negative and therefore, would be expected to have a more favorable response to neoadjuvant chemotherapy (66, 67).

Resection margin status has also been correlated with IBTR rates. In a series from the Institut Gustave Roussy, the 10-year rate of an IBTR following neoadjuvant chemotherapy, breast-conserving surgery, and radiation was 17% for negative margins, 32% for margins ≤ 2 mm and 24% for positive margins (63).In the MD Anderson series (53) the 5-year locoregional failure rate was 8% for those with negative margins compared to 11% for those with positive margins. Only 4% of the 340 patients had positive margins. In a series from Milan, the 3-year IBTR rate was 5% for negative margins following quadrantectomy compared to 13% for those with positive margins.(68) The 8-year overall survival was 60% for positive margin patients compared to 78% for those with negative margins. Pathologic assessment of resection margin status is more complex in patients receiving neoadjuvant

chemotherapy. Invasive cancers may decrease in a concentric fashion with partial or complete disappearance of the invasive component with or without residual DCIS, or shrink in a pattern in which there are noncontiguous foci of invasive cancer and/or DCIS interspersed amidst noncancerous breast tissue (69).Surgical excision following neoadjuvant chemotherapy should remove all residual foci of clinically and/or radiographically evident disease with negative margins. The excision volume is the postchemotherapy volume rather than the prechemotherapy volume. Patients with a multifocal pattern of residual disease may have false negative margins of resection because viable cells may remain at a significant distance from the original nidus. Pathologic multifocal residual disease after neoadjuvant chemotherapy has been shown to be a significant risk factor for IBTRin women with T3 to T4 tumors (53). However, clinical multifocal breast cancer as assessed by mammogram, ultrasound, or physical exam prior to neoadjuvant chemotherapy was not an independent risk factor for locoregional recurrence (70). Patients with multicentric disease are not considered candidates for breast-conserving surgery even with neoadjuvant chemotherapy.

Investigators at MD Anderson established the following criteria for patients who should not be considered for breast-conserving surgery after neoadjuvant chemotherapy: (a) inflammatory breast cancer, (b) presence of diffuse or extensive malignant appearing calcifications, (c) multicentric disease, (d) extensive invasive lobular cancer, (e) residual disease > 5 cm, and (f) the inability to achieve negative margins with acceptable cosmesis. Similarly, initial T3 tumor size, invasive lobular cancer, multicentricity, and post chemotherapy residual disease > 3 cm predicted for mastectomy in the experience of the Institute Curie (63). Therefore, women whose initial disease extent is amenable to breast-conserving surgery should remain candidates for breast-conserving surgery after neoadjuvant chemotherapy in the absence of disease progression and selected patients who otherwise would have had mastectomy may be candidates for breast-conserving surgery. It is important to recognize that local control impacts long-term disease-free survival and overall survival (71). A retrospective analysis of patients treated with neoadjuvant chemotherapy, conservative surgery, and radiation at the Institute Curie reported IBTR as an independent and highly significant predictor of distant disease with a relative risk of 5.34 (63). The risk of distant metastases after an IBTR at 2 years was 31% and at 5 years was 60%.

Radiation

Radiation in patients undergoing breast-conserving surgery following neoadjuvant chemotherapy consists of treatment to the entire breast with total doses of 45 to 50 Gy in 1.8 to 2.0 Gy fractions. These patients are not candidates for accelerated partial breast irradiation (72). The role of the boost to the primary site is unknown especially in patients who have a pCR. However, for patients with residual disease in the breast, indications for adding the boost may be extrapolated from the adjuvant setting (i.e. young age and high-grade tumors) (73). Consideration may be given to omitting the boost in women who have a pCR without residual DCIS.

The absence of the original pathologic nodal status (i.e. node negative vs. node positive) and the number of positive nodes complicates decisions for regional node irradiation. The generally accepted indication for regional node irradiation is the finding of four or more positive axillary nodes. Regional node recurrences in the NSABP B-18 randomized trial were similar when comparing the adjuvant to neoadjuvant chemotherapy arms (42). None of these patients or those in the NSABP B-27 trial received regional node irradiation. Axillary recurrence rates were 0.7% for adjuvant chemotherapy compared to 1% for neoadjuvant chemotherapy. The supraclavicular recurrence rate was 2.9% for adjuvant chemotherapy compared to 1.6% for neoadjuvant chemotherapy and the internal mammary node recurrence rate was 0.2% for the adjuvant chemotherapy arm compared to 0% for the neoadjuvant chemotherapy arm. In an update of the NSABP B-18 and B-27 trials, Mamounas (74) reported an 8-year regional node failure rate of 1% in patients who had a pCR (245 patients) or were node negative (644 patients) and had breast-conserving surgery and radiation. The regional node recurrence rate was 3% for those who were path node positive. Omission of regional node irradiation in Stage II patients who are clinically and pathologically node negative has not been associated with an increased risk of regional node failure or a decreased disease-free or overall survival (75, 76). Indications for regional node irradiation in women with one to three positive axillary nodes after neoadjuvant chemotherapy are not well defined. While in the adjuvant setting, nodal rations (number of positive nodes to number of nodes examined) have been used to account for differences in the extent of axillary surgery and have been shown to be a significant predictor for locoregional recurrence (77, 78) and their use in the neoadjuvant setting may

be limited. Fewer axillary nodes are identified after neoadjuvant chemotherapy (79–81) and because the reliability of the nodal ratio decreases as the number of nodes examined decreases, the use of nodal ratios for indications for regional node irradiation can be questioned. The recently reported results of the MA.20 trial (82) suggest a benefit for regional node irradiation in women with one to three positive axillary nodes undergoing breast-conserving surgery, radiation, and adjuvant systemic therapy. However, the trial did not control for systemic therapy and the small numerical benefit could be related to variations in systemic treatment. In an era of tailored therapy, emphasis should be placed on the selective use of regional node irradiation. Regional node irradiation is indicated in women with four or more positive axillary nodes after neoadjuvant chemotherapy. Its role in women with one to three positive axillary nodes has not been defined. Data to date would suggest it is not indicated in pathologic node negative women.

■ NEOADJUVANT CHEMOTHERAPY AND POSTMASTECTOMY RADIATION OPERABLE BREAST CANCER

While PMRT is an integral component of the treatment of locally advanced breast cancer, its role in women with clinical Stage I to III noninflammatory breast cancer who undergo neoadjuvant chemotherapy is less well defined. Established guidelines for PMRT in the adjuvant setting are based on the pathological extent of disease at the time of initial surgery. Because neoadjuvant chemotherapy may result in a decrease in the extent of the disease both in the breast and the axilla, it is possible that this downsizing may obscure indications for PMRT. There are no randomized trials or meta-analyses of PMRT in the neoadjuvant setting. Most of the reported series are retrospective from single institutions and present outcome at 5 years. A single exception is the analysis of locoregional failure patterns in patients entered onto the NSABP B-18 and B-27 trials of neoadjuvant chemotherapy (83). The National Cancer Institute sponsored a multidisciplinary conference in 2007 whose purpose was to review the science for neoadjuvant therapy and identify avenues for future research. Buchholz and colleagues (84) published a statement regarding the issues of locoregional treatment in 2008. They concluded that PMRT should be considered for patients with initial clinical Stage III disease regardless of pathologic response. The panel recognized the complex issues related to pretreatment staging and acknowledged that the role of PMRT in patients with clinical Stage II disease was not well defined. Unlike the adjuvant setting, initial clinical stage and postchemotherapy pathologic stage have been shown to correlate with postmastectomy locoregional recurrence rates in patients receiving neoadjuvant chemotherapy (83, 85, 86). This finding emphasizes the importance of accurate clinical staging.

Investigators at MD Anderson have published a number of studies evaluating the role of PMRT in women receiving neoadjuvant chemotherapy in their prospective clinical trials of systemic therapy. In a comparison of outcome of 542 patients who received neoadjuvant chemotherapy, mastectomy, and radiation with those of 134 patients treated with neoadjuvant chemotherapy and mastectomy, they reported 10-year locoregional recurrence rates of 11% with radiation and 22% without radiation (p = .0001) (87). These groups were not equally matched with more advanced stages selectively referred for radiotherapy. Radiation significantly reduced locoregional recurrences in patients with clinical T3/T4 tumors, Stage IIB and higher, residual disease > 2 cm and ≥ 4 axillary lymph nodes containing disease. For clinical T4, Stage IIIB or higher or ≥ 4 positive lymph nodes after chemotherapy, the addition of radiation also improved cause specific survival (p = .007). In patients with a favorable response defined as having < 5 cm of disease and fewer than four positive lymph nodes, the locoregional recurrence rates were 9% with radiation and 20% for those not receiving radiation. In an analysis of postmastectomy locoregional recurrence rates following neoadjuvant chemotherapy in the NSABP B-18 and B-27 trials, the 8-year cumulative incidence of a locoregional failure was 8% for women with residual disease in the breast and negative nodes compared to 15% for those with positive nodes (61, 74). Thirteen percent of the patients in the B-18 trial had primary tumors > 4 cm compared to 45% in the B-27 trial. Therefore, similar to the adjuvant setting, the finding of four or more positive nodes, initial T4 disease or Stage IIIB of IIIC disease would prompt a recommendation for PMRT.

Indications for PMRT in patients with clinical Stage II disease who do not have four or more positive axillary nodes are less well defined. Factors to consider include patient's age, molecular subtype, the presence or absence of lymphovascular invasion (LVI), extracapsular extension (ECE), response to systemic therapy and axillary nodal status (node negative vs. one to three positive nodes) (Table 3). Women with initial Stage IIA disease who have a pCR or negative axillary nodes have a low risk of

TABLE 3 Locoregional recurrence rates, neoadjuvant chemotherapy and mastectomy without radiation

Stage	No. of Patients	Risk Factor	LRF and/or DM (%)	Follow-Up (years)	Institution/Reference Number
I to III	270	ypN0	8	8 CI	NSABP B-18, B-27 (61)
	447	ypN1	15	8 CI	NSABP B-18, B-27 (61)
	132	All	20	10 act.	MDA (91)
IIA to III	63	All	17	3	Emory (96)
II[a]	181	All	3	5 act.	MDA (90)
	83	ypN0	7	5 act.	René Huguenin (93)
	9	ypN0 age < 35	35	5 act.	MDA (88)
	NS	ypN0 TN	1	5 act.	MDA (89)
	NS	1–3+ nodes	5	5 act.	MDA (90)
	NS	1–3+ TN	37	5 act.	MDA (89)
	11	1–3+ age < 35	30	5 act.	MDA (88)
	NS	≥ 4+	20	5 act.	MDA (90)
	NS	≥ 4+ TN	57	5 act.	MDA (89)
	6	≥ 4+ age < 35	37	5 act.	MDA (88)
	8	ECE+	29	5 act.	MDA (91)
	NS	LVI+	23	5 act.	MDA (91)
IIB T3N0	32	ypN0	14	5 act.	MDA (94)
	11	ypN1	53	5 act.	MDA (94)
	17	Grade 1–2	13	5 act.	MDA (94)
	19	Grade 3	37	5 act.	MDA (94)
III T3N1	12	ypN0	10	5 act.	René Huguenin (93)
I to III	68	Path CR	6	8 CI	NSABP B-18, B-27 (61)
	34	Path CR	10	10 act.	MDA (19)
	10	Path CR	11	3 act.	Emory (96)
IIA	13	Path CR	0	10 act.	MDA (19)
I-II TN	NS	Path CR TN	0	5 act.	MDA (89)
IIB T3N0	4	Path CR	0	5 act.	MDA (94)
III	12	Path CR	33	10 act.	MDA (94)

[a] Young age excludes stage IIA and includes IIB to III, triple negative (TN) includes Stage I to III.
NSABP = National Surgical Adjuvant Breast and Bowel Project; MDA = MD Anderson; ECE = extracapsular extension; LVI = lymphovascular invasion; LRF = locoregional failure; DM = distant metastasis.

locoregional recurrence without radiation regardless of age or triple negative status (88–90). For women with Stage II disease and one to three positive nodes, MD Anderson (91, 92) reported a 5-year locoregional recurrence rate of 8% in 42 patients who did not receive postoperative radiation. For patients with T1 to T2 tumors and one to three positive nodes without extracapsular extension, > 10 nodes removed, and negative margins, the 5-year locoregional failure rate was 9% and the 10-year locoregional failure rate was 12%. This study suggests that these patients are at a relatively low risk for locoregional recurrence. However, Stage II patients with LVI or ECE were reported to have LRF rates of 15% and 29% respectively (90, 91). Molecular subtype has also been correlated with LRF rates in women with one to three positive nodes. Settle et al. (89) reported a 37% 5-year LRF in women with triple negative tumors and one to three positive nodes. Therefore, indications for PMRT in women with Stage II disease and one to three positive nodes include the presence of LVI, ECE, triple negative

subtype, and young age (see below) based on the limited data available. An additional consideration may be the presence of a close or positive mastectomy margin although there are no data to address this issue in the neoadjuvant setting.

Women with Stage IIB disease (T1–2 clinical N1 disease) who receive neoadjuvant chemotherapy and are converted to pathologic node negative disease appear to be low risk with LRF rates of 1% and 7% (90, 93). Therefore, the presence of a clinically positive node by itself may not support a recommendation for PMRT in these women. Nagar et al (94) reported outcome in women with initial T3N0 disease. At 5 years, LRF rates were 14% without radiation compared to 5% with radiation for those whose axillary nodes were negative, 0% for pCR, and 53% for path node positive. The presence of multifocal/multicentric disease without other risk factors does not appear to increase the risk of locoregional failure when compared to unicentric disease (70). A single study reported LRF rates of 10% at 5 years in T3N1 patients who were converted to path node negative (93).

As previously noted, young women receiving neoadjuvant chemotherapy and undergoing breast-conserving surgery and radiation appear to have an increased risk of locoregional recurrence. Similar findings have been noted in these young women who undergo mastectomy without radiation. Garg et al (88) reported 5-year locoregional recurrence rates of 35% in women < 35 years of age with Stage IIB to III disease who received neoadjuvant chemotherapy followed by a mastectomy and had negative axillary nodes. The rate was 30% for those with one to three positive nodes and 37% for those with four or more positive nodes. None of four women with initial Stage IIA disease experienced a LRF when radiation was omitted. Therefore, young age appears to be a risk factor for locoregional failure regardless of nodal response to chemotherapy in women with Stage IIB to III.

Data regarding the role of PMRT in patients receiving neoadjuvant chemotherapy who experience a complete pathologic response are limited. In a study at MD Anderson Cancer Center, the locoregional recurrence was 33% in patients with initial Stage III disease who achieved a pathologic complete response underwent mastectomy without radiation (12 patients) compared to 7% with radiation (62 patients) (19). The majority of the failures were in patients with Stage IIIB and IIIC disease. The locoregional failure rate for patients with clinical Stage I or II disease who achieved a pathologic complete response was 0%. In the NSABP B-18 trial post mastectomy, LRF rates were 6% for the patients who experienced a pCR (61, 74). Therefore, patients with clinical Stage IIIB and IIIC disease who experience a pathologic complete response should be considered for postoperative radiation. The role of PMRT in patients with Stage IIIA disease who have a pCR is unresolved.

Investigators from the MD Anderson recommend PMRT for all patients with clinical T3 or T4 tumors or clinical Stage III disease, including those who have a pathologic complete response, the presence of four or more positive axillary nodes, and residual invasive cancer > 5 cm. Factors which may prompt a recommendation for PMRT in patients with T1 to T2 disease and one to three positive nodes include young age, a close or positive mastectomy margin, lymphovascular invasion, ECE, or triple negative subtype. After a pCR, radiotherapy does not appear to benefit clinical Stage I to II but the limited evidence to date supports radiotherapy for clinical Stage IIIB to Stage IIIC disease. Its role in clinical Stage IIIA who have a pCR has not been established.

Locoregional failure rates with PMRT following neoadjuvant chemotherapy range from 5% to 15% (19, 87, 88, 90, 91, 93–96). Huang et al (97) identified five factors associated with locoregional failure rates in women with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiation. These factors included skin/nipple involvement, supraclavicular disease, ECE, no tamoxifen, and estrogen receptor negative disease. The 10-year locoregional failure rate was 4% for those with none or one factor, 8% for two factors, and 28% for three factors. For women with Stage I to III disease, the high-risk group included those with ER negative disease or LVI+ and a residual tumor burden ≥ 2 (34). 5-year LRF rates in this cohort were 20%.

Radiation

PMRT following neoadjuvant chemotherapy includes the chest wall in all patients. Indications for regional node irradiation are not well defined in women with negative nodes or one to three positive nodes. Investigators at MDA routinely include the regional nodes (level III axillary and supraclavicular nodes and/or internal mammary nodes) in all patients. However, no survival or disease-free survival benefit has been demonstrated with regional node irradiation in Stage II patients who are clinical and pathologic node negative with regional node

irradiation (75). The omission of supraclavicular radiation has also not resulted in an increased risk of locoregional failure in these women (76). In the absence of positive axillary nodes, treatment may be limited to the chest wall and/or reconstructed breast based on the limited available data. Regional nodes failures in the NSABP B-18 and B-27 trials were < 5% in the postmastectomy setting without radiation (74). The use of a separate posterior axillary field is generally not indicated. Treatment of clinically positive IMN nodes that are not resected and have a complete clinical response (imaging) with chemotherapy has resulted in IMN control rates of 96% (98). Radiation dose and technique are similar to that used in the adjuvant setting. The dose to the chest wall is 50 Gy. The use of tissue equivalent bolus and a scar boost varies considerably among institutions (99). Bolus should be used at a minimum of every other day. The dose to the regional nodes is 45 to 50 Gy and the nodes should be contoured for treatment planning.

SUMMARY

The neoadjuvant systemic therapy approach initially reserved for Stage III patients has now been expanded to Stage II patients. It offers valuable translational research opportunities to identify clinical, pathological, and molecular markers of response and long-term outcome. Pathologic complete response has become the intermediate endpoint for evaluating the efficacy of systemic agents and targeted therapies. Emphasis is now placed on tailoring preoperative systemic therapy to specific tumor subtypes based on hormone and epidermal growth factor receptor status, molecular subtypes, and gene expression profiles. Downstaging of the disease in the breast and/or axilla has complicated decisions for locoregional treatment. While the randomized trials of neoadjuvant vs. adjuvant systemic therapy have confirmed the role of breast-conserving surgery and radiation in these patients, uncertainty remains as to whether all patients receiving neoadjuvant therapy are candidates for breast conservation and which factors should influence this decision. Similarly, the role of PMRT in the neoadjuvant setting is not well defined given the absence of randomized trials or consensus guidelines to aid in the decision-making process. Data are limited mostly retrospective from single institutions and with small numbers of patients in subgroups. The 10-year analysis of locoregional failures in the NSABP B-18 and B-27 trials has been presented at national meetings but has not been published (83). While lack of response to systemic therapy appears to affect both locoregional and distant recurrence, quantitating this response in the breast and/or regional nodes has not been standardized. Therefore, it is important to recognize these limitations in the context of the above discussion. Decisions for locoregional therapy should be tailored to the risk of locoregional recurrence and should parallel the more tailored approach used for systemic therapy. As additional data become available, recommendations may change.

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Postmastectomy Radiotherapy and Breast Reconstruction: Emerging Trends and Controversies

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■ ABSTRACT

Breast reconstruction has been shown to provide physical, psychosocial, and emotional benefits to breast cancer patients who undergo mastectomy. Over recent years, there continues to be a steady, upward trend in the total number of breast reconstructive procedures performed in the United States annually. Simultaneously, the crucial role of postmastectomy radiation therapy in patients with locally advanced disease has been established, with more recent data suggesting that patients with less advanced disease may also benefit from treatment. As a result, it is becoming increasingly important to understand and anticipate the consequences of combining these two treatment modalities. This review article discusses heavily debated issues including the optimal sequencing, technique, and integration of breast reconstruction and postmastectomy radiation. Recent studies demonstrating current treatment patterns and resultant oncologic and reconstructive outcomes are presented.

Keywords: breast cancer, reconstruction, implant, autologous flap, postmastectomy radiation therapy

■ INTRODUCTION

Postmastectomy radiation therapy (PMRT) plays a critical role in the management of locally advanced breast cancer. Multiple randomized trials have demonstrated that PMRT significantly reduces the risk of local recurrence in the chest wall and regional draining lymphatics (1–3). The 2005 Oxford overview by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that this decrease in local recurrence translates into a statistically significant improvement in overall survival for women with positive axillary lymph nodes (4).

In 2007, the EBCTCG presented a subgroup analysis of patients with one to three positive axillary nodes that demonstrated an improvement in 15-year breast cancer mortality rate with PMRT, suggesting that patients with less advanced disease benefit from treatment (4). Based on these data, the indications for PMRT continue to evolve. Although no routine guidelines for PMRT in the one to three node-positive subset exist, clinicians utilize high-risk patient and tumor characteristics such as young age, extranodal extension, lymphovascular invasion, and skin or nipple involvement to guide treatment decisions (5).

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In parallel with the expanding indications for PMRT, breast cancer patients are increasingly opting for breast reconstruction. With the abrupt loss of a breast mound, mastectomy can have significant psychological consequences such as low self-esteem, poor self-image, anxiety, and depression (6,7). Breast reconstruction has been associated with enhanced quality of life in breast cancer survivors, as it can improve cosmetic satisfaction and allow patients to maintain their sense of femininity and sexuality (8–11). According to the American Society of Plastic Surgeons, the number of breast reconstructive procedures performed in the United States each year continues to increase steadily, with greater than 93,000 reconstructive procedures performed in 2010 (Figure 1) (12).

Despite the individual merits of PMRT and breast reconstruction, the optimal integration of these two modalities has generated considerable controversy over the past decade. Topics such as optimal sequencing, technique, and manner of integration, as well as the resultant oncologic and reconstructive outcomes will be discussed in this review.

■ TECHNIQUES OF BREAST RECONSTRUCTION

Breast reconstructions can be implant-based, autologous tissue flap-based, or a combination of both. Varieties of anatomic and treatment-related factors are considered when selecting the optimal reconstruction type, making this decision highly individualized to the patient. These include the size and shape of the desired breast mound, donor site availability, size and location of the index tumor, patient's medical and prior radiation history, type of adjuvant therapy and most importantly, patient preference. Nationwide statistics show that over 75% of breast reconstructive procedures performed in breast cancer patients in 2010 consisted of tissue expanders (TEs) and implants or implants alone. Of the autologous flaps, transverse rectus abdominis muscle (TRAM) flaps were most commonly used (12).

The pros and cons of each type of reconstruction are summarized in Table 1. Advantages with implant reconstruction include shorter surgical procedure and recovery times, lack of functional deficits, and the potential to achieve good cosmetic results, particularly in patients who undergo contralateral mastectomy and desire bilateral symmetry. Disadvantages include the limited lifespan of implants and the aging of implants with time. Autologous flaps can more accurately mimic the natural shape and texture of the breast compared to implants. They also tend to offer superior long-term cosmetic results and patient satisfaction rates (13,14). However, autologous flaps require more complex and lengthier surgeries that can result in donor site morbidity (15).

Implant-Based Reconstructions

Implants are constructed from saline or silicone and are available in either a round or teardrop shape. A recent study demonstrated significantly higher patient satisfaction rates with silicone compared to saline reconstructions (16). Implant-based reconstructions can be performed with several approaches: a) single-stage, b) two-stage following the placement and inflation of a TE, or c) in combination with autologous tissue.

Single-Stage

Single-stage implant reconstructions are performed infrequently. They are limited to patients

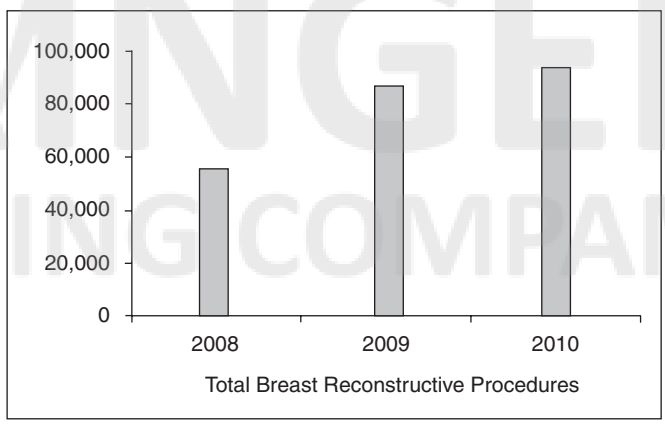

FIGURE 1 Recent trends in breast reconstruction from the American Society of Plastic Surgeons.
Source: Adapted from Ref. (12).

TABLE 1 Advantages and disadvantages of tissue expander/permanent implant versus autologous flap reconstruction

	Advantages	Disadvantages
Tissue expander/ permanent implant	• Shorter surgery and recovery times • No functional deficits • Good cosmetic results, particularly with bilateral breast construction	• Limited lifespan of the implant • Aging of the implant with time • Less natural in shape and consistency
Autologous flap	• More natural in shape and texture • Superior long-term cosmetic results and patient satisfaction rates	• More complex and lengthier procedures • Risk for donor site complications (i.e., abdominal hernia)

who desire small, nonptotic breasts and have adequate amounts of skin and muscle tissue to permit the immediate placement of an implant without prior expansion. The advantage of this method lies in the convenience of a single surgical procedure. Unfortunately, aesthetic outcomes with this approach are suboptimal and often require subsequent revision procedures (17).

Two-Stage

The majority of implant-based reconstructions are performed in two-stages with TEs (12). At the time of mastectomy, the TE is placed under the pectoralis major and serratus anterior muscles. The expander is consecutively inflated for 6 to 8 weeks and in a second procedure, exchanged for a permanent implant (PI). Expansion can occur concurrently with the administration of chemotherapy. Specific details regarding median time intervals between each step of this process when integrated with PMRT will be discussed below.

Autologous Flap Combined With Implant

Implants are combined with an autologous flap, usually a latissimus dorsi myocutaneous flap, when there is inadequate skin for expansion. This technique is often reserved for patients who had large amounts of skin resected during mastectomy or received prior radiation therapy, which can also limit the quality of skin. Because the addition of an autologous flap adds considerable complexity and risks to the reconstructive procedure, it is used only in highly selected patients (17,18).

Autologous Flap Reconstructions

During autologous flap reconstructions, a flap consisting of the patient's own skin, muscle, and fat is transferred to the chest wall defect in order to create a breast mound. Donor sites include the abdomen, back, buttocks, and thighs. These flaps are transferred either as a pedicled flap that contains its own blood supply or as a free flap, which would require microvascular reattachment of the principal blood vessels to those in the chest wall.

Patients whose body habitus does not allow for adequate tissue donation are not candidates for this procedure. Additionally, patients with a history of smoking, obesity, diabetes, or any other disease that can compromise the vasculature are at higher risk for complications, such as poor wound healing and fat necrosis (17).

■ SEQUENCING OF BREAST RECONSTRUCTION WITH PMRT

When integrated with radiation therapy, breast reconstruction can be performed immediately at the time of mastectomy and prior to PMRT, or it can be delayed as a separate surgical procedure, months following PMRT. Each sequence has its distinct set of advantages and disadvantages.

Immediate Reconstruction

Performing a reconstruction immediately following mastectomy provides multiple benefits to the patient. The surgical process can be streamlined into one procedure, which is convenient and potentially cost-effective (19). Cosmetic results are often improved, as anatomical structures including the natural inframammary fold and skin envelope can be preserved (17). Finally, patients experience greater psychosocial benefits from immediate reconstruction compared to delayed reconstruction because they emerge from surgery with a breast mound (20).

Delayed Reconstruction

Delaying breast reconstruction can simplify radiation therapy, as treatment planning is less complex with a relatively flat chest wall surface. Patients are also candidates for postmastectomy electron beam radiotherapy, a technique that allows for the delivery of conformal treatment using a relatively simple and reproducible clinical setup (21).

However, patients may experience more profound psychological effects associated with their altered anatomy and body image, as they are denied the benefits of reconstruction until months after the completion of radiation. Patients also must undergo a second major surgery following mastectomy. In those who require PMRT, this second procedure can be more challenging because of radiation-induced fibrosis at the surgical site.

Delayed-Immediate Reconstruction

The need for PMRT is not always known preoperatively, particularly in patients who present with clinical Stage II disease. Although delaying reconstruction until pathology is available is one approach, not all patients are in favor of postponing reconstruction until after PMRT. With the intent of preserving the aesthetic benefits of immediate reconstruction while avoiding the complications associated with irradiating a reconstructed breast, investigators from the MD Anderson Cancer Center (MDACC) developed the "delayed-immediate" technique (22) (Figure 2). During Stage I, a partially inflated TE is placed at the time of mastectomy. After pathology is reviewed, patients who will not receive PMRT proceed to definitive breast reconstruction within 2 weeks (Stage II). Patients who will require PMRT

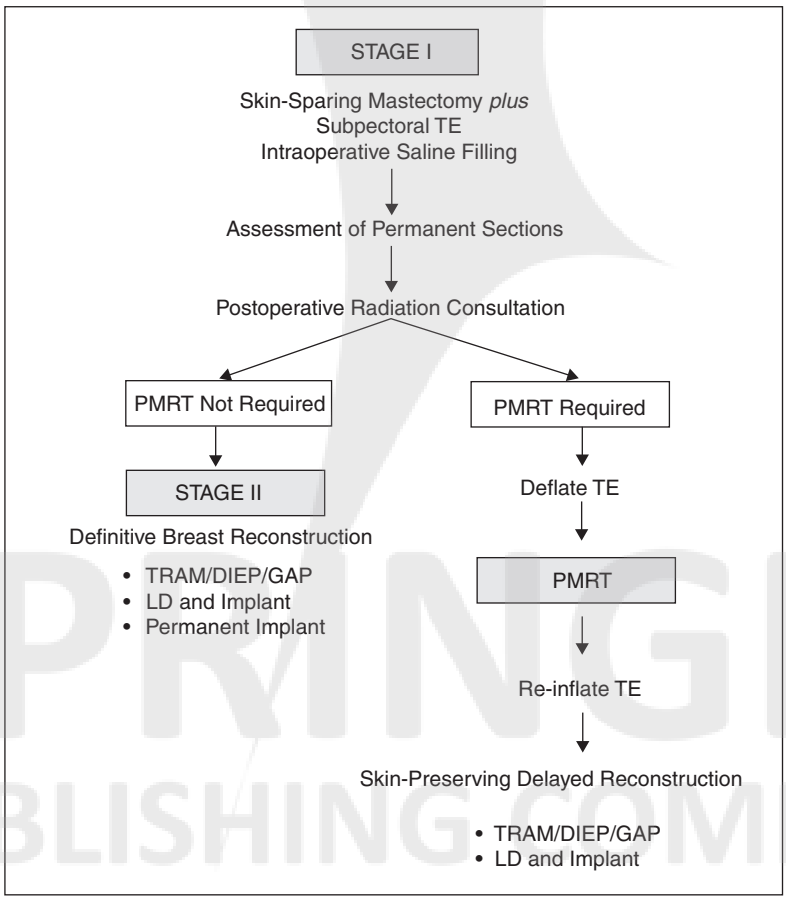

FIGURE 2 MD Anderson Cancer Center algorithm for delayed-immediate reconstruction.
DIEP = deep inferior epigastric perforator; GAP = gluteal artery perforator; LD = latissimus dorsi; PMRT = postmastectomy radiation therapy; TE = tissue expander; TRAM = transverse rectus abdominis muscle.

have their expanders deflated while they are still left in place to preserve the shape of the breast skin envelope. Reinflation of the TE begins 2 weeks after the completion of radiation. Approximately 3 months following PMRT, the expander is removed, and the patient undergoes definitive reconstruction.

A disease-matched controlled study of patients who received neoadjuvant chemotherapy was performed comparing 47 patients who underwent skin-preserving delayed reconstruction according to the delayed-immediate protocol, matched to 47 controls. All patients in the control group underwent standard delayed reconstruction without preservation of the breast skin. The protocol group received radiotherapy with a deflated TE in place, while the control group received treatment only to the chest wall. With a median follow-up of 40 months, the overall complication rate in the delayed-immediate group was 24% compared to 38% in the control group. TEs were lost in 32% of patients in the delayed-immediate group, a majority (60%) of which occurred during reinflation after PMRT secondary to infection or an irregular fold in the expander. Wound-healing complications occurred in 3% of the delayed-intermediate group compared to 10% of the control group. Three-year recurrence-free survival was 92% in the protocol group and 86% in the control group ($P = .87$) (23).

■ OUTCOMES FOLLOWING BREAST RECONSTRUCTION AND PMRT

Implant-Based Reconstruction and PMRT

It is difficult to collectively interpret existing studies on radiation and immediate implant-based reconstruction, as many studies included only a small number of patients with irradiated implants and treatment techniques and sequencing were inconsistent among them. Mean follow-up intervals were relatively short, and study endpoints were variably defined. These limitations resulted in a wide spectrum of reported complication rates ranging from 5% to 48% (Table 2), underscoring the need for reliable data with lengthy follow-up in homogeneously treated patients who received immediate implant-based reconstruction and radiation (18,24–29).

