Quality of Life in Urinary Bladder and Prostate Cancer Patients

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As I am not a doctor, I have been having some difficulties with understanding the clinical background and management of treatments. Thank you Albert for your help and explanations, and the coffee in front of *Hospital del Mar*.

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And the only words I can say (*con mucho cariño*):

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Summary

The overall objective of this thesis was to describe the evolution of Health-Related Quality of Life in Spanish patients with urologic tumours; and to the examine clinical and treatment-related factors associated with changes in Health-Related Quality of Life during the first year of treatment. The EMPARO project is an observational, multicenter, prospective study on patients diagnosed with bladder cancer (n=326) and prostate cancer (n=472). Consecutive patients were enrolled in 7 Spanish hospitals, and evaluations (conducted before treatment, at 6 and 12 months after) included the SF-36 health questionnaire and a specific instrument for each tumour location. In patients with bladder cancer, what becomes outstanding among the results is the distinctive pattern of improvement according to the intravesical therapy combined with transurethral resection. In prostate cancer, our results did not show any better results in patients treated with the new modalities of treatment, neither in surgery nor in external radiation therapy. Only brachytherapy stands out due to its lack of sexual side effects.

Resumen

El objetivo global de esta tesis fue describir la evolución de la Calidad de Vida Relacionada con la Salud en los pacientes españoles con tumores urológicos; y examinar los factores clínicos y de tratamiento asociados con el cambio en la Calidad de Vida Relacionada con la Salud durante el primer año de tratamiento. El proyecto EMPARO es un estudio observacional, multicéntrico, prospectivo de pacientes diagnosticados de cáncer de vejiga urinaria (n= 326) y cáncer de próstata (n=472). Se reclutaron los pacientes consecutivos en 7 hospitales españoles, y las evaluaciones (realizadas antes del tratamiento, 6 y 12 meses después) incluyeron el cuestionario de salud SF-36 y un cuestionario específico para cada localización tumoral. En los pacientes con cáncer de vejiga, entre los resultados encontrados destaca el patrón distintivo de mejoría según la terapia intravesical que se combina con la resección transuretral. En cáncer de próstata, nuestros resultados no muestran mejores resultados en los pacientes tratados con las nuevas modalidades de tratamiento ni en cirugía ni en radioterapia externa. Únicamente destaca la braquiterapia por su falta de efectos secundarios a nivel sexual.

Preface

This doctoral thesis is designed following the instructions given by the Department of Experimental and Health Sciences of the Universitat Pompeu Fabra. It is presented as a compendium of scientific manuscripts that are either already published in indexed peer reviewed journals or are currently under revision.

All these manuscripts have been produced within the EMPARO project, a Spanish multicentre prospective cohort study of patients with prostate cancer and urinary bladder cancer. EMPARO is composed by four subprojects focused on: evaluation of the clinical care process; estimation of models for predicting cancer recurrence and progression; economic evaluation; and quality of life assessment. The general objective of the project is to describe the clinical situation and health care process of patients with these urologic tumours in Spain. The thesis reports the quality of life of Spanish urinary bladder and prostate cancer patients.

In the introductory part, a narrative review summarizes the current evidence. It contains information regarding epidemiology and quality of life in urinary bladder and prostate cancer patients, as well as a general description of the methods used for quality of life assessment and interpretation.

The following body of the thesis is composed by four scientific manuscripts. The first and second manuscripts can be understood as 'field work' because they were addressed to solving research questions

about which quality of life instruments to use in the EMPARO project. They also provide an insight into the concept and methods of quality of life assessment. The third and fourth manuscripts deliver the actual results of the cohort study, presenting original research data, which contribute to the body of evidence about quality of life in prostate and bladder cancer. Finally, the annex, which contains two further publications, completes the research circle on quality of life assessment.

The first manuscript deals with the identification and evaluation of quality of life measures designed for patients with prostate cancer. It illustrates the problem of having of several instruments available and addresses the question about how to choose the 'best' measure for a specific research purpose.

> *Schmidt S, Garin O, Pardo Y, Valderas JM, Alonso J, Rebollo P, Rajmil L, Garcia-Forero C, Ferrer M; the EMPRO Group.* ***Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments****. Qual Life Res. 2014 Apr 19. [Epub ahead of print]*

The second manuscript describes the translation and evaluation of a quality of life measure that was developed originally for another language and culture. It gives the reader of this thesis an overview on the process and methods followed in order to maintain the equivalence with the original instrument.

Schmidt S, Riel R, Frances A, Lorente Garin JA, Bonfill X, Martinez-Zapata MJ, Morales Suarez-Varela M, dela Cruz J, Emparanza JI, Sánchez MJ, Zamora J, Goñi JM, Alonso J, Ferrer M; EMPARO-CU Study Group. ***Bladder cancer index: cross-cultural adaptation into Spanish and psychometric evaluation****. Health Qual Life Outcomes. 2014 Feb 15;12:20. doi: 10.1186/1477-7525-12-20.*

The third and fourth manuscripts present the results and conclusions about the quality of life in Spanish bladder and prostate cancer patients, respectively. The study design, strategy of analysis and results are described and put into context with former published research.

Schmidt S, Frances A, Lorente Garin JA, Juanpere N, Lloreta Trull J, Bonfill X, Martinez-Zapata MJ, Suarez-Varela MM, de la Cruz J, Emparanza JI, Sánchez MJ, Zamora J, Pijoan JI, Alonso J, Ferrer M. ***Quality of Life in Bladder Cancer Patients: 1-Year Results of a Multicentre Prospective Cohort Study****. (Submitted)*

Schmidt S, Frances A, Lorente Garin JA, Juanpere N, Lloreta Trull J, Bonfill X, Martinez-Zapata MJ, Suarez-Varela MM, de la Cruz J, Emparanza JI, Sánchez MJ, Zamora J, Pijoan JI, Alonso J, Ferrer M. ***Quality of Life in Prostate Cancer Patients: 1-Year Results of a Multicentre Prospective Cohort Study****. (Under review)*

Interpretation of quality of life scores is a key factor to promote the use of these instruments in research and clinical practice. The question arises if the score change is true and important, and therefore requires

a change in the clinical management of a patient or in the health-care system at a population level. The following two contributions to this topic are given to the reader as additional information as these publications describe the norm-based interpretation strategy which was later applied to the results of the cohort study.

> *Schmidt S & Pardo P.* ***Normative Data****. In: Michalos AC (ed.),* ***Encyclopedia of Quality of Life and Well-Being Research****. 1st ed. Springer; 2014. ISBN 978-94-007-0752-8.*

> *Schmidt S, Vilagut G, Garin O, Cunillera O, Tresserras R, Brugulat P, Mompart A, Medina A, Ferrer M, Alonso J. [****Reference guidelines for the 12-Item Short-Form Health Survey version 2 based on the Catalan general population****]. Med Clin (Barc). 2012 Dec 8;139(14):613-25. doi: 10.1016/j.medcli.2011.10.024.*

I hope the results of this doctoral thesis will find their way into clinical practice and will help future patients and clinicians to optimize their treatment. I also hope that other research projects will start from this base and continue the investigation in order to widen the body of evidence of the quality of life in urologic tumours, and to empower the patients by focusing attention on their voice. I further hope that this work can make health care practitioners, health care policy makers, and health researchers aware of the importance and benefit of assessing quality of life.

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1. INTRODUCTION

Cancer is a major health problem around the world. It is one of the most prevalent diseases in developed countries and therefore, contributes to a large personal, societal and economic burden.

In the European Union (EU-27), 2.45 million people were diagnosed with cancer and 1.23 million died because of this disease in 2008 (Luengo-Fernandez 2013). In the EU-27, the economic burden for all types of cancer was estimated to reach 126 billion Euros in 2009 (Luengo-Fernandez 2013); with a large proportion of costs associated to health care spending (40%), as well as productivity losses due to early death and lost working days.

In Spain, cancer is the leading cause of death in men and the second in women. In 2006, it accounted for a total of 98.048 deaths (61.184 in men and 36.862 in women) (Cabanes 2009). This means that 3:1.000 men and 2:1.000 women died because of cancer. In terms of individual lifetime risk, one in five Spanish men and one in six Spanish women will be diagnosed with cancer at some point in their life (Ferlay 2013a). Half of them will survive their disease during the next five years.

1.1 Urologic tumours

Urologic tumours contribute to a large proportion to the global cancer burden. These so called genitourinary cancers can affect the prostate, bladder, kidney, urethral, testicular, and penile location.

While other tumours have been studied in much detail, such as breast, lung, or colon, less investigation exists regarding bladder and prostate cancer. However, bladder and prostate cancer belong to the most prevalent tumours among Spanish men. Together with lung cancer, they contribute to the most frequent registered cancer sites in Spanish cancer registries, and account for between 55.6% and 62% of all registered cancer cases (Cabanes 2009). Therefore, the EMPARO study was addressed to these less studied tumour sites: urinary bladder and prostate.

a) Epidemiology, diagnosis, and treatment of bladder cancer

Urinary bladder Cancer (C67 after ICD-10) affects men and women worldwide, though it is more common in the Western world. In the USA and Europe it is the fourth most common cancer diagnosed in men, and is placed at seventh and eighth position in cancer-related mortality, respectively in the USA (Siegel 2014) and EU-27 (Ferlay 2013b). The tumour appears three to four times more frequently in men than in women (Shariat 2010). For men, the highest age-standardized incident rate estimates in Europe have been reported for Spain, with 39.0 versus 29.1 for EU-27 per 100,000, respectively. For

women, incidence rates in Spain were lower than the mean for the EU-27, with 5.5 versus 6.1, respectively (Ferlay 2013b). Five-year relative survival rates in Europe are around 68% for both sexes (De Angelis 2014), but it has been noted that men are only twice as likely to die from the disease (Shariat 2010). Age, tobacco smoking, and exposure to cancerous substances have been reported so far as risk factors (Burger 2013).

Approximately 75% of the newly diagnosed cases are non-muscle invasive bladder cancers, where the tumour affects only the mucous membrane (also called superficial bladder cancers) (Babjuk 2013). About 25% of diagnosed patients have muscle invasive cancer and will have poorer health outcomes even after treatment. The prevalence of bladder cancer is high, as the tumour recurs frequently after initial treatment. Therefore, this cancer is very bothersome to patients, as they remain under long-term monitoring, and also very costly for the health care system (Svatek 2014).

Urinary cytology to detect micro haematuria, ultrasound, or cystoscopy are the diagnostic techniques that might indicate the presence of a bladder cancer. Definitive diagnosis depends on the histopathological findings of bladder biopsy. Therefore, in the transurethral resection (TUR), suspicious tissue is removed from the inside of the bladder. The strategy of resection depends on the size of the lesion. If the lesions of the bladder wall are small, the tumour can be resected totally. Complete and correct TUR is essential to achieve a good prognosis, with less risk of residual disease and early recurrence (Babjuk 2013). If the tumour affects greater parts of the bladder and

possibly invades muscle layer, cystectomy would be the treatment of choice. The risk of cancer progression and recurrence after transurethral resection is estimated by six clinical and pathological factors: number of tumours, tumour size, prior recurrence rate, T category, carcinoma in situ, and grade (Sylvester 2006). This might help urologists to determine further treatment and the frequency of follow-up visits.

Tumour staging is based on the international Tumour Node Metastasis (TNM) system (see Table 1).

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 1: Tumour Node Metastasis (TNM) classification of bladder cancer (Sobin 2009).

Bladder Cancer stages proposed by the American Joint Committee on Cancer is shown in Table 2.

Stage 0a	Stage 0is	Stage I	Stage II	Stage III	Stage IV
Ta, N0, M0	Tis, N0, M0	T1, N0, M0	T2a, N0, M0	T3a, N0, M0	T4a, N0, M0
			T2b, N0, M0	T3b, N0, M0	Any T, N1, M0
				T4a, N0, M0	Any T, N2, M0
					Any T, N3, M0
					Any T, any N, M1

Table 2: Bladder cancer staging (American Joint Committee on Cancer 2002).

For the histological grading of bladder cancer, the WHO 2004, former WHO 1979, is used (see Table 3). Figure 1 illustrates the differences.

1973 WHO grading	2004 WHO grading
Urothelial papilloma Grade 1: well differentiated Grade 2: moderately differentiated Grade 3: poorly differentiated	**Flat lesions** Hyperplasia (flat lesion without atypia or papillary aspects) Reactive atypia (flat lesion with atypia) Atypia of unknown significance Urothelial dysplasia Urothelial CIS is always high-grade (HG)
	Papillary lesions Urothelial papilloma (completely benign lesion) Papillary urothelial neoplasm of low malignant potential (PUNLMP) Low-grade (LG) papillary urothelial carcinoma High-grade (HG) papillary urothelial carcinoma

Table 5: WHO histological grading classifications (Montironi 205).

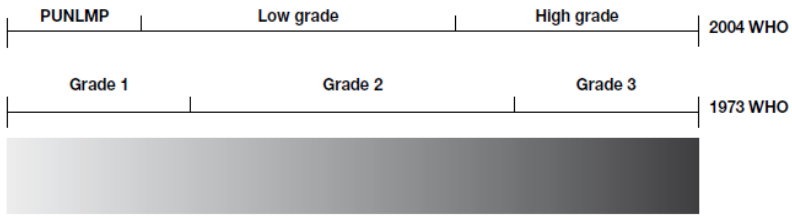

Figure 1: Differences in tumour grading according to the WHO 1973 and 2004 classification systems (McLennan 2007).

The clinical pathway in the treatment and management of non-muscle invasive bladder cancer is shown in Figure 2.

The follow-up or surveillance of urinary bladder cancer patients is important in order to early detect recurrent tumours. Frequent cystoscopy and cytology are nowadays the best strategies. Urinary markers are used additionally to cystoscopy, because of their low sensitivity to detect low-grade recurrences. So far, no urinary marker can replace cystoscopy during follow-up and further research in this field is needed.

The goal of TUR in Ta and T1 is to make the correct diagnosis and remove all visible lesions. TUR by itself can eradicate Ta and T1 tumours completely. However, if it is incomplete, tumour recurrence could appear, and this explains the high variability of recurrence rate at three months (Brausi 2002). Therefore, current guidelines recommend considering adjuvant therapy in all patients.

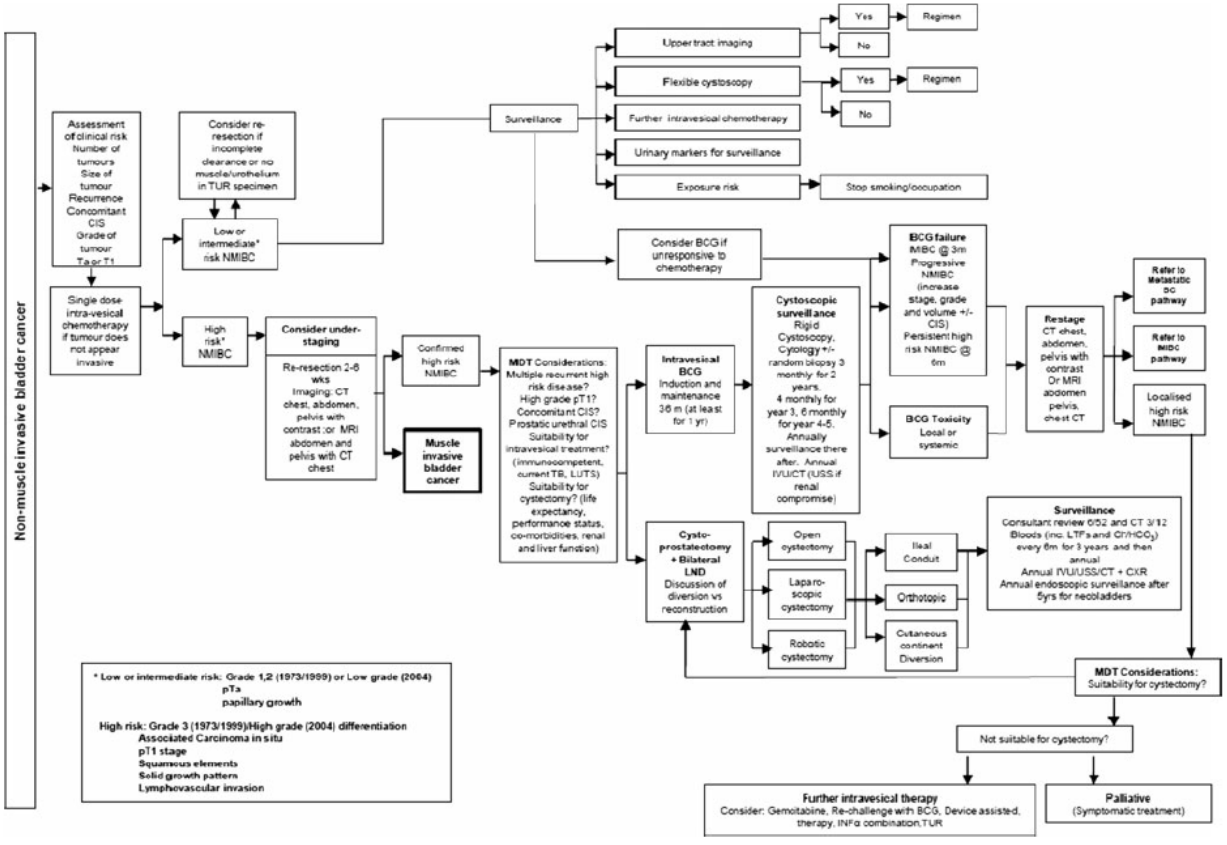

Figure 2: Clinical pathway in the treatment of non-muscle invasive bladder cancer (McLennan 2011).