With the exception of one study that reported one locoregional recurrence in 92 patients (30), the studies on PMRT and immediate breast reconstruction have focused largely on cosmetic outcomes and complication rates rather than disease control. Recently, Memorial Sloan-Kettering Cancer Center (MSKCC) evaluated long-term disease outcomes in a cohort of 151 patients with Stage II to III breast cancer who underwent immediate two-stage expander/implant reconstruction with the following treatment algorithm: (a) a modified radical mastectomy with immediate placement of the TE(s), (b) initiation of chemotherapy with expansion of the TE(s) performed throughout treatment, (c) exchange of the TE(s) for PI(s) after the completion of chemotherapy, and (d) initiation of PMRT (Figure 3). The median time interval from mastectomy to the beginning of PMRT was 8 months, and the median interval from the end of chemotherapy to PMRT was 8 weeks. The mean follow-up was 86 months. After 7 years, there were only two reported chest wall-failures demonstrating excellent locoregional control in the study cohort. These data suggest that immediate reconstruction with the two-stage expander/implant approach performed in the described sequence and timeline does not compromise clinical outcomes in patients with locally advanced breast cancer (31).

In addition to disease outcomes, 7-year PI removal and replacement rates were also assessed. Overall, the 7-year combined PI removal or replacement rate was 29%. The most common causes for PI failure were severe capsular contracture and infection. Mechanical issues including implant shift, leak, or rupture comprised a minority of removal or replacements. Infection was a major cause of implant removal, whereas capsular contracture was the most dominant cause for implant replacement (31).

Capsular contracture is a common late complication of implant-based reconstruction. Radiation is a known risk factor for the development of capsular contracture (29,32). A study from MSKCC looked at long-term capsular contracture rates of two-stage TE/implant reconstructions in 315 patients with 410 reconstructions. At a median follow-up of 36.7 months, 32 (10%) of 309 nonirradiated reconstructions developed Baker's grade III/IV capsular contracture compared to 36 (50%) of 71 radiated reconstructions ($P < .001$) (33). Other series have reported Baker's grade III/IV capsular contracture rates ranging from 0% to 14% in nonirradiated patients and 15% to 42% in patients who undergo radiotherapy following reconstruction (26,29,34,35).

Despite the increased risk of surgical complications with radiotherapy, satisfactory cosmetic outcomes following immediate implant reconstruction and PMRT have been demonstrated (29,34). Another series from MSKCC evaluated complication rates and aesthetic results in both irradiated and nonirradiated

TABLE 2 Select studies of implant reconstruction and PMRT

Author (Year)	Total N (PI + RT)	Reconstruction Sequencing	Median FU (mo)	Endpoint	Endpoint Rate in RT Patients
Spear (2000) (18)	80 (40)	9 Delayed 19 Concurrent with RT 5 Immediate 7 Prior lumpectomy & RT	28	Implant loss	47.5%
Krueger (2001) (20)	81 (19)	2 Delayed 10 Immediate 7 Prior lumpectomy & RT	31	Reconstruction failure	37%
Chawla (2002) (40)	48 (18)	7 Delayed 31 Immediate 10 Prior lumpectomy & RT	32	Complication rate	53%
Tallet (2003) (42)	77 (55)	8 Delayed 47 Immediate	25	Reconstruction failure	24%
Cordeiro (2004) (29)	687 (81)	Immediate	34	Implant removed or replaced	11%
Anderson (2004) (27)	85 (50)	15 Delayed 70 Immediate	28	Major complications	5%
Ascherman (2006) (28)	104 (27)[a]	8 Premastectomy 19 Delayed	28	Major complications	18.5%
Wong (2008) (50)	62 (15)	6 Delayed 9 Immediate	10	Major corrective surgery	40%
Whitfield (2009) (32)	110 (41)	Immediate	51	Severe capsular contracture	19.5%
Kronowitz (2010) (22)	77 (77)[a]	Delayed-Immediate	32	TE loss	14%
Cowen (2010) (51)	141 (141)[a]	Delayed-Immediate	37	Implant removed or replaced	23%
Ho (2011) (31)	151 (151)	Immediate	86	Implant removed or replaced	30.5%

[a] Included irradiation of tissue expanders

RT = radiation therapy; FU = follow-up; mo = months; PI = permanent implant.

patients with implant reconstruction. Eighty-one patients were irradiated according to the institutional algorithm previously described (Figure 3). The control group included 75 patients who had similar reconstructions but did not receive PMRT. At a median follow-up of 34 months, 68% of irradiated patients developed capsular contracture compared to 40% of nonirradiated patients (P = .025). However, acceptable aesthetic results were achieved in 80% of irradiated patients compared to 88% of nonirradiated patients (P = NS). Nine (11%) irradiated implants were removed, four because of implant exposure or leakage and three because of infection. Notably, 72% of irradiated patients reported that they would choose the same reconstruction again (29).

Similar complication rates and cosmetic outcomes have been shown in studies comparing TE and PI irradiation. The Fox Chase Cancer Center assessed reconstructive outcomes following PMRT in a group of 74 patients. Sixty-two patients received radiation to a TE, and 12 patients were treated with PIs in place. The primary endpoint was a major complication requiring corrective surgery or reconstruction loss. With a median follow-up of 48 months, there

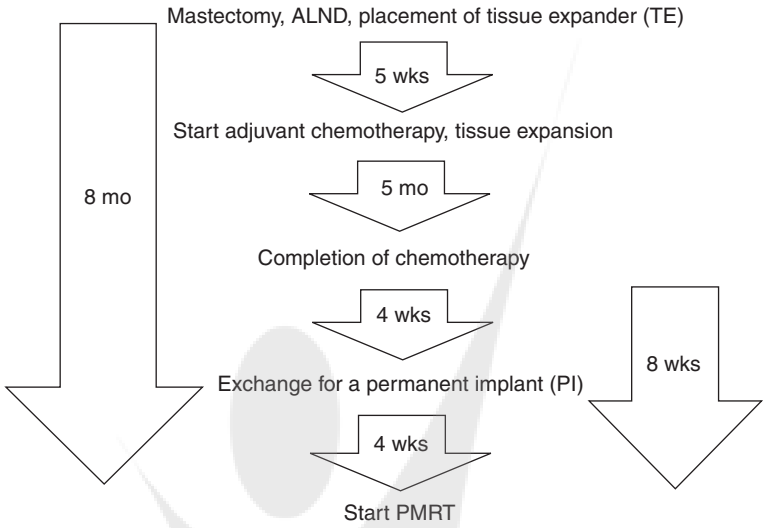

FIGURE 3 The Memorial Sloan-Kettering Cancer Center treatment algorithm for the integration of immediate two-stage tissue expander-permanent implant reconstruction and postmastectomy radiation (PMRT). ALND = axillary lymph node dissection.

was no significant difference in the rate of major complications between the TE and PI groups. No PIs were lost, while three patients lost their TEs. Patients achieved good or excellent cosmetic scores in 80% of the PI group and 90% of the TE group, a difference that was not significant (36).

Tissue expansion and PI placement in previously irradiated patients is rarely performed. Radiation-induced fibrosis of the chest wall and thinning of the mastectomy flaps greatly increase the risk for complications when tissue expansion is attempted. Patients who are not appropriate candidates for autologous flap reconstruction are therefore limited in their options if reconstruction is delayed. Preoperative coordination and assessment by both plastic surgeon and radiation oncologist is crucial so that patients who may desire implant-based reconstruction receive this in the immediate setting.

Data on irradiated patients who subsequently undergo implant-based reconstruction is limited. A retrospective review from Yale University evaluated nine patients (10 breasts) who underwent two-stage implant reconstruction following a salvage mastectomy for local recurrences after initial treatment with breast-conservation therapy and radiation to an unreconstructed chest wall. The average time interval from radiation treatment to placement of the TE was 4.6 years. Overall, six (60%) patients experienced some sort of complication. The TE was extruded in one patient (10%). In two patients (20%), expansion was difficult and the final reconstruction lacked projection. One patient (10%) required removal of the PI because of infection, and two patients (20%) developed Baker class III or IV capsular contracture (37).

Autologous Flap Reconstruction and PMRT

In the acute setting, radiation-associated complications of autologous tissue flaps are similar to those seen with whole breast radiation and include erythema and desquamation of the skin. Long-term complications unique to flap reconstructions are primarily cosmetic and include fat necrosis and flap atrophy (38).

A study at the University of Rochester Medical Center evaluated 76 patients who underwent autologous breast reconstruction followed by PMRT. Seventy percent of patients experienced complications within the first year after radiation treatment. Twenty percent had parenchymal complications including fat necrosis or parenchymal fibrosis, and 30% had skin complications including retraction and hypertrophic scarring. In 28% of cases, general dissatisfaction was reported by either the patient or physician. Parenchymal complications were associated with smoking (OR = 9.3, $P = .03$), type II diabetes mellitus (OR = 8.5, $P = .02$), and age (OR = 1.1, $P = .02$) (39).

The MDACC group examined the outcomes of immediate and delayed TRAM flap reconstructions

in patients undergoing PMRT. Early and late complications were compared between 32 patients with immediate TRAM flap reconstruction and 70 patients with delayed TRAM flap reconstruction. Early complications included vessel thrombosis, partial or total flap loss, skin flap necrosis, and wound-healing problems. Late complications included fat necrosis, flap volume loss, and contracture. While there was no significant difference in the incidence of early complications between the two groups, the incidence of late complications was significantly higher in the immediate TRAM flap reconstruction group (P = .000). Twenty-four (75%) immediate reconstruction patients experienced flap contracture, and nine (28%) required an additional flap or an external prosthesis for correction of contour and volume deformities (38).

At the Georgetown University Medical Center, the reconstructive outcomes of 171 pedicled TRAM reconstructions in 150 patients were evaluated. Forty-two TRAM flap reconstructions were performed after radiation (delayed reconstruction), 38 were completed before radiation (immediate reconstruction), and the remainder did not receive any radiation (control). Total flap complications were seen in 57.1% of delayed reconstruction patients, 50% of immediate reconstruction patients, and 49.5% of control patients (P = NS). The control group had significantly better overall aesthetic outcomes compared to both irradiated groups. While aesthetic outcome scores were superior in patients with delayed reconstructions compared to immediate reconstructions, this difference was not significant (40).

A study from the Beth Israel Deaconess Medical Center evaluated complication rates and patient satisfaction in 114 patients who underwent autologous tissue-based or implant-based reconstruction and received PMRT. Fifty-seven patients had immediate reconstruction and 57 had delayed reconstruction. Reconstructive techniques were highly variable within the study cohort, with a majority of patients undergoing autologous flap reconstruction. Thirty-nine percent of patients received a pedicled or free TRAM flap, 20% received a deep inferior epigastric perforator (DIEP) flap, and 26% received a latissimus dorsi muscle flap. Patients with immediate reconstructions had a higher complication rate compared to delayed reconstructions although the difference was not statistically significant (44% vs. 32%, P = .176). Late complication rates were significantly higher in the immediate reconstruction group (33% vs. 14%, P = .009), while early complications were more frequent in the delayed reconstruction group (18% vs. 11%, P = .210). General and aesthetic satisfaction rates were similar between the two groups (41).

Cosmesis following irradiation of DIEP flaps have been examined by a group at Tulane University. A matched pair analysis of 60 patients who underwent DIEP flap reconstruction with or without PMRT was performed. The follow-up time from surgery was 19.9 months in the irradiated group and 17.4 months in the nonirradiated group. Patients who received PMRT had significantly higher rates of fat necrosis (23% vs. 0%, P = .006), fibrosis or shrinkage (57 vs. 0%, P < .001), and flap contracture (17% vs. 0%, P = .023) compared to nonirradiated patients. Preirradiation and postirradiation photographs were taken in 10 patients and compared to 10 matched controls to evaluate aesthetic outcomes. A five-point scale was used to evaluate symmetry, aesthetic proportion, and the superior pole. While nonirradiated patients had an overall increase of 0.5 points in their aesthetic scores, irradiated patients had an overall decrease of 0.56 points (42).

As demonstrated by the above data, complication rates are relatively high in the setting of autologous flaps irradiation. While some centers in the United States may utilize this technique, many tend to favor alternative approaches secondary to concerns regarding suboptimal cosmesis following radiation therapy. Irradiation of autologous tissue flaps is performed in other countries, where favorable cosmetic results of irradiated autologous flaps have been reported. In a large series performed at Kaohsiung Medical University Hospital in Taiwan, 82 patients who underwent immediate TRAM flap reconstruction followed by PMRT were examined. At a median follow-up of 40 months, flap contracture rate was seen in 36% of patients and fat necrosis in 8.5%. There was no total flap loss reported. Seventy percent of patients reported good or excellent cosmetic outcomes, while only 7% reported poor cosmetic outcomes (43).

Breast Reconstruction and PMRT in Patients Receiving Neoadjuvant Chemotherapy

While the feasibility of two-stage expander/implant reconstruction in the setting of adjuvant therapy has been demonstrated, studies regarding the integration of PMRT with reconstruction in the context of neoadjuvant chemotherapy are also slowly emerging. Given that many patients who are candidates for neoadjuvant chemotherapy have high-risk disease features, there is concern that the delay of PMRT initiation can compromise locoregional control. Some groups have approached this by performing rapid

expansions of the TE following mastectomy and initiating PMRT with the expander rather than a PI.

Reconstructive failure rates using this approach were recently reported by the Instituto Nazionale Dei Tumori in Italy from a prospective study on 257 PMRT patients separated into three groups. Group one included 109 patients who underwent mastectomy with immediate TE placement, initiation and completion of adjuvant chemotherapy during expansion, exchange for a PI, and finally PMRT with the PI in place. Group two included 50 patients who received neoadjuvant chemotherapy, underwent mastectomy with TE placement, received PMRT with the TE in place, and finally had the TE exchanged for a PI more than 6 months after completing radiation treatment. Group three was a control group of 98 nonirradiated patients who underwent two-stage immediate breast reconstruction. The primary endpoint of the study was reconstruction failure defined by removal of the implant or change to a flap-based technique. A secondary endpoint was capsular contracture.

The median follow-up was 50 months. The reconstruction failure rate was 40% in group two, 6.4% in group one, and 2.3% in the control group ($P < .0001$), suggesting that radiotherapy during tissue expansion may significantly compromise reconstructive outcomes in patients who received neoadjuvant chemotherapy. The overall capsular contracture rate was significantly higher in both irradiated groups compared to the control group. The Baker grade IV capsular contracture rate was 13.3% in group two, 10.1% in group one, and 0% in the control group ($P = .0001$) (44).

Impact of Breast Reconstruction on the Technical Delivery of PMRT

The compatibility of PMRT and immediate breast reconstruction has been questioned by clinicians who hypothesize that immediate reconstruction can complicate the technical delivery of radiation (45). The presence of a reconstruction, whether implant or autologous flap-based, significantly alters the chest wall contour from a relatively flat to a sloping surface. The sloping contour can lead to an imprecise geometric match of radiation treatment fields and in turn dose heterogeneity. Potential dosimetric consequences include suboptimal target coverage and increased critical organ toxicity.

A matched pair analysis from the MDACC evaluated the impact of immediate reconstruction on radiation treatment planning in breast cancer patients receiving PMRT. Treatment plans from 216 patients were evaluated, 110 with reconstruction and 106 without reconstruction. The majority of reconstructed patients (96%) had TRAM flap reconstructions. Four categories were assessed: chest wall coverage, internal mammary node (IMN) coverage, minimization of irradiated ipsilateral lung volume, and avoidance of the heart. Notably, all patients from this study received treatment to the IMNs. A goal was set for each category, and a scoring system was developed so that points were awarded to plans when the goals were met and deducted when they were not. Based on the total number of points accrued, plans were deemed severely compromised, moderately compromised, or optimal.

Over half of the treatment plans for reconstructed patients were compromised. About 33% versus 6% of plans were moderately compromised and 19% versus 1% majorly compromised in reconstructed versus unreconstructed patients (both $P < .001$). Major compromises occurred more commonly with left-sided cancers. Reconstructed patients had significantly higher rates of suboptimal chest wall coverage ($P < .0001$), IMN coverage ($P < .0001$), and minimization of irradiated lung volume ($P = .0015$). Avoidance of the heart was similarly achieved in both groups ($P = .14$). Based on these results, the MDACC group concluded that the potential for compromised radiation treatment planning should be considered when deciding between immediate and delayed reconstruction (45).

The MSKCC group performed a similar study comparing 247 unreconstructed and reconstructed patients who received PMRT. Fifty-one patients did not undergo any reconstruction, and 196 patients underwent immediate implant reconstruction. Rather than treatment plan evaluation, dose -volume histogram data was used to assess ipsilateral lung dose, heart dose, and target coverage. All reconstructed patients were treated with tangential photons, while unreconstructed patients were treated using en-face electrons (Figure 4). In contrast to the MDACC study, only 49 patients (20%) in this cohort received treatment of the IMNs (23 reconstructed and 26 unreconstructed patients).

Reconstructed patients had lower ipsilateral lung doses and similar heart doses compared to unreconstructed patients. A majority of reconstructed patients had excellent coverage of the chest wall demonstrating that normal tissue doses were not achieved at the expense of adequate coverage. Among the 49 patients who received treatment to the IMNs, reconstructed patients also had superior IMN coverage compared with unreconstructed patients. Finally, the dosimetric impact of IMN treatment was assessed within

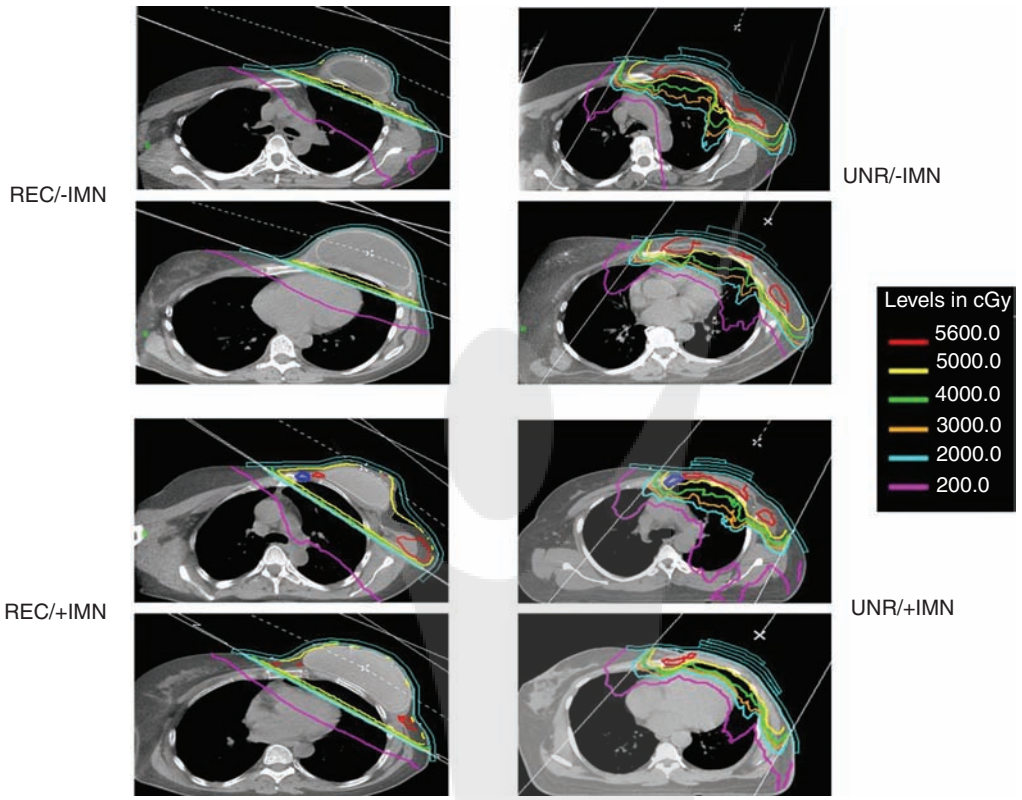

FIGURE 4 Axial views at the central axis (bottom) and 6 cm superior to the central axis (top) showing isodose lines from representative left-sided treatment plans of unreconstructed and reconstructed patients with and without IMN treatment. Dark blue = IMN contour.

the reconstructed and unreconstructed groups. All measured heart and lung parameters significantly increased with IMN treatment in the reconstructed group (all $P < .05$), whereas none of the parameters significantly changed in the unreconstructed group (all $P > .05$). The following conclusions were drawn: (a) immediate implant reconstruction does not compromise the technical quality of PMRT when the IMNs are excluded and (b) treatment technique, not reconstruction, is the primary determinant of normal tissue doses and target coverage (46).

Both studies illustrate the dosimetric consequences of IMN treatment, which appear to be particularly magnified in patients with breast reconstruction. The value of IMN irradiation in locally advanced breast cancer patients remains tremendously controversial, and any potential gains in clinical outcomes may be offset by treatment-related toxicities (47). Twenty-four of the 25 PMRT studies in the EBCTCG meta-analysis included the IMNs in the radiation treatment fields, suggesting that the benefits of PMRT may be related to their treatment (4). However, opponents argue a lack of survival benefit and increased toxicities with IMN irradiation compared to treatment with traditional three-field radiation plans (47–49).

■ CONCLUSION

Significant advances in the integration and delivery of PMRT in the setting of breast reconstruction have been witnessed over the past decade. Acceptable long-term complication rates and excellent locoregional control with immediate implant-based breast reconstruction and PMRT are achievable using a coordinated multidisciplinary approach. When autologous reconstruction is planned, delayed reconstruction is usually performed, secondary to suboptimal cosmesis following irradiation of tissue flaps. The future areas of investigation include elucidating the timing of PMRT in patients who receive neoadjuvant

chemotherapy and receive immediate reconstruction with implants.

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Local Recurrence and Biological Subtypes of Breast Cancer

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■ ABSTRACT

Estimation of the risk of local and regional recurrence after treatment for early stage breast cancer has long relied on traditional clinical and pathologic prognostic factors, but these remain imprecise. With the discovery of intrinsic breast cancer subtypes based on gene expression profiling, there has been great interest in determining the value of these subtypes as prognostic and predictive factors. Several retrospective reports have now examined the risk of local and regional recurrence after breast-conserving therapy or mastectomy according to immunohistochemistry-based approximations of the molecular subtypes. Luminal breast cancers, defined by hormone receptor positivity, have been found to have markedly improved local outcomes as compared to nonluminal breast cancers. Further work is required to prospectively validate the use of breast cancer subtypes as prognostic and/or predictive markers for eventual clinical use with individual patients.

Keywords: breast cancer, subtype, local recurrence, locoregional recurrence, breast-conserving therapy, mastectomy, luminal, HER2, triple negative

■ INTRODUCTION

The management of breast cancer (BC) has changed substantially over the past several decades, including the widespread adoption of screening programs, use of systemic hormonal therapy and chemotherapy, and wide acceptance of breast-conserving therapy (BCT). Randomized clinical trials have demonstrated equivalent survival outcomes after mastectomy compared with BCT (1) for early stage BC, and local control (LC) after BCT has improved markedly over time. The reason for this improvement is multifactorial, and appears attributable to a combination of a) advancements in mammography that have allowed visualization of more subtle radiologic changes, b) increasing attention to margin status after surgical resection, c) improved delineation of the postoperative lumpectomy cavity for radiotherapy (RT) planning, and d) widespread use of adjuvant systemic therapy, which has been shown to decrease the risk of local recurrence (LR). The Early Breast Cancer Trialists' Collaborative Group showed in a landmark meta-analysis that one death from BC is prevented at 15 years for every four LR prevented at 5 years (2). With longer follow-up, the same group has recently

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reanalyzed the data and found that after BCT, one death is prevented at 15 years for every four recurrences (local or distant) prevented at 10 years (3). These findings highlight the importance of LC and understanding the factors that contribute to LR.

Estimation of the risk of LR after BCT or mastectomy has long relied on traditional clinical and pathologic prognostic factors, which continue to be widely used in clinical decision-making. Relevant factors include patient's age, tumor size, axillary lymph node status, histologic grade, and margin status after lumpectomy. While each of these factors has been shown to influence the risk of LR among women with early stage BC, they remain imprecise. It has long been recognized that BC is a heterogeneous disease. For example, only patients with estrogen receptor (ER) positive tumors have been found to derive benefit from tamoxifen (3), essentially a form of targeted therapy, which can lead to substantially improved outcomes compared to other tumors.

In the year 2000, researchers from Stanford University and Norway made significant advances to our understanding of this heterogeneity within BC by identifying several distinct BC subtypes based on gene expression patterns from different patient tumors (4). Since that seminal publication, ongoing characterization of BC subtypes over the past decade has led to a growing understanding of the genetic diversity of invasive BCs, including correlation with clinical outcomes (5). Thus in the modern era of genomic information, there has been growing optimism that molecular data for an individual patient may lead to a personalized, accurate prognostic evaluation of BC outcomes that might eventually supplant traditional clinico–pathologic risk factors. While there is a substantial literature on the association of genomic features with overall survival in BC, there is less data on the relationship between these features and LC. This review will outline the evolution of BC subtypes and then focus on our current understanding of the relationship between subtypes and LC.

■ IDENTIFICATION OF INTRINSIC BC SUBTYPES WITH GENE EXPRESSION PROFILING

The characterization of BC made an important leap forward with the discovery by Perou et al of intrinsic gene expression patterns unique to multiple different BC subtypes (4). In this study, complementary DNA microarrays representing more than 8,100 genes were used to analyze mRNA from breast tumors from 42 different individuals to ascertain the gene expression patterns for each tumor. Tumors included 36 infiltrating ductal carcinomas, 2 lobular carcinomas, 1 ductal carcinoma in situ, 1 fibroadenoma, and 3 normal breast samples. Approximately half of the women had their tumor biopsied both before and after receipt of 16 weeks of doxorubicin chemotherapy, and two patients had samples taken from both the primary tumor and an axillary lymph node metastasis. Among all samples, hierarchical clustering was used to group genes based on variations in expression pattern seen among all samples.

The gene expression profiling results exhibited striking variation between tumors, with gene expression patterns that were found to be characteristic of newly-defined "intrinsic" breast tumor subtypes. Luminal epithelial cells and basal epithelial cells are two different epithelial cell types in breast tissue, and Perou et al observed clear differences in gene expression between these two cell types. In particular, the luminal cells had characteristic clustering of gene expression of the ER. In addition to the luminal and basal-like BC subtypes, they found a third distinct subtype characterized by HER2/neu oncogene (also known as Erb-B2) over expression and related gene sets. Interestingly, subset testing revealed the gene expression patterns did not change substantially after treatment with doxorubicin, or between primary tumor and axillary lymph node metastasis, suggesting that these patterns were intrinsic to the tumor itself, and not just a particular tumor sample.

Additional work by this group went on to identify that luminal epithelial/ER-positive breast tumors could be further divided into two or three groups with a distinct expression profile (5). These include luminal A tumors that were characterized by the highest expression of the ERα gene, and luminal B and luminal C tumors that showed more moderate expression of the luminal-specific genes including the ER cluster. Subsequent work in the past decade has confirmed that with repeated experiments and different microarray platforms, there indeed appear to be four intrinsic BC subtypes characterized by gene expression patterns (6,7). In summary, luminal A and luminal B cancers exhibit high expression of hormone receptor-related genes (such as ER), with luminal A tumors having somewhat higher expression of these hormone receptor genes and lower expression of proliferation genes as compared to luminal B cancers. The HER2 cancers demonstrate high expression of HER2/neu and low expression of hormone receptor-related genes. Basal-like cancers are distinguished by high expression of proliferation

genes and low expression of hormone receptor or HER2/neu-related genes.

■ CORRELATION OF MOLECULAR BC SUBTYPES WITH CLINICAL CHARACTERISTICS AND OUTCOMES

Soon after identification of these intrinsic BC subtypes, correlation between the molecular subtypes and clinical outcomes was first reported in retrospective series (5,8,9). Sørlie et al examined 49 patients with locally advanced BC and with a median follow-up on 66 months observing a highly significant difference in overall survival between the BC subtypes, with basal-like and HER2 subtypes being associated with the shortest overall and relapse-free survival (5). Furthermore, luminal A tumors appeared to have the most favorable characteristics among all the BC subtypes, with higher relapse-free survival even when compared to luminal B tumors.

In addition to survival outcomes, the BC subtypes have been shown to be associated with different clinical and pathologic characteristics. Overall, luminal BC are the most common subtype, representing approximately two-thirds of BC (9). The basal-like subtype has been found to be significantly more prevalent among premenopausal African American women (39%) compared to postmenopausal African American women (14%) and non-African American women of any age (16%), with the luminal A subtype being correspondingly much less prevalent in this group of women. Also, compared with luminal A as baseline, basal-like tumors exhibited significantly higher mitotic index, more marked nuclear pleomorphism, higher grade, and more TP53 mutations.

Other traditional BC prognostic factors, such as patient's age, have also been shown to be associated with the intrinsic BC subtypes. It has long been observed that young women with BC have poorer outcomes as compared to older patients (10,11), and with the introduction of genomic data, it was believed that young women with BC exhibited a fundamentally different disease on a molecular level. For example, Anders et al demonstrated that BC in women 45 years of age or younger exhibit significantly lower ERα mRNA, ERβ mRNA, and PR expression but higher HER2 and epidermal growth factor receptor (EGFR) genomic expression, with more than 350 gene sets related to multiple oncogenic signaling pathways that distinguish BC in young women (12). However, recent work from this same group evaluated the distribution of molecular BC subtypes by age to assess for potential confounding effects on the distribution of supposed age-associated genes (13). Their work showed that genes associated with intrinsic subtype and grade appeared to strongly influence the biologic differences observed among tumors in young versus older women, and that age alone did not confer additional biologic complexity above that imparted by molecular subtype. This suggests that as BC continues to be better characterized at the genomic level, the prognostic importance of age, or other traditional clinico–pathologic factors may decline substantially.

■ BC SUBTYPE APPROXIMATION BY IMMUNOHISTOCHEMISTRY

While the discovery of intrinsic BC subtypes and their associations with clinical outcomes was a breakthrough in understanding the biology of BC, a practical limitation with gene expression profiling was the cost, expertise, and availability of performing microarrays on individual patients. Moreover, it remains to be further characterized whether such information might be not only prognostic of outcome, but also predictive of response to various treatments (14). It was recognized early on that molecular BC subtypes could be approximated using readily available clinical receptors, specifically ER, progesterone receptor (PR), and HER2/neu status of the primary tumor as defined by immunohistochemical (IHC) staining. The intrinsic BC subtypes have thus been approximated as follows : luminal A (ER+ or PR+ and HER2–), luminal B (ER+ or PR+ and HER2+), HER2 (ER– and PR– and HER2+), and basal (ER– and PR– and HER2–) (8).

A limitation of using IHC to approximate the BC subtypes is that the approximations are not genotype-based, and there is not a perfect correlation between IHC results and genotype data. For example, in the Carolina Breast Cancer Study (9), Carey et al reported that only 30% to 50% of luminal B tumors defined by genotyping were HER2+ on IHC (or fluorescence in situ hybridization). While this remains a limitation, recent refinements in distinguishing the luminal subtypes have led to incorporation of not only ER, PR, and HER2 status but also the cell proliferation marker Ki-67, which has been found to more accurately distinguish the luminal subtypes and add prognostic information (15). As a result, several groups are now employing a classification scheme that specifies five BC subtypes, with either Ki-67 index or histologic grade as the additional marker used to categorize tumors

(16–18) as follows: luminal A (ER+ or PR+, HER2–, and grade 1 or 2 [or Ki-67 index < 14%]), luminal B (ER+ or PR+, HER2–, and grade 3 [or Ki-67 index ≥ 14%]), luminal-HER2 (ER+ or PR+ and HER2+), HER2 (ER– and PR– and HER2+), and triple negative (ER– and PR–, and HER2–).

Moreover, other reports have suggested that the triple negative subtype can also be further subdivided into two subcategories using not only ER, PR, and HER2, but also CK 5/6 and EGFR markers (19,20). Data suggests that triple negative tumors that express the basal markers CK 5/6 and/or EGFR have significantly inferior outcomes including distant metastasis rate and death. Ongoing work is required to determine the optimal number and combination of IHC-based markers for BC subtype approximation, which balances availability of the markers for general, routine use on the one hand, with improved discrimination in outcomes based on multiple markers on the other.

■ LR AFTER BCT ACCORDING TO SUBTYPE

As previously outlined, estimating the risk of LR after BCT or mastectomy has relied for decades on traditional prognostic factors, including patient's age, tumor size, axillary lymph node status, histologic grade, and margin status. The advent of BC subtyping and its association with disease progression and survival led to the question of whether the local behavior of the tumor after surgical resection might also be influenced by BC subtype. An initial study to examine this question in women who had received BCT came from our institution in 2008, which investigated 793 consecutive women with early stage BC who received BCT between 1998 and 2001 and had information available regarding ER, PR, and HER2 status (21). After a median follow-up of 70 months, there were 18 isolated LR, with an overall 5-year LR rate of 1.8%. However, significant differences were observed in the risk of LR according to four BC subtypes ranging from 0.8% for luminal A and 1.5% for luminal B, up to 8.4% for HER2 and 7.1% for basal subtype (Table 1). Notably, BC subtype was the only variable that remained significant in the final multivariable model for association with risk of LR. Specifically, with luminal A as baseline, the HER2 and basal subtypes were associated with increased LR risk with adjusted hazard ratios of 9.2 (1.6–51, $P = .012$) and 7.1 (1.6–31, $P = .009$), respectively.