Systematic reviews of randomized clinical trials with meta-analysis indicated that adjuvant intravesical Bacillus Calmette-Guérin (BCG) with maintenance treatment is effective for the prophylaxis of tumour recurrence in superficial bladder cancer (Han 2006, Shelley 2010); it is superior to chemotherapy in terms of complete response and disease-free survival (Shelley 2010); and intravesical chemotherapy is recommended for patients failing or unsuitable for BCG therapy (Shelley 2010). Nevertheless, BCG causes significantly more side effects than chemotherapy does (Shang 2011). These systematic reviews also highlighted the lack of conclusive evidence in terms of overall survival (Shelley 2010).

b) Epidemiology, diagnosis, and treatment of prostate cancer

Prostate cancer (C61 after ICD-10) is the most common diagnosed tumour and the second or third cause of cancer-related deaths respectively in American (Siegel 2014) and European (Ferlay 2013b) men (see Figure 1). In Spain, prostate cancer ranks at first in incidence (Ferlay 2013a) and at third place of cancer-related deaths (Ferlay 2013a).

The probability of developing an invasive prostate cancer from birth to death is 1:7 and increases significantly with age (Siegel 2014). The estimated age-standardised rates of cancer incidence for EU-27 for 2012 were 110.8 per 100,000, compared to 96.8 in Spain (Ferlay 2013b).

The European mean age-standardised 5-year relative survival for prostate cancer increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 (De Angelis 2014). These survival advances can be partly related to earlier diagnosis, as well as to better diagnostic imaging, genetic profiling, and treatment techniques (Kapiteijn 2002). The 5-year relative survival of 84.7% in Spain is slightly above the EU mean (83.4%) (De Angelis 2014). Due to a lack of evidence, no recommendation regarding preventive strategies can be given.

Prostate cancer is suspected on the basis of digital rectal examination and prostate-specific antigen test (PSA) levels. Definitive diagnosis depends on the histopathological findings of prostate biopsy (Heidenreich 2014a, Heidenreich 2014b). The PSA, which measures a protein that is produced by the prostate gland, is increasingly used from the 90th on. The PSA has been used since then to screen men, which led to a so called "stage migration" (Makarov 2007): patients are diagnosed at younger ages and mostly at clinical asymptomatic disease stages. Nowadays, about 90% of patients are diagnosed at these localized stages of disease (Heidenreich 2014a, Heidenreich 2014b).

Prostate cancer screening is one of the most controversial topics in urological literature due to a debate of treatment-related harms and benefits. The two big randomized controlled trials (Andriole 2009, Schröder 2009) that studied the effectiveness of cancer screening on mortality yielded inconsistent results in USA and Europe. So far, the evidence form meta-analyses of clinical trials does not find a significant reduction in prostate cancer-specific or overall mortality in the treatment of screen-detected cases (Ilic 2013). Moreover, there is

substantial information that overdiagnosis and overtreatment are common and are associated with frequent and medium to severe treatment-related harms (Ilic 2013).

Tumour staging is based on the international Tumour Node Metastasis (TNM) system (Sobin 2009) showed in Table 4.

T - Primary tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Clinically inapparent tumour not palpable or visible by imaging
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
T2		Tumour confined within the prostate[1]
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3		Tumour extends through the prostatic capsule[2]
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4		Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes[3]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M - Distant metastasis[4]		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

Table 4: Tumour Node Metastasis (TNM) classification of prostate cancer (Sobin 2009).

The Gleason score is calculated from the histopathologic results of the biopsies taken in order to evaluate the tumour grade. It ranges from grade 1 (well differentiated) to grade 5 (very poorly differentiated).

The classical score is derived by adding the two most prevalent pattern grades, yielding a score ranging from 2 to 10 (see Table 5) (Epstein 2005).

Gleason 2–6	The tumor tissue is well differentiated
Gleason 7	The tumor tissue is moderately differentiated
Gleason 8–10	The tumor tissue is poorly differentiated or undifferentiated

Table 5: Gleason score for prostate cancer grading.

D'Amico risk-group classification (D'Amico 1998) (see Table 6) is used to predict the risk of biochemical tumour recurrence after treatment with curative intent, as well as the likelihood of tumour progression into metastatic disease and cancer specific and overall survival. It can be used in order to select among available treatment options.

Low-risk	**Intermediate-risk**	**High-risk**
PSA <10 ng/mL and Gleason < 7 and cT1-2a	PSA 10-20 ng/mL or Gleason <7, or cT2b	PSA > 20 ng/ mL, or Gleason > 7, or cT2c-3a

Table 6: Classification into risk groups for localized prostate cancer.

The TNM classification and Gleason score calculation are used for constructing the prostate cancer staging proposed for the American Joint Committee on Cancer, which is showed in Table 7.

Stage I	Stage II	Stage III	Stage IV
T1a, N0, M0, G1	T1a, N0, M0, G2-4	T3, N0, M0, any G	T4, N0, M0, any G
	T1b, N0, M0, any G		Any T, N1, M0, any G
	T1c, N0, M0, any G		Any T, any N, M1, any G
	T, N0, M0, any G		
	T2, N0, M0, any G		

Table 7: Prostate cancer staging (AJCC 2002).

The different available treatment options and clinical pathways for localized prostate cancer are shown in Figure 3.

Active surveillance implies to maintain the patient under close monitoring in order to time properly the curative treatment. This approach is increasingly used since the last decade, as the debate of overtreatment arose. The disease is not treated immediately and so the harms of treatment at this asymptomatic stage of low grade disease are delayed, too.

Radical prostatectomy has been the traditional treatment applied to localized prostate cancer patients. The prostate gland is removed radically together with the resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin.

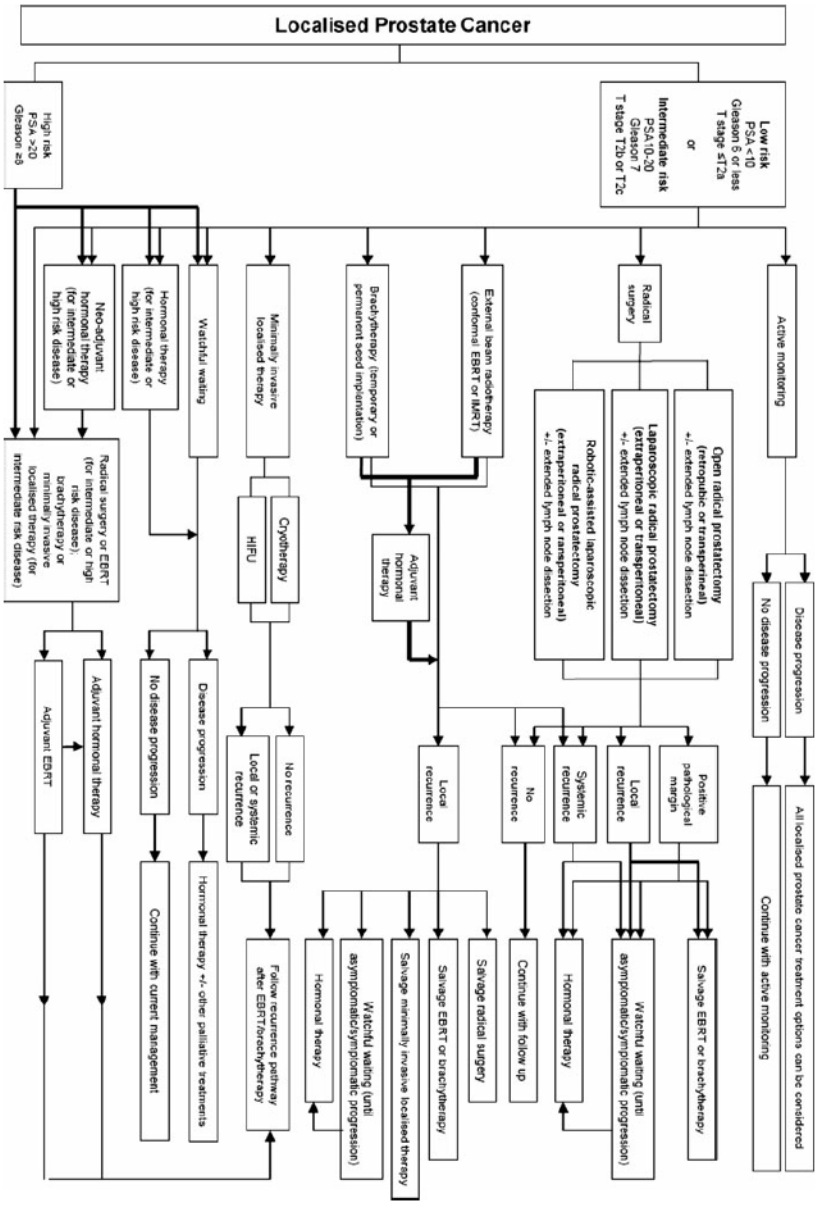

Figure 3: Clinical pathway in the treatment of localized prostate cancer (McLennan 2011).

Different treatment modalities are used, including retropubic radical prostatectomy, laparoscopic radical prostatectomy, and robot-assisted laparoscopic prostatectomy.

Recent systematic reviews showed that robot-assisted laparoscopic prostatectomy is associated with less blood loss and transfusion rates in comparison with retropubic prostatectomy (Ficarra 2012), but there are only minimal differences in terms of overall post-operative complications (Novara 2012a, Novara 2012b). Well-designed comparative effectiveness studies that show the superiority of one technique over the other are still outstanding due to the recent introduction of robots and because existing studies suffer from methodological limitations (Montorsi 2012).

External radiotherapy has traditionally been used mainly for more advanced disease stages or for patients not suitable for surgery treatment because of health problems. It can be applied as monotherapy or in combination with surgery. The most common form of external-beam therapy is 3-dimensional conformal radiation therapy (3D-CRT). Recently, the intensity-modulated radiation therapy (IMRT) delivering a single dose of radiation whereby the intensity of the radiation beams can be changed during treatment sessions has been introduced. IMRT can reduce the risk of side effects as the radiation can be focused on the specific areas where treatment is needed and therefore affects less the surrounding normal tissues (National Cancer Institute 2014).

External-beam radiation therapy is usually delivered to patients in repeated treatment sessions over several weeks. In contrast to this approach, internal radiation therapy consists of introducing radioactive material within the tumour tissue in a single session. This approach is called brachytherapy or seed implantation, as the radioactive material (isotopes) is placed inside the body using a needle, catheter or any other delivery device. These seeds remain in the body, and after a few weeks or months the isotopes decay completely and so the radiation stops automatically.

Hormones can be used as neo-adjuvant or adjuvant combination therapy with surgery or radiotherapy, or as monotherapy. Synthetic hormones or other drugs are used to either slow or stop the growth of the tumour by blocking the body's natural hormones.

Watchful waiting (or symptom-guided treatment) is a form of palliative treatment used to alleviate the patients' symptoms (Heidenreich 2014b). This term was introduced before 1990 and refers to the conservative management of prostate cancer until the disease progressed locally or systemically and would require palliative treatment.

1.2 Health-related quality of life

The concept of quality of life was introduced in medicine in the 70^{ths}. This innovative approach was enhanced by the broadening of the definition of the "health" concept by the World Health Organization, as well as the epidemiological transition of disease in the industrialized countries, with increasing chronic conditions that require long-term interventions.

a) Concepts and definitions

'Quality of life', 'health-related quality of life' (HRQL), 'health status', 'functional status', and 'well-being' are expressions often interchangeably used in the medical literature. All these terms belong to the umbrella concept of patient-reported outcomes (PROs) (Taillefer 2003, Ferrans 2010, Smith 1999). This term was introduced around the year 2000 in order to avoid terminology misuse and confusion (McKennan 2011). Now it is clear that all quality of life measures can be considered PRO measures, but not all PRO measures assess quality of life.

The term PRO emphasises the expression of subjective information about something that can affect a person's life. Qualitative information is gathered in a quantitative and standardized way. It includes a wide spectrum of concepts, such as disease symptoms, satisfaction with life in general or with the delivery of care, limitations

in daily life performance, general health perception, mental wellbeing, and quality of life. All these concepts have in common that the information comes directly from the patient and is not modified by any other person. As stated in the Food and Drug Administration's definition (FDA 2009) "A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else". This stands in contrast to the clinician-reported outcomes, where the doctor rates and interprets a patient's health state, such as range of motion or other clinical scales.

HRQL is a subtype within the PRO concept. One of several HRQL definitions come from Patrick and Erickson and refers to "the value assigned by individuals, groups, or society to the duration of survival as modified by impairments, functional states, perceptions, and social opportunities influenced by disease, injury, treatment, or policy" (Patrick 1993).

The US National Institutes of Health defined HRQL measures as: "(…) patient outcome measures that extend beyond traditional measures of mortality and morbidity, to include such dimensions as physiology, function, social activity, cognition, emotion, sleep and rest, energy and vitality, health perception, and general life satisfaction. (Some of these are also known as health status, functional status, or quality of life measures.)" (NIH 2014).
The content of the HRQL instrument may vary greatly, not only among generic, disease-specific, and cancer-site specific instruments, but also within each category of measure.

Figure 4 shows a comprehensive model that aims to incorporate health outcomes and can be understood as a common framework for classifying PRO measures regarding their content (Valderas 2008a). It incorporates the Wilson and Clearly model (Wilson 1995) and the International Classification of Functioning Disability and Health (World Health Organization 2001) conceptual models.

The number of HRQL instruments has increased tremendously in the last decades, and standards and recommendations for their selection and appropriate use have emerged (Ahmed 2012, Aronson 2001, FDA 2009). Although there is no gold standard definition, consensus exits that HRQL is a multi-conceptual and evaluative approach that reflects the subjective view of the patient. As well as the definition of health, it includes physical, mental, and social aspects of a person´s life, under the perspective of general well-being and the ability to function in daily life activities. It is therefore used as an indicator of the effect of disease or treatment upon a person.

Today, quality of life data are used in epidemiologic studies (e.g. in population surveys to monitor the health of a population), in clinical setting to facilitate informed treatment decision making and to enhance patient-doctor communication, in evaluative research to assess the effect of treatment, and in politics to assess the quality and costs of care and to inform policymaking in health care.

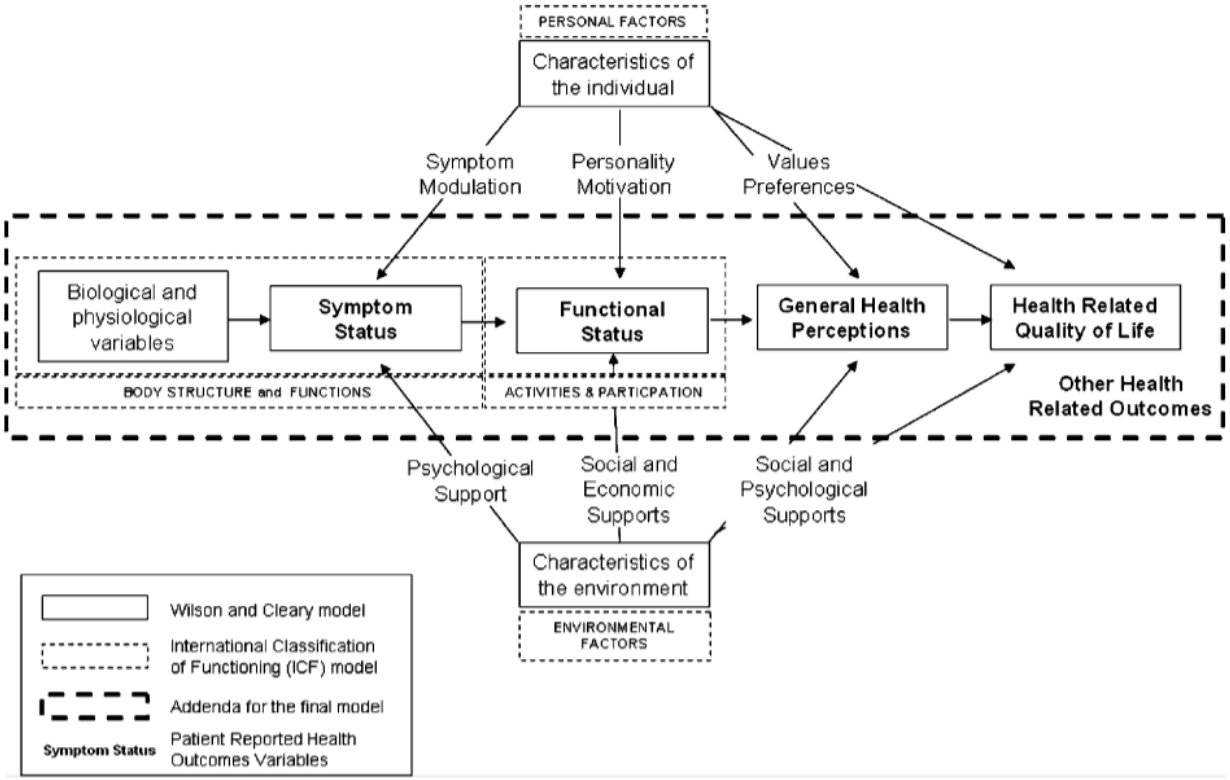

Figure 4: A descriptive model for health outcome concepts (Valderas 2008a).

b) Measurement instruments

The value of a HRQL instrument depends on various factors: it needs a valid conceptual framework and measurement methodology, as well as known interpretation strategies and grade of applicability (Guyatt 1994).

HRQL measurement can be based on psychometric or econometric development methods (Velikova 1999). Psychometric-based instruments measure the unobservable construct of HRQL with individual responses of questions that represent this construct and are aggregated to summary scores. They are helpful in describing or monitoring the health of populations, as well as in evaluating the effect of medical interventions or health services. Instruments using the econometric approach are based upon decision theory, and were originally developed to facilitate decision making for health care providers. They are able to weight individual preferences for a certain state of health and therefore are used for cost-effectiveness analysis and resource allocation. Quality-Adjusted-Life-Years (QALYs) are used as indicators of effectiveness as they combine the burden of disease with survival length.

In order to make HRQL instruments a valuable source of information about the effect of treatment, and thus let them become an indicator to facilitate treatment decision, they need to fulfil rigorous quality criteria (Varricchio 2006, Aaronson 2002, Guyatt 1993a). Conceptual and measurement model, reliability, validity, responsiveness, interpretability, and respondent and administrative burden are all

important attributes that should be reviewed before including the HRQL instrument in a clinical study (see Figure 5). They should also be considered when interpreting the instruments' scores in order to prevent misinterpretation.