These findings, demonstrating a relationship between BC subtype and risk of LR after BCT, have been confirmed in other studies. An Australian study analyzed 688 women receiving BCT enrolled in a randomized trial evaluating the benefit of an RT boost to the lumpectomy cavity, with tissue blocks available for IHC analysis on 498 of the patients (22). Patients were categorized into five approximated BC subtypes, which included luminal A, luminal B, HER2, basal, and unclassified (19,20). With a median follow-up of 84 months, the 5-year LR rates ranged from 1.0% for luminal A tumors and up to 9.6% for basal tumors. Compared to other subtypes, luminal A tumors had a trend toward a lower rate of LR with a hazard ratio of 0.433 (0.186–1.005; $P = .051$), though with a low overall LR rate in the entire cohort. In addition, the authors reported that BC subtype was associated with significant differences in locoregional recurrence (LRR) ($P = .012$), distant disease-free survival ($P = .0035$), and BC-specific death ($P = .0482$).

In addition, Yu et al presented data in abstract form on the risk of LR among 644 patients who received neoadjuvant chemotherapy before BCT from 1997 to 2005 (23). With a median follow-up of 65 months, the authors report that among four BC subtypes, HER2 and triple negative tumors had a significantly higher rate of achieving a pathologic complete response compared to the luminal subtypes (16%–17% for HER2 and triple negative vs. 2% for luminal A and luminal B; $P < .001$). Despite this, the risk of LR at 5 years was significantly higher among patients with HER2 (15%) and triple negative (10%) subtypes in contrast to luminal A (3%) and luminal B (2%; $P < .001$).

One study has examined the location of LR within the ipsilateral breast according to subtype, which is further suggestive of differences in biological behavior between BC subtypes (24). In this report, 1,223 women with invasive BC treated with BCT and followed for a median of 70 months, with 24 patients developing LR. The authors examined whether the LR was a true recurrence, defined as within the same quadrant and within 3 cm of the initial primary tumor, or an elsewhere recurrence. They found that triple negative and HER2 tumors had higher rates of true recurrence at 4.4% and 9.0% respectively compared to luminal B (1.2%) or luminal A (0.2%; $P < .0001$) subtypes. On multivariate analysis, triple negative subtype was the strongest independent predictor of true recurrence, with a hazard ratio of 4.8 ($P = .01$). Based on these data, the authors concluded that strategies to reduce true recurrences

TABLE 1 Risk of local, regional, and locoregional recurrence according to breast cancer subtype

Study	Number of Patients	Median Follow-Up (years)	Luminal A (%)	Luminal B (%)	Luminal-HER2 (%)	HER2 (%)	TN (%)
Nguyen (21)							
5-year LR (BCT)	793	5.8	0.8	1.5	–	8.4	7.1
Arvold (17)							
5-year LR (BCT)	1,434	7.1	0.8	2.3	1.1	10.8	6.7
Millar (22)							
5-year LR (BCT)	498	7.0	1	4.3	–	7.7	8.8
5-year LRR (BCT)			2	4.3	–	15.3	14.7
Yu (23)							
5-year LR (Chemo◇BCT)	644	5.4	3	2	–	15	10
Voduc (16)							
10-year LR (BCT)	1,271	12.0	8	10	9	21	11
10 year RR (MRM)	1,283		3	8	5	16	10
Kyndi (25)							
15-year LRR (MRM)	486	17.0	32	48	–	33	32
15-year LRR (MRM◇RT)	510		3	3	–	21	15
Abdulkarim (26)							
5-year LR (BCT)	319	7.2	–	–	–	–	6
5-year LRR (MRM)	287		–	–	–	–	15

Abbreviations: HER2 = human epidermal growth factor receptor 2; TN = triple negative; LR = local recurrence; BCT = breast-conserving therapy; Chemo = chemotherapy; RR = regional recurrence; MRM = modified radical mastectomy; LRR = locoregional recurrence; RT = radiotherapy.

among triple negative tumors were warranted, such as increased RT boost doses or concurrent chemotherapy with RT.

Finally, we recently updated of our institutional experience of BCT with a focus on LR according to patient's age and BC subtype (17). In this report, 1,434 consecutive women with clinical Stage I or II invasive BC treated with BCT from 1997 to 2006 were examined, with an analysis of five BC subtypes including luminal A, luminal B, and luminal-HER2, using histologic grade to distinguish three luminal subtypes as outlined previously. After a median follow-up of 85 months, the Kaplan Meier 5-year cumulative incidence (CI) of LR was 0.8% for luminal A, 2.3% for luminal B, 1.1% for luminal HER2, 10.8% for HER2, and 6.7% for triple negative. On multivariate analysis, HER2 subtype (adjusted hazard ratio = 5.15; 95% CI, 1.76–15.05; $P = .003$) and triple negative subtype (adjusted hazard ratio = 3.94; 95% CI, 1.72–9.01; $P = .001$) were independent predictors of LR, and luminal B subtype (adjusted hazard ratio = 2.14; 95% CI, 0.95–4.85, $P = .067$) showed a nonsignificant trend toward increased risk of LR. Analysis according to age quartile and BC subtype revealed that age appears to be important within each BC subtype, with highest crude rates of LR among luminal B (8.1%), HER2 (13.3%), and triple negative (10.2%) tumors among the youngest age quartile in contrast to very low rates of LR among the oldest age quartile for luminal B (0%) and HER2 (0%) tumors, for example.

■ LRR AFTER MASTECTOMY ACCORDING TO SUBTYPE

While the preponderance of the recent literature on LR according to BC subtype has focused on women who received BCT, several publications have included sizable numbers of patients who received mastectomy. A British Columbian study examined 2,985 women treated for early stage invasive BC between 1986 and 1992, all of whom had intrinsic molecular subtype approximated using six biomarkers including Ki-67, CK 5/6, and EGFR, in addition to the standard ER, PR, and HER2 (16). Mastectomy alone was performed on 44% of the women, and 42% received BCT. After a median of 12 years of follow-up, both

mastectomy patients and BCT patients with luminal A tumors had significantly lower rates of both LR (8% for both mastectomy and BCT) and regional recurrence (4% for mastectomy, 3% for BCT) at 10 years compared to other subtypes. For women who received mastectomy, all nonluminal A subtypes, except for nonbasal-like triple negative, were significant independent predictors of a chest wall recurrence, and of regional nodal recurrence, on multivariate analysis.

Kyndi et al investigated 996 of the 3,083 women with high-risk BC who were randomized in the Danish 82b and 82c postmastectomy RT (PMRT) trials, which ran from 1982 to 1990, and reported outcomes according to four BC subtypes (25). On multivariate analysis of prognostic factors, HER2 and triple negative subtypes were significantly associated with increased rate of both LRR and overall mortality among all patients. When analyzed according to receipt of PMRT, only women with triple negative tumors had a significantly increased risk of LRR after PMRT ($P = .01$), whereas women with either HER2 or triple negative subtypes who did not receive PMRT had a significantly increased risk of LRR ($P < .001$ and $P = .004$, respectively). Interestingly, the authors examined the predictive value of BC subtype and found that the luminal A tumors derived a greater LRR benefit from PMRT when compared to HER2 ($P = .003$) and triple negative tumors ($P = .02$).

An intriguing recent study from the University of Alberta has reported on outcomes of women with BC who underwent mastectomy versus BCT, specifically among patients with triple negative tumors defined as ER–, PR–, and HER2– (26). They examined 768 women from a single institution treated between 1998 and 2008, of whom 37% had received mastectomy alone and 42% had received BCT, with a median follow-up of 7.2 years. Among all patients, compared with BCT, mastectomy was associated with an increased risk of LRR (adjusted hazard ratio = 3.44, 95% CI, 2.04–5.80, $P < .001$) on multivariate analysis, whereas there was no significant difference among patients treated with BCT versus those treated with mastectomy plus adjuvant RT. A subgroup analysis of just the T1–2N0 patients revealed that receipt of mastectomy was the only independent prognostic factor associated with LRR, with an adjusted hazard ratio of 2.53 (1.12–5.75, $P = .0264$) when compared to BCT. While there was no survival difference between BCT and mastectomy alone patients, these data point to the question of whether and how treatment recommendations should be tailored for patients with more aggressive BC subtypes.

■ LIMITATIONS

The intrinsic BC subtypes have added greatly to our understanding of the molecular characterization of the heterogeneity of BC, yet there are some limitations raised in the data we have outlined above. Classification according to ER, PR, and HER2 status are only approximations of gene expression profiling-based molecular BC subtypes, and even with the addition of other markers such as Ki-67 or histologic grade, CK 5/6, or EGFR, IHC-based categorizations cannot fully approximate those that utilizing gene expression profiling. With regard to the correlations between BC subtypes and clinical outcomes, nearly all of the published data comes from the pretrastuzumab era, and thus, it is not clear that the present risk of LR and LRR for HER2+ BC subtypes is accurately conveyed in the existing literature. In the two largest randomized trials, adjuvant trastuzumab decreased the risk of LR among HER2-positive patients by almost 50% (27, 28) although LR was not a specific endpoint, and thus the risk of LR for HER2+ subtypes may be shown to be substantially lower.

More generally, most of the literature on the risk of LR or LRR after BCT or mastectomy still reports data on patients treated in the 1970s, 1980s, and early 1990s, and thus the published risks of local failure for early stage BC may be higher than what is observed clinically in the modern era. Advances in the past decade include better preoperative breast imaging and postoperative delineation of the lumpectomy cavity for RT planning, greater attention to obtaining negative surgical margins, incorporation of a RT boost, and perhaps most importantly the prevalent use of adjuvant systemic therapy, which has been shown to reduce rates of LR (29). In our experience, we have observed that while there is marked variability in LC according to BC subtype, the overall rate of LR is currently only on the order of 2% to 3% at 5 years (17). Therefore, strategies to reduce LR in the modern era should increasingly be focused specifically on the BC subtypes that behave the most aggressively from a local standpoint, namely the HER2 and triple negative subtypes.

■ CONCLUSIONS AND FUTURE DIRECTIONS

Local outcomes after treatment for localized BC have steadily improved over time, but as demonstrated, there remains substantial heterogeneity in

outcome. The intrinsic BC subtypes have been an important breakthrough into the biology underlying the varying behavior of BC in different patients. The approximation of these subtypes by IHC has yielded a convenient and widely available tool to categorize tumors among BC patients, and there is now a growing literature examining local outcomes after both BCT and mastectomy according to subtype. The better outcomes observed among luminal cancers compared with nonluminal cancers likely reflects both lower innate biological aggression, as well as responsiveness to systemic hormonal therapy.

Recent work has suggested that even within BC subtypes, there is striking heterogeneity among tumors. Transcriptome analysis has revealed six subgroups within the triple negative subtype with divergent sensitivities to different chemotherapies or targeted inhibitors (30). Given this apparent diversity of subgroups within BC subtypes, ongoing research is necessary to further characterize and refine our ability to not only categorize heterogeneity of BC, but also eventually treat each subgroup in a targeted, specific manner. While we are starting to better understand the prognostic importance of BC subtype, more work will be required to evaluate the degree to which BC subtypes are prognostic and/or predictive such that management decisions might eventually be reliably based on this type of molecular information for a given patient. Before clinical decisions can be made reliably based on these subtypes, prospective randomized studies must be conducted which incorporate BC subtyping and potentially validate their use.

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Adjuvant Breast Radiotherapy Using Intensity-Modulated Radiation Therapy: Should It Be Used Routinely?

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■ ABSTRACT

In contrast to other tumor sites, breast intensity-modulated radiation therapy (IMRT) has been evaluated for its ability to improve dose homogeneity rather than to improve dose conformality. Three randomized clinical trials and a number of prospective series have shown that breast IMRT improved radiotherapy tolerance. The clinical outcomes have been consistent. All series and trials showed a reduction of acute dermatitis and moist desquamation which are acute side effects of radiation treatment, and also improvements in associated pain and quality of life outcomes. For women with large breasts, breast IMRT improved the cosmetic result and reduced permanent delayed side effects of the skin such as telangiectasia. It is currently unknown if breast IMRT reduces the risk of chronic breast or chest wall pain or has an impact on long-term quality of life. There is consensus that either forward- or inverse-planned breast IMRT should be the standard in Canada, but there is a debate in the United States on the economic value of the clinical benefits. The cost of a course of radiation therapy doubles when the Medicare "inverse planning code" is used. This funding issue currently undermines the ability for the clinical community to achieve consensus on the role of IMRT to improve homogeneity during radiation therapy for breast cancer. Although highly likely, there is no direct evidence addressing whether breast IMRT will further improve breast hypofractionation tolerance. Women with large breasts, who are experiencing over 50% of moist desquamation even with the use of breast IMRT, may benefit from the combination of a prone technique with breast IMRT to further improve treatment tolerance.

Keywords: breast cancer, radiotherapy, intensity-modulated radiation therapy

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BACKGROUND

Breast cancer is the most frequent cancer in women. The systematic introduction of screening mammography has created a shift in the initial presentation of breast cancer, with the early stages representing the majority of the cases today (1,2). Current Surveillance, Epidemiology, and End Results (SEER) program reported data demonstrate that 60% of breast cases were diagnosed at a localized stage, defined as a disease confined to the primary site but not spreading regionally or distantly (3). The overall 5-year relative survival for 2001 to 2007 was 89.1% and for patients with localized disease stage, the 5-year relative survival was 98.6%.

In this population of women with early stage breast cancer, the treatment objective is to ensure local control of the tumor with acceptable cosmesis (4). Breast conserving therapy (BCT), including limited breast surgery followed by whole breast radiotherapy, is the current standard treatment for early stage breast cancers. Based on large randomized clinical trials and meta-analyses, this treatment provides locoregional control equivalent to mastectomy with better cosmesis and without compromising the overall survival (4–7). Because a cosmetically viable alternative to BCT would be a mastectomy followed by breast reconstruction, it is important not only to ensure an optimal cosmetic result but also to prevent any treatment-induced acute or delayed toxicities.

Breast radiation techniques have dramatically changed because of the introduction of CT simulation, three-dimensional dose distribution planning, multileaf collimator, and intensity-modulated radiation therapy (IMRT). Since its introduction in 1999 (8), breast IMRT has been widely investigated. Over 500 articles have been published. However, breast IMRT is still not accepted as a standard treatment for whole breast radiotherapy. The purpose of this chapter is to review current evidence regarding the use of this technique.

WHAT IS BREAST IMRT AND WHAT ARE THE CLINICAL GOALS?

Definition and Objective of IMRT

There are many radiation techniques that modulate the radiation intensity across a beam direction but not all of them would be considered to be "IMRT." From a purely technical point of view, IMRT could be defined as a radiotherapy technique using an "intelligent" modulation of the radiation flux across multiple irradiation fields to produce a three-dimensional dose distribution achieving a set of predetermined dosimetry constraints. "Intelligent" means that an iterative trial-and-error optimization process is used to optimize the dose distribution. In 2007, Purdy (9) pointed out that the objective of IMRT is not limited to the improvement of the dose *conformality* around the target, but it can also be used to improve the dose *homogeneity*, which means a reduction of the hot and cold spots inside the treated volume. There were two major impetuses to develop a breast IMRT technique. The first was to reduce radiation-induced toxicities by removing hot spots from the treated volume. The second was to enable improved local control through dose escalation. It is noticeable that, almost 15 years after the introduction of the IMRT technique, randomized studies have focused on radiation-induced toxicity reduction rather than improving tumor control (10).

IMRT to Improve the Breast Dose Homogeneity

Because the breast has an uneven three-dimensional shape, for many decades wedges, either physical or virtual, were used to compensate for missing breast tissue. The selection of the wedge angle was based on a two-dimensional dose distribution, often a single slice through the midtangential plane. This technique tended to create hot spots in the inframammary fold, at the nipple and in the axillary tail (Figure 1). It also created relative cold spots in the midplane of the breast, close to the pectoralis fascia. There have been many techniques reported to improve dose homogeneity during irradiation of the breast (11,12). The simplest and most efficient of these is breast IMRT (8,13–19).

It is unclear whether avoiding posteriorly located cold spots may lead to any clinical benefit of breast IMRT. However, evidence that local control has a dose–response relationship (20,21) suggests that elimination of cold spots in the breast could reduce the risk of local recurrence in some patients. Conversely, there is a significant amount of clinical data demonstrating that eliminating hot spots can reduce radiation-induced acute breast side effects (16,22). There are also data suggesting the association of acute side effects with permanent and delayed ones (23). Since these toxicities are frequent, easy to measure, and occur acutely, breast IMRT clinical trials have primarily focused on evaluating the clinical significance of IMRT to improve dose homogeneity.

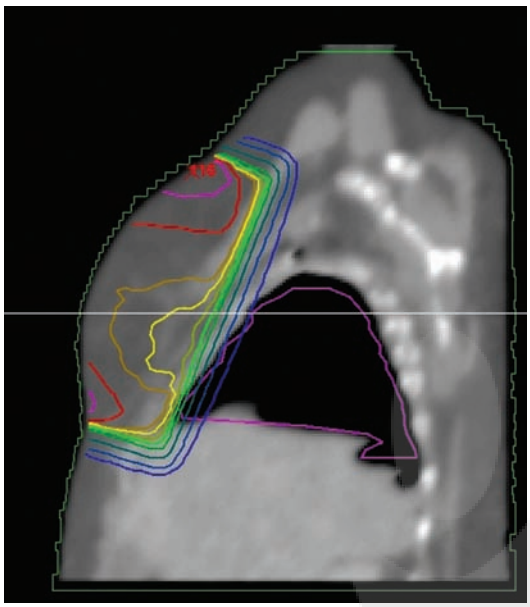

FIGURE 1 Typical dose distribution on a sagittal plane using standard wedged radiotherapy. Due to the uneven three-dimensional shape, dose hot spots are generated in the inframammary fold and the axilla, and dose cold spots are generated in the center of the breast.

IMRT to Improve the Breast Dose Conformality

Many authors have evaluated the dosimetry benefits of conformal breast IMRT (24–29). They generally focused on the reduction of dose to the heart and the improved coverage of the internal mammary chain. Some have also shown that conformal breast IMRT reduced the volume of lung receiving a high dose and improved coverage of the breast expansions laterally and medially (27). To improve conformality, breast IMRT requires more than two opposed beams, such that some beams are directed toward the chest wall. This eventually increases the median dose to intrathoracic critical structures and the integral dose to the body.

For the lung, the dose–volume histograms show a reduction of the high-dose region at the expense of the low-dose region (27). The clinical consequences of this change are currently unknown. For example, it is unclear if this could reduce the risk of symptomatic radiation pneumonitis, a relatively uncommon event, at the cost of a potentially higher risk of secondary lung cancers.

Some authors have advocated using multibeam, conformal breast IMRT for women with a large heart volume included in the standard tangential fields (24,27). In this situation, the left anterior descending artery is in the high dose volume, which raises concerns about an increased risk of myocardial infarction. This technique may be beneficial in particular for patients receiving cardiotoxic drugs like anthracycline or Trastuzumab. While the potential dosimetric advantages of multi-beam conformal breast IMRT have been demonstrated on numerous occasions, clinically its use remains sporadic. The reality is that it is difficult to formally demonstrate a clinical benefit since cardiac events are rare and occur many decades after treatment. In the absence of data from Phase III trials, the development of rigorous constraints for heart and lung doses could lead to the use of conformal breast IMRT for specific clinical situations.

■ PLANNING OF BREAST IMRT FOR DOSE HOMOGENEITY

Breast IMRT Simulation and Planning

Breast IMRT requires the same planning steps as any other form of IMRT. However, several simplifications have been suggested. Following clinical assessment, patients are booked for a computed tomography (CT) simulation to acquire breast volumetric data and the location of nearby critical structures including the lung and heart. The target volume can be contoured on each CT slice, but initial studies have demonstrated that the target volume can be more simply defined as the volume receiving over 95% of the prescribed dose (30). This volume classically excludes the first 5 mm below the skin surface and the *pectoralis fascia*. For IMRT planning, many protocols have been reported to define the beam segments. Initially, it was proposed to define beam segments on equivalent path length maps of the irradiated volume (18), and further work proposed using the dose distribution of open beams to define the segment shapes along the 5% isodose lines on a plane generated perpendicularly to the beam axis (15). True pencil beam weight optimization leading to beam segmentation has been proposed (19). Among the multiplicity of methods, it is difficult to choose one over another, especially since in most publications the dosimetry evaluations were made using different parameters. In 2008, Donovan investigated different breast IMRT techniques. Each technique was applied to a retrospective cohort of 14 patients with breast volumes ranging from 500 to 2200 cm^3. Most methods improved dose homogeneity compared with

a standard wedge technique but none demonstrated a clear advantage over another (31).

Forward and Inverse Breast IMRT Planning

When segments are defined based on open beam isodoses, their weights can be calculated in two different ways. The first method, called "forward-planning," delivers 5% of the dose using each beam segment shaped on the 5% isodose contours, and the remaining dose with open beams (15). The weight of each segment can eventually be slightly modified to optimize the dose distribution. Alternately, an "inverse-planning" can be used to select a limited number of points inside the breast volume, including areas where cold or hot spots are generally found but avoiding build-up areas. The weight of each segment is then automatically adjusted using an inverse algorithm to achieve doses values within a few percentages on each selected point (32). Our team compared a forward and inverse breast IMRT technique on a prospective cohort of 30 patients referred for adjuvant breast radiotherapy. The study showed that the forward-planned technique better improved the dose distribution in the breast central plane, and more efficiently reduced the hot spots in the inframammary fold and the nipple, but the inverse-planned technique reduced hot spots in the axillary tail. While those differences were statistically significant, their absolute values were small and unlikely to produce significant clinical differences (32).

Breast IMRT Planning Automation

The use of breast IMRT does not impact the duration of each treatment fraction, but the planning time is longer and may impact workload. A major advance in breast IMRT planning is represented by planning automation. Purdie et al. (33) reported a study on 158 patients receiving adjuvant radiotherapy to the whole breast. Using a rigorous simulation protocol, with the placement of markers and wires on well-defined positions around the breast, a fully automated breast and critical structure segmentation algorithm was used, followed by automated beam placement and eventually IMRT planning. Using this automated planning algorithm took less than 7 min, on average, to generate a breast IMRT plan. Those plans were compared in a double-blinded fashion to plans generated using standard breast IMRT planning. The automated plans were deemed clinically acceptable in 99% of cases and superior to the standard ones in 87% of cases. Automating the whole planning procedure may alleviate a major hurdle in the adoption of breast IMRT. Since treatment of patients with breast cancer generally represents the largest tumor site for most radiation center, an efficient, automated technique to derive an optimally homogeneous treatment plan could have a major resource benefit.

Constraints and Quality Assurance

One caveat in the use of breast IMRT is the lack of consensus regarding dose constraints to critical structures and quality assurance procedures. In addition to the heart and lung, critical structures for breast IMRT include the skin and breast glandular tissues. It is not clear what dose constraint should be applied for the skin or glandular tissue to prevent acute and/or delayed side effects. To add to the difficulty, the skin is located in the build-up area where the dose calculation is not accurate. Similarly, no standard quality assurance procedures have been published for breast IMRT. Compared with conformal IMRT in other tumor sites, it is unlikely that breast IMRT three-dimensional dose distributions should be physically checked on phantoms, but common sense suggests that segment shapes and weights should be checked for each patient.

Total Body Dose for Breast IMRT

In 2003, Hall and Wuu (34) estimated that the use of conformal IMRT could double the risk of secondary cancers compared with that of standard radiation therapy. Their reason was that conformal IMRT involves the use of more beam directions, and results in a larger volume of normal tissue exposed to low-dose radiation. Also, the use of multiple field segments shaped by multileaf collimators induces a parallel increase of the number of monitor units by a factor of 2 to 3 which increases the body exposure to radiation due to head leakage. While those conditions are true for conformal IMRT, they are not true for the breast IMRT used to improve dose homogeneity. When using IMRT solely to improve dose homogeneity, two opposed parallel beams are set tangentially to the chest wall. In fact, breast IMRT may be safer than standard radiotherapy using physical wedges which scatter photons outside the primary beam direction and increase total body exposure (35,36). Conversely, breast IMRT blocks those

scattered photons in the multileaf collimator or primary jaws. There have been several reports showing a decreased total body exposure using breast IMRT. In 2006, our group showed in a prospective cohort of 120 women receiving adjuvant breast radiotherapy that the use of breast IMRT resulted in a threefold decreased radiation exposure to most parts of the body compared with that of a comparable treatment plan using physical wedges (36). Those results were confirmed using Monte Carlo simulation and also that breast IMRT reduced the scattered dose to most internal organs (37).

■ CLINICAL BENEFIT

Radiation-Induced Side Effects to the Breast

Radiotherapy induces acute and generally temporary as well as delayed and generally permanent side effects to the breast and surrounding organs at risk. Acute side effects include skin erythema, dryness, edema, changes in pigmentation, and moist desquamation. More rarely, radiation impacts on adjacent organs like the lung, inducing symptomatic or radiographic pneumonitis. Permanent delayed side effects include skin telangiectasia, erythema, dryness, and discoloration. There are also subcutaneous side effects including chronic edema, indolent or painful indurations, fat necrosis, and breast scaling. All delayed side effects can impact negatively on the cosmetic result. Chronic pain has been reported in up to 43% of patients (38). The patient's quality of life can be reduced by poorer cosmetic outcome and pain (39,40). Less frequently, radiotherapy can induce side effects such as lymphedema, myocarditis, rib fractures, or symptomatic lung fibrosis (41).

Moist desquamation is a severe acute side effect that is an exclusive consequence of radiation treatment. The incidence of moist desquamation peaks 1 to 2 weeks after the end of radiotherapy. Patients need to be assessed during this early interval following radiation therapy to accurately capture the magnitude of this side effect (39,42). Depending on the timing of assessment, the reported rate of moist desquamation varies considerably (Table 1). Moist desquamation occurred most frequently in the inframammary fold and is statistically associated with pain and a reduction of the patient's quality of life (71).

In 2007, Lilla analyzed the factors associated with late normal tissue complications following breast radiotherapy. Skin telangiectasia and subcutaneous induration were the most frequent permanent side effects with reported rates of 31.4% and 6.7%, respectively (27). The patient's age, the occurrence of moist desquamation, the radiation dose, and heavy smoking were significantly associated with the occurrence of telangiectasia. Patients with moist desquamation had a higher risk of developing telangiectasia with an odds ratio of 1.8 (95% confidence interval 1.0–3.1) (27). Bentzen and Overgaard (47) reported the same odds ratio for the development of telangiectasia following moist desquamation after postmastectomy radiotherapy.

Benefit of Breast IMRT Reported From Cohort Studies

The team at William Beaumont Hospital was the first to report the clinical outcomes of breast IMRT in a cohort of 10 patients (15). During the radiation treatment, no patient experienced more than a Grade 2 Radiation Therapy Oncology Group (RTOG)

TABLE 1 Rate of moist desquamation for standard wedged breast radiotherapy depending on the timing of assessment reported in various series

Author	Rate of Moist Desquamation (%)	Maximum Assessment Time (Weeks)
Roy et al. (43)	23	<6
Boström et al. (44)	20	<5.5
Pignol et al. (39)	26.7	<6
Back et al. (45)	31.2	<7
Freedman et al. (46)	38	<7
Pignol et al. (39)	47.8	>7

skin side effects. In 2002, they reported immediate tolerance results on a larger prospective cohort of 281 patients with only 43% experiencing a Grade 2 and 1% experiencing Grade 3 RTOG skin toxicity. On a subset of 94 patients followed up to 12 months after radiotherapy, none experienced skin telangiectasia, fibrosis, or breast pain (30). In 2007, the same team compared the tolerance outcomes of 93 patients treated with breast IMRT to 79 patients treated with standard wedged technique (48). There was an absolute reduction of 44% in Grade 2 acute dermatitis using breast IMRT. Furthermore, there was also a significant impact on acute and chronic edema. However, that study may have underestimated the true benefit of breast IMRT since it captured radiation dermatitis using weekly review notes filled by the patient's nurse or treating radiation oncologists but did not capture skin toxicity after the end of the treatment.

In 2006, similar results were reported for a cohort of 73 patients treated with breast IMRT at the Fox Chase Cancer Center (46). Those patients were matched for breast volume to 58 patients treated with standard wedged radiotherapy. An absolute reduction of 17% in the rate of moist desquamation using breast IMRT was shown (46). In 2009, this group published a larger cohort of 399 patients receiving breast IMRT and compared the outcomes with 405 patients receiving standard wedged radiotherapy. It was reported that 23% fewer patients experienced Grade 2 or Grade 3 dermatitis using breast IMRT (49).

In 2008, the Emory University School of Medicine reported the outcomes of 121 patients treated with breast IMRT. These outcomes were compared with 124 patients treated with standard wedged radiotherapy (50). The irradiation technique and boost prescription were left to the discretion of the treating physician. That study found 11% fewer Grade 2 or Grade 3 acute dermatitis using breast IMRT. There was no statistically significant difference between arms in term of local recurrence at 7 years.

Benefit of Breast IMRT Reported From Randomized Trials

There have been three randomized clinical trials that have evaluated the clinical benefits of breast IMRT. In 2007, the Royal Marsden Hospital reported the long-term results of a prospective Phase III trial (51). A total of 306 patients estimated to be at higher risk than average for normal tissue changes after radiotherapy because of breast size or shape were randomized to receive breast IMRT or standard wedged radiotherapy. The 5-year cosmetic outcomes were available for 240 patients. Significantly fewer patients receiving breast IMRT had breast induration and permanent visible changes in the breast were 18% less frequent. Patients with dose distribution hot spots exceeding 105% had a 2.6-fold increased risk of detrimental breast cosmetic changes.

In 2008, we reported the results of a Canadian, multi-center, randomized controlled trial (37). The trial evaluated the rate of acute dermatitis for 331 evaluable patients out of 358 patients accrued. Eligible patients were randomized to receive whole breast radiotherapy delivering 50 Gy in 25 fractions using either breast IMRT of standard wedged treatment. The randomization was blocked on breast volume and the delivery of a boost to ensure that the treatment arms were balanced. Skin assessments were done weekly during the radiation treatment and up to 6 weeks after treatment by a research assistant blinded to the treatment arm. The study showed a 17% absolute reduction in moist desquamation using breast IMRT. On multivariate analysis, the breast volume and the treatment technique were the two factors significantly associated with the occurrence of moist desquamation.

In 2011, the University of Cambridge reported the results of another Phase III study on 814 patients presenting significant inhomogeneity on a standard plan. Those patients were randomized to receive either breast IMRT or standard wedged radiotherapy. At 2 years, there was no difference between arms in the breast size due to the radiation treatment, but a significantly higher rate of telangiectasia was found in the standard group ($P = .009$) (52).

■ THE BREAST IMRT BILLING AND DEFINITION CONTROVERSIES

Until the end of 2011, breast and head and neck were the only tumor sites where IMRT was supported by several randomized trials (10). For head and neck cancer, IMRT is considered to be the standard of care (53), but for breast cancer the use of IMRT as a standard remains debated. In May 2009, the American Society for Therapeutic Radiation and Oncology (ASTRO) convened an intersociety meeting to debate the status and future directions of Radiation Oncology. The objective was to review the role of emerging technologies and their benefit in regards

to economic constraints. The panel concluded that "*breast IMRT continues to be a controversial issue awaiting both data and decisions from payers*" (54).

The controversy at that time was about the proper definition of IMRT and about the use of a code for inverse planning which had direct implications for reimbursement in the United States. The controversy started in 2002 after the second publication of the William Beaumont Hospital reported prospective data showing improved tolerance of breast radiotherapy using breast IMRT (30). In an editorial, Potters questioned the use of the term "IMRT" for the breast irradiation technique used at William Beaumont Hospital (72). First, he pointed that the American Medical Association Current Procedural Terminology refers to IMRT when highly conformal dose planning is indicated. Second in 2002, there was insufficient data to justify widely adopting the technique since "there are some private (insurance) carriers that are insisting on prospective, randomized data to substantiate their reimbursement and refuse to pay for IMRT". Vicini et al. (55) in a response letter defined IMRT as a complex planning process including CT simulation, target definition, three-dimensional treatment planning, and the use of multileaf collimators to modulate the intensity of radiation across the beam. In the case of breast IMRT, the objective is that all points within the breast receive the prescribed dose following a predetermined set of dosimetry constraints. He also cautioned on defining a technique based on economic issues.

In 2011, an analysis of breast IMRT costs in 16 geographic catchment areas of SEER was reported in the *Journal of the National Cancer Institute* along with an editorial and a press release (56–58). The original report examined the billing data for 26,163 women treated from 2001 to 2005 and showed an increase of breast IMRT billing codes from 0.9% to 11.2%. After adjustment for inflation, this resulted in an increase in the average cost of breast care from $21,674 to $29,366. The cost of a breast IMRT course was calculated at $15,230 compared with $7,179 for standard breast radiotherapy. This chapter also examined radiation technique evolution over time in areas where the Medicare reimbursement scheme was "favorable" toward breast IMRT. Over the time of the study, there was a five times larger increase in the use of breast IMRT billing in "favorable" areas compared with "unfavorable" areas. There were also 36% more breast IMRT billings in freestanding radiation centers compared with hospital-based centers.

Although this chapter's conclusion emphasized the need to harmonize Medicare reimbursement policies between regions, the authors also acknowledged that the use of breast IMRT has led to a significant advance for breast radiotherapy with respect to lowering risks of both acute and late toxic effects associated with radiation therapy (56). This chapter concluded that for patients treated in areas with Medicare codes favorable to breast IMRT, the reimbursement policy has helped to improve the quality of breast radiation. On the other hand for patients treated in regions with unfavorable Medicare codes, the reimbursement policy has served to control cost.

The accompanying editorial and press release were more negative toward breast IMRT, adding much confusion regarding its definition, clinical purpose, and benefit. Despite the large number of cohort studies and Phase III trials published, the editorial stated that the "current level of evidence to support this growing practice is weak, and the benefit of IMRT observed in the randomized trials could likely be achieved with simple segmentation using two tangential fields that have been three-dimensionally planned." The simpler technique referred to is the forward-planned breast IMRT technique used in many trials and cited in the Smith et al. report. The confusion in the editorial and the press release could be related to Smith et al.'s method of identifying the breast radiation technique for a given patient: the billing code of "inverse planning" was frequently used as a surrogate to identify breast IMRT cases (56). In their report, Smith et al. acknowledged that this strategy may not capture all the instances where patients received breast IMRT without being billed as such.

Beside these controversies and confusions, the important question raised by the Smith et al. report is about the dollar value of the clinical benefits demonstrated in randomized trials and the justification for an incentive to adopt this technique. In 2011 in North America, most adjuvant breast radiotherapy is delivered following CT simulation, dosimetry calculations using three-dimensional treatment planning, and the treatment is delivered using a linear accelerator equipped with multileaf collimators. For breast IMRT, most of the planning, dosimetry, and treatment steps have been simplified such that this technique may not increase the manpower needs. Also the public is aware of the benefits of this technique and it seems controversial to justify not using available planning information and an optimal radiation technique to improve treatment tolerance.

Outside the United States, other strategies have been followed to define breast IMRT as the standard

for adjuvant radiotherapy after breast conserving surgery. As noted by Smith et al. (56), there is in Ontario, Canada, only a 1% difference in cost between breast IMRT and standard wedged breast radiotherapy. Following an independent review process by Cancer Care Ontario to establish evidence-based guidelines, breast IMRT was massively adopted in the province and today over 80% of patients receives this technique a standard (59). A similar process has been established in British Columbia, Canada, where reimbursement and staffing resource allocations are independent of whether forward-planned, inverse-planned breast IMRT or standard wedged breast tangent radiotherapy are employed.

■ EVOLUTIONS BEYOND BREAST IMRT

Hypofractionated Regimens

Traditionally, low daily doses have been recommended for breast radiotherapy and a dose of 50 Gy delivered over a period of 5 weeks in daily fractions of 2 Gy has been the most frequently reported dose-fractionation scheme (5,6). Protocols delivering 42.5 Gy in 16 treatments have been proposed following radiobiological models suggesting that larger daily dose given over a shorter time may be as effective (60–62). The hypofractionated schedule was more convenient for patients and consumed fewer resources. A large, Canadian, multicenter, controlled clinical trial showed no difference in the rates of local control, delayed side effects or cosmetic outcome at 5 and 10 years after treatment (62,63). While it is unlikely that breast IMRT used in combination with a hypofractionated regimen would present any additional risks in terms of local recurrence, it is possible that the combination may reduce acute side effects because a lower total dose is used. In the randomized trial, the traditional (50 Gy/25fractions) and hypofractionated (42.5 Gy/16 fractions) arms were shown to be radiobiologically and clinically equivalent in terms of long-term toxicity and cosmetic outcomes. The use of breast IMRT in combination with hypofractionation may present additional advantages in regards to these endpoints since hot spots in the dose distribution may be more harmful when higher doses per fractions are used. Hypofractionated whole breast radiotherapy using forward-planned or inverse-planned IMRT is considered the new "standard" in many Canadian jurisdictions.

Prone Breast Techniques

Although breast IMRT improves the tolerance for patients whatever the breast size, the absolute benefit varies with the breast volume (Table 2). Even using breast IMRT, women with large breast sizes, defined as a D bra cup or greater, had a 52% risk of developing moist desquamation which was frequently severe, painful, and extensive. Women undergoing adjuvant radiotherapy are generally treated in the supine position, which is a more comfortable position for patients, allows for visualization of skin markings, and provides a simple, reproducible immobilization. In large-breasted women, however, this position results in the horizontal spreading of the breast, increasing the separation from the medial to the lateral aspect of the breast and often the inframammary fold is not eliminated, resulting in a "self-bolusing" effect in the fold (Figure 2). These anatomic considerations make it difficult to achieve dose homogeneity even with the use of IMRT (63,64). Recent research has examined the impact of better patient positioning including the prone position (65–67). Prone breast radiotherapy uses gravity to pull the breast downward, lengthening and narrowing it, effectively removing the breast target volume away from the chest wall. The dose distribution becomes more homogeneous.

The majority of the published prone breast studies have focused on the dosimetry aspects of treatment and the reduction of the exposure to organs at risk including the lung and the heart. Using breast IMRT along with the prone position results in a very homogeneous dose distribution throughout the breast (68,69). Clinical experience with prone breast radiotherapy has been reported by several authors. In 2000, Grann et al. (65) reported the Memorial Sloan Kettering preliminary tolerance data in 56 patients with large breasts. Only one patient required a treatment break

TABLE 2 Rate of moist desquamation for whole breast radiotherapy using either a standard wedge technique or breast IMRT in function of the breast size

Bra Size	*N*	Mean V_{95} (cc)	Wedges (%)	IMRT (%)
Small (32A/B, 34A/B, 36A)	56	534	14	3
Medium (32C, 34C, 36B/C, 38A/B/C)	165	942	32	23
Large (larger sizes)	110	1,412	59	52

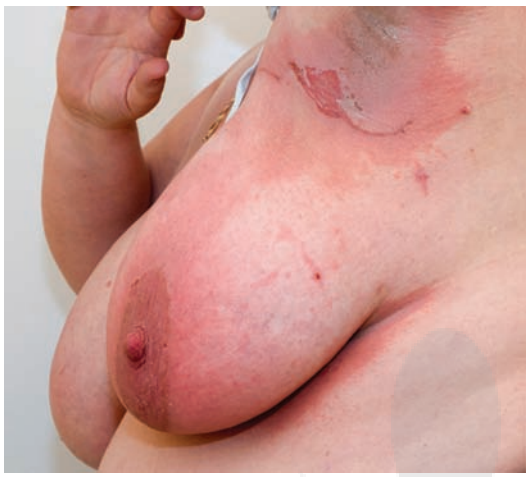

FIGURE 2 Patient with large breast volume presenting at the end of her treatment. Significant moist desquamation is seen in the axillary tail, the inframammary fold, and the nipple area. Those are areas where dose distribution hot spots are created using standard wedge technique.

due to severe moist desquamation. In 2002, Mahe et al. (66) reported excellent treatment tolerance in 35 patients with large breasts with no treatment interruptions and limited skin side effects noted in one-third of the patients. In 2007, the Memorial Sloan Kettering experience was updated with 245 women. Only 16% experienced acute RTOG Grade 2 skin toxicities and 2% had Grade 3 toxicity (70). There are currently two randomized studies, one in Belgium and one in Ontario, comparing prone versus supine techniques for large-breasted women.

CONCLUSIONS

Breast IMRT has been used to improve dose homogeneity rather than dose conformality. Compared with other tumor sites, there is a substantial amount of Level 1 and Level 3 clinical data that demonstrate that breast IMRT improves the tolerance of radiotherapy. There is considerable consistency in the clinical outcomes reported. All single institution series and the three published randomized trials showed a significant reduction in acute dermatitis, including moist desquamation which is a side effect directly related to the radiation treatment and that is associated with pain and a reduction in the quality of life for women receiving breast tangent radiotherapy. For women with large breasts, breast IMRT improves the cosmetic result and reduces permanent skin side effects like telangiectasia. It is currently unknown if breast IMRT could have an impact on chronic breast pain and long-term quality of life. There is currently a debate about the economic value of these clinical benefits, since the cost of a radiation treatment doubles when the Medicare "inverse planning code" is used. While consensus has been reached to use breast IMRT as a standard in Canada, the economic debate is blocking the adoption of this innovation in the United States.

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Proton Radiation for Breast Cancer

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■ ABSTRACT

Proton therapy allows for radiation delivery to targeted areas with decreased radiation dose to healthy surrounding tissues when compared with standard radiation. For many malignancies, the goal of using proton therapy is to decrease the side effects from radiation therapy. Clinical experience for the use of protons for breast malignancies to date is limited. Given the increased access to this form of therapy and the potential for long-term survival for breast cancer patients, we are beginning to explore the potential benefits of this form of radiation. Clinical trials are starting to explore the best indications for this more expensive form of radiation treatment.

Keywords: proton radiation, breast cancer

■ INTRODUCTION

Proton radiation therapy is a form of particle radiation therapy, which, a decade ago, was available only at three radiation centers in the United States. Over the past several years, the advantages of this radiation modality over the standard radiation therapy have been recognized. Despite substantial capital and operational costs, there are currently nine operational proton facilities in the United States and several others—in both the private and academic sectors—are in the planning or construction phases. Furthermore, several companies are actively researching to develop more efficient, smaller, and less expensive proton delivery systems. Given increased access to this treatment, it is now possible and imperative to explore the potential benefit of proton radiation for additional malignancies, such as breast cancer. The use of proton therapy for the treatment of breast cancer has the potential to decrease cardiac and pulmonary toxicity and better spare any nontarget tissue while delivering the same therapeutic radiation dose to areas requiring treatment. It is, however, crucial to recognize that modern standard radiation treatments for breast cancer are very well tolerated. Proton therapy is, and will likely continue to be, substantially more expensive than standard radiation treatments (1). In the current health care climate, it is crucial that we select patients with the greatest potential to benefit from proton radiation and provide evidence of an advantage over standard radiation treatments.

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■ PROPERTIES OF PROTON RADIATION

Proton radiation is a form of charged particle radiation. Protons enter tissue, delivering a small and constant dose until near the end of the proton range, where the majority of dose is delivered; this is referred to as the Bragg peak (2). Beyond this region, no dose is delivered, allowing for complete sparing of tissues and organs distal to the target volume. Photons used for standard radiation treatments have no charge or mass and continue to deliver dose to tissues beyond the target volume until they exit the body. Biologically, proton radiation should be no different from photon radiation. Proton radiation is prescribed in Gray (RBE) as opposed to Gray, which is used for prescribing photon radiation. This takes into account the slightly higher Relative Biological Effectiveness (RBE) of protons. Thus, with this correction for a given prescribed dose, the biological effect in tissues should be the same for protons and photons. The advantage for protons comes from the physical properties of the proton beam (3–5).

At present, the predominant mode of proton delivery is through passive beam scattering methods or "three-dimensional conformal" proton therapy. Compensators and apertures are designed to shape the proton beam and deliver a homogeneous dose distribution to the target with optimal dose conformity at the distal target region for each field (2). Figure 1 shows patient specific hardware used for a three-dimensional conformal proton treatment to the chest wall following mastectomy. A brass aperture is used to shape the field in the beam's eye view, and a Lucite™ compensator is used to modify the distal range and compensate for tissue heterogeneity. Field size limitations exist, and, similar to photon radiation, separating the target volume into two radiation fields is sometimes necessary (i.e., supraclavicular [SCV] field and chest wall field). Three-dimensional conformal protons may also deliver a higher than desired skin dose. While the skin is often considered a less critical structure than more vital organs such as the heart, lung, and brain, it is a principal concern for patients with breast cancer, particularly for those patients that have undergone breast-conserving therapy. Increased modulation is possible through pencil beam scanning techniques, though these techniques have become available only recently. Pencil beam scanning delivers homogenous dose to the target through the superimposition of individually inhomogeneous fields or individual Bragg peaks (6). Although this increases the complexity of the plan, it allows for both increased dose-shaping capabilities with optimal conformity, not only at the distal region of the target, but also to the proximal target edge and allows for an inhomogenous dose distribution within the target, if desired. Intensity modulated proton therapy (IMPT) allows for the treatment of large areas without matching of fields and, if desired, a decrease in the dose to skin. Figure 2 depicts an IMPT plan for a woman with a silicone breast implant.

FIGURE 1 Patient specific brass aperture and Lucite™ compensator for chest wall treatment following mastectomy. The brass aperture allows for shaping of the field in the beam's eye view (similar to the use of multileaf collimator or cerrobend blocks used for photons). The Lucite™ compensator allows for distal shaping of the proton beam and accounts for heterogeneity of the tissue in the path of the beam.

■ PROTONS FOR PARTIAL BREAST IRRADIATION

Accelerated partial breast irradiation (APBI) is being extensively studied as a more convenient and targeted form of radiation for patients undergoing breast-conserving therapy. Multiple phase I/II trials have shown excellent local control and minimal toxicity for women with early favorable breast cancers, and guidelines for delivering APBI were recently established to assist in patient selection and delivery of treatment outside of the clinical trial setting (7–9). The Phase III NSABP B39/RTOG 0413 trial has rapidly accrued patients with early breast cancer and will allow for comparison of APBI with modern whole breast irradiation. When the results of this trial become available, the standard of care for many women undergoing breast-conserving

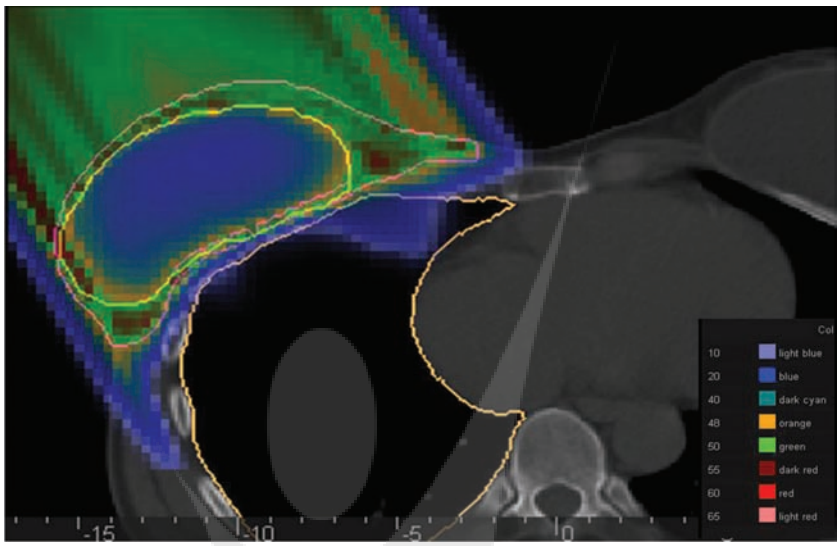

FIGURE 2 Pencil beam scanning plan for PMRT following breast reconstruction allows for excellent target volume coverage without any technical limitations introduced by a silicone implant.

therapy may be redefined. Although early experience was limited to brachytherapy, external beam radiation (EBRT) has proven a more attractive delivery method for APBI. The advantages to EBRT include the ability to review final pathology prior to radiation, decreased invasiveness, decreased risk of infection, and ease of availability with minimal specialized training. EBRT also provides a very homogeneous dose distribution. The downside of EBRT compared to brachytherapy is its inferior conformality. Proton radiation offers the convenience of a noninvasive form of radiation therapy with superior conformality compared with external beam photon or photon/electron techniques. In the earlier years of proton therapy, when the machine time was extremely valuable and only two treatment centers in the United States with full treatment capabilities existed, APBI represented an attractive use for proton radiation. For these reasons, the majority of clinical experience to date for the use of proton therapy for breast cancer patients is for APBI.

Massachusetts General Hospital Experience

The Massachusetts General Hospital Phase I/II APBI trial allowed for treatment with proton radiation (10,11). Twenty-five patients received proton radiation. All patients had unifocal breast cancer with margins ≥ 2 mm. APBI was delivered 4 Gy per fraction, twice daily to a dose of 32 Gy (RBE). Twenty-four patients had three-dimensional photon/electron plans generated for dosimetric comparison. An optimal photon/electron plan could not be generated for one patient due to the inability to abduct her arm, and, therefore, she was excluded from this analysis. All plans delivered the prescribed dose to the tumor bed with homogeneous target volume coverage. Proton radiation provided a very small but significant benefit in sparing cardiac and pulmonary tissues. The largest benefit from protons was the sparing of breast tissue outside of the target volume. The breast volume receiving 50% of the prescribed dose was decreased by 40–45% by using protons. In addition, successful delivery of APBI to the patient, for whom it was unable to abduct her arm, demonstrates the potential for the use of protons for technically difficult patients. Most patients were treated with two to three fields, but a solitary field was used for three patients. Increased skin toxicity was noted in patients treated with a single field. This was likely attributable to the combination of having the entire entrance dose in the same area of the skin, hypofractionation, and the increased skin dose that can result from three-dimensional conformal proton radiation. Figure 3 demonstrates a single field proton APBI treatment. Based on this experience, multiple fields and the delivery of each fraction with more than one field are recommended for proton APBI. Pencil beam

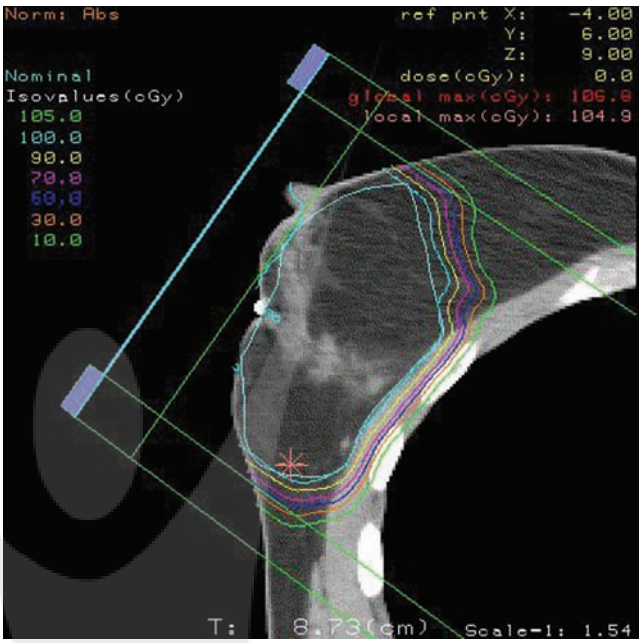

FIGURE 3 Proton APBI with a single field spares much of the uninvolved breast tissue but delivers full dose to the skin.

scanning may allow for better skin sparing, resulting in a decrease in acute skin toxicity, and improved cosmetic results for patients treated with proton APBI. Pencil beam scanning would also be expected to further decrease the dose to uninvolved breast tissue.

Loma Linda Experience

Loma Linda also examined the role of proton radiation for APBI (12). They enrolled 50 patients on a Phase I/II trial. Prone position was chosen to minimize respiratory motion (13). Two to four beams were used for treatment. The surgical bed with a 1 cm margin was targeted and prescription dose was 40 Gy in 10 fractions over 2 weeks. The treatment was well tolerated and disease free survival was 92% at a median follow up of 48 months. Long-term toxicities included three grade 1 telangiectasias. Normal tissue sparing was superior to photon plans run for dosimetric comparison. The authors concluded that proton radiation was feasible, and that toxicities may be less than reported for invasive APBI techniques.

Overall, APBI may not represent the best indication for the use of protons. There are several APBI techniques that provide excellent sparing of uninvolved tissues. Compared to other EBRT techniques, use of protons leads to very modest decreased dose to cardiac and pulmonary structures. Although follow up for ABPI trials is not yet long enough to fully evaluate cardiac toxicity, cardiopulmonary toxicity has been exceedingly rare (14). Selected cases that are technically difficult to plan may benefit from protons. For this reason, the use of proton therapy has not been widely adopted.

■ PROTONS FOR POSTMASTECTOMY RADIATION

Postmastectomy radiation therapy (PMRT) is indicated for several women reported with lymph node positive or locally advanced breast cancer (15–18). Conventional treatment delivers radiation to the chest wall and regional lymphatics, including the supraclavicular region, axillary apex, and, sometimes, the internal mammary lymph nodes. Depending on patient anatomy, it is often technically difficult or impossible to provide homogeneous coverage of the target volume, while producing acceptable doses to the heart and lung, and it is often necessary to compromise coverage of target volumes in order to avoid toxicity.

Older radiation trials reported increased cardiac morbidity and mortality, predominantly in patients treated for left-sided breast cancer (19–21). This increased mortality due to ischemic heart disease may even be the reason that a survival benefit was not observed during some of the earlier postmastectomy radiation trials (22,23). More recent postmastectomy studies, utilizing modern techniques, do not yet show

an increase in cardiac mortality but do report a survival benefit for PMRT (24,25). Acceptable parameters using three-dimensional planning are still being developed, but we do have some data to guide treatment. The risk of cardiovascular disease increases with increasing mean heart dose, and doses in excess of 30 to 40 Gy to small volumes of the heart, as felt by some authors, are to increase a patient's risk of cardiovascular disease (26). Doses of 25 Gy have been shown to induce temporary perfusion defects, and ≥ 5% to 6% of the heart receiving ≥ 25 to 27 Gy has been accepted by some to define "unfavorable cardiac anatomy" based on correlation of this heart volume to the Stockholm trial for patients with left-sided tumors that showed a high rate of cardiac morbidity and mortality (19–21,27,28). The aforementioned toxicities and parameters are derived from trials, excluding cardiotoxic chemotherapy (29,30). Currently, Doxorubicin, Paclitaxel, and Herceptin, the known cardiotoxic agents, are included in standard chemotherapeutic regimens and are often administered in combination (31). It is not yet known if radiation therapy in the setting of these agents will have a synergistic effect on toxicity. Maximal cardiac sparing achieved through proton therapy has the potential to decrease this risk by decreasing mean heart dose as well as heart volume receiving 40 Gy and 25 Gy for patients with left-sided breast cancer. For patients with breast cancer that is curable, improved cardiac sparing without the compromise of target coverage may be of substantial benefit for selected patients.

Protons will also decrease lung dose, although to a lesser degree than cardiac tissue, because of decreased proton stopping power in lung. Radiation pneumonitis is a well-known subacute side effect of breast and chest wall irradiation (32). When irradiating the chest wall and regional lymphatics, 20% to 30% of ipsilateral lung may receive radiation to a dose of 20 Gy. In addition, data from lung cancer patients treated with radiation report increased toxicity from large volume/low dose irradiation (5 Gy or 10 Gy) (33). Although the reason of this, for patients with breast cancer, is less clear, it is important to note that the techniques using electron radiation and/or some intensity modulated photon therapy (IMRT) techniques generally decrease the volume of lung receiving 20 Gy but increase the volume of lung receiving lower doses of radiation. Protons are capable of reducing both high and low doses of radiation to the lung. Radiation pneumonitis is reported in approximately 1% to 5% of patients treated for breast cancer without concurrent chemotherapy (29,34,35). However, the risk of radiation pneumonitis has been shown to increase with treatment of the regional lymph nodes and/or concurrent chemotherapy, and rates as high as 20% have been reported (36–38). Radiation pneumonitis generally resolves without treatment but may require hospitalization or a course of steroids.

Comparison planning studies using three-dimensional conformal protons and pencil beam scanning for PMRT have been performed and have demonstrated superior target coverage with improved sparing of cardiac and pulmonary structures. Figure 4 shows a three-dimensional conformal proton plan, showing more homogeneous coverage of the chest wall and excellent coverage of the internal mammary lymph nodes (IMN) with improved cardiac and pulmonary sparing as compared to a photon and photon/electron technique. Figure 5 shows average DVH data for the heart and chest wall for eight patients planned with three-dimensional conformal protons, photons, and photon/electron plans. The

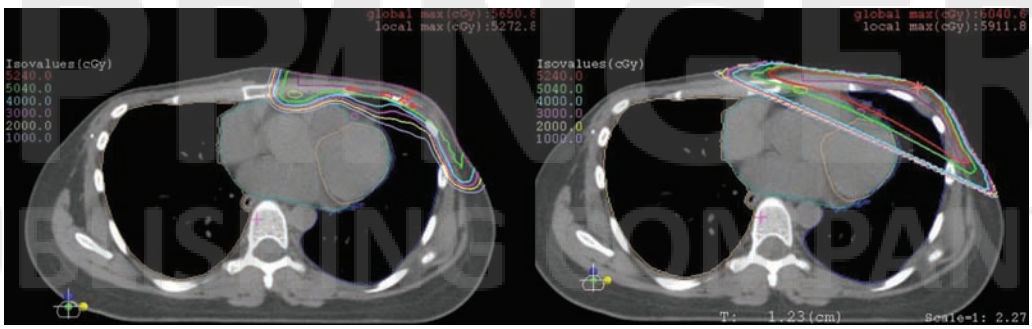

FIGURE 4 Three-dimensional conformal protons for chest wall irradiation compared to photon irradiation with partially wide tangent fields. Protons allow for improved sparing of cardiac and pulmonary structures for patients with unfavorable cardiac anatomy.

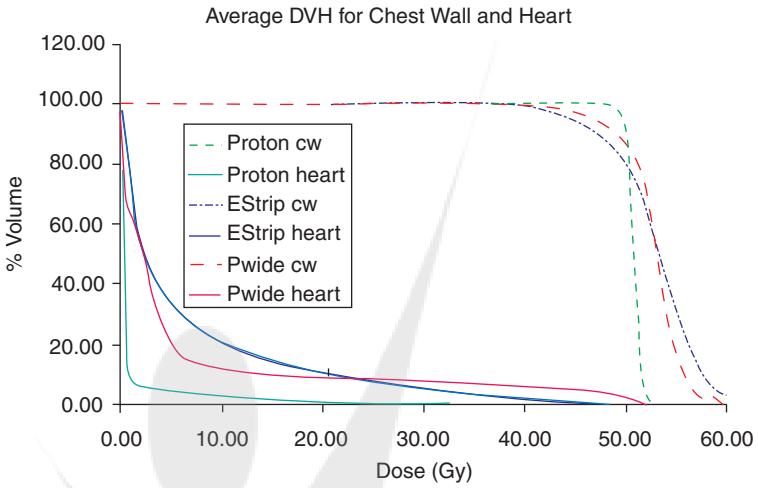

FIGURE 5 Dose Volume Histograms showing average DVH data for eight patients for chest wall and heart. Patients were planned for PMRT with protons (green), photon/electron technique (EStrip, blue), and partially wide tangent fields (Pwide, magenta). Protons provide the most homogeneous coverage of the chest wall and minimize dose received by any volume of the heart.

Paul Scherrer Institute published dosimetric comparisons for 20 patients with locally advanced breast cancer, with several receiving PMRT, showing the potential benefit of pencil beam scanning or IMPT over standard photon therapy and IMRT (39).

Women that have undergone breast reconstruction following mastectomy represent perhaps the most technically challenging cases for radiation planning (40). It is not uncommon for these women to require manipulation or removal of the implant prior to radiation to allow for comprehensive coverage of the target volume without excessive radiation dose to the heart or lung. In addition, some women are denied of immediate reconstruction, when it is known that they are likely to require PMRT, for fear that the reconstruction will be suboptimal or interfere with radiation delivery. Delaying reconstruction can have a negative psychological impact on the patient and increase the number of procedures required for the patient and also increases the final cost of the reconstruction. In addition, more women are opting for bilateral mastectomies and reconstruction, further increasing the complexity of radiation delivery (41–43). At the Massachusetts General Hospital/Francis H. Burr Proton Therapy Center, we have performed treatment planning for eight breasts in patients with bilateral breast reconstruction or bilateral cosmetic implants using IMPT, photons with partially wide tangent fields, and photon/electron plans. Plans were performed to achieve 95% coverage of target volumes (chest wall, IMN, SCV, and axilla), while maximally sparing cardiac and pulmonary structures. Priority was given to target volume coverage. IMPT plans were markedly more homogeneous. Figure 6 shows axial images at the level of the IMN for a particularly challenging treatment plan.

Although no clinical data has been reported yet, a clinical trial for PMRT has been opened at the Massachusetts General Hospital. Given the increased complexity of these plans, the greater potential for cardiac and pulmonary sparing, and the possibility of increased skin toxicity with protons, PMRT seems the rational indication to explore at this time. Patients with locally advanced cancer, unfavorable cardiac anatomy, breast reconstruction, and internal mammary node involvement are some of the most technically challenging patients and may represent the population with the most to gain from proton therapy.

■ PROTONS FOR LOCALLY ADVANCED BREAST CANCER FOLLOWING BREAST CONSERVATION

Similar to PMRT, the treatment of patients with advanced breast cancer following breast conservation can be technically challenging if nodal regions, particularly the IMN, are targeted. There is no clinical experience to date for this group of patients, but several dosimetric comparison studies have been performed. The Paul Scherrer Institute has published multiple planning studies comparing IMRT, IMPT, and standard three-dimensional photon radiation (39,44). IMRT improved homogeneity, target coverage, and sparing of normal tissues from higher doses of radiation as compared with three-dimensional photons. However, this was at the cost of increased integral dose as would be expected with IMRT. IMPT provided plans superior to both photon modalities. In addition, IMPT allowed for superior sparing of the contralateral breast. The authors concluded that IMPT may be of clinical benefit in the

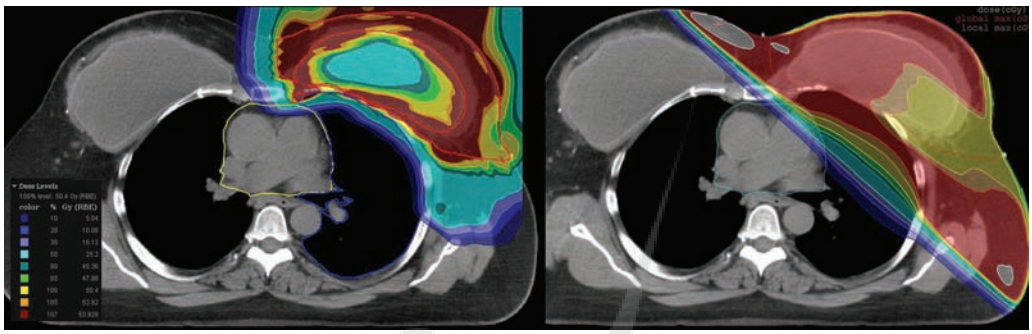

FIGURE 6 IMPT for patient with bilateral implants. IMPT plan demonstrates improved homogeneity, better avoidance of the contralateral breast tissue, and improved homogeneity. IMPT may enable some patients to receive PMRT without manipulation or removal of a breast implant.

setting of complex target volume coverage, particularly when IMN coverage is desired. Johansson et al., from the University of Uppsala, also reported results for comparative planning using conventional photons or photon/electron plans, IMRT, and protons. They evaluated target coverage and used the normal tissue complication probability model (NTCP) to evaluate cardiac mortality and radiation pneumonitis. The cardiac mortality NTCP was 6.7%, 2.1%, and 0.5% for the photon/electron plan, IMRT plan, and proton plan, respectively. Although IMRT decreased the cardiac NTCP, this modality increased the NTCP for radiation pneumonitis compared to the photon/electron technique (28.2% for IMRT and 14.7% for photon/electron). IMPT decreased this to 0.6%.

■ WHOLE BREAST IRRADIATION FOR EARLY BREAST CANCER

While standard whole breast irradiation for early stage breast cancer and ductal carcinoma in situ is the most common indication for radiation, it may very well be the last indication to be explored for proton radiation due to the importance of cosmetic outcome and the potential for increased skin toxicity with protons. If clinical trials for patients with locally advanced breast cancer treated to the whole breast demonstrate acceptable cosmetic outcomes, the benefit for selected patients with left-sided breast cancer will likely be explored.

■ COST EFFECTIVENESS

In our current health care climate, cost is becoming increasingly important. Cancer care is expensive, but chronic health problems in cancer survivors can also be a burden on the health care system. It will likely be required in the coming years that we provide evidence of not only clinical benefit, but also cost effectiveness of cancer therapies. The upfront cost of proton radiation will always be greater than photons, but potential cost savings from protons will come from a decrease in late morbidity. For breast cancer patients, this will take years to decades to recognize. Models evaluating cost effectiveness for the treatment of breast cancer with protons, albeit with their limitations, do exist. Lundkvist et al used a Markov cohort simulation to evaluate the cost effectiveness for the treatment of a left-sided breast cancer (45). Increased cardiac and pulmonary risks were assumed. Protons were not judged to be cost effective for the average breast cancer patient. However, for patients with double the risk of cardiac disease, proton therapy was considered to be cost effective by the measures used in this study. Additional studies are needed to evaluate the cost-effectiveness of proton therapy. In addition, as more efficient and less expensive treatment centers become available, the scales may tip in favor of protons being beneficial in terms of overall health care costs.

■ CONCLUSIONS AND FUTURE STUDIES

The use of proton radiation for breast cancer is currently in its infancy. Many planning studies have shown potential benefits, but little clinical data exists. The patients that may have the most to gain are likely those that require regional nodal irradiation, particularly IMN irradiation in the setting of

unfavorable cardiac anatomy or breast reconstruction. A clinical trial, for evaluating the feasibility of delivering PMRT for patients with locally advanced breast cancer and unfavorable cardiac anatomy and/or breast reconstruction that would require manipulation or removal for radiation therapy, has been opened at the Massachusetts General Hospital and is currently accruing patients.