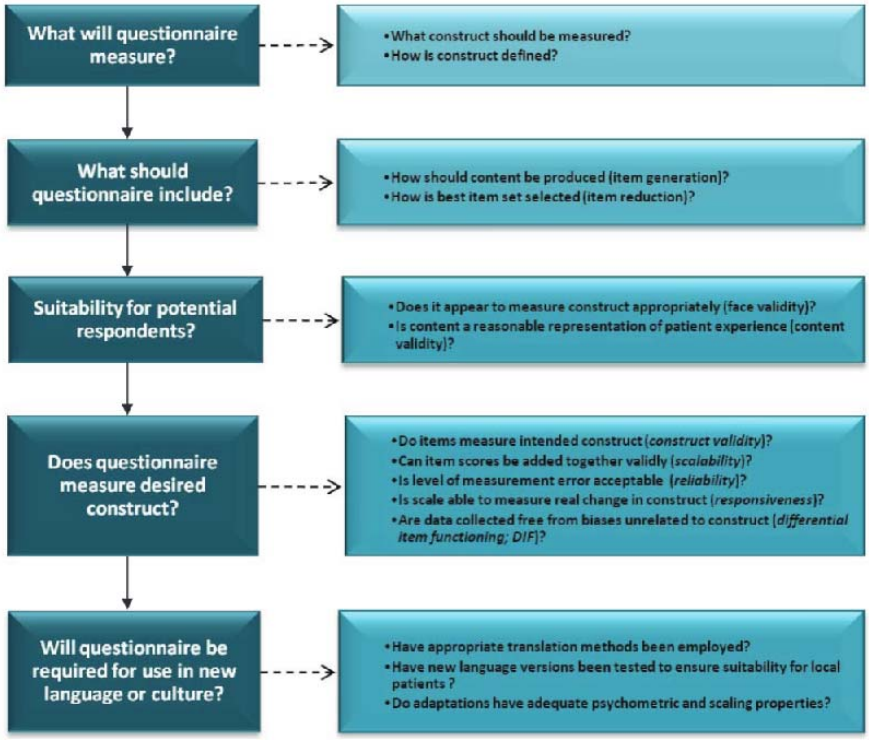

Figure 5: Considerations when chosing an instrument for HRQL assessment (McKenna 2011).

c) Interpretation of health-related quality of life data

Given the multi-dimensional approach of HRQL, the interpretation of score changes is not self-evident and the lack of a gold standard makes it difficult to calibrate the results (Guyatt 1993b). Without relating the

change of scores to an interpretation strategy, HRQL usefulness is limited in clinical practice. Knowing how to interpret a HRQL instrument score and its change is important. Is the impact of a certain treatment on HRQL small but important, extremely important, trivial, or of moderate magnitude?

This need led to the development of different interpretation strategies, which can be classified as: distribution-based, anchor-based, or reference population-based approaches (Testa 2000, Guyatt 2002).

The distribution-based approach uses effect sizes (Cohen 1988) or standard error of measurement in order to relate the magnitude of change to the variability in stable subjects. Here, differences between treatment and control group are related to some measurement of variability. Cohen's recommendation for "small", "medium" and "large" changes correspond to effect sizes (ES) of 0.2, 0.5, and 0.8, respectively. Effect size is one strategy for interpretation useful for outcomes measured by continuous variables and that has been suggested as appropriate for HRQL instruments.

The anchor-based approach relates the changes observed in HRQL scores to another type of independent clinical results, so called 'anchors', that is self interpretable. These anchors examine the relationship between the scores and an independent measure to evaluate the meaningfulness of a score change (Guyatt 2002). One example is the "minimal important difference" (MID), which is proposed to clearly distinguish between statistical and clinical differences (Norman 2001). The MID is defined as "the smallest

difference in scores in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patients management." (Juniper 1994). While the ES is almost entirely based on statistical criteria, the MID is based on a patient judgment of the HRQL change experienced.

The norm-based approach uses reference values, or so called population norms, to facilitate score interpretation. Norm data indicates how the characteristic of interest "should" be distributed (average data is considered as normality), and therefore permits the identification of variations when HRQL data is compared to this reference. Norms are obtained by representative populations and this strategy is mainly applied for the interpretation of generic HRQL measures. Norm data can be used to discriminate between "sick" and "healthy" populations, to provide information at individual level, to facilitate clinical decision making, or to detect vulnerable subgroups within a population.

There is no superior interpretation strategy and probably the use of multiple strategies would enhance the interpretability of the HRQL measures.

1.3 Health-related quality of life in oncology

HRQL assessment in oncology has the longest tradition. In the treatment of chemotherapy, some questions arose: Will adding years of life be sufficient? Will the value of these added years be important when facing the treatment decision? In other words, are the gains in lifespan worth the cost of decrease in well-being? Thus, the evaluation of treatment effects has gone beyond the clinical endpoints of lengths of survival and tumour response.

The specialty of oncology was a pioneer in the field of HRQL measurement, and the first standardized questionnaire of this type to be described is Karnofsky's scale, which was developed in 1949 to assess the impact of chemotherapy in cancer patient. HRQL evaluation allows assessing the impact of the disease and the effects of treatments from the patient's point of view. The growing interest in measuring HRQL and its incorporation into the efficacy and effectiveness studies have been partly related to survival improvements. At present, there is a clear consensus on the need, in cancer patients, for information on HRQL and not only on survival.

HRQL has shown to be a reliable predictive indicator of survival in cancer patients (Varricchio 2010). Global domains (such as physical or social functioning or global health), as well as disease-specific domains (such as symptom distress, appetite loss, pain, or fatigue), were the most important indicators in predicting survival duration in cancer patients (Montazeri 2009). They were even more strongly associated than traditional clinical indicators, like tumour response (Carey 2008,

Montazeri 2001, Varricchio 2010). Therefore, the common recommendation is to routinely collect HRQL data in oncological randomized clinical trials (FDA 2009).

In cancer care, HRQL information could help patients to plan individual care and to choose among available treatment options. Furthermore, it facilitates informed clinical decision making and incorporates the individual preferences of patients, improving thus satisfaction with treatment. For the clinician, this data can help in order to answer the patient's questions regarding the impact of treatment and the expected benefit, as well as to monitor the patient's clinical evolution during the treatment and follow-up process.

Now, cancer treatment has three main objectives: increasing the recovery rate, lengthening the survival period, and improving quality of life. However, despite this early and important history, articles published on oncology rarely assess the benefits in HRQL and only 10% of published cancer clinical trials include it as one of the main outcomes.

Among the reasons for a limited use of HRQL measures in clinical research, it is important to remark some methodological limitations, such as the instrument's administration mode and metric characteristics, the periods in which the assessment is conducted, and the statistical analysis and interpretation of scores. A paper (Efficace 2007) reviewing the quality of clinical trials that evaluate HRQL in oncology showed that only 39% of articles published between 1990 and 2000 were rated as methodologically robust, although this

percentage rose to 64% in articles published after 2000. This learning curve suggests that the development of recent methodological research can now allow overcoming these limitations. Therefore, it is expectable for information on HRQL to have a greater impact on clinical management, deciding among different therapeutic options, and health planning.

The most established strategy to measure HRQL in patients with cancer is the combination of generic instruments, such as the SF-36, with cancer-specific questionnaires that were specifically designed for patients with some tumour location. In this context, the two most used instruments are the 'Functional Assessment of Cancer Therapy - FACT' and the 'European Organization for Research and Treatment Cancer - EORTC'. Both contain items that assess symptoms that are important to cancer patients and assess the effects of the disease or the treatment and tumour location-specific modules.

With the exponential growth of HRQL questionnaires in recent years (more than 1275 instruments in English) (Valderas 2008b), the quality of these instruments and the rigor with which their metric properties were studied can vary considerably. In this context, it is necessary to follow a strict and validated selection process to include the most appropriate instrument for the intended purpose or study.

a) Health-related quality of life in bladder cancer

Bladder cancer is still an unrecognized public health problem (Kaplan 2014). In comparison to other urologic tumours, it presents the smallest progress in survival (Siegel 2011). Funding for this tumour is far behind investment in other oncological diseases, resulting in poor scientific advancement and few randomized trials (Lotan 2009). Also, HRQL assessment is hampered by inappropriately used questionnaires and few available bladder cancer-specific instruments (Gerharz 2005).

Radical cystectomy and the subsequent urinary diversion (see Figure 5) are complex surgical procedures in urology. Most of HRQL studies in bladder cancer include patients with muscle-invasive disease that have undergone cystectomy, focusing on the impact of different types of urinary diversion. These studies are biased by preoperatively selection of the most appropriate diversion (Hautmann 2013).