Many advances in the field of breast cancer are anticipated to occur over the next several years. As breast cancer survival is increased, providing local disease control without long-term toxicities becomes of paramount importance. Despite the increased cost of the actual therapy, if long-term chronic complications can be avoided, protons may prove cost effective and allow for improved quality of life for selected patients with breast cancer.

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Radiation-Induced Heart Disease in Women Receiving Adjuvant Radiation Therapy for Breast Cancer: Pathophysiology, Epidemiology, and Prevention

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■ ABSTRACT

Breast cancer is the most common cancer diagnosed in women and is second only to lung cancer as the leading cause of cancer-related death in women. The use of adjuvant radiation therapy (RT) following either breast conserving surgery or mastectomy has been shown in comprehensive meta-analyses to reduce the risk of local recurrence by approximately 75%. These same studies have established that for every four local recurrences avoided by the use of adjuvant RT, approximately one death from breast cancer is averted. Unfortunately, the reduction in death due to breast cancer seen in irradiated women may be partially offset by increase in death due to cardiovascular disease. Radiation exposure to the heart causes a wide variety of acute and late effects that appear to depend primarily on the volume of heart exposed to RT and on the dose to which that volume is exposed. Studies of breast cancer survivors treated with older RT methods, which exposed large volumes of heart to substantial doses of radiation have consistently demonstrated increases in cardiac morbidity and mortality 10 to 20 years after RT. However, more recent studies of patients treated with modern RT methods, which have greatly reduced both the volume and dose of cardiac exposure, have generally not detected increases in cardiovascular morbidity and mortality. In this chapter, we review the pathophysiology, epidemiology, and prevention of radiation-induced heart disease in women undergoing adjuvant RT for breast cancer.

Keywords: radiation therapy, breast cancer, cardiac toxicity

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INTRODUCTION

Breast cancer is a common diagnosis in women with an estimated diagnosis of 207,000 new cases made in 2010 with an additional diagnosis of 54,000 cases of carcinoma in situ. Approximately 40,000 women are expected to die from breast cancer annually (1). The use of adjuvant radiation therapy (RT) following either breast conserving surgery (BCS) or mastectomy has been shown in comprehensive meta-analyses to reduce the risk of local recurrence by approximately 75%. These same studies have established that for every four local recurrences avoided by the use of adjuvant RT, approximately one death from breast cancer is averted. Unfortunately, the reduction in death due to breast cancer seen in irradiated women may be partially offset by increase in death due to cardiovascular disease (CVD). The full spectrum of radiation-induced heart disease (RIHD) includes pericarditis, cardiomyopathy, coronary artery disease, pericardial effusions or constriction, myocarditis, myocardial fibrosis, valvular defects leading to murmurs, and conduction abnormalities leading to arrhythmias (2). In this chapter, we review the pathophysiology and epidemiology of RIHD, as well as advances in treatment planning and delivery of breast that can be used to reduce the risk of RIHD by minimizing incidental cardiac exposure during adjuvant breast.

MECHANISMS OF RIHD

Pathophysiology of RIHD

Virtually, any cell within the heart or great vessels can be injured by radiation exposure. The major structures that can be affected include the pericardium, coronary vessels, myocardium, and heart valves. Radiation injury to the heart includes several common potential pathways of damage including endothelial cell and microvascular damage, direct damage to myocytes, and late fibrosis of the pericardium and myocardium (2).

The pericardium is often affected more than the myocardium itself. Acute radiation injury can lead to rapid extravasation of fibrin-rich fluid causing pericarditis which typically presents with fever, chest pain, and diastolic dysfunction within weeks of treatment, or even tamponade (3). In addition, microvascular injury may inhibit production and resorption of pericardial fluid leading to decreased pericardial drainage, and ultimately pericardial constriction-induced cardiac failure. Late pericardial fibrosis is typically caused by collagen deposition in the parietal pericardium, which leads to pericardial thickening and decreased compliance of the pericardial sac.

Myocardial injury due to radiation may result in diffuse interstitial fibrosis (4). A common mechanism of damage appears to be microvascular damage in the myocardium. Using a rabbit model of myocardial injury, Fajardo and Stewart observed three phases of damage. A neutrophilic inflammatory infiltrate develops within the first 6 hours of radiation injury in the small- and medium-sized vessels in the heart (2,5). Two days after exposure, fibrosis begins to occur. On a microscopic level, endothelial cell damage and lumen obstruction lead to myocardial ischemia. In the late stage, beginning approximately 70 days after exposure, the animals begin to die. Autopsy demonstrates extensive fibrosis in the heart. Fibrous lesions can be anywhere from several millimeters to several centimeters in size, although they usually do not affect the entire myocardium. The spectrum of clinical manifestations of RIHD in the rabbit model includes systolic dysfunction leading to decreased cardiac output, impairment of the conducting myocytes, and diastolic dysfunction (6–8).

Premature atherosclerosis is thought to be a major mechanism by which incidental irradiation of the heart leads to excess cardiovascular morbidity and mortality. Because it is frequently included within tangential RT fields that treat the left breast or chest wall, the left anterior descending (LAD) coronary artery is likely the coronary vessel most frequently affected by RT. The mechanism by which RT promotes atherosclerosis has been investigated in a number of animal models. RT has been shown to cause endothelial cell damage and may induce postapoptotic cell death in the endothelium of the coronary vessels. Endothelial cell damage can lead to intimal wall fibrosis due to proliferation of myofibroblasts. Lipid-laden macrophage deposition also occurs, with these deposits eventually resulting in thrombosis and vessel luminal occlusion (9). This radiation-related mechanism results in a final common pathway similar to coronary artery disease due to atherosclerosis from other causes (10,11). Clinical manifestations are dependent on the degree of occlusion, but include angina pectoris, unstable angina, chronic ischemic heart disease (IHD), and myocardial infarction (MI). These complications may necessitate medical or surgical intervention in the coronary arteries to alleviate symptoms or prevent life-threatening events (12).

Finally, the heart valves may also be affected by radiation. In a case series of five patients who received chest radiotherapy to a dose of at least 40 Gy, stenosis of the entire pulmonary outflow tract has been reported (13). In addition, pathologic changes in the valves may occur as a result of damage elsewhere in the heart. However, it is less clear by what mechanism valvular damage may occur, as the heart valves are avascular structures (14,15).

■ CARDIAC MORBIDITY AND MORTALITY IN WOMEN TREATED WITH OLDER RT METHODS

The adverse effects of older radiation techniques on the heart have been well documented through the meticulous and laborious efforts of researchers to investigate the phenomenon of RIHD. These studies are reviewed in detail below.

Meta-Analyses

Two meta-analyses have shown that cardiovascular mortality was increased in women who received RT in the 1970s and 1980s, particularly those with left-sided disease. The Early Breast Cancer Trialists Collaborative Group conducted a meta-analysis of 40 major randomized clinical trials (RCTs) encompassing 19,582 women treated for breast cancer in the 1970s and 1980s (16). This meta-analysis found that the addition of radiotherapy to breast cancer treatment reduced breast cancer mortality by 13.2% (standard error [SE], 2.5%), but that mortality from other causes increased by 21.2% (SE, 5.4%) (17). The increase in nonbreast mortality was primarily due to vascular causes (death rate ratio, 1.3; SE, 0.09), and the bulk of the nonbreast cancer deaths occurred in women in whom both the breast and chest wall and regional lymph nodes were included in the radiation fields.

Cuzick et al. conducted a similar meta-analysis of 10 RCTs of mastectomy with or without radiation initiated before 1975 and involving nearly 8,000 patients. The majority of these patients were treated with what would now be considered outdated radiation techniques including Cobalt-60 and orthovoltage machines. There was a nonsignificant improvement in all-cause mortality seen in the irradiated population; however, any improvements in breast cancer mortality were completely offset by increases in cardiac mortality after 10 years (18,19).

Observational Data

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program data, 27,000 women were found treated with RT for breast cancer from 1973 to 1989, and there was a significant difference in 15-year mortality due to IHD in women with left-sided breast cancer, 13.2%, versus those with right-sided breast cancer, 10.2% (20). In a study using data from the SEER program, Paszat et al. identified over 200,000 women with localized invasive breast cancer between 1973 and 1992. In women treated with radiation for left-sided breast cancer, the relative risk (RR) for fatal MI was 1.17 (95% CI, 1.01–1.36) compared with those treated for right-sided breast cancer. In women younger than age 60, the RR for fatal MI was increased in patients with left-sided cancer compared with those with right-sided cancer (RR, 1.98; 95% CI, 1.31–2.97). However, the RR of fatal MI was significantly greater only in the cohort of patients who had survived at least 10 to 15 years after the diagnosis of breast cancer, illustrating the long latency to between cardiac irradiation and subsequent cardiac morbidity (21).

In a series of 25,000 women treated in the early 1980s in the Canadian province of Ontario, Paszat et al. (22) observed a RR for fatal MI among patients receiving left-sided postlumpectomy RT which was 2.10 times higher than that seen in women undergoing right-sided treatment. Gyenes et al. (23) later reported that patients with a high dose–volume of cardiac exposure had a significant increase in IHD.

Randomized Controlled Trials

Data from several RCTs of breast radiotherapy also indicate increased rates of cardiac morbidity and mortality in women undergoing adjuvant RT for breast cancer. Houghton et al. reported the long-term outcomes of 2,800 patients treated on a trial between 1970 and 1975 of postmastectomy radiation therapy (PMRT) conducted by the United Kingdom Cancer Research Campaign Breast Cancer Trials Group. With 5 years of follow-up, a significant increase in cardiovascular mortality was seen (RR, 1.52; 95% CI, 1.01–2.29); in addition, an increased risk of cardiac death was observed in patients with left breast cancer compared with surgical controls (RR, 1.92; 95% CI, 1.09–3.39). Again, the increased RR of cardiac mortality in patients undergoing left-sided RT was seen in patients treated with orthovoltage RT (RR, 2.34;

95% CI, 1.25–4.37) but not in those treated with megavoltage techniques (24).

Jones et al. reported on the late effects observed in 1,461 patients who were randomized after mastectomy to immediate postoperative radiotherapy or delayed radiotherapy after recurrence between 1949 and 1955. In the first 15 years of follow-up, there was no statistically significant difference ($P = .37$) in mortality between the two groups. After 15 years of follow-up, however, significantly increased mortality was in the irradiated group (RR 1.43; 95% CI, 1.13–1.81; $P = .0025$). This increase in mortality was largely attributable to deaths from CVD, not including cerebrovascular disease (25).

Rutqvist et al. studied the impact of RT on cardiovascular mortality in a group of 960 women with primary breast cancer randomized to pre- or postoperative RT versus surgery alone. Surgery consisted of modified radical mastectomy. Radiation was delivered to the preoperative breast using Cobalt-60 tangents covering the breast, chest wall, and internal mammary nodes (IMN). In patients treated postoperatively, the chest wall and IMN were irradiated using an oblique electron field. With 16 years of follow-up, there was a nonsignificant overall survival difference in the irradiated versus nonirradiated patients. However, a subset of patients who received left-sided treatment had a significantly increased risk of death from IHD (relative hazard, 3.2; $P < .05$). Right-sided cancer patients and those treated with electrons were not subject to this increased risk (26).

■ CARDIAC MORBIDITY AND MORTALITY IN WOMEN TREATED WITH MODERN RT METHODS

Overview

While studies of patients treated with older methods have consistently demonstrated increased risks of CVD in women receiving adjuvant RT for breast cancer (especially left-sided breast cancer), increased rates of CVD have generally not been observed in studies conducted in women treated with more contemporary methods. The results of these studies are summarized below.

Observational Data

Using the SEER database, Giordano et al. (20) evaluated the impact of RT on risk of death from IHD in 27,283 women treated between 1973 and 1989. There were 13,998 women with left-sided, and 13,285 with right-sided breast cancer. For women diagnosed in 1973 to 1979, there was a significant difference ($P = .02$) in 15-year mortality in women with left-sided (13.1%, 95% CI = 11.6–14.6) versus right-sided cancers (10.2%, 95% CI = 8.9–11.5). However, this difference was eliminated in patients diagnosed between 1980 to 1984 and 1985 to 1989.

Patt et al. (27) also used the SEER data to compare 8,363 women with nonmetastatic left-sided breast cancer, and 7,907 with right-sided breast cancer, all of whom underwent breast surgery and received adjuvant RT from 1986 to 1993 with up to 15 years of follow-up. There was no significant difference in hospitalization for IHD, valvular disease, arrhythmias, or heart failure in patients treated for left-sided versus right-sided breast cancer.

In a large retrospective series from a single institution, Nixon et al. (28) examined the rates of cardiac mortality among 745 patients treated between 1968 and 1986 with BCS and RT. With a minimum follow-up among surviving patients of 12 years, there were no significant differences in death from breast cancer or death from nonbreast cancer causes, including CVD, among patients treated for left- versus right-sided breast cancer.

Randomized Controlled Trials

Højris et al. (29) assessed morbidity and mortality from IHD in patients who were treated on the Danish 82b and 82c randomized trials of PMRT. In these landmark trials, conducted from 1982 to 1990, 3,083 women identified as high risk for local–regional recurrence after mastectomy were treated with adjuvant systemic therapy and then randomized to PMRT ($n = 1,538$) or observation ($n = 1,545$). The chest wall and IMN were treated with anterior electron fields, while the supraclavicular and axillary nodal regions were treated with anterior photon fields. A total dose of 48 to 50 Gy was delivered in 22 to 25 fractions. At 10 years of follow-up, there was no difference in either the relative hazard for morbidity from IHD (0.86, 95% CI = 0.6–1.3) or the relative hazard for death from IHD (0.84, 95% CI = 0.4–1.8) among patients in the radiotherapy versus no-radiotherapy group.

Imaging Studies

Although observational data and data from RCTs suggest that modern RT methods do not increase

the risk of CVD, concerns about the risk of RIHD have persisted due to uncertainty regarding the normal tissue tolerance of the heart and its substructures and the absence of prolonged follow-up in many of the studies of patients treated with modern RT methods. Given the long latency for RIHD, investigators have attempted to define the dose–response relationship for RIHD using surrogate endpoints of RIHD that are observable shortly after completion of RT as opposed to the clinical endpoints of cardiac morbidity and mortality that typically do not appear until 10 to 20 years after RT. Most of these studies have used abnormalities seen on post-RT imaging (compared with pre-RT baseline scans) to define surrogate endpoints. The results of these studies are summarized below.

Imaging studies to detect cardiac injury include echocardiography, single-photon emission computed tomography (SPECT), angiography, and catheterization. Perfusion defects have been observed as soon as 6 months following radiation exposure (30,31). However, any increase in cardiac morbidity is typically not observed until 10 to 15 years after RT, and an increase in cardiac mortality is usually not seen sooner than 15 to 20 years after RT. Perfusion studies detect local or global changes in cardiac blood flow, relating it to myocardial contractility and viability.

Marks et al. (31) performed pre- and post-RT cardiac SPECT in 114 women undergoing RT for left-sided breast cancer. Following RT, SPECT scans were obtained every 6 months for 24 months. Cardiac perfusion defects developed in 50% to 60% of patients within 24 months of completing RT, but this risk depended on the volume of heart irradiated: 25% of patients who had modest volumes of the left ventricle (1%–5%) in the RT field developed new perfusion defects following RT, versus 55% of patients who had a larger (>5%) volume of the left ventricle exposed. In patients with perfusion defects, 12% to 40% had wall motion abnormalities, compared with only 0% to 9% who did not have abnormalities if there was no perfusion defect. However, these wall motion abnormalities were not associated with significant changes in global cardiac function as measured by ejection fraction. In a follow-up study of 44 patients who continued on the study up to 6 years following RT, the incidence of perfusion defects at 3, 4, 5, and 6 years was 52%, 71%, 67%, and 57%, respectively. However, these perfusion defects did not correlate with regional wall motion abnormalities or ejection fraction abnormalities at 3 to 6 years after treatment (30).

Erven et al. (32) investigated early radiation-related changes in cardiac region using strain rate imaging (SRI) by Doppler echocardiography. Strain describes a relative length change in the myocardium, while strain rate quantifies the speed at which the change occurs. SRI has been shown to detect changes in cardiac function before it can be detected by conventional techniques. Twenty left-sided and 10 right-sided breast cancer patients were studied using standard echocardiography and SRI at baseline, immediately after treatment completion, and 2 months after treatment to the intact breast or chest wall. The imaging findings were compared with regional radiation dose. Left-sided patients had significantly decreased strain immediately after RT ($S_{\text{post-RT}}$) and 2 months after RT (S_{FUP}) compared with baseline ($S_{\text{post-RT}}$: –19.5% ± 2.1% vs. S_{FUP}: –17.6% ± 1.5% vs. S_{baseline}: –17.4% ± 2.3%, respectively; $P < .001$), but not strain rate. Right-sided patients did not show this change. The changes in strain post-RT and at follow-up compared with baseline were more prominent in regions of the heart receiving >3 Gy ($S_{\text{post-RT}}$: –18.9 ± 2.6% vs. S_{FUP}: –16.1 ± 1.6% vs. S_{baseline}: –15.8 ± 3.4%, respectively; $P < .001$). The authors concluded that SRI can detect dose-related regional changes in myocardial function immediately after RT and at follow-up.

Molecular Markers

Molecular methods to detect immediate cardiac damage include troponins, lactate dehydrogenase, and creatine kinase. These markers are typically released after myocardial cell damage. The data on release of these biomarkers are limited in breast cancer, and conclusions regarding the utility of these markers are mixed. Hughes-Davies et al. (33) compared pre- and post-RT levels of serium troponin T levels in women receiving adjuvant whole breast RT with Stage I and II breast cancer. The group found no significant differences between pre- and posttreatment levels, and all women had either normal or undetectable levels of the marker at both time points. However, cardiac dosimetry was not provided in the study, so the degree of cardiac exposure to radiation is unclear.

Nellessen et al. (34) studied the release of troponin I and brain natriuretic peptide (BNP) in 23 patients receiving radiation to the chest. Levels were taken before treatment, and weekly during treatment. The levels of both troponin I and BNP increased significantly during the study; however, the mean and absolute values of each marker remained

relatively low during the course of the entire study (mean pre- and postradiation troponin I: 0.007 ± 0.008, 0.014 ± 0.01 ng/ml; mean pre- and postradiation BNP: 123 ± 147, 159 ± 184 pg/ml). Furthermore, only 5 of the 23 patients in this study were treated for breast cancer; all others had lung cancer. The use of cardiac biomarkers remains an interesting and important area of further study in breast cancer treatment.

Dose–Response Relationship for RIHD

The shapes of the dose–response curve (DRC) for most of the clinical manifestations of RIHD including cardiomyopathy, coronary artery disease, valvular disease, and conduction system abnormalities have not been described. The shapes of the DRC for the pericarditis and the global endpoint of long-term excess cardiac mortality after RT for breast cancer have been characterized, but only crudely using limited clinical data and mathematical models.

Acute Pericarditis

In a seminal publication reviewing the tolerance of normal tissues to radiation, Emami et al. (35) suggested that the TD5/5 for pericarditis occurred at a heart V33 of 60 Gy, heart V66 of 45 Gy, and heart V100 of 40 Gy. The TD50/5 was estimated at a heart V33 of 70 Gy, heart V66 of 55 Gy, and heart V100 of 50 Gy. These doses/volumes of cardiac exposure are far greater than is generally ever encountered in the adjuvant radiation of breast cancer patients. Nevertheless, Muren et al. (36) used the tolerance doses proposed by Emami to estimate the risk of pericarditis in women with breast cancer treated with either standard tangential irradiation (STI) or conformal tangential irradiation (CTI). The Emami tolerance doses, fitted to two radiobiological models (the probit and relative seriality models), were applied to calculate the normal tissue complication probability (NTCP). For STI, the estimated risk of pericarditis ranged from 0% to 0.7% in the various models. For CTI, the estimated risk ranged from 0% to 0.3%.

Death From Cardiovascular Causes

In a publication by Gagliardi et al., clinical data on long-term cardiac mortality among breast cancer patients included in two randomized trials of PMRT of RT as an adjunct to primary surgery were analyzed using the "relative seriality" model of radiation response (26,37,38). (The relative seriality model is one of several mathematical models commonly used to describe the relationship between radiation exposure to an "organ at risk" (OAR) and the corresponding risk of a clinically defined toxicity endpoint.) Analysis of the Stockholm trial has shown a 7% excess risk of cardiac mortality at 15 years for left-sided patients compared with surgical controls and no excess for right-sided patients; while data from the Oslo indicate an 8% and 3% excess risks of cardiac mortality for patients treated for left- and right-sided breast cancers, respectively.

The original treatment plans from patients enrolled on the Stockholm study were recalculated on a group of model patients using a modern three-dimensional treatment planning system. A mean dose–volume histograms (DVH) was calculated for each treatment technique employed in the Stockholm study. Both whole heart and myocardium alone were investigated as at-risk organs. The DVH data were related to incidence data on excess cardiac mortality to derive DRCs. The authors found that the relative seriality model could be used to describe the incidence data. Below a dose of 20 Gy, the excess cardiac mortality was negligible, regardless of the volume of heart within the field. Treatment of 20%, 33%, 60%, and 100% of the heart to a dose of 30 Gy was associated with a probability of excess cardiac mortality of 1%, 1.5%, 3%, and 4%, respectively. The D50 (i.e., the dose resulting in a 50% complication probability) was 52.3 Gy.

In a similar publication by Eriksson et al. (39), clinical data on long-term cardiac mortality among Hodgkin's disease survivors treated with mediastinal RT at the Karolinska Hospital were also analyzed using the relative seriality model. Of the 157 patients, 13 (8.3%) died due to IHD. Analysis of DVH showed an increasing risk with increasing dose to a larger volume fraction. Treatment of 33% of the heart to a dose of 30 or 40 Gy was associated with an excess risk of cardiac mortality of approximately 1.5% and 4%, respectively.

Using the dose–response parameters for the relatively model determined by Gagliardi and Eriksson, several authors have estimated the excess risk of cardiovascular mortality associated with modern breast RT methods. Muren et al. (36) calculated heart and lung DVHs in 31 patients who underwent three-dimensional planning for tangential breast irradiation. They then used NTCPs from several probit and relatively seriality model and the probit model (an alternative mathematical model of radiation injury) to estimate the risk of excess cardiac mortality. The mean and range of predicted excess cardiac mortality for STI

in the three models used were 0.4% (0–0.8), 0.5% (0–1.2), and 0.7% (–0–1.5). For CTI, the predictions were 0.2% (0–0.8), 0.3% (0–1.2), and 0.3% (0–1.6). Hurkmans et al. (40) conducted a planning study of 17 patients with left-sided breast cancer treated with tangents using either optimized wedges without blocks, wedges with conformal blocks, or IMRT. The NTCP for excess cardiac mortality after 10 to 15 years was calculated by applying the relative seriality model with parameters as derived by Gagliardi et al. The NTCP values for late cardiac mortality for the three techniques were 6%, 4%, and 2%, respectively.

■ RADIATION TECHNIQUES TO REDUCE CARDIAC EXPOSURE

Clinical Target Volumes

The utility of different RT techniques in reducing cardiac exposure may vary considerably with the clinical target volume (CTV) being treated in a given case. The CTV is the anatomic region considered to be at substantial risk of harboring microscopic disease. In women receiving adjuvant RT for breast cancer, the CTV may differ substantially depending on the clinical scenario. Some women with biologically favorable disease may be candidates for accelerated partial breast irradiation (APBI); in such cases, the CTV is confined to the tumor bed with a 1- to 2-cm margin of surrounding breast tissue. For young women or older women with intermediate to high-risk cancer, the CTV usually depends on the surgery that has been performed and the extent of nodal positivity: (a) women with negative nodes who have undergone BCT are treated with whole breast RT; (b) women with more than minimal node involvement who have undergone BCT with axillary lymph node dissection, are treated with RT fields that encompass the whole breast and the regional nodes; and (c) for women undergoing mastectomy who are felt to be at substantial risk of local-regional recurrence, the CTV will generally include the chest wall and regional nodes in most cases (occasionally treatment will be directed at the chest wall only). Treatment of the IMN remains somewhat controversial but the IMN have been treated in almost every RCT reported to date of postmastectomy RT and of whole breast RT with our without regional node irradiation (29,41). Because of the proximity of the IMN and the heart, treatment of the IMN with older RT methods (e.g., deep tangents or "hockey-stick" method) led to incidental irradiation of large volumes of heart. One major area of progress in reducing incidental heart exposure has been the development of techniques to treat the IMN while minimizing cardiac exposure. These and other technical innovations are discussed below.

Two-Dimensional RT

Following the realization that treating large volumes of heart to high doses could substantially increase the risk of RIHD, the traditional RT techniques used to treat the IMN (deep tangents, hockey-stick method, etc.) were abandoned in favor of techniques capable of treating the IMN with substantially reduced cardiac exposure.

In the mixed-beam approach to treating the IMN, a combination of en face electrons and anteroposterior (AP) photons are used. The beam is typically weighted so that the ratio of electrons to photons is at least 2 to 1. The electron energy required to treat the IMN depends on their depth but typically ranges from 6 to 16 MeV depending on the thickness of the chest wall. If the patient has undergone mastectomy without reconstruction and is thin, a gantry angle of 0° (pure AP) is usually used. If the patient has an intact breast, has undergone reconstruction, or is obese, then angling of the IMN field by 15° to 25° will reduce the size of the so-called "cold triangle" (area of underdosage between the IMN field and tangential fields which are matched to it) (42).

The other two-dimensional innovation in treating the IMN was to use "partially wide tangents," also known as partially deep tangents (Figure 1). In this technique, pioneered by Marks et al. (43), tangential fields are used that are deep superiorly to include the superior IMN but shallow inferiorly to reduce exposure of the heart to radiation in left-sided cases. Treatment of the superior IMN (first three intercostal spaces) only is based on data demonstrating IMN involvement rarely extended beyond the first three intercostal spaces in patients with IMN involvement (44–47).

Three-Dimensional Conformal RT

With the advent of RT treatment planning software capable of performing virtual simulation using CT scan datasets, RT treatment planning evolved from two-dimensional techniques in which target volumes and fields were established using fluoroscopic imagers and were largely based on bony anatomy

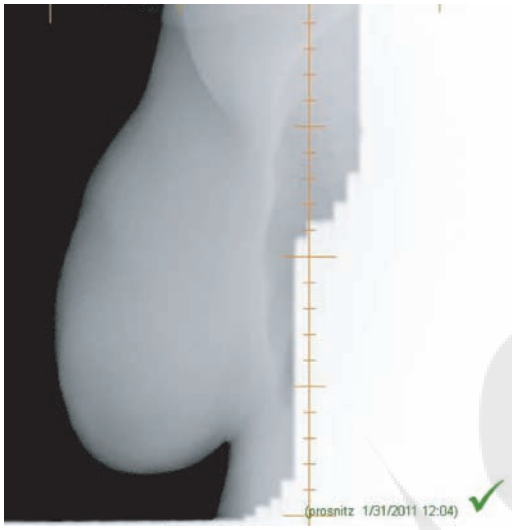

FIGURE 1 Portal image of a partially wide tangential field. The fields are wide superiorly to include the IMN (first three intercostal spaces) and narrow inferiorly to exclude the heart and lung while still treating the entire breast or chest wall.

and/or placement of markers or instillation of contrast into organs such as the bladder, rectum, or stomach, to much more sophisticated three-dimensional techniques in which target volumes and normal organs could be contoured on the axial images of CT scans and three-dimensional conformal RT fields established through beam's eye view (BEV) virtual simulation. With three-dimensional conformal radiotherapy, it became possible for the first time to quantify coverage of target volumes and exposure to normal organs using DVH (Figure 2).

With three-dimensional CRT, the intact breast or chest wall is still treated with tangential RT fields. However, visualization of the target volumes and OAR such as the heart allows one to modify the fields to reduce cardiac exposure by adjusting the medial and lateral field borders and/or shielding the heart using a heart block (or the multileaf collimator [MLC] on current linear accelerators), assuming that such a block or MLC pattern does not compromise coverage of the clinically relevant portions of the target volume (Figure 3).

Muren et al. (36) found three-dimensional conformal treatment reduced the volume of heart receiving >50% of the prescription dose (PD) by 42%, and the mean dose by 36% compared with STI. This reduction in cardiac exposure was associated with a 50% reduction in average excess cardiac mortality using several different NTCP models.

Another advantage of three-dimensional treatment planning was that the cardiac sparing approaches to treating the IMN that were first implemented with two-dimensional planning methods (as described above) could be applied with greater accuracy, ensuring coverage of the target volumes (e.g., breast, regional nodes) while minimizing dose to the heart and the lung (Figure 4) (45–47).

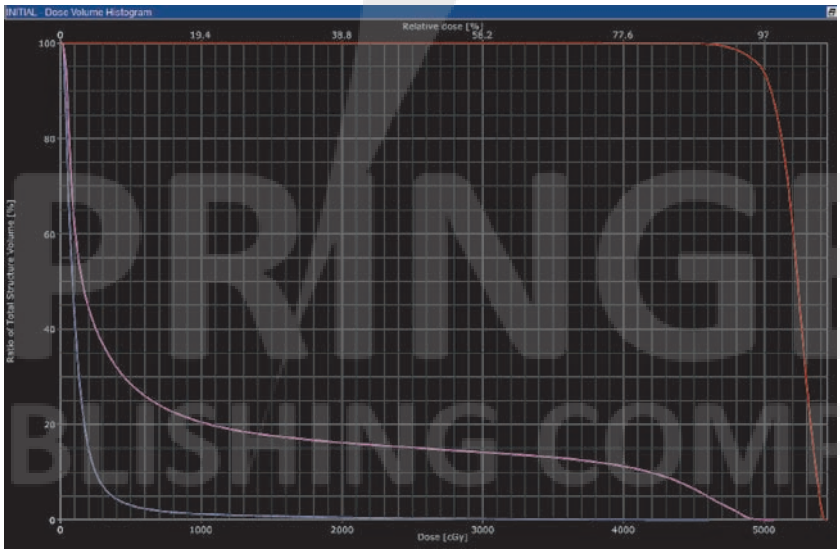

FIGURE 2 DVH for a patient receiving tangential RT to the left breast. The DVH for the breast PTV, the left lung, and the heart are shown in red, purple, and blue, respectively.

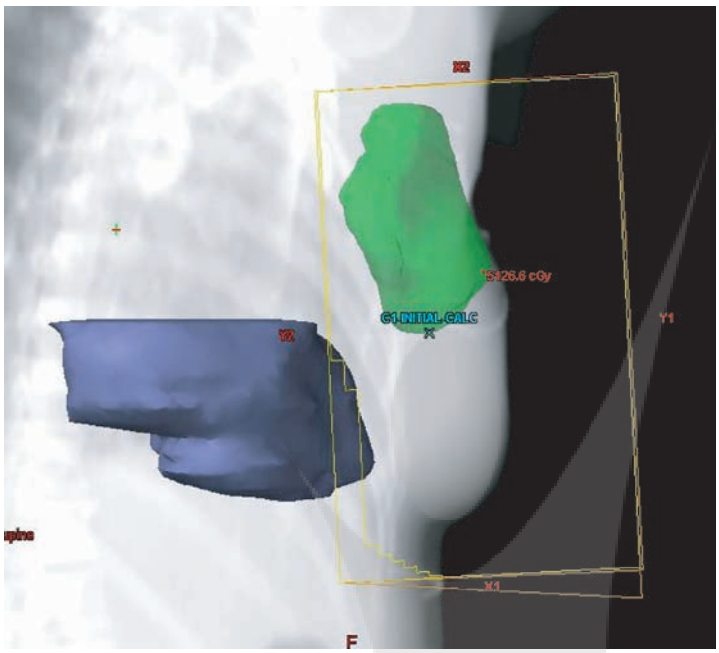

FIGURE 3 BEV of the medial tangential field in a patient undergoing RT for left breast cancer. A heart block was used in this case since it did not compromise coverage of the tumor bed, which was in contour in the upper outer quadrant of the breast.

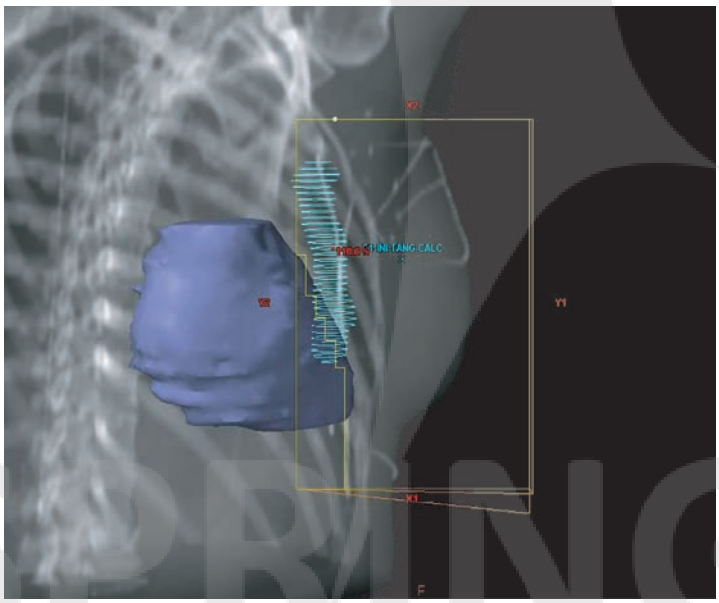

FIGURE 4 BEV of the left medial partially wide tangential field in a patient undergoing treatment to the left breast and regional nodes. The IMN target volume and the heart are shown. The deep field edge is defined by the MLC (stagger-step line).

Deep Inspiration Breath-Hold and Respiratory Gating

The premise behind deep inspiration breath-hold (DIBH) is that inhalation expands the chest cavity volume such that the breast and chest wall move anteriorly and greater separation is achieved between the chest wall and the heart. Inspiration also pulls the diaphragm down, and since the pericardium is securely attached to the diaphragm, the heart is subsequently pulled inferiorly as well (Figure 5). A number of systems have been tried or are available in respiratory gating of radiotherapy for breast cancer including fluoroscopy, ultrafast CT, magnetic sensors, breathing-activated devices and cameras (48).

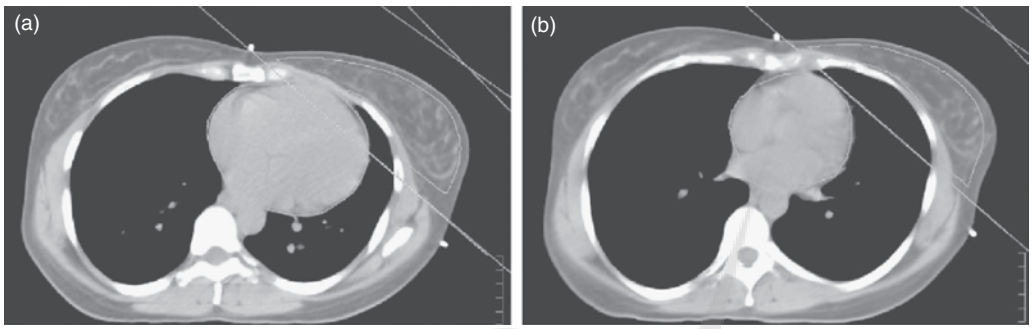

FIGURE 5 Axial CT images showing the path of the tangential fields in (A) free breathing and (B) DIBH in a patient undergoing treatment for left-sided breast cancer. At deep inspiration, the volume of heart in the RT fields was substantially reduced.
Source: Reproduced with permission from Ref. (52).

Chen et al. studied how the respiratory cycle altered irradiated cardiac volume in left-sided treatment portals. Fourteen healthy female volunteers underwent chest MRI in a position as close as possible to the usual RT treatment position. Cardiac volume was measured during breath-hold at end-tidal volume, deep inspiration, and forced expiration. Of the 14 patients, 13 had a significant portion (20.9 cm^3, range 1.3–88.4 cm^3) of cardiac volume in the fields prior to deep inspiration. Deep inspiration in these 13 patients reduced cardiac volume in the portals by 10.7 cm^3 (40.2%), and expiration significantly increased cardiac volume in the fields by 4.0 cm^3 (21.5%) (49).

Another study of 15 patients with breast cancer who were planned using CT found that irradiated heart volume was reduced by as much as 86% with deep inspiration. In seven of the patients, the heart moved completely out of the tangent fields during deep inspiration. The authors found that the patients were comfortable holding their breath for 20 seconds at a time (50). Even when a conscious effort was made to avoid the heart during placement of radiation fields, deep inspiration still significantly reduced involved cardiac volume. Sixel et al. (51) studied five patients using a device-activated breath-hold, instead of patient coordinated, and similarly concluded that deep breath-hold decreased cardiac volume in both standard and wide tangents.

Remouchamps et al. (52) studied moderate DIBH using the Active Breathing Coordinator (Elekta Oncology) device combined with step-and-shoot IMRT to increase homogeneity in five early stage breast cancer patients. The heart V30 Gy ranged from 2.3% to 9.7%, and was reduced to 0% to 0.6% at moderate DIBH. The median NTCP for the heart decreased 1.5% in absolute terms. A number of other studies have been published with similar findings (53–56).

Although planning studies have shown reduced NTCP for the heart in DIBH, the impact of this technique on the volume/fraction of lung in the RT field and the subsequent is unclear. Some studies have found that expansion of the chest cavity increases the volume of lung tissue irradiated, while others have shown that the fractional volume of the left lung in the fields is the same before and after breath-holding (50,51). With current techniques, radiation pneumonitis is a now an uncommon complication of breast radiotherapy; therefore, with new techniques, a similarly low rate of radiation pneumonitis must be confirmed.

Multifield IMRT

Intensity-modulated radiation therapy (IMRT) is a relatively new RT technology that relies on innovations in treatment planning software and in treatment delivery hardware (e.g., the MLC) to vary the intensity of the photons or "fluence" within a given RT field to create dose distributions that conform more tightly to target volumes and/or reduce the dose of radiation to nearby organs (Figure 6). A simpler form of IMRT can also be used to improve the homogeneity of dose within the treatment field by acting as a customized three-dimensional tissue compensator. In the treatment of women with breast cancer, IMRT has been clearly shown to improve dose homogeneity compared with standard two-dimensional planning.

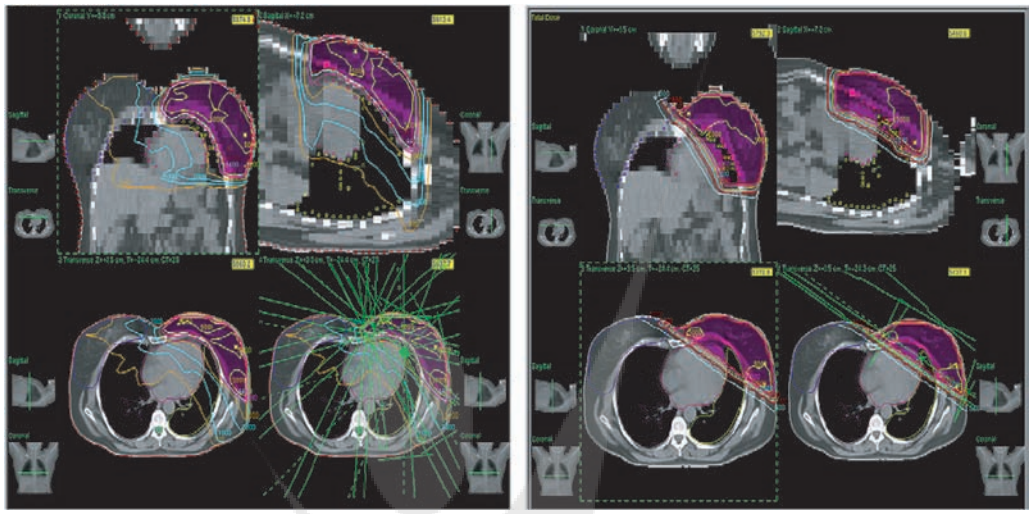

FIGURE 6 Dose distributions in the transversal, coronal, and sagittal planes for (left) IMPT radiotherapy and (right) three-dimensional conformal plans.

The role of IMRT in reducing cardiac exposure has been investigated in a number of planning studies. When IMRT is used and the beam orientation is restricted to traditional opposed tangential field, the extent of cardiac sparing achieved with IMRT is roughly equivalent to the degree of sparing achieved with a simple heart block. The downside of both approaches is also similar: both compromise coverage of the portion of the planning target volume (PTV) that lies in the "shadow" of the heart.

Landau et al. compared heart blocks in standard wedged tangents to tangential and multifield IMRT in 10 left-sided breast cancer patients with unfavorable cardiac anatomy, defined as >1.0 cm of maximum heart depth within the posterior border of the tangent field. Plans generated included standard wedged tangents with and without partial or complete cardiac blocks, and two-, four-, and six-field IMRT. It was found that all patients benefitted from some form of cardiac shielding compared with unshielded tangents, although full cardiac shielding did compromise PTV coverage. IMRT was also able to reduce the heart dose compared with unshielded tangents, although tangent IMRT could not spare the heart further than wedged tangents with a partial cardiac block. Additional IMRT fields using a four- and six-field technique did also reduce the heart dose compared with unshielded tangents, although there was increased low-dose radiation to the heart, lung, and contralateral breast (57).

In our own series, we compared tangent three-dimensional CRT to tangent inverse-planned, sliding window IMRT in 14 left-sided breast cancer patients with unfavorable cardiac anatomy, defined as maximum heart depth >1.0 cm (58). Three-dimensional CRT was planned using tangent RT with dynamic wedges, segments, and a physician-designed partial cardiac block with the dual goals of optimizing PTV coverage and protecting the heart. The inverse-planned IMRT was designed to provide comparable PTV coverage compared with three-dimensional CRT, with the goal of reducing high-dose radiation exposure to the heart any further. We found that there was no significant difference in the V30 Gy for the heart (1.7% vs. 1.8%, $P = .8$) between the two modalities, but IMRT delivered significantly more monitor units.

When multiple fields, some of which are nontangential, are used to create an IMRT plan, the volume of heart receiving a high dose of radiation (e.g., the V30) can be reduced without compromising coverage of the PTV, but only at the expense of increasing low-dose exposure to the heart, lungs, and contralateral breast. In a representative study, Beckham et al. (59) showed that, in women receiving treatment to the whole breast and IMN, the heart V30 was reduced from 12.5% to 1.7%, but the volume of normal tissues receiving >5 Gy was substantially increased. In another representative study of women receiving adjuvant RT to the intact left breast, Coon et al. (60) showed the heart V35 was reduced from 3.6% with three-dimensional CRT to 0.7% with IMRT but that the heart V20 was significantly increased from 15% to 22% with the use of IMRT.

Given the concern regarding the potential adverse effects of low-dose irradiation of the heart, lungs, and contralateral breast (e.g., impairment of organ function, development of second malignancies), multifield IMRT has been evaluated in planning studies but has not been implemented widely in the clinic.

Accelerated Partial Breast Irradiation

APBI refers to any one of several techniques for delivering RT to the tumor bed and a small region of surrounding normal breast tissue in a compressed time (accelerated) and with large doses per fraction (hypofractionated). The three main techniques for delivering APBI are external beam, catheter-based brachytherapy (most commonly an inflatable balloon with a single or multiple channels), and interstitial implantation. In patients who are at low risk of having microscopic disease extending more than 1 to 2 cm beyond the excision cavity, APBI may be as effective as whole breast irradiation (WBI) in reducing local recurrence. Consensus guidelines have been published which divide patients into "suitable," "cautionary," and "unsuitable" categories based on their clinicopathological characteristics (61). However, until the results of NSABP B-39 (a large randomized trial of WBI versus APBI) are available, APBI will remain investigational, especially for women who fall into the cautionary or unsuitable categories as defined by the consensus guidelines.

Although increased patient convenience and reduced acute toxicity are usually cited as the primary advantages of APBI, the utility of APBI in reducing the risk of RIHD has also been evaluated in a number of studies. Stewart et al. (62) compared MammoSite (high-dose rate brachytherapy delivered using a saline-filled balloon inserted into the lumpectomy cavity) to whole breast tangent RT in 15 left-sided patients. They delivered 3.4 Gy per fraction for 10 fractions to 1 cm from the balloon surface. Using standard dosimetric parameters, MammoSite decreased the maximum dose to the heart from 44.1 to 16.6 Gy. The percent volume of heart receiving >20 Gy was decreased from 3.7% to 0.1%. The dose distribution for a typical MammoSite case is shown in Figure 7.

Lettmaier et al. (63) studied the dose to OAR in 16 women treated with multicatheter interstitial brachytherapy (low dose rate or high dose rate [HDR] brachytherapy delivered in a single- or double-plane implant of the lumpectomy cavity). Brachytherapy outperformed external beam therapy in every category of heart sparing: mean volume receiving >50% of the PD was 51.07 cm^3 in external beam RT, compared with 0.18 cm^3 in brachytherapy, and no volume of heart received >90% of the PD. The low dose to the heart reported in this study is consistent with the results of other studies of multicatheter brachytherapy (64). The authors argue that the multicatheter method offers superior cardiac sparing compared with MammoSite because the multiple catheters allow for more flexibility in shaping the dose distribution.

APBI can be also be delivered by external beam methods including three-dimensional CRT, tomotherapy, IMRT, and conformal proton therapy. The three-dimensional CRT APBI method was first developed at the William Beaumont Hospital. In this approach, which was later adopted for use in B-39, the lumpectomy cavity is expanded by 1.5 cm to create a clinical treatment volume (CTV) and by an additional 1 cm to create a PTV. In four left-sided breast cancer patients, the volume of the heart receiving >10% of the PD was substantially lower in three-dimensional CRT APBI compared with WBI (65). In a planning study of 19 patients with left-sided breast cancer comparing different external beam APBI methods, Moon et al. (66) found the average heart volume receiving greater than 20% of the PD was 8%, 1.5%, and 1.2% for tomotherapy, three-dimensional CRT, and IMRT APBI, respectively.

Proton Therapy

Protons are highly energetic charged particles that can be accelerated to high speeds using a machine called a cyclotron. The therapeutic use of protons in treatment of malignancy was proposed in 1946 and then clinically implemented in 1954 at the Lawrence Berkeley Laboratory. Because of their unique physical properties, protons can be used to create dose distributions that are not achievable with conventional x-ray (photon) therapy. In contrast to x-ray beams, which are gradually attenuated as they pass through tissue, proton beams deposit the majority of their energy at a fixed distance which depends on the energy of the beam and density of the tissue through which it passes. This phenomenon, referred to as the "Bragg Peak," allows for delivery of the prescribed radiation dose to a deep target with minimal exit dose beyond the target. The theoretical advantages of proton beam therapy over conventional x-rays in the treatment of ocular, pediatric, skull base, CNS,

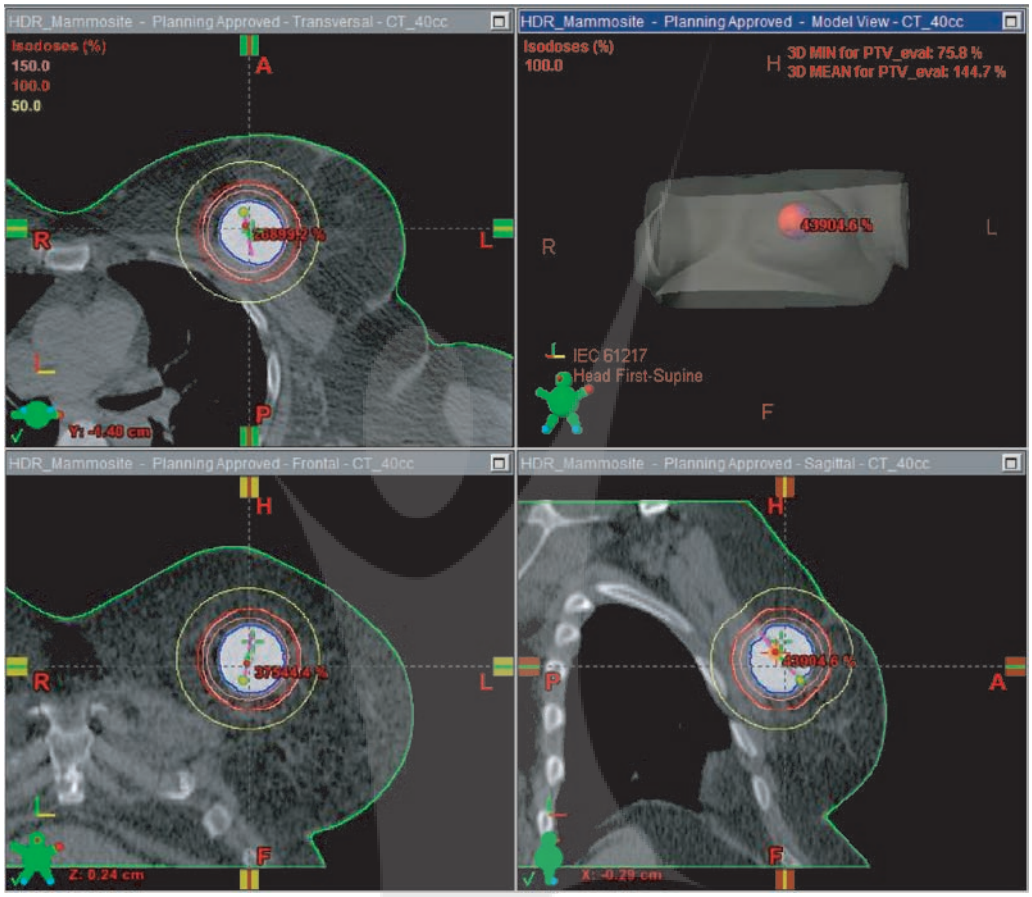

FIGURE 7 Dose distributions in the transverse, coronal, and sagittal planes for a MammoSite HDR brachytherapy plan in a patient with left breast cancer.

head and neck, and prostate cancers has been extensively evaluated (67). In general, these studies have suggested that proton therapy may improve the therapeutic ratio in these diseases by reducing the risk of acute and/or late toxicity. More recently, a few studies have investigated the potential of proton therapy in reducing the risk of RIHD in women undergoing adjuvant RT for breast cancer.

Fogliata et al. (68) compared two- and three-field field photon therapy, two- and three-field IMRT, and single-field proton therapy in five breast cancer patients (three left-sided) with unfavorable lung anatomy. A dose of 50 Gy was prescribed to the PTV for each technique with the goal of minimizing lung dose while keeping PTV coverage high. Although the heart was not intentionally avoided in treatment planning, the authors reasoned that the risk of cardiac toxicity was low when the IM nodes are not treated. The study found that heart dose was significantly reduced in patients treated with proton therapy: in the three left-sided cases, mean doses to the heart were 2.7, 2.9, and 2.2 Gy for two-field conventional, two-field IMRT, and proton therapy, respectively. Maximum doses to the heart were 33.5, 33.2, and 19.3 Gy for two-field conventional, two-field IMRT, and proton therapy, respectively. The authors concluded that proton therapy provided superior PTV coverage and normal tissue sparing compared with both conventional and IMRT plans.

Further improvements in OAR sparing have been found in proton-based APBI and intensity-modulated proton therapy (IMPT). Ares et al. (69) performed a planning study in which IMPT was compared with three-dimensional CRT and IMRT in 20 patients, with increasingly demanding regional nodal irradiation requirements. The first plan was designed to cover the chest wall and intact breast, the second added the supraclavicular and Level III

axillary nodes, and the last plan added the internal mammary chain. Comparing IMRT with IMPT, it was found that IMPT reduced low-dose (V5) radiation by a factor >2.5, and IMPT reduced high-dose (V22.5) radiation to the heart by a factor >20. The authors concluded that complex IMRT may increase the integral dose compared with three-dimensional CRT in patients with increasingly complex target volumes, and proton therapy may increase the therapeutic ratio while allowing for organ-sparing. In a similar planning comparison with 11 patients, Johansson et al. (70) calculated the mean NTCP for the cardiac mortality to be 0.5%, 2.2%, 2.1%, and 6.7% for protons, IMRT, patched photons, and standard tangents, respectively. The dose distributions for three-dimensional CRT, IMRT, and IMPT plans for a representative patient are shown in Figure 8.

Moon et al. (66) compared proton beam APBI against x-ray APBI modalities and found that the mean V20 Gy of the heart was 8.0%, 1.5%, 1.2%, and 0% and the mean V10 Gy was 19.4%, 3.1%, 4.0%, and 0% in tomotherapy, IMRT, three-dimensional CRT, and proton therapy, respectively.

Although proton therapy has been shown to have dosimetric advantages compared with x-ray-based techniques in planning studies, clinical experience to date is extremely limited and has raised a cautionary note. An initial dosimetric study in 2006 by Taghian et al. with a clinical implementation update by Kozak et al. explored the potential utility of proton-beam APBI (71,72). This is the only clinical trial reported to date. A total of 20 patients with Stage I breast cancer were treated using proton APBI on a Phase I/II clinical trial. There were no recurrences with median 12 months of follow-up and 100% of both physicians and patients rated global cosmesis as good to excellent at 12 months. However, almost 80% had moderate to severe immediate skin changes at 3 to 4 weeks posttreatment, 22% severe desquamation, 3% rib tenderness, and 1% a documented rib fracture. Although cosmesis and local control appear excellent, there remain significant technical challenges to reduce acute skin and rib toxicity.

Assuming techniques can be developed that reduce acute skin toxicity to acceptable levels, the widespread implementation of proton therapy will likely be hindered by its costs, which at present are significantly greater than the costs of x-ray-based techniques due the high cost of building and operating a proton therapy center.

Patient Positioning (Prone and Decubitus)

Most patients with breast cancer are treated in the supine position with their arms abducted overhead. However, this position may not be ideal for women with large, pendulous breasts. Supine treatment of patients with large pendulous breasts may lead to large volumes of heart and lung being included within the tangential fields, the development of moist desquamation in the inframammary skin fold, and dose inhomogeneity within the breast that may increase the risk of late fibrosis and poor cosmesis (73). Although prone positioning of patients clearly reduces acute skin toxicity, and improves homogeneity in patients with large pendulous breasts, its impact on dose to the heart is less clear (74–76).

Several studies using CT-based planning have shown that cardiac dose is decreased in prone

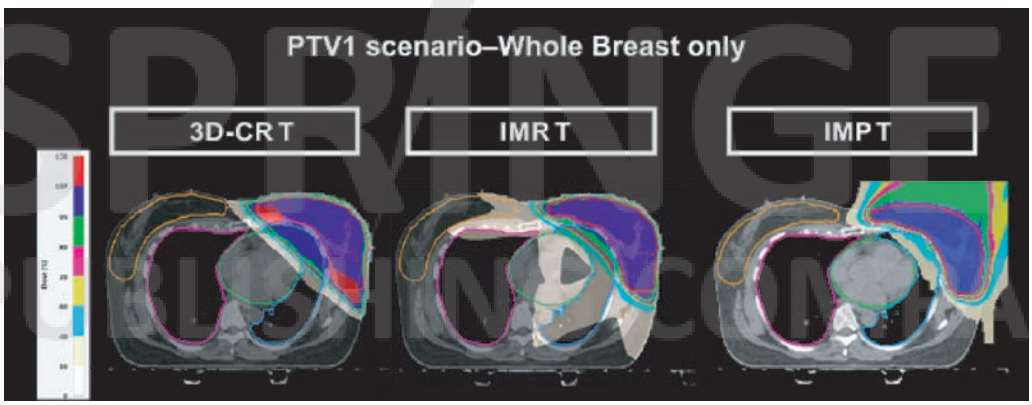

FIGURE 8 Representative axial image showing dose distributions for three-dimensional CRT, IMRT, and IMPT. *Source:* Reproduced with permission from Ref. (69).

positioning compared with a supine setup. Formenti et al. (75) compared prone and supine positioning in 90 patients, 50 with left-sided cancers, treated with hypofractionated IMRT. The authors found that their IMRT constraint of <5% of the heart receiving >18 Gy was more frequently achieved with prone positioning and that the median volume of heart in the field was significantly lower with prone setup when comparing with other studies. Although the authors did not specifically study prone versus supine dosimetry in this study, early results of an institutional trial show that prone positioning provides superior heart sparing dosimetry. Kirby et al. (77) compared dose with the LAD artery and heart in prone and supine positioning in both partial and WBI. Although the V30 Gy to the LAD was reduced in 19/30 whole breast cases by a median of 6.2 Gy, it was increased in 8/30 cases by a median of 9.5 Gy. Prone positioning decreased the dose to the LAD in more cases than it reduced the dose. Breast volume was a major determinant of benefit from prone breast RT; in patients with whole breast (CTV) volume greater than 1,000 cm^3, prone positioning significantly reduced cardiac dose in both whole and partial breast therapy. Finally, Buijsen et al. (78) showed a nonsignificant difference between heart doses in most measures, although the V95% was significantly lower in the seven left-sided breast cancer patients in the prone position.

While some studies have indicated that prone positioning reduces cardiac exposure, a number of reports have found either no impact or a potentially adverse impact of prone positioning on cardiac dose. In a planning study of 20 patients (12 with left-sided disease), Alonso-Basanta et al. (79) found that both supine and prone positioning both provided excellent PTV coverage and that the mean heart volume receiving >30 Gy was low with both approaches (0.56% supine vs. 0.30% prone, P = NS). In a study of 19 patients evaluated in the prone position, Chino and Marks (80) found the superior and lateral aspects of the anterior pericardium moved a mean 19 mm closer to the anterior chest wall potentially negating the benefit of reduced breast separation typically achieved by prone positioning. Griem et al. (81) found the volume of heart exposed to clinically relevant doses of radiation did not consistently change between prone and supine positioning. A study by Varga et al. (82) also found that the dose to heart did not vary consistently between prone and supine planning. Axial images of the patient treated in the prone position are shown in Figure 9.

Other alternative treatment positions have been also been studied, most notably the lateral decubitus (LD) position. In a series of 644 patients treated at the Institut Curie in Paris, where treatment has routinely been administered in the LD position for large-breasted patients for over 40 years, Fourquet et al. found that the mean dose to the heart was <10% of the PD (83). Despite the favorable results reported from the Institut Curie, treatment in the LD position had never been widely adopted due to concerns about reproducibility.

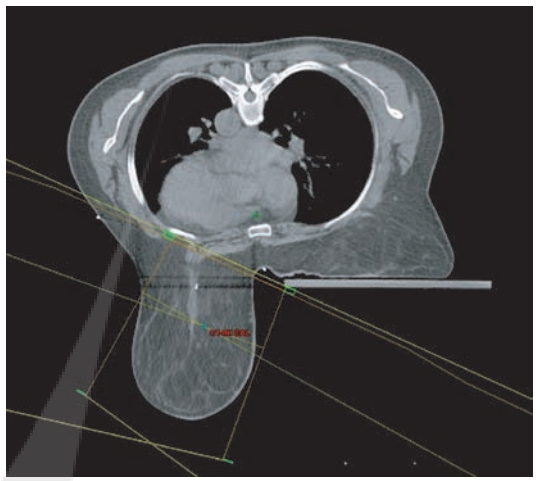

FIGURE 9 Axial image showing path of tangential beams in a patient undergoing left breast RT in the prone position. For patients with large pendulous breasts, prone positioning may be advantageous in reducing heart and lung exposure and in decreasing acute radiation dermatitis.

■ SYNERGISTIC EFFECTS OF RT AND CARDIOTOXIC SYSTEMIC AGENTS

Anthracycline Chemotherapy

Anthracycline chemotherapy agents have formed the backbone of adjuvant chemotherapy for breast cancer for the past two decades. Enthusiasm for their continued use, however, has been tempered by concern regarding their potentially cardiotoxic effects. The overall incidence of doxorubicin-induced cardiotoxicity ranges from 1.7% to 6.8%, and is largely dependent on the dose administered. Although some toxicity has been reported in doses as little as 180 mg/m^2, a much higher incidence of cardiotoxicity occurs at cumulative doses between 450 and 550 mg/m^2. Anthracycline-induced cardiotoxicity often has a rapid and insidious onset, generally

appearing within the first 8 weeks of the final dose of the agent and presents with symptoms typical of biventricular failure including shortness of breath, tachycardia, lower extremity edema, jugular venous distension, and pleural effusions. Early trials reported fatality rates as high as 70% to 80% in patients developing anthracycline-induced cardiac toxicity, mostly due to complications arising from severe progressive congestive heart failure (84).

The major cardiotoxic effects of anthracyclines are thought to be due to free radical generation in the myocytes, although the exact mechanism of action is not entirely well characterized. These damaging particles result in vacuole formation, disorganization of the myofilaments, and destruction of myofibrils leading to functionally impaired myocytes. Ultimately, the cells die and the heart is subject to diffuse myocardial fibrosis, which is the same end-result as occurs in radiation-induced toxicity to the heart, although the mechanism is different; RT appears to have a much greater effect on endothelial cells compared with chemotherapy (2).

Early studies reported that patients receiving mediastinal irradiation for Hodgkin lymphoma were at greater risk of subsequent doxorubicin-induced cardiotoxicity, even at subcritical doses of the agent (85). A pathological analysis of 12 patients who received doxorubicin and mediastinal radiation in doses from 600 to 5,700 cGy found that there were more severe pathological changes consistent with cardiomyopathy in this combined modality group compared with doxorubicin dose-matched controls who did not receive mediastinal radiation (86). Animal models suggest that doxorubicin and radiation may have synergistic cardiotoxic effects (87).

Hardenbergh et al. studied cardiac perfusion changes with SPECT imaging in patients with left-sided breast cancer treated with RT, with and without doxorubicin. A total of 22 patients in this study received pre-chemotherapy, pre-RT, and 6 months post-RT. All patients received 45 to 50 Gy of tangent breast RT and approximately half received doxorubicin-based chemotherapy. Sixty percent of all patients had new cardiac perfusion defects at 6 months after RT completion. There was a dose-dependent perfusion defect at 6 months with up to a 20% decrease in regional perfusion seen at doses of 41 to 50 Gy (88).

A study by Shapiro et al. (89) assessed the cardiac effects of RT and doxorubicin in a cohort of patients prospectively randomized to receive either five or ten cycles of adjuvant cyclophosphamide and doxorubicin. Of the 299 patients in the study, 121 also received RT, and cardiac dose was estimated as low, moderate, or high. In median follow-up of 6.0 years, it was found that the estimated risk of cardiac events for 100 patient-years was significantly higher in patients who had received the 10 cycles of chemotherapy compared with the 5 cycles. In the population of patients who received 10 cycles, the incidence of cardiac events was significantly increased compared with the Framingham Heart Study population in patients who also received moderate and high-dose volume cardiac RT.

Targeted Agents

Trastuzumab (Herceptin, Genentech, San Francisco, CA), a biologic agent that targets the HER2/neu protein, is now standard of care for the 20% of women with cancers that overexpress this cell surface molecule (90,91). Although trastuzumab reduces the risk of relapse by around 50%, this agent has been shown to have cardiotoxic effects in a significant proportion of patients. Specific cardiotoxic effects of trastuzumab include heart failure, cardiomyopathy, and decreases in left ventricular ejection fraction. Although adverse cardiac events are relatively infrequent in patients receiving trastuzumab monotherapy, Phase III trials of trastuzumab and combined chemotherapy have shown a much higher rate of cardiac events. In the NSABP B-31 trial, the cumulative incidence of patients with New York Heart Association Grade III/IV congestive heart failure was 0.8% in the control group, and 4.1% in the trastuzumab group. In the N9831 trial, the incidence of class III/IV congestive heart failure at 3 years was 0% in the control group, and 2.9% in the trastuzumab group (91,92). In a 4-year follow-up of the joint analysis of the B-31 and N9831 trials of trastuzumab and combined chemotherapy for operable breast cancer, adjuvant trastuzumab was found to have consistent survival benefits that outweighed these adverse effects (93).

Since trastuzumab and RT are both potentially cardiotoxic, concerns have arisen that the potentially cardiotoxic effects of RT may be amplified by the sequential or concurrent administration of trastuzumab. However, the data are limited and early studies do report differing results. In a series of patients with advanced breast cancer who received trastuzumab, it was found that 7% of women who received RT to the right side experienced a cardiac event, compared with 26% of women who received RT to the left side (94). In another study of trastuzumab with RT in the N9831 trial, Halyard et al. (95) found that concurrent

administration of RT and trastuzumab was not associated with increased cardiac events. At a median follow-up of 3.7 years, RT with trastuzumab did not increase cardiac events, regardless of the treatment side. The cumulative incidence of cardiac events was 2.7% with trastuzumab and combined chemotherapy, with or without concurrent RT. Although the independent potential cardiotoxic effects of RT and trastuzumab are well documented, further study is clearly needed to confirm any synergistic or additive cardiotoxic effects of trastuzumab and radiotherapy.

MANAGEMENT OF RIHD

Prevention is still the best strategy to manage potential RIHD, with modern radiation equipment and treatment planning with heart-sparing strategies in mind. The clinical manifestations of RIHD vary tremendously and may have a long latency period between treatment completion and disease presentation. Management of radiation-related cardiac toxicity is specific to that disease, and largely follows standard therapy for that particular disease. For example, acute pericarditis may be seen within weeks of treatment completion. The symptoms often resolve quickly without severe sequelae after treatment with nonsteroidal antiinflammatory medications. However, more severe cases leading to cardiac tamponade or recurrent effusions may require more intensive interventions. Radiation-related cardiomyopathy follows standard management of other causes of cardiac failure. In addition, radiation-related coronary artery disease also is managed using standard therapy, with medical management of patient risk factors and percutaneous coronary or surgical bypass intervention, should it be required (3).

SUMMARY AND CONCLUSIONS

Older RT methods used in the adjuvant treatment of women with breast cancer often exposed large volumes of heart to high doses of radiation. As a result, increases in late cardiovascular morbidity and mortality were subsequently observed in women treated with these methods. As these data emerged, the older RT methods were abandoned in favor of techniques that dramatically reduced the volume of heart exposed to high doses of radiation. Consequently, most studies of women treated with modern RT techniques have not shown an increase in late cardiovascular morbidity and mortality. While these studies have been reassuring, concern about the RIHD persists and remains justified in light of cardiac imaging studies that have shown radiographic abnormalities in cardiac perfusion and function shortly after completion of RT, and in view of the frequent use of potentially cardiotoxic systemic agents. Furthermore, although the literature indicates a strong association between dose and volume of cardiac exposure the risk of developing RIHD, the precise dose–response relationship for RIHD has not been defined, and it is unclear if there is a safe threshold for cardiac irradiation. Given the concerns raised by imaging studies and the lack of a clear safe threshold for cardiac irradiation, a wide array of RT techniques have been developed to further reduce incidental cardiac exposure. Until a safe threshold for cardiac irradiation is established, clinicians are advised to use RT techniques that minimize cardiac exposure while maintaining adequate coverage of the tissues at risk for harboring residual microscopic disease and respecting the normal tissue tolerances of other organs at risk in the thoracic region.