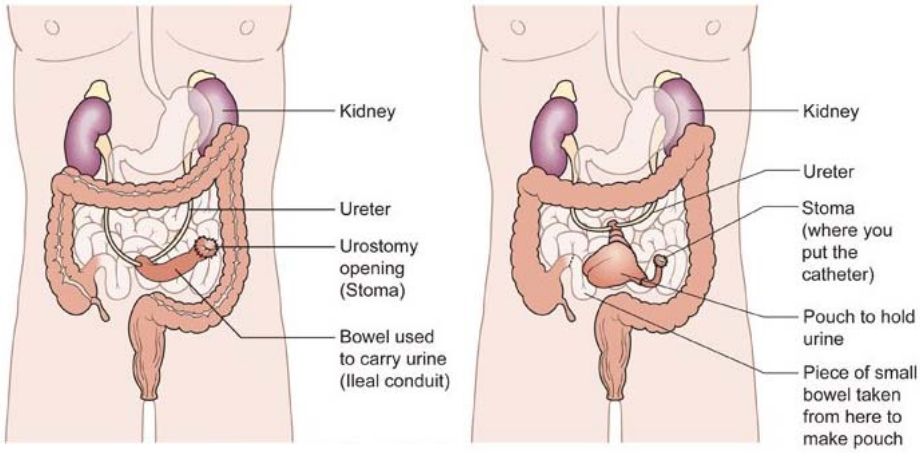

Figure 5: Types of urinary diversion. Left: schema of ileal conduit, right: continent urinary diversion (Cancer Research UK 2014).

Nowadays, approximately 70% of the patients are diagnosed at a non-muscle invasive stage. Though being the most relevant group, HRQL assessment is scarce. Yet this measurement in these patients is important, as the non-muscle invasive tumour has a high chance of recurrence, meaning that the patient remains under long-term clinical monitoring. This imposes not only a physical, but also a mental burden to the patient and his family.

Singer et al. (Singer 2013) investigated which domains were usually affected by bladder cancer treatment. They showed that patients reported especially worse physical and role functioning, as well as increased fatigue compared to the general population, using the SF-36 questionnaire and the cancer-specific EORTC QLQ-C30.

Among patients who underwent cystectomy (Singer 2013), HRQL depended on the type of urinary diversion, and was furthermore associated with appetite loss and nausea and vomiting; chemotherapy treatment was associated with dyspnoea and nausea and vomiting; and radiotherapy with decreased social functioning, increased pain, dyspnoea, constipation, and appetite loss.

Allareddy et al. (2006) reported with the FACT-BL no variations in long-term (between 7-16 years) HRQL among patients who had received cystectomy with any type of urinary diversion, or bladder preservation treatments, but identified that sexual functioning scores were worse in the cystectomy group.

b) Health-related quality of life in prostate cancer

In the absence of a "gold-standard" therapy and with a similar survival among different available treatment methods, the assessment of treatment-related side effects and their impact on patients' HRQL has become specially important in prostate cancer (Eton 2002, Kollmeier 2012, Singh 2010).

Moreover, through the widespread PSA-screening patients are diagnosed at younger ages and thus live longer with the disease or the side effects of treatment. To present, there is considerable controversy regarding possible overdiagnosis and overtreatment not only in the medical scientific literature but also in the media. Nowadays, the optimal management for localized prostate cancer remains uncertain. Randomized clinical trial data is scarce, and the data obtained by observational studies present some inconsistencies.

Ideally, treatment decision should be based on clinical (general health status, life expectancy, comorbidities, disease stage, Gleason score) as well as personal factors (individual preferences, prior cancer experiences). A review about treatment decision aids for patients suggested that the existing treatment decision variability is not only due to patients' preferences, but rather due to differences regarding the content and methods of communicating this information (Zeliadt 2006).

The disease-specific domains mostly affected by prostate cancer and its treatment have been proven to be urinary, bowel, sexual, and

hormonal. Cohort studies which followed prospectively since pre-treatment (Sanda 2008, Pardo 2010) have shown a consistent and distinctive pattern of adverse effects and their HRQL impact for localized prostate cancer attempted curative treatments at two or three years of follow-up: radical prostatectomy produced greater urinary incontinence, while brachytherapy presented higher urinary irritative-obstructive symptoms and external radiotherapy caused also bowel side effects. Sexual dysfunction was a common adverse effect in all treatments with a varying impact over time and among different studies. Relevant differences between treatment groups remained up to 5 years of follow-up (Ferrer 2013). Treatment-related side effects influenced the outcomes on satisfaction with treatment among patients and their spouses or partners (Sanda 2008).

2. RATIONALE FOR THIS THESIS

Cancer is one of the most prevalent diseases in developed countries. In Spain, cancer is the leading cause of death in men and the second in women, accounting for 27.5% of the total in 2012. In terms of individual risk, one in five Spanish men and one in six Spanish women will be diagnosed with cancer at some point in their lives, and half of them will survive their disease for over five years.

Although rates in all cancer mortality have decreased by 13% in Spain over the past twenty years, this decline is lower than in other European countries and the United States. Furthermore, a significant geographic variation has been reported within the country regarding mortality, clinical procedures and assistance, such as discharge rates and average hospital stay.

The information about health care processes and outcomes currently available in Spain is limited or confined to a local level. It has been recognized as a significant gap regarding its potential value for health services users, providers and also for the sustainability of the health system itself. This gap is even more relevant when considering information on Patient Reported Outcomes such as Health-Related Quality of Life (HRQL).

The EMPARO project was designed to describe the health care process and outcomes on prostate and bladder cancers because both tumours are very prevalent in our country (the leading and third cancers in males, respectively), and even less studied than other neoplastic diseases. The good prognosis of prostate and bladder cancers, with a relative survival at 5 years of 83% and 68% in Spain, make HRQL become one of the main variable outcomes.

Bladder cancer patients continue experiencing treatment-related bother over a long period of cancer monitoring, but its HRQL impact is still poorly known. Most HRQL literature addresses muscle-invasive bladder patients, having therefore few published studies available on non-muscle invasive tumours although patients are mostly diagnosed at this stage.

There are a great number of treatment options for prostate cancer, including radical prostatectomy and external radiation among others. New modalities of these treatments, such as robot assisted surgery, brachytherapy or intensity modulated radiotherapy, have already started to be applied with the hope of improving patient outcomes. Given the novelty of these technologies, it is not clear whether differences in their extension could produce outcome variations within Spain.

Finally, we would like to highlight that the development of the disease-specific HRQL instruments for prostate and bladder cancer presented major differences. In the last decades there has been an exponential development of prostate cancer-specific instruments, which complicates the knowledge and generalized understanding needed for making a selection among the numerous instruments available nowadays. Bladder cancer-specific HRQL instruments are more scarce, and usually designed for specific grades of tumour infiltration and types of treatment. Only the Bladder Cancer Index was created to be comprehensive across a wide range of bladder cancer patients, independent of tumour infiltration and treatment applied.

Therefore, the EMPARO project provides useful HRQL information for patients, clinicians and health care policy makers in Spain. It means also a methodological contribution summarizing the strengths and limitations of existing instruments designed for patients with prostate cancer, and developing the Spanish version of the Bladder Cancer Index.

3. OBJECTIVES

Global objective:

To describe the evolution of Health-Related Quality of Life (HRQL) in Spanish patients with urologic tumours (prostate and bladder cancer); and to examine the clinical and treatment-related factors associated with changes in HRQL during the first year of management.

Specific objectives:

To obtain a systematic and standardized evaluation of the available evidence on development processes, metric properties and administration issues of prostate cancer-specific HRQL instruments which are currently applicable to patients with early-stage disease.

To linguistically and culturally adapt the Bladder Cancer Index for its use in Spain, and to test the acceptability, reliability, validity, and responsiveness of this adapted version.

To describe the evolution over time of Spanish bladder cancer patients' HRQL (measured by generic and disease-specific instruments); and to examine the clinical and treatment-related factors associated with changes in HRQL during the first year of bladder cancer management.

To describe the evolution of HRQL over time in Spanish prostate cancer patients (measured by generic and disease-specific instruments); and to examine the clinical and treatment factors associated with changes in HRQL during the first year of prostate cancer management.

4. SCIENTIFIC ARTICLES

4.1 **Manuscript 1:** Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments

4.2 **Manuscript 2:** Bladder cancer index: cross-cultural adaptation into Spanish and psychometric evaluation

4.3 **Manuscript 3:** Quality of Life in Bladder Cancer Patients: 1-Year Results of a Multicentre Prospective Cohort Study

4.4 **Manuscript 4:** Quality of Life in Prostate Cancer Patients: 1-Year Results of a Multicentre Prospective Cohort Study

Schmidt S, Garin O, Pardo Y, Valderas JM, Alonso J, Rebollo P, Rajmil L, Garcia-Forero C, Ferrer M; EMPRO Group.. Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments. Qual Life Res. 2014 Oct;23(8):2169-81. doi: 10.1007/s11136-014-0678-8

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Quality of Life in Bladder Cancer Patients: 1-Year Results of a Multicentre Prospective Cohort Study.

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Abstract

New modalities of radical prostatectomy and radiotherapy, such as robot-assisted surgery or intensity modulated radiotherapy (IMRT), have started to be applied with still limited evidence of their advantages.

Objective: We aimed to describe the evolution of HRQL over time in Spanish prostate cancer patients, and to examine the clinical and treatment factors associated with changes in HRQL during the first year of management.