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RMR RADIATION MEDICINE ROUNDS

Individualizing Risk of Locoregional Recurrence With Molecular and Genomic Classifiers

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■ ABSTRACT

Gene expression profiling has emerged as a useful tool for assessing risk of distant recurrence in patients with early stage breast cancer and has provided additional prognostic information to that obtained from traditional histopathologic factors and biomarkers. Locoregional recurrence (LRR) is a significant predictor of distant recurrence but despite significant progress in identifying genomic profiles associated with risk of distant recurrence, risk assessment for LRR is still primarily based on traditional anatomic and histopathologic factors. Several studies have evaluated genomic classifiers and molecular subtypes as predictors of risk of LRR in patients with early stage breast cancer. In summary, the above studies suggest that (a) genomic profiling by DNA microarrays can be used in mastectomy patients in order to define low-risk and high-risk patients for LRR but such an association is less pronounced in patients treated with breast-conserving surgery (BCS) plus radiation therapy (XRT); (b) reverse transcription polymerase chain reaction-based gene expression profiling (such as the 21-gene recurrence score) predicts risk of LRR in node-negative, estrogen receptor (ER) positive patients treated with tamoxifen alone or with tamoxifen plus chemotherapy, and the association appears to be more straightforward in mastectomy patients compared with patients treated with BCS plus XRT, suggesting that XRT may be more effective as risk for LRR increases; and (c) studies that categorize tumors according to immunohistochemistry-based subtypes suggest that compared with luminal A subtype, the HER-2 subtype, and the basal-like subtype are associated with significant increase in risk of LRR whether patients are treated with mastectomy or with BCS plus breast XRT. However, compared with luminal A subtype, luminal B subtype is associated with increased risk of LRR primarily in patients treated with mastectomy (without chest wall XRT) and not in those treated with BCS plus XRT, indicating that perhaps the luminal B subtype is more sensitive to XRT than the basal and HER-2 neu subtypes. As genomic profiling becomes integrated in the management of early stage breast cancer, the association between genomic classifiers and risk for LRR may also have important clinical implications. It is envisioned that in the near future, we may be able to use existing or future genomic classifiers in order to make therapeutic recommendations on the optimal locoregional management of patients with early stage breast cancer.

Keywords: locoregional recurrence, genomic profiling

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■ INTRODUCTION

Gene expression profiling has emerged as a useful tool for assessing risk of distant recurrence in patients with early stage breast cancer and has provided additional prognostic information to that obtained from traditional histopathologic factors and biomarkers (1–6). Several gene expression signatures have been reported to predict risk of distant recurrence in both untreated patients and those treated with hormonal therapy and/or chemotherapy (1–7).

Locoregional recurrence (LRR) is a significant predictor of distant recurrence (8–10). All types of LRR (ipsilateral breast tumor recurrence, chest wall recurrence, and regional nodal recurrence) have been associated with a significant increase in risk for subsequent distant recurrence, although the magnitude of risk varies depending on the type of LRR (8,10).

Despite significant progress in identifying genomic profiles associated with risk of distant recurrence, risk assessment for LRR is still primarily based on traditional anatomic and histopathologic factors (such as tumor size, grade, pathologic nodal status, and presence of lymphovascular invasion). Given the strong association between LRR and distant recurrence, several investigators have hypothesized that genomic profiles that predict risk of distant recurrence will also predict risk of LRR (11–13).

■ REVIEW OF THE LITERATURE

Cheng et al. (13) first reported on the association between gene expression profiles and LRR in 94 breast cancer patients who underwent mastectomy without radiotherapy between 1990 and 2001 and had DNA microarray study on the primary tumor. The cohort of patients was randomly split into training and validation sets. Statistical classification tree analysis and proportional hazards models were developed to identify and validate gene expression profiles that related to LRR. Two sets of gene expression profiles were identified (one with 258 genes and the other 34 genes) that were significant predictors of LRR. The overall accuracy of the prediction tree model in the validation sets was estimated to be 75% to 78%. In the validation data set, the 3-year local recurrence (LR) control rate derived from the 34-gene prediction model was 91%, in the low-risk group and 40% in the high-risk group ($P = .008$, Figure 1).

Multivariate analysis of all patients revealed that the estrogen receptor (ER) and the genomic predictive index were independent prognostic factors of LR control. The authors concluded that using gene expression profiles effectively identifies breast cancer patients who are at high versus low risk for LRR and that this gene expression-based predictive index can be used to select patients for postmastectomy radiotherapy.

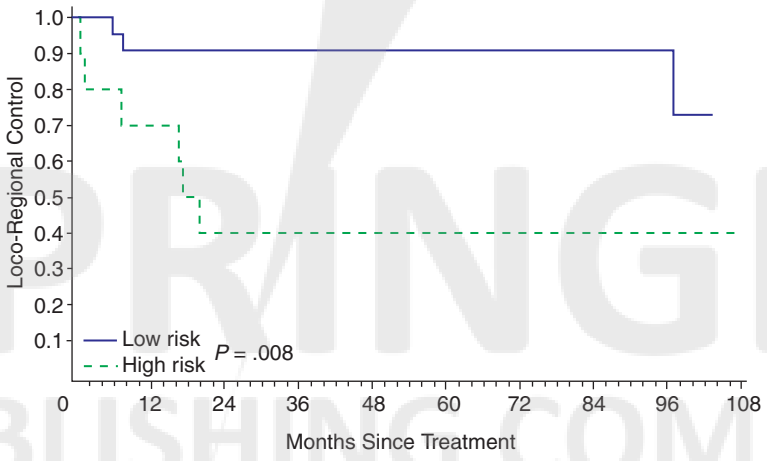

FIGURE 1 Kaplan–Meier survival estimates for locoregional control in validation data set by the 34-gene prediction tree model. Blue line indicates patients with the predictive index more than 0.8; green lines indicates patients with the predictive index 0.8 or lower. The differences between these two subgroups from both prediction models are statistically significant.
Source: Adapted from Ref. (13).

Mamounas et al. (14) evaluated the association between the 21-gene recurrence score (RS) in node-negative, ER-positive breast cancer patients from two National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials (B-14 and B-20) in patients treated with no adjuvant therapy, tamoxifen and tamoxifen plus chemotherapy. The primary objective of the study was to examine the relationship between the RS and risk of LRR in tamoxifen-treated patients (from NSABP B-14 and B-20). Secondary objectives included the evaluation of the relationship between RS and LRR in placebo-treated patients (from NSABP B-14) and in chemotherapy plus tamoxifen-treated patients (from NSABP B-20). Since patients with ER-positive breast cancer are currently treated with hormonal therapy with or without chemotherapy, we will limit our discussion of the study findings to those from patients treated with tamoxifen or with tamoxifen plus chemotherapy. In 895 evaluable patients treated with tamoxifen, the 21-gene RS was significantly associated with risk of LRR (log-rank test *P*-value < .001). The 10-year K–M estimates of the proportion of patients with LRR were 4.3% for patients with low RS, 7.2% for those with intermediate RS, and 15.8% for those with high RS (Figure 2).

Similarly, in 424 evaluable patients treated with chemotherapy plus tamoxifen from B-20, the 21-gene RS was significantly associated with LRR (log-rank *P*-value = .028). The 10-year K–M estimates of the proportion of patients with LRR were 1.6% for patients with low RS, 2.7% for those with intermediate RS, and 7.8% for those with high RS (Figure 3).

Although the above data suggest that the risk of LRR appears to be reduced with chemotherapy across all RS categories, the number of events was too small for formal statistical comparisons. Of interest, however, is the observation that even in chemotherapy plus tamoxifen-treated patients there was still a 5-fold increase in LRR between patients with low versus high RS.

The results of this study further suggested that in tamoxifen-treated patients who underwent mastectomy the association between the 21-gene RS and LRR was straightforward and independent of age (Figure 4). Patients with low RS had very low 10-year rates of LRR whether they were <50 years of age (1.5%) or >50 years (2.6%). Similarly, patients with high RS had a significant risk for LRR (10-year rates of 23.8% for patients <50 years and 12.8% for those >50 years). On the other hand, the association between the 21-gene RS and LRR was less straightforward in patients treated with lumpectomy plus breast radiation (L+XRT), where patients <50 years with a low RS had still a 12.5% 10-year rate of LRR (mostly in-breast recurrences) versus 27.7% for patients with an intermediate RS and 26.5% for those with a high RS (*P* = .001). For L+XRT patients over 50, there was no significant association between the 21-gene RS and LRR (10-year rate of LRR: 3.6% for patients with low RS, vs. 3.7% for those with intermediate RS and vs. 4.7% for those with high RS [*P* = .67]). One possible explanation for the apparent different patterns of association between RS and LRR in mastectomy versus L+XRT-treated patients may be that the effect of XRT is not uniform across RS categories but that XRT may be more effective as RS increases (Figure 4).

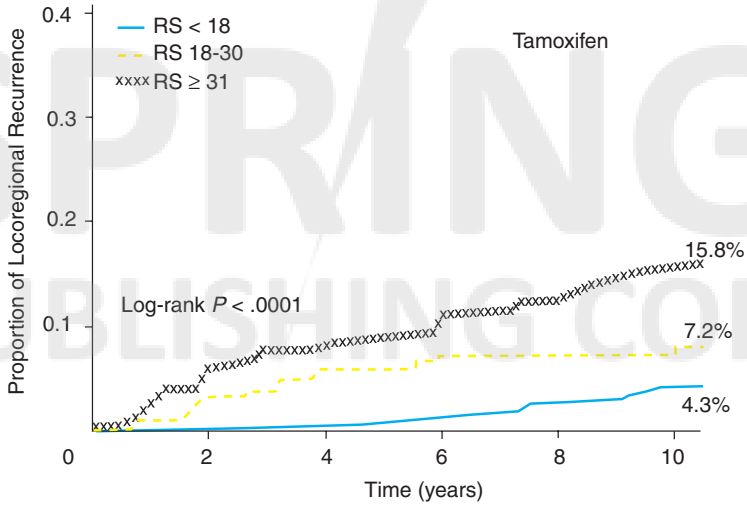

FIGURE 2 Cumulative incidence of LRR according to RS in patients from NSABP B-14 and B-20 treated with tamoxifen. *Source:* Adapted from Ref. (14).

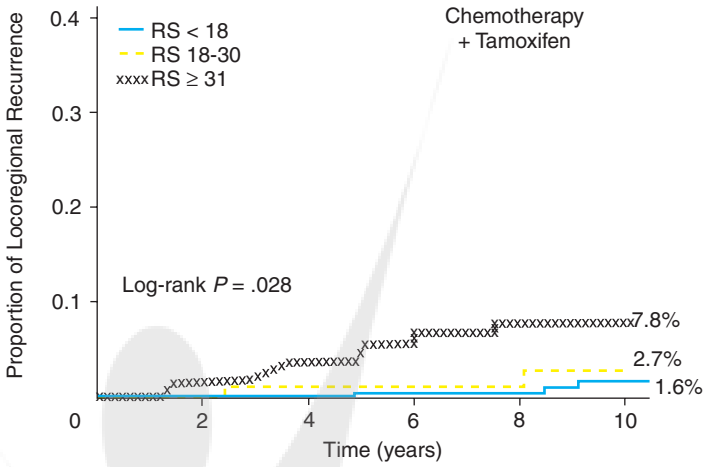

FIGURE 3 Cumulative incidence of LRR according to RS in patients from NSABP B-20 treated with tamoxifen plus chemotherapy.
Source: Adapted from Ref. (14).

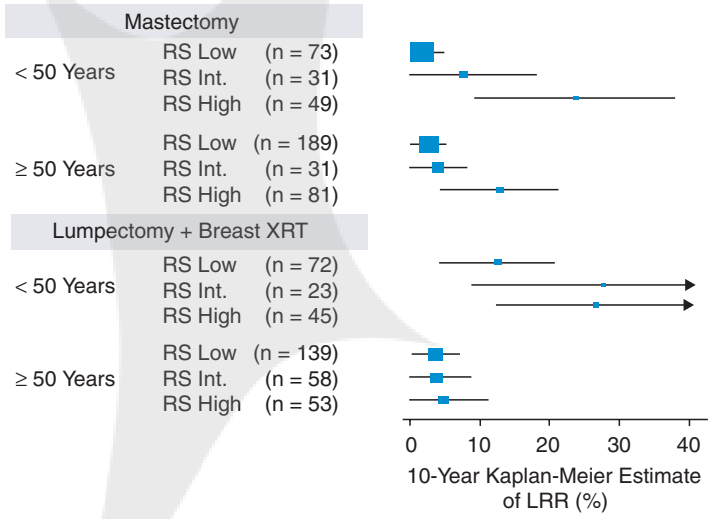

FIGURE 4 Ten-year Kaplan–Meier estimates of the proportion of LRR according to RS, initial locoregional treatment, and age in the 895 tamoxifen-treated patients in NSABP B-14/B-20 trials.
Source: Adapted from Ref. (14).

Nuyten et al. (12) evaluated microarray-based gene expression profiles with proven value in predicting metastasis-free and overall survival (wound–response signature, 70-gene prognosis profile, and hypoxia-induced profile) as predictors of LRR in patients treated with breast-conserving surgery (BCS) plus radiotherapy. Only the wound–response signature (after gene set enrichment analysis) independently separated patients at high (29%) versus low (5%) risk of LRR at 10 years. Although these findings indicate that gene expression profiling can identify subgroups of patients at increased risk of developing LRR after breast-conserving therapy, the association does not appear to be as straightforward as in previous studies of patients treated with mastectomy where no XRT was used.

Nguyen et al. (15) evaluated whether breast cancer subtype determined by immunohistochemistry (IHC) is associated with LRR after lumpectomy and radiation therapy. They studied 793 consecutive patients with invasive breast cancer. Receptor status was used to approximate subtype: ER or progesterone receptor (PR) positive and human epidermal growth factor receptor 2 (HER-2) negative = luminal A; ER+ or PR+ and HER-2+ = luminal B; ER– and PR– and HER-2+ = HER-2; and ER– and PR– and HER-2– = basal. With median follow-up of 70 months, the 5-year cumulative incidence of LR was 0.8% for luminal A, 1.5% for luminal B, 8.4% for HER-2, and 7.1% for basal (Figure 5).

On multivariate analysis with luminal A as baseline, HER-2 (adjusted hazard ratio [AHR] = 9.2,

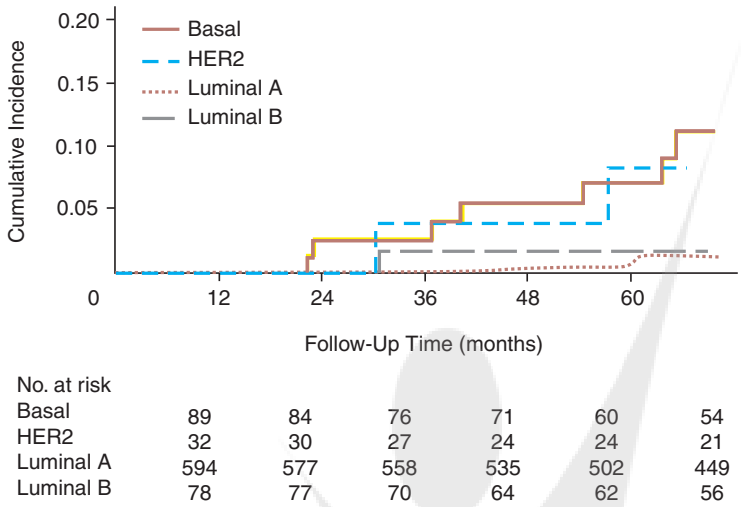

FIGURE 5 Cumulative incidence of LRR according to breast cancer subtype in patients treated with BCS and breast XRT.
Source: Adapted from Ref. (15).

$P = .012$) and basal (AHR = 7.1, $P = .009$) subtypes were associated with increased risk of LR. On multivariate analysis, luminal B (AHR = 2.9, $P = .007$) and basal (AHR = 2.3, $P = .035$) were associated with increased risk of distant metastases. The findings of this study are interesting as they suggest that although luminal B patients were at increased risk of distant recurrence compared with luminal A, there were no significant differences in the risk of LRR. The increased benefit from breast XRT in the luminal B subtype may be one of the reasons for this observation.

Alvord et al. (16) from the same group of investigators as above recently examined the effect of age and breast cancer subtype on LRR in 1,434 consecutive patients with invasive breast cancer who received BCS plus breast XRT. Ninety-one percent received adjuvant systemic therapy but no patients received trastuzumab. Five breast cancer subtypes were approximated: ER or PR positive, HER-2 negative, and Grades 1 to 2 (luminal A); ER positive or PR positive, HER-2 negative, and Grade 3 (luminal B); ER or PR positive, and HER-2 positive (luminal HER-2); ER negative, PR negative, and HER-2 positive (HER-2); and ER negative, PR negative, and HER-2 negative (triple negative). Median follow-up was 85 months. The 5-year cumulative incidence of LR was 5.0% for age quartile 23 to 46 years; 2.2% for ages 47 to 54 years; 0.9% for ages 55 to 63 years; and 0.6% for ages 64 to 88 years (Figure 6 [left]).

The 5-year cumulative incidence of LR was 0.8% for luminal A; 2.3% for luminal B; 1.1% for luminal HER-2; 10.8% for HER-2; and 6.7% for triple negative (Figure 6 [right]). On multivariate analysis, increasing age was associated with decreased risk of LR (AHR, 0.97; 95% CI, 0.94–0.99; $P = .009$). Based on these findings, they concluded that in the era of systemic therapy and breast cancer subtyping, age remains an independent prognostic factor after BCT. However, the risk of LR for young women appears acceptably low. These data further support the observation that for patients treated with BCS plus breast XRT, the incidence of LRR was similar in luminal A, luminal B, and luminal HER-2 patients and considerably higher for those with HER-2 positive and triple-negative tumors.

In a similar study, Millar et al. (17) attempted to determine the clinical utility of intrinsic molecular phenotypes in predicting LRR following BCS and whole-breast XRT with or without a cavity boost. They included 498 patients with invasive breast cancer who were enrolled into a randomized trial of BCS with or without a tumor bed XRT boost. Tumors were classified by intrinsic molecular phenotype as luminal A or B, HER-2, basal-like, or unclassified using a five-biomarker panel: ER, PR, HER-2, CK5/6, and epidermal growth factor receptor (EGFR). A total of 394 patients were classified as luminal A, 23 were luminal B, 52 were basal, 13 were HER-2, and 16 were unclassified. With a median follow-up of 84 months, the 10-year rate of LRR was 4.8% for luminal A tumors, 8.6% for luminal B tumors, 17.3% for basal tumors, and 15.3% for HER-2 positive tumors ($P = .012$, Figure 7). These findings confirm that the basal and the HER-2 subtypes are associated with the highest risk for LRR following BCS plus beast irradiation. On the other hand, there are small differences in LRR between the luminal B and the luminal A subtypes, possibly reflecting a larger effect of breast XRT in luminal B tumors.

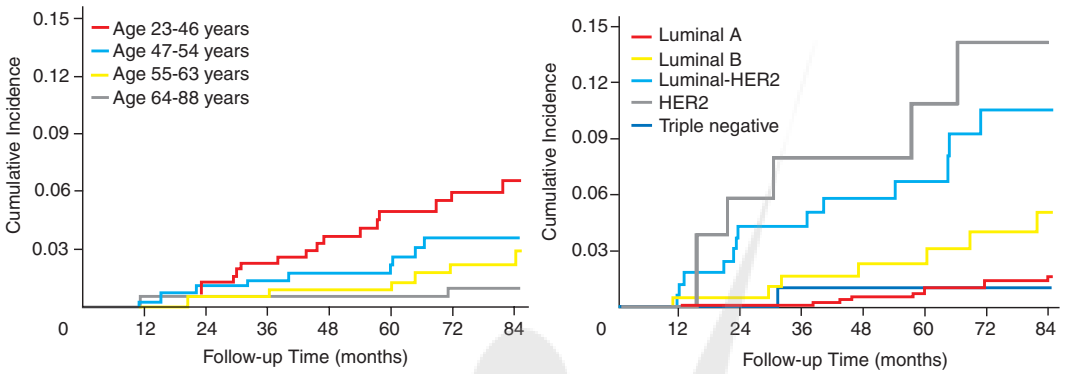

FIGURE 6 Unadjusted cumulative incidence of LR by age quartile (left) and by breast cancer subtype (right) on the basis of competing risks analysis; HER-2, human epidermal growth factor receptor 2.
Source: Adapted from Ref. (16).

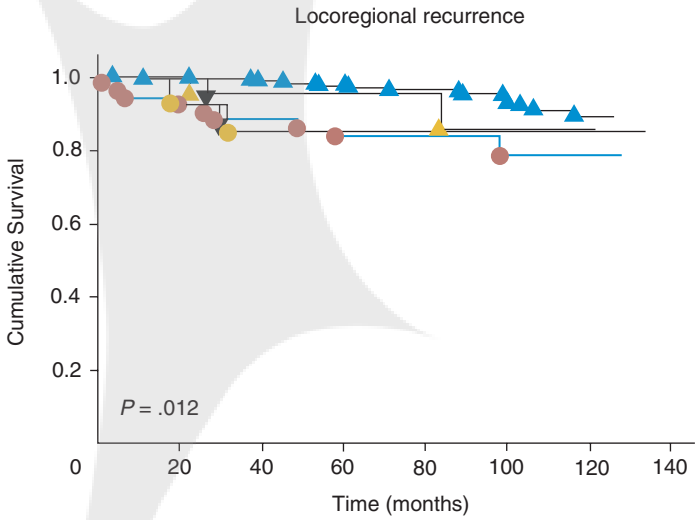

FIGURE 7 Kaplan–Meier estimates (log-rank test) for LRR according to intrinsic molecular subtype. Luminal A (blue triangle; *n* = 394), luminal B (yellow triangle; *n* = 23), basal (red circle; *n* = 52), HER-2 (yellow circle; *n* = 13), and unclassified (black triangle; *n* =16).
Source: Adapted from Ref. (17).

Finally, similar observations were made more recently by Voduc et al. (18). They evaluated the risk of LRR associated with each breast cancer molecular subtype in a large cohort of patients with breast cancer. Subtype assignment was accomplished using a validated six-marker IHC panel (ER, PR, Ki-67, HER-2, EGFR, and cytokeratin [CK] 5/6) was performed on tissue microarrays constructed from 2,985 patients with early invasive breast cancer. Patients were classified into the following categories: luminal A, luminal B, luminal HER-2, HER-2 enriched, basal-like, or triple-negative phenotype-nonbasal. Multivariable Cox analysis was used to determine the risk of local or regional relapse associated the intrinsic subtypes, adjusting for standard clinicopathologic factors. With median follow-up of 12 years, luminal A tumors (ER or PR positive, HER-2 negative, Ki-67 < 1%) had the best prognosis and the lowest rate of local or regional relapse.

For patients undergoing breast conservation, HER-2-enriched and basal subtypes demonstrated an increased risk of regional recurrence, and this was statistically significant on multivariable analysis. After mastectomy, luminal B, luminal HER-2, HER-2-enriched, and basal subtypes were all associated with an increased risk of local and regional relapse on multivariable analysis. Based on these findings, the authors concluded that luminal A tumors are associated with a low risk of local or regional recurrence and that molecular subtyping of breast tumors using a six-marker IHC panel can identify patients at increased risk of local and regional recurrence. It is

of interest that this study also showed that compared with luminal A, luminal B tumors have increased risk of LRR in mastectomy-treated patients but not in patients treated with BCS and breast XRT. These results are supportive of the observations made in other studies as outlined above.

In summary, the above studies suggest the following:

1. Genomic profiling by DNA microarrays can be used in mastectomy patients in order to define low-risk and high-risk patients for LRR. In separate studies, such an association was less pronounced in patients treated with BCS plus XRT.
2. The 21-gene RS (based on reverse transcription polymerase chain reaction) predicts risk of LRR in node-negative, ER-positive patients treated with tamoxifen alone or with tamoxifen plus chemotherapy but the association appears to be more straightforward in mastectomy patients than in patients treated with BCS plus XRT, suggesting that XRT may be more effective as risk for LRR increases.
3. Studies that evaluate patients according to IHC-based breast cancer subtypes suggest that compared with luminal A subtype, the HER-2 subtype and the basal-like subtype are associated with significant increase in risk of LRR whether patients are treated with mastectomy or with BCS plus breast XRT. However, compared with luminal A subtype, luminal B subtype is associated with increased risk of LRR only in patients treated with mastectomy (without chest wall XRT) but not in those treated with BCS plus XRT indicating that perhaps the luminal B subtype is more sensitive to XRT than the basal and HER-2 neu subtypes.

■ DISCUSSION

A major limitation of most of the above studies (which are not based on data from randomized clinical trials) is that adjuvant systemic therapy was left at the discretion of the treating physician and it was not uniform. Thus, the effect of systemic therapy on LRR cannot be controlled in these studies unless patients are treated uniformly as part of a randomized clinical trial. Also, although some of the above reported studies included only patients with negative nodes, others included both node-negative and node-positive patients. This reduces the impact of some of the above observations on the clinical management of patients and makes it difficult to incorporate the results from genomic profiling into everyday clinical practice.

Another important limitation in most of the existing studies is that for node-positive patients, the use of chest wall XRT after mastectomy and regional nodal XRT after BCS or mastectomy is left at the discretion of the treating physician. This is true not only for studies that report on cohorts of patients from nonrandomized studies but also for some of the studies that report on randomized clinical trial data.

Although most studies suggest that following BCS plus XRT, the LRR rate for the basal subtype is higher than that for the luminal A and B subtypes and similar to the HER-2 subtype, two studies have shown no differences in the risk of LRR between triple-negative and nontriple-negative subtypes (19,20). Haffty et al. (19) sought to determine the prognostic significance of triple-negative breast cancers with respect to LRR and distant metastasis in conservatively managed breast cancer patients. Of 482 patients with all three markers available (ER/PR/HER-2 neu), 117 were classified as triple negative. Although at 5 years, the triple-negative cohort had a poorer distant metastasis-free rate compared with the other subtypes (67% vs. 82%, respectively; $P = .002$), there was no significant difference in local control between the triple negative and other subtypes (83% vs. 83%, respectively) (Figure 8).

Similarly, Dent et al. (20) compared the clinical features, natural history, and outcomes for women with triple-negative breast cancer with those of women with other types of breast cancer in a cohort of 1,601 patients with breast cancer diagnosed between 01/87 and 12/97. One hundred

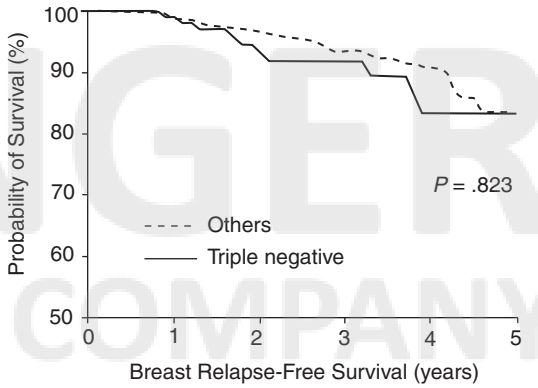

FIGURE 8 Breast relapse-free survival as a function of subtype.
Source: Adapted from Ref. (19).

patients (11.2%) had triple-negative breast cancer, and median follow-up was 8.1 years. Although compared with other women with breast cancer, women with triple-negative breast cancer had an increased likelihood of distant recurrence (hazard ratio [HR]: 2.6; $P < .0001$) and death (HR: 3.2; 2.3–4.5; $P < .001$) within 5 years of diagnosis, LR rates were similar between the two groups (13% for triple negative vs. 12% for other).

Effect of Postmastectomy XRT

From the above-described studies, it is evident that for patients treated with mastectomy without chest wall XRT, patients with luminal A subtype or those with low 21-gene RS have very low rates of LRR (14,15,18). On the other hand, patients with luminal B tumors or those with high 21-gene RS have high rates of LRR which sometimes approximate those of basal and HER-2 subtypes. This increased risk for LRR is not observed for luminal B tumors or for those who have high RS if they are treated with BCS plus breast XRT but it is still observed for the basal and HER-2 subtypes even when treated with BCS plus XRT. This potentially indicates that luminal B tumors or those with high 21-gene RS are quite sensitive to XRT and that basal and HER-2 subtypes may be less sensitive. These observations lead to the question of whether similar associations exist in patients who are treated with mastectomy followed by chest wall XRT. Kyndi et al. recently addressed this question indirectly when they studied the importance of ER, progesterone receptor (PgR), and HER-2 by constructing subtypes in a large study randomly assigning patients to receive or not receive postmastectomy XRT (21). This analysis included 1,000 of the 3,083 high-risk breast cancer patients randomly assigned to postmastectomy XRT in the Danish Breast Cancer Cooperative Group protocol 82 trials b and c. Tissue microarray sections were stained for ER, PgR, and HER-2. Median follow-up time for patients alive was 17 years. Comparing HRs and 95% CIs, significantly smaller improvements in LRR control after postmastectomy XRT were found for ER-negative and PgR-negative tumors compared with the ER-positive and PgR-positive tumors ($P = .003$ and .04, respectively), and for the triple negative ($P = .02$), and the hormonal receptor-negative/HER-2 positive subtypes ($P = .003$) compared with the hormonal receptor-positive/HER-2 negative subtype (Figure 9).

Furthermore, a significantly improved overall survival after postmastectomy XRT was seen only among patients characterized by good prognostic markers such as hormonal receptor-positive and HER-2-negative patients. No significant overall survival improvement after postmastectomy XRT was found among patients with a priori poor prognosis, the hormonal receptor-negative and HER-2-positive patients, and in particular the hormonal receptor-negative/HER-2-positive subtype (Figure 10).

Based on these findings, the authors concluded that hormonal receptor status, HER-2, and the constructed subtypes may be predictive of LRR and survival after postmastectomy XRT. These findings are in agreement with the observations from studies of molecular subtypes and LRR in patients treated with BCS plus XRT and indicate potentially higher sensitivity of the high-risk ER-positive tumors to XRT.

■ FUTURE DIRECTIONS

One of the remaining critical locoregional therapy questions in breast cancer relates to the use of postmastectomy XRT (or regional nodal XRT after lumpectomy) in patients with one to three positive nodes. Despite data showing a survival improvement with the addition of postmastectomy XRT in node-positive patients (22–24) (including those with one to three nodes), this approach has not been uniformly accepted and in most clinical trials where this decision is left at the discretion of the treating physician, about 50% of patients with one to three positive nodes receive postmastectomy XRT (or regional nodal XRT after lumpectomy). Also, although postmastectomy XRT is recommended for all patients with >4 positive nodes, it is conceivable that there may be favorable subsets of such patients at low risk for LRR in which postmastectomy XRT can be withheld.

More recently, benefit from adding regional nodal XRT to breast XRT was also demonstrated by Whelan et al. (25) based on the results from the NCIC MA.20 trial. That trial randomized patients with one to three positive nodes (or high-risk node-negative), who were treated with BCS to receive either breast XRT or breast and regional nodal XRT. The results showed a significant improvement in LRR-free survival, disease-free survival, and distant disease-free survival in favor of the group randomized to receive regional nodal XRT. There was also a nonsignificant trend toward improvement in overall survival with the addition of regional nodal XRT. These results will probably expand the use of regional nodal XRT

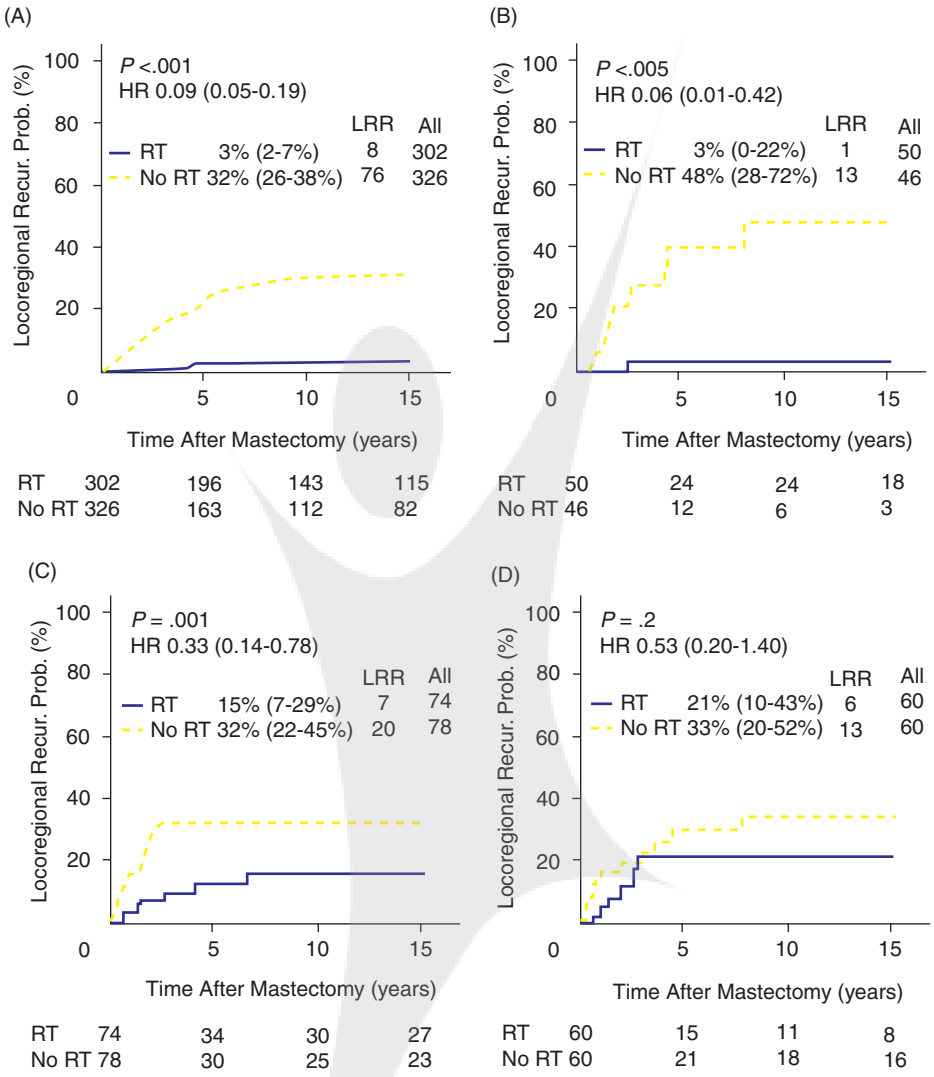

FIGURE 9 Kaplan–Meier probability plots of LRR probabilities in high-risk breast cancer patients as a function of randomization to postmastectomy radiotherapy (RT) within the four different subtypes: (A) Hormone receptor negative/HER-2 negative. (B) Hormone receptor negative/HER-2 positive. (C) Triple negative. (D) Hormone receptor negative/HER-2 positive. Ninety five percent CIs are presented for HRs.
Source: Adapted from Ref. (21).

in patients with one to three positive nodes treated with BCS plus breast XRT. Thus, it is also important to identify subsets of those patients for which rates of regional nodal recurrence are low with breast XRT only and in which the addition of regional nodal XRT can be omitted.

The data on the independent association between genomic classifiers and risk of distant recurrence in node-positive patients (6,26–28) coupled with the data on the association between genomic classifiers and risk of LRR in node-negative and node-positive patients (treated with hormonal therapy alone or with chemotherapy plus hormonal therapy) are supportive of the hypothesis that an association between genomic classifiers and risk of LRR will also exist in node-positive patients treated with adjuvant chemotherapy. If this is the case, it is possible that we can use these genomic classifiers in order to make therapeutic decisions on locoregional treatment of node-positive patients (i.e., whether or not to add postmastectomy XRT or post

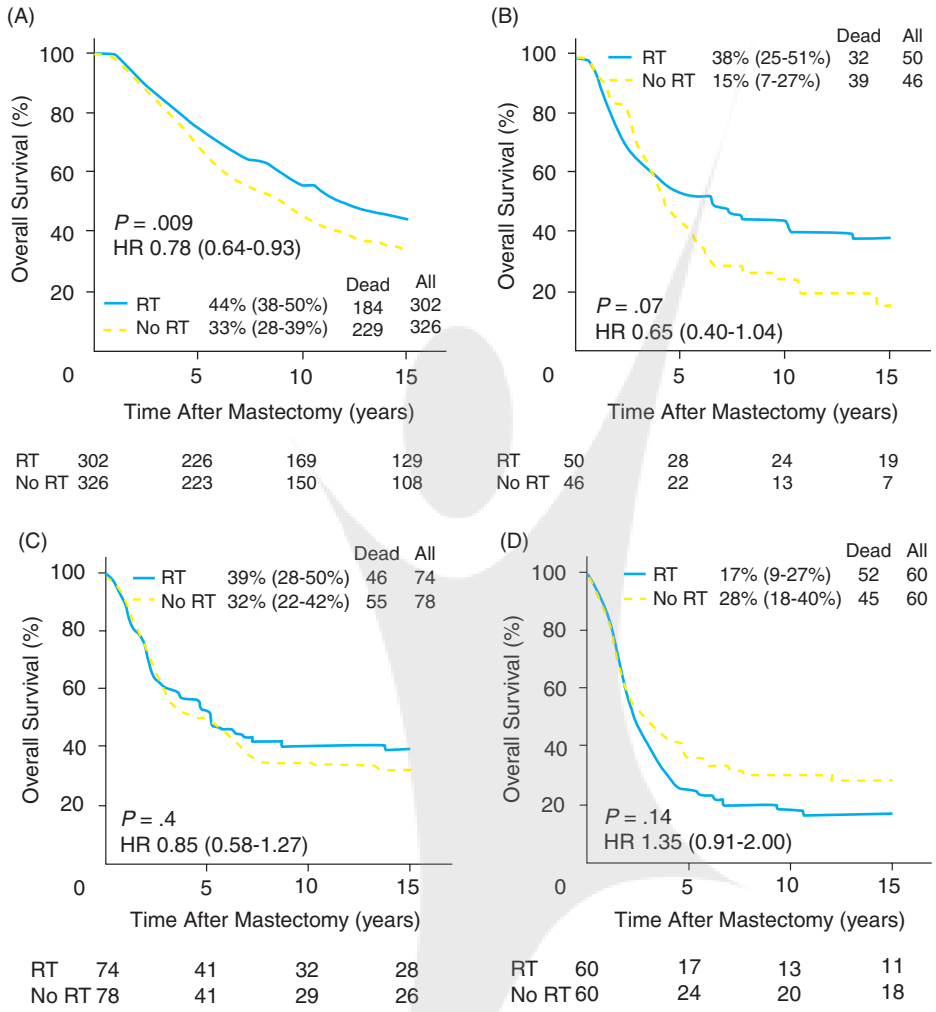

FIGURE 10 Kaplan–Meier probability plots of overall survival probabilities in high-risk breast cancer patients as a function of randomization to postmastectomy radiotherapy (RT) within the four different subtypes: (A) Hormone receptor negative/HER-2 negative. (B) Hormone receptor negative/HER-2 positive. (C) Triple negative. (D) Hormone-receptor negative/HER-2 positive. Ninety-five percent CIs are presented for HRs and 15-year survival probabilities.
Source: Adapted from Ref. (21).

BCT regional nodal XRT) in subgroups of patients with 1 to 3 positive nodes or whether or not to withhold it in subgroups of those with >4 positive nodes.

■ CONCLUSIONS

As genomic profiling becomes integrated in the management of certain subtypes of breast cancer, the association between genomic classifiers and risk for LRR becomes one with important potential clinical implications. As we currently use genomic classifiers in order to decide on appropriate systemic therapy, it is envisioned that in the near future we can also use existing or future genomic classifiers in order to make therapeutic recommendations on the optimal locoregional management of the disease.

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Current and Future State of Breast Radiation Therapy

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■ ABSTRACT

Radiotherapy is frequently used in the treatment of breast cancer. In this chapter, the role of radiation against breast cancer is discussed based on not only patient's pathologic factors, but also side effects and techniques. Where there is a tendency for less treatment in conservatively treated patients, for instance, with partial breast irradiation in low-risk patients, but in mastectomy patients, there is a tendency to extend radiotherapy indications to the intermediate risk group. In neoadjuvant chemotherapy treatment, the absolute indications for radiation have become less clear. Distinctive lymph node areas and radiotherapy indications have been commented as well as the development and more common use of hypofractionation in breast cancer.
Keywords: breast cancer, radiotherapy, indications, hypofractionation, side effects, radiation techniques

■ INTRODUCTION

Breast cancer is the most frequent form of tumor occurring among women in the Western World. In today's clinical practice, radiotherapy is given for curative or palliative intent in the majority of breast cancer patients. For curative intent, radiotherapy is usually given in combination with surgery and systemic therapy (hormonal therapy, chemotherapy, and immunotherapy). In this chapter, we discuss the present and future role of radiotherapy in the treatment of breast cancer.

■ LOCAL CONTROL AND OVERALL SURVIVAL

Radiotherapy reduces local recurrence (LR) rates in breast cancer treatment by 60% to 70% in all patients (1). This relative reduction appears to be independent of patient, histologic, and treatment factors. The initial risk on LR in patients varies; therefore, the absolute benefit of radiotherapy should be taken into account in clinical decision making. Radiation is given to the whole breast after following the breast-conserving therapy (BCT). In the case of radical surgery, radiotherapy is given in the case of risk factors

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(positive lymph nodes, tumor size, etc.). It has long been thought that radiation only improved local control. In the late 90s, publications showing overall survival benefit in irradiated patients appeared. Meta-analysis of randomized clinical trials with 15 years of follow-up showed that one breast cancer death is avoided for every four LRs prevented in the first years (1). It is assumed based on this analysis that radiotherapy is expected to improve survival in subgroups, where the absolute risk reduction for LR is ≥10% (Figure 1). The demonstrated improvement of overall survival has led to adaptation of the radiotherapy indications, especially after radical surgery, as discussed later.

■ BREAST-CONSERVING THERAPY

Multiple prospective randomized trials with over 20 years of follow-up have confirmed the equivalence of lumpectomy and whole-breast irradiation (i.e., BCT) to modified radical mastectomy with respect to overall survival. Many risk factors for LR are known: young age is an important factor (2–6). Particularly, patients below 35 years are at high risk for LR. In these patients, 10-year LR rates of 30% or higher are reported (2,4). Other risk factors for local relapse are high-grade tumors, lymph-angiovascular invasion (which, however, is not so predominant as after radical surgery), and positive resection margins of the excision. In several older studies (2,7), extensive intraductal component is found to be a risk factor for LR, but is shown to lose its predictive value for an LR after radical resection (7,8). When an additional boost of 10 to 16 Gy is employed to whole-breast irradiation, LR is reduced with a relative risk reduction of about 50%, as shown in the results of the 10-year randomized Boost versus no Boost European Organization for Research and Treatment of Cancer (EORTC) trial (6). A boost dose, however, has an impact on impaired cosmetic outcome (9). The individual decision on adding a boost should be taken by assessing the risk of impaired cosmesis versus the individual risk for LR. Also, the addition of systemic therapy should be taken into account as this reduces a patient's local relapse risk by 50%. Nomograms were developed for both estimating the chance on fibrosis and LR after a boost dose of 16 Gy (10,11). Over the years, significant improvement of local control after BCT was observed in several studies; nowadays, an LR rate of 0.5% per year or less is reported. This improvement in local control is also observed in high-risk young women, as is shown in Figure 2. In this figure, local control results are shown for patients from three large prospective randomized trials: (a) the BCT arm from the early EORTC 10801 study (12) mastectomy versus BCT; (b) the boost arm of patients of 50 years of age or less from the boost–no boost study (6); and (c) the recently closed Young Boost trial, which randomized patients of ≤50 years after BCT and 50 Gy whole-breast irradiation between low (16 Gy) and high boost (26 Gy). It is shown that, over the years, local control in high-risk young patients is largely improved. Most likely, this is the result of better standards for surgery and radiotherapy as well as the additive effect of adjuvant chemotherapy. Besides classical patient and histopathologic factors, more recently, gene expression profiling studies have identified prognostic gene expression profiles to predict outcome in breast cancer patients (13,14). There are also several studies that have attempted to identify a gene expression profile that is predictive for LR (15–17). Although interesting results have been found, clinical risk assessment

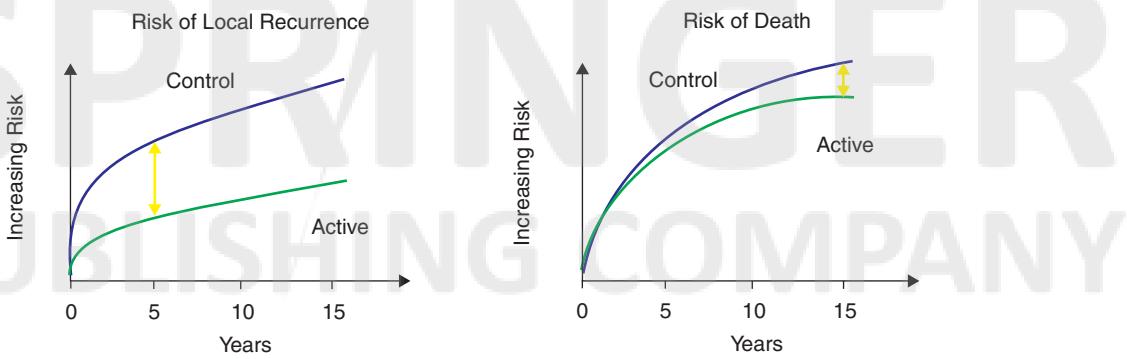

FIGURE 1 Effect of a reduction in the 5-year risk of LR on breast-cancer mortality at 15 years.
Source: Adapted from Punglia et al. *N Engl J Med.* 2007;356(23):2399–2405. With permission.

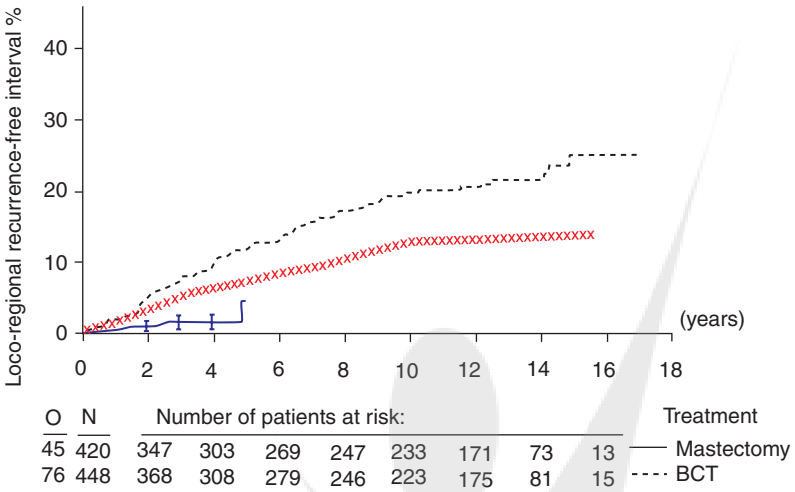

FIGURE 2 LR rate in prospective randomized trials from 1980 to 2011. Black dashed line, BCT arm of the BCT–mastectomy trial; red cross-hatched line, boost arm patients <50 years from the Boost versus no Boost trial; blue line, Young Boost trial.

for LR is still primary and is based on traditional clinical and histopathologic factors.

■ PARTIAL BREAST IRRADIATION

The rationale for partial breast irradiation (PBI) is that 70% to 80% of the LRs after BCT is present at the original tumor bed; therefore, in PBI, only the tumor bed is irradiated. Benefit of PBI is less irradiation to the breast tissue and the surrounding organs, such as lung and heart. Also, because a limited volume is irradiated, hypofractionation is used, resulting in a treatment period of single fractionation to 1 to 2 weeks, instead of conventional 3 to 6 weeks of radiation. After surgery, because of lack of anatomical boundaries in the breast, it is difficult to define the target area for radiotherapy, as is shown in several delineation studies (18); however, the placement of surgical clips has improved the accuracy of lumpectomy cavity delineation in three-dimensional APBI (19). Because of the difficulty defining the target area in postoperative setting, PBI is mostly performed with invasive techniques during the tumorectomy procedure, such as brachytherapy and intraoperative applicators. The results of PBI using various methods published so far are very satisfying, resulting in very good local control rates and good cosmesis. Vicini et al. (20) published the largest series using brachytherapy with the longest follow-up and good local control (3.8% local relapses in 10 years). Also, some randomized trials have been published (21,22). Polgar et al. randomized patients between brachytherapy PBI and whole-breast irradiation; in 5 years, nonsignificant local relapse rates were found as 4.7% versus 3.4%. Also, the ELIOT series (23,24) from Milan have shown low relapses of 2.1% in the low-risk group (according to the American Society of Therapeutic Radiology and Oncology [ASTRO] guidelines, see further). Many randomized trials are being run at present, including trials using external beam irradiation. Recently, the Targit randomized trial is published, where whole-breast irradiation is compared with intraoperative PBI. At a median follow-up period of 2 years, 0.9% and 1.2% local relapses were found. It should be noted that in this study, apart from the short follow-up time, numerous low-risk patients were included (median age 63 years, 90% estrogen positive, and <2 cm tumor). Also, over 60% of the patients were given hormonal treatment.

The most important issue in PBI is patient selection. ASTRO has developed a consensus statement, addressing patient selection criteria and the best practices for the application of PBI outside clinical trials based on the results of a systematic literature and expert opinion (25). Defined suitable patients are patients who are ≥60 years old with tumors ≤2 cm, completely resected, N0, estrogen receptor positive, and no extensive DCIS component.

■ RADIOTHERAPY AFTER MASTECTOMY

After mastectomy, radiotherapy is indicated for high-risk patients (i.e., large tumor size [T3–T4] and ≥4 positive lymph nodes) (1). Whether intermediate risk patients (N1–N3, or N0 associated with risk factors for local relapses as Grade 3 and lymph-angio invasion) should be treated with radiotherapy is controversial.

With the impact shown of adjuvant radiotherapy on overall survival, the discussion of radiotherapy for intermediate risk patient has started a new era. A subgroup analysis of the DBCG 82b&c trials reported a 15-year locoregional failure rate of 27% in a one-to-three positive lymph node group and 51% in a more than four positive lymph node group, for patients who did not receive postmastectomy chest wall and nodal irradiation. Radiotherapy use was associated with the greatest reduction in locoregional recurrence in the ≥4 lymph node group (41%), but was also significant in the 1-to-3 positive lymph node group (23%). The 15-year relative survival benefit was similar (9%) in both groups (26). Locoregional recurrence risks in node-positive patients after mastectomy and systemic therapies without radiotherapy are no longer as high as those reported by the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) data. Better attention to surgical technique in the axilla and widespread adoption of anthracyclines, taxanes, trastuzumab, and hormonal therapy are responsible for substantial reduction in LRs (27,28). On the other hand, the effect of radiotherapy on overall survival was neutralized by excessive deaths from radiation-induced cardiovascular problems from the earlier series. With new radiation techniques allowing avoidance of irradiation of (part of) the heart (see later), the effect of radiotherapy on overall survival may be greater. Therefore, the selection of patients who benefit from radiation therapy, nowadays, is still a matter of debate.

The ongoing SUPREMO fase III trial (29) is designed to evaluate the results of chest-wall irradiation in mastectomy patients with pT1N0M0 or pT2N0-1M0 breast cancer. These patients are treated according to high standard today's breast cancer care. In this trial also molecular markers will be studied to identify patients at risk for local relapse.

■ CONSEQUENCES OF NEOADJUVANT CHEMOTHERAPY FOR POSTOPERATIVE RADIATION

Neoadjuvant chemotherapy used to be reserved for patients with locally advanced disease. In recent years, an increase in the use of neoadjuvant chemotherapy is also shown for patients with earlier stages of breast cancer; although no studies have been reported that neoadjuvant chemotherapy leads to a superior survival compared with adjuvant chemotherapy (30,31). An advantage of this policy is that neoadjuvant chemotherapy can shrink the tumor volume, allowing for a higher percentage of BCT (31). A disadvantage of neoadjuvant chemotherapy is however that the classical indications for postoperative radiotherapy are based on studies in which where locoregional recurrences were correlated to the pathologic Tumor (T) and Nodal (N) stage in patients who had not been treated with neoadjuvant chemotherapy. Since neoadjuvant chemotherapy is affecting the pathologic T and N stages, the indications for postoperative radiotherapy in these patients have become uncertain.

Buchholz et al. (32) showed that prechemotherapy clinical and postchemotherapy factors influence the individual locoregional recurrence rate independently. Therefore, for radiotherapy indications, the cTNM and the ypTNM (TNM after chemotherapy and operation) are of importance. In a study of 542 patients treated with prospective neoadjuvant chemotherapy trials, followed by mastectomy without irradiation (33), it was shown that radiotherapy positively influenced the LR rate in cT3–T4 tumors, Stage IIB tumors (T2N1, T3N0), and pathologic residual disease >2 cm. Garg et al. (34) showed that patients treated with cT3, ypT3, or ypN2–3 had a very high risk for local relapse, while patients with one to three positive nodes after chemotherapy had an intermediate risk for LR. In these series, patient's age of under 40 was also found to be a risk factor. The role of radiotherapy after neoadjuvant chemotherapy and conservative or radical surgery for high-risk patients as cT3–T4; ypT3–T4 and cN2–N3; and ypN2–N3 is clear; independent of pathologic response (including complete response), these patients need to be irradiated (33–35). McGuire (35) also showed that besides improvement in local control, postoperative radiotherapy was associated with improved disease-free and overall survival in Stage III patients, achieving complete pathologic response.

The problem for radiotherapy indications arises for the cT1–2N1 tumors treated with neoadjuvant chemotherapy. In principle, the same indications are applied for radiotherapy without neoadjuvant chemotherapy. However, well-known risk factors for local relapse as tumor grade, tumor size, and lymph-angio invasion are influenced by neoadjuvant chemotherapy in the final pathologic review. Also, the number of lymph node metastases can be influenced by systemic therapy. The role of pre- or postchemotherapy sentinel nodes is also unclear in this issue. In general, downstaging by neoadjuvant chemotherapy seems not to be associated with better local control (32,33). At this moment, few studies have focused on this issue, resulting in impossibility

to identify all patients who benefit from radiation therapy. Because of this uncertainty, overtreatment as well as undertreatment results in daily practice. In T1–2N1 patients treated with neoadjuvant chemotherapy, it seems to be justifiable to advise radiotherapy to ypN1 patients (36). The role of other clinical and histologic factors in this intermediate risk patient group is unfortunately yet unclear.

■ LYMPH NODE IRRADIATION

Lymph node treatment in breast cancer patients has changed dramatically over the past years. The axilla was used to be operated and used as staging for chemotherapy and radiotherapy indication. After treatment, the axilla local relapses are rare, mostly presenting in the first few years after treatment (37). In this study of Louis-Sylvestre, 658 patients with ≤3 cm N0 breast tumors were treated with axillary dissection or radiation of the axilla; low axillary recurrence rates were found 1% versus 3%, with no differences at 15 years of follow-up. With the present sentinel node procedures, an axillary dissection can be prevented in many patients. In the case of positive sentinel node in T1–2N1 (sn) patients, the AMAROS trial (38) randomized over 4,800 patients between axillary dissection and radiotherapy. No results are available yet, but low axillary recurrence rates were found in both arms, resulting in extension of accrual of number of patients during the study. Recently, the Z-11 study was published (39). In this study, it was found that in patients treated with lumpectomy followed by whole-breast irradiation, there was a low axillary recurrence rate in sentinel node-positive patients without the further treatment of the axilla. It should be stated, however, that all patients were treated with radiation without 3 D-CT planning, but with conventionally simulated breast fields, known to have the axillary levels I -II to be included in the radiation fields in most of the patients. Therefore, these results should be interpreted with caution.

Different indications for postoperative radiotherapy such as ≥4 lymph nodes, nodal ratio ≥50%, and extranodal growth are used widely but have never been studied in randomized trials. If a relapse occurs in the regional lymph nodes, it is mainly a periclavicular recurrence. Therefore, the supra- and infraclavicular regions are usually irradiated in high-risk patients. The internal mammary chain is a distinct area; relapses are found in only 1% of irradiated as well as nonirradiated patients. In meta-analysis (1), showing a survival benefit of radiation, the internal mammary chain was irradiated in 24/25 of the trials. The benefit of internal mammary chain irradiation, so far, is unclear. The risk of internal mammary chain irradiation is, however, widely known, as all possible techniques are associated with substantial dose to the heart and the associated vascular damage. Recently, the French internal mammary chain study was presented (40), where no benefit was shown of overall survival at 8 years of follow-up for irradiated patients. Longer follow-up might change these results, as well as other randomized trials focusing on this issue as the EORTC study 22922/10925. Of interest is the recent presentation of data from Whelan et al. (41), where the addition of regional nodal irradiation to whole-breast irradiation was studied. Women with high-risk node-negative or node-positive breast cancer treated with BCT and adjuvant chemotherapy and/or endocrine therapy were randomized to whole-breast irradiation (50 Gy in 25 fractions with or without boost irradiation) or to whole-breast irradiation plus regional nodal irradiation (45 Gy in 25 fractions) to the internal mammary, supraclavicular, and high axillary lymph nodes. Between the years 2000 and 2007, 1,832 women were randomized. After a median follow-up period of 62 months, additional regional nodal irradiation has reduced the risk of locoregional and distant recurrence and improved disease-free survival with a trend in improved overall survival.

■ HYPOFRACTIONATION

Standard fractionation for curative radiotherapy is usually 1.8 to 2.0 Gy per fraction. Recently, several randomized trials have been published, showing hypofractionated schemes (>2 Gy per fraction) to be equivalent to conventional schemes in terms of local control and side effects as fibrosis, as well as disease-free and overall survival (42–44). Also, at 10-year follow-up, no difference was shown (42). The equivalence of hypofractionation seems to be for pT1–3aN0–1 breast tumors, however, subgroups are studied with small patient numbers. Whelan (42) studied LRs in subgroups; high-grade tumor was shown to be associated with higher relapse rate in the hypofractionation arm (16.6% vs. 4.7%). This could not be confirmed at 8-year follow-up in the START trials (45).

No excess heart damage, known to be partly based on fraction size, was shown in the randomized trials. It should be stated, however, that vascular damage is not seen until 15 to 20 years of follow-up,

while follow-up of these trials are limited to 5 to 10 years. Another concern is the more frequent use of cardiotoxic systemic treatment, such as anthracyclines and trastuzumab, as was the case during the hypofractionation trials.

■ TECHNIQUES TO LOWER THE SIDE EFFECTS

Irradiation of the breast or chest wall is traditionally performed using opposing wedge fields. With the introduction of intensity-modulated radio therapy (IMRT), more homogeneous dose distribution can be achieved, resulting in less side effects (less acute skin reaction and improved cosmesis) as shown in two randomized trials (46,47). Another development is the use of a simultaneous integrated boost (SIB) technique, resulting in less volume irradiated to high dose, and, therefore, it is expected to improve cosmetic results. Vascular damage as well as associated heart morbidity and death is known to be a risk factor in left-sided breast cancer patients, as shown in several studies. In the earlier meta-analysis of EBCTCG, the overall survival was shown to be worse in irradiated patients because of excess vascular deaths, while breast cancer specific survival was found better. Although the survival benefit of radiotherapy has been stated already, radiation can be improved for left-sided breast cancer patients, such as by using techniques as the 'deep inspiration breath hold technique' (48). With this technique, patients are irradiated during maximal inspiration with additional caudal movement of the diaphragm and heart. Radiation plans can be achieved, resulting from less to no heart volume to be irradiated (Figure 3). With

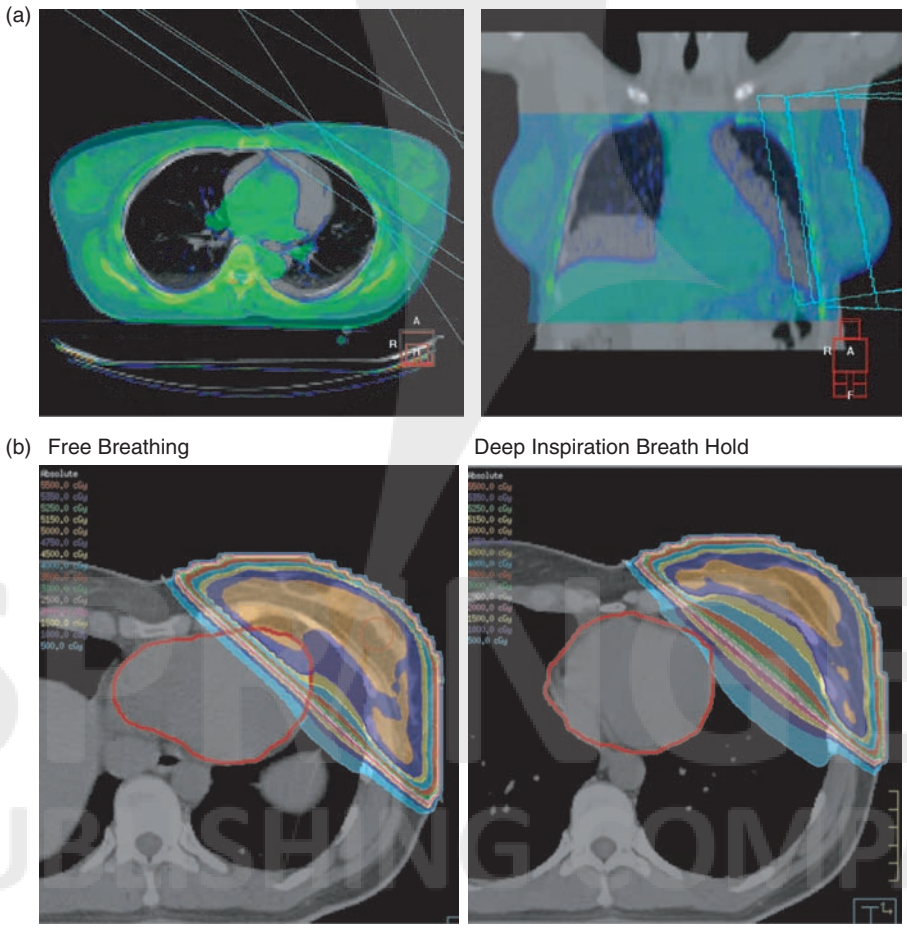

FIGURE 3 Deep inspiration breath hold technique. Match of the free breathing (gray) and deep inspiration breath hold (green) CT scan. During inspiration, the heart has moved caudal and dorsal. Radiotherapy can be planned without significant reduction in heart dose.

the more expanded use of these techniques in radiotherapy departments, radiotherapy results, including survival benefit, will be improved in the future.

■ RADIOTHERAPY IN COMBINATION WITH NOVEL AGENTS

The therapeutic implications of DNA damage in cancer therapy form the basis of cytotoxic chemotherapy and radiation treatment. Interaction of chemotherapy and radiotherapy is known, and in breast cancer treatment these modalities are sequentially used because of higher incidence of acute and late side effects with combined use. With the more frequent use of trastuzumab in HER-2-positive patients, there is a focus on possible synergistic effect of radiotherapy when combined with trastuzumab. Although it is not shown in studies so far, it is known that vascular damage after radiotherapy develops after long follow-up (15–25 years), therefore, it might be too early to state that there is no interaction between these agents and radiotherapy. An interesting agent in breast cancer is a novel class of DNA repair defect targeted therapeutics that inhibits poly (ADP ribose) polymerase (PARP). In BRCA mutation associated breast cancer in combination with chemotherapy in triple negative breast cancer, exciting preliminary results have been found (49). Since radiotherapy and cytotoxic chemotherapy exert their antitumor defect through the production of DNA damage, inhibition of DNA repair with a PARP inhibitor can be used to sensitize tumor cells to overcome treatment resistance.

■ CONCLUSION

Radiotherapy in breast cancer decreases the LR rate and improves overall survival. Over the past decades, for breast cancer care, radiotherapy has become more targeted. In BCT, more factors for LR are known to detect the high-risk patients, who can benefit from an additional boost after whole-breast irradiation. With proper patient selection, 0.5% to 1% recurrences per year are found. Studies focusing on molecular markers may contribute to even better selection in future. In low-risk patients, radiation can be limited to the tumor bed alone as is used in PBI. Many trials are presently in progress, which will result in more detail for suitable patient selection and technique differences.

In patients treated with radical surgery, there is a tendency to expand the radiotherapy indication. Partly, this is based on long-term meta-analysis, showing the survival benefit in intermediate risk patients also. Trials are being run to study whether historical results are comparable with today's practice.

Standard regional irradiation is limited in postoperative setting and limited to high-risk areas. Primary irradiation after positive sentinel node will become a standard practice. Improvement of techniques in radiation as IMRT, SIB technique, and deep inspiration breath hold technique has resulted in a lower incidence of acute as well as important late side effects, such as vascular damage. Interesting developments of radiotherapy in combination with novel agents as PARP inhibitors might change radiotherapy doses in the future.

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BREAST CANCER

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Alphonse G. Taghian, MD, PhD
Michele Y. Halyard, MD, Guest Editors

Radiation Medicine Rounds is a trinary, hard cover, periodical designed to provide an up-to-date review of a dedicated radiation medicine topic of interest to clinicians and scientists who are involved in the care of patients receiving radiotherapy. It is intended to serve as both a reference and instructional tool for students, housestaff, fellows, practicing clinicians, medical physicists, cancer biologists, radiobiologists, and interdisciplinary colleagues throughout the oncology spectrum. This issue of ***Radiation Medicine Rounds*** discusses the more salient topics surrounding the role of radiation therapy in breast cancer. The specialty of radiation therapy has increased in complexity over the years, yet as technology improves, the goal of improving outcomes while decreasing toxicity remains critical. ***Breast Cancer*** provides the practitioner with a full current overview of the present best practices and recent research in management of this complex and challenging cancer.

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