Methods and materials: Observational multicenter prospective inception cohort study conducted in urologic departments of 7 Spanish hospitals. A consecutive sample of 472 patients with anatomopathologically confirmed prostate cancer, recruited from October 2010 to September 2011, was followed during the diagnostic process, and 6 and 12 months later. HRQL was assessed by generic and disease-specific instruments: the SF-36 (covering Physical and Mental health) and the Expanded Prostate Cancer Index (EPIC), which measures urinary, bowel, sexual and hormonal domains (scores ranging 0-100). Bivariate analysis and Generalized Estimating Equation (GEE) models were separately constructed for surgery and radiotherapy patients to assess change in HRQL score according to treatment modalities.

Results: Most patients were diagnosed at stage II (68%); primary treatment was radical prostatectomy for 48%, radiotherapy for 32%, hormonotherapy for 17%, and 3% received no treatment. Adjusted HRQL score changes from baseline to 12 month follow-up estimated with GEE models showed deterioration, regardless of the surgical modality applied, on urinary incontinence (-10.2; 95%CI -17.8, -2.7) and sexual domain (-26 laparoscopic, and -15 radical retropubic prostatectomy). No statistically significant differences were observed among radiation modalities in adjusted EPIC score changes with the exception of sexual domain (+23.1; 95%CI 9.0, 37.2).

Conclusions: Our results did not support the expected better results for new modalities of surgery. Similarly, HRQL evolution did not show any advantage in favour of IMRT. It is noteworthy that brachytherapy differs from external radiotherapy modalities due to its better sexual results.

Background

Prostate cancer is the second most commonly diagnosed cancer in men worldwide, and the second leading cause of cancer-related death in males in the western world.[1] Among Spanish men, it is the most prevalent and incident[2] cancer, but the third in cancer-related mortality due to its relatively good prognosis. The Prostate-Specific Antigen (PSA) has led to diagnosing tumours that previously would have remained clinically undetectable, therefore moving diagnosis to earlier disease stages. The European study EUROCARE showed increased relative survival at 5 years from 65% [3] to 85% [4] between the periods 1992-94 and 2000-07 in Spain.

There is a great number of treatment options for prostate cancer[5] including surgery, radiotherapy, cryoablation, androgen deprivation, active surveillance, and observation, among others. Radical prostatectomy and external radiation have traditionally been the most common,[6,7] followed more recently by interstitial radiotherapy[8] (brachytherapy) mainly for patients with low risk tumours. Also new modalities of these treatments, such as robot-assisted surgery or intensity modulated radiotherapy (IMRT), have already started to be applied with the hope of improving patient outcomes. However, given the novelty of these technologies, the evidence is still limited.[9-11]

Although rates in all cancer mortality have decreased by 13% in Spain over the past twenty years,[12] this decline is lower than in other European countries and the United States. Furthermore, a significant geographic variation regarding mortality,[13] clinical procedures, and assistance, such as discharge rates and average hospital stay, has been reported. For example, since 2005 the number of da Vinci robots has increased rapidly in a few autonomous communities, and nowadays, radical prostatectomy is carried out by robotic or non-robotic surgery according to where treatment is performed.

In recent years Patient Reported Outcomes such as Health-Related Quality of Life (HRQL) have been used by health systems to assess and compare providers' performance.[14] Nevertheless, this utilization of HRQL data is still

uncommon and largely restricted to England, Sweden, and United States. HRQL allows assessing the effects of disease and treatments from the patient's perspective, and it could be useful to evaluate the impact of the clinical practice variations on patients' health.

We aimed to describe the evolution of HRQL over time in Spanish prostate cancer patients, and to examine the clinical and treatment factors associated with HRQL change during the first year of management. Our hypothesis is that prostate cancer patients' HRQL is associated with the modality of treatment received. Consequently, differences in the extension of novel technologies such as brachytherapy and robot-assisted surgery could produce outcome variations within Spain.

Material and methods

EMPARO-CU is an observational multicenter prospective inception cohort study in Spain focused on the clinical care process and health outcomes of patients with urologic tumours. Participants were consecutively enrolled from October 2010 to September 2011 in the urologic departments of 7 hospitals in 5 Spanish autonomous regions. The inclusion criteria for PC patients were 1) having an anatomopathological confirmation of first PC diagnosis during the study period, 2) being diagnosed and treated in one of the study hospitals, and 3) agreeing to participate in the study through written informed consent. The study was approved by the ethic committees of each hospital.

Information on diagnostic tests, biopsy, and therapeutic procedures, among other variables, were collected from medical records. Interviews including socio-demographic characteristics and patient self-completed HRQL questionnaires were performed at the outpatient visits, after diagnosis (baseline), and 6 and 12 months later. Generic and disease-specific HRQL questionnaires, such as the Health Survey SF-36 version 2 and the Expanded Prostate Cancer Index (EPIC), were administered. The SF-36 covers eight health dimensions, which are summarized in a physical and mental component summary score (PCS and MCS, respectively). Summary components have a mean of 50 points (standard deviation of 10) in the USA general population.[15] SF-36 norms, stratified by gender and age groups, were used to interpret the results.

EPIC[16] was designed to assess the impact of prostate cancer and treatment side effects on patients' HRQL. The EPIC instrument (50 items) was constructed by expanding the UCLA-PCI to measure four domains: urinary (12 items), bowel (14 items), sexual (13 items), and hormonal (11 items). A summary score was constructed for each domain, and also two urinary scales distinguishing irritative/obstructive symptoms and incontinence, as recommended by the developers of the questionnaire. All EPIC items are answered on a 5-point Likert scale. Scores were obtained by transforming item responses into a 0-100 scale, and calculating the mean when at least 80% of the items were completed, with higher scores indicating better HRQL. The Spanish versions of both instruments have shown appropriate psychometric properties.[17,18]

Data analyses

Means, standard deviations, and percentages were calculated to describe the characteristics of the sample. Differences in HRQL score changes (from baseline to 12 months) among groups defined by socio-demographic, clinical and treatment variables were tested with one-way analysis of variance.

To explore the relationship between treatment and HRQL change, figures showing the evolution of SF-36 and EPIC scores during follow-up per each modality of treatment were separately constructed for patients treated with surgery and radiotherapy. We compared SF-36 score means with USA general population norms to examine the impact of prostate cancer on patients' HRQL. Differences in HRQL among treatment modalities at each evaluation were tested with one-way analysis of variance.

To estimate the HRQL change over time according to treatment modality, Generalized Estimating Equation (GEE) models were constructed to account for correlation among repeated measures. For each EPIC score (included as dependent variable) a model was constructed for surgery and another one for radiotherapy. Treatment modality was included as the explanatory variable, selecting the most frequently applied to use as reference category. Time and interactions between time and treatment modalities were included in the models, in order to assess change. The GEE models included as adjusting factors the hospital and some baseline patient characteristics: age as a continuous variable, tumour classification (T, N, M), hormonal therapy, and any other variables significantly associated with HRQL change in the bivariate analysis. These variables were chosen because their clinical significance is clear in practice and in the literature on prostate cancer treatment. Effect sizes were calculated (ES= Beta coefficients/standard deviation at baseline) to quantify the magnitude of estimated change, and the following ES categorization guidelines were applied:[19] small 0.2, moderate 0.5, and large 0.8.

Analyses were carried out with SPSS version 12[20] and SAS version 9.2[21] statistics software.

Results:

We recruited 502 PC patients, and 30 were excluded as they did not meet the inclusion criteria. Of the remaining 472 patients, 426 completed HRQL questionnaires at baseline (90.3% response rate), 346 at 6 (73.3 %) and 385 at 12 month of follow-up (81.6 %). The mean age and PSA serum level were 68 years, and 25.5 ng/dL, respectively (Table 1). Most patients were classified at stage II (68%). Almost half of them were treated with surgery, 32% with radiotherapy, 17% with hormones, and 3% received no primary treatment. Radical prostatectomy was mainly laparoscopic (n=89), retropubic (n=71), or robot-assisted (n=19). The radiotherapy applied was mainly external, using 3-D conformal radiation (n=53) or IMRT (n=31), and 41 patients received interstitial radiotherapy.

----------Table 1----------

Table 2 shows the results of the bivariate analysis of HRQL score changes from baseline to 12 months. In general, no differences were found by age, education, number of comorbidities, TNM, and tumour stage. Statistically significant differences were found by treatment for the SF-36 Physical component and EPIC sexual, bowel, and hormonal domains. Patients treated with hormones or radiotherapy presented physical decline ($p<0.001$), and the latter also bowel worsening ($p=0.008$). Radical prostatectomy patients presented the highest sexual decline ($p<0.001$), and the highest worsening on hormonal domain was observed among patients treated with hormones ($p<0.001$).

----------Table 2 ----------

Figure 1 shows that physical health of prostate cancer sample was significantly better than the SF-36 reference norms' group of men aged 65-74 years, and remained stable during follow-up. Mental health was quite similar to this reference norms' group. No significant differences in SF-36 Physical and Mental Component summaries were observed among surgical modalities. Radiotherapy techniques only presented statistically significant differences in

the Physical component at 12 months of follow-up, where brachytherapy showed better results than 3D conformal external radiotherapy.

----------Figure 1----------

EPIC presented several significant differences at baseline by surgical modality (Figure 2, left column), but no differences after treatment. For example, patients undergoing robot-assisted prostatectomy presented before treatment the highest scores (best HRQL) in urinary incontinence, and those with open prostatectomy the worst. A clear decline was observed in urinary incontinence and sexual EPIC scores regardless of the surgical modality applied. Patients treated with radiotherapy also showed a clear sexual decline (Figure 2, right column), except for those treated with brachytherapy, who were significantly better than those with external radiation at 6 and 12 months of follow-up. No differences by radiotherapy modality were observed in the other EPIC domains.

----------Figure 2----------

The adjusted EPIC score changes from baseline to 6 and 12 month follow-up (estimated with GEE models) are shown in blue and purple, respectively, in Figure 3. Detailed results of GEE models are available in the Appendix 2. The left column of Figure 3 shows the change in patients treated with radical prostatectomy according to the surgical modality applied. Patients treated with laparoscopic technique experienced significant urinary incontinence deterioration over time with beta coefficients of -28.5 and -10.2 at 6 and12 months, respectively. Compared to this group, used as reference in the GEE model, change experienced by patients undergoing open and robot-assisted prostatectomy did not statistically differ. Sexual deterioration was statistically significant for patients treated with laparoscopic technique at 6 and 12 months (beta coefficients of -36.1 and -26.4, respectively). The evolution of patients with retropubic prostatectomy was better than the laparoscopic group (deterioration was 20.1 and 11.4 points lower); while patients undergoing robot-assisted technique did not statistically differ from those with laparoscopy. No statistically significant change was observed in urinary irritative-obstructive and bowel scores in any of the surgical modalities.

----------**Figure 3** ----------

The right column of Figure 3 shows change in patients treated with different modalities of radiotherapy. No statistically significant change was observed in urinary incontinence, urinary irritative-obstructive, or bowel scores in any of the radiotherapy modalities. For the sexual domain, patients treated with 3-D CRT presented a statistically significant change of -19 and -21 points at 6 and12 months, respectively, which indicated large worsening (ES$\geq$0.8). Patients treated with brachytherapy showed a significantly better evolution. The beta coefficients at 6 and 12 months indicated +16 and +23 points of less deterioration for brachytherapy compared to 3-D CRT (reference group), which translates into recovering pre-treatment sexual scores.

Discussion:

This Spanish multicenter prospective cohort study showed a similar HRQL evolution pattern among patients treated with radiotherapy, regardless of the modality applied, except for brachytherapy which did not present sexual side effects. Similarly, significant differences among surgical modalities were only found in sexual outcomes, radical retropubic prostatectomy being the technique showing the best results. The outstandingly better SF-36 physical health of the prostate cancer sample compared to the general population norms could reflect a selection bias of healthier men towards PSA detection.

Both laparoscopic and radical retropubic prostatectomy were standard techniques in the hospitals of study, representing 41% and 33% of surgical patients, respectively. Only one hospital with a da Vinci surgical system applied minimally invasive robotic prostatectomy to 19 patients of the study. The three surgical modalities presented a similar impact on urinary incontinence of around -10 points, reflecting an almost moderate worsening (0.4 ES). Sexual deterioration was large (1 ES) among patients treated by laparoscopy and moderate (0.6 ES) for those with radical retropubic prostatectomy. A systematic review[22] identified eight studies comparing urinary continence between laparoscopic and retropubic prostatectomy, and three comparing them regarding erectile function. In both comparisons the available data suggested similar results between these two surgical modalities. An ongoing Cochrane review aims to compare the laparoscopic with the radical retropubic prostatectomy for the treatment of localised prostate cancer.[23]

Regarding results of robot-assisted prostatectomy, our study has obviously no statistical power to detect HRQL differences in this small group of 19 patients. However, it is interesting to remark that the magnitude of both urinary incontinence and sexual worsening is very similar to what was observed among patients treated with laparoscopic prostatectomy. These results are in disagreement with the findings from recent systematic reviews showing a better urinary continence recovery[9] and potency rates 12 months after surgery for

robot-assisted prostatectomy.[10] The definition of potency in the primary studies included remains, though, a non-standardized parameter.

The majority of hospitals included in the study applied the three radiation modalities, 3D-CRT being the most frequent and IMRT the least, representing 36% and 21% of patients undergoing radiotherapy, respectively. The three presented non significant, small (ES <0.2) impacts on both urinary domains, incontinence and irritative obstructive. Patients treated with 3-D conformal radiation showed a bowel change of 4 points, reflecting between moderate and large worsening (0.7 ES); while IMRT technique showed better results at 6 months, but a similar deterioration at 12 months. Our results are consistent with findings reported by a systematic review,[11] which identified 13 non-randomised studies comparing IMRT with 3D-CRT, and showed an advantage for IMRT in gastro-intestinal toxicity, but no differences in HRQL.

The only significant difference among radiation modalities was observed on sexual deterioration, which was large (0.8 ES) among patients treated by 3-D CRT and IMRT and did not appear at all among those with brachytherapy. It is important to point out that this difference could be explained in part by the clinical profile of patients undergoing external or interstitial radiotherapy (age…). However, there were no differences in pretreatment sexual scores between them. Likewise, the results of the GEE models that allowed us to adjust for pretreatment differences on the main prognostic variables are consistent with the results obtained from bivariate comparison. Furthermore, this finding is consistent with the better result of brachytherapy compared to 3-D CRT in previous comparative high quality studies.[24-26]

Lost to follow-up and missing data is the main limitation of longitudinal studies with repeated measurements. Of the 472 patients included, only 16 patients were lost during the 12 months of follow-up, and the average missing HRQL data in the three evaluations was 18.3%. Furthermore, GEE allows the presence of missing values in the repeated measurements of the dependent variable, without having to exclude individuals with incomplete data and with no need of imputation methods (even though missing completely at random does

not hold).[27] Second, we did not report the HRQL evolution of patients under observation because it was a very small group (n=13), reflecting the poor application of active surveillance in Spain. Furthermore, one year is a short follow-up to expect any change in these patients taking into account that 2/3 parts were diagnosed at T1. Third, there were numerous patients treated only with androgen deprivation therapy, which were not showed in figures because comparing different hormonal protocols was out of this manuscript's focus. Finally, our study is only able to assess short-term benefits and harms related to primary treatments, longer follow-ups are needed to evaluate long-term effects.

In conclusion, our study provides multicenter, prospective one year follow-up results for Spanish patients with prostate cancer undergoing treatment by either standard or novel modalities of surgery and radiotherapy. Our findings did not support the expected better results for new modalities of surgery. Similarly, HRQL evolution did not show any advantage in favour of IMRT when compared to 3-D conformal radiation. Therefore, it is unlikely that variations in the incorporation of these new technologies could have a major impact on the HRQL of Spanish prostate cancer patients. Obviously, there are other relevant outcomes, such as perioperative complications, hospital stay, lost of working days, and oncologic control, which also merit attention when evaluating updated modalities. Finally, we would like to highlight that brachytherapy differs from external radiotherapy modalities in its better sexual results. This finding supports the relevance of offering brachytherapy as an alternative to external radiation (when indicated by clinical and tumour characteristics) to patients who were seeking to limit the risk of sexual deterioration. Since this is not a comparative effectiveness study, treatment modality differences should not be interpreted in terms of efficacy, but can be useful to generate hypotheses to test in future studies.

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Table 1. Patient's socio-demographic and clinical characteristics.

	All patients (n = 472)
Age (yrs), mean (*SD*)	67.8 (7.6)
Education, n (%)	
Incomplete studies	47 (10.1%)
Primary or secondary studies	350 (75.4%)
Superior studies	67 (14.4%)
Comorbidities, n (%)	
None	255 (54%)
1	146 (30.9%)
2	54 (11.4%)
≥3	17 (3.6%)
Prior cancer disease, n (%)‡	37 (7.8%)
Gleason, mean (SD)	6.5 (1.2)
histological grade, n (%)	
I	17 (4.1%)
II	182 (44.2%)
III/IV	162 (39.3%)
Unknown	51 (12.4%)
PSA serum level, mean (SD)	25.5 (209.1)
Hormonoterapia, n (%)	28 (5.9%)
Prostate size, mean (SD)	45.3 (28.2)
T: Primary clinical tumour, n (%)	
Tx	1 (0.2%)
T1	194 (40.6%)
T2	189 (40.0%)
T3	74 (15.7%)
T4	8 (1.7%)
N lymph nodes, n (%)	
Nx	125 (26.5%)
N0	336 (71.2%)
N1	11 (2.3%)
M metastasis, n (%)	
Mx	94 (19.9%)
M0	368 (78.0%)
M1	10 (2.1%)
Tumour stage, n (%)	
I	58 (12.5%)
II	315 (68.0%)
III	69 (14.9%)
IV	19 (4.1%)
Unkown	2 (0.4%)
Primary medical treatment, n (%)	
Surgery	216 (47.5%)
External Radiotherapy	107 (23.5%)
Brachitherapy	41 (9.0%)
Hormonotherapy	78 (17.1%)
No treatment	13 (2.9%)
Unkown	17 (3.6%)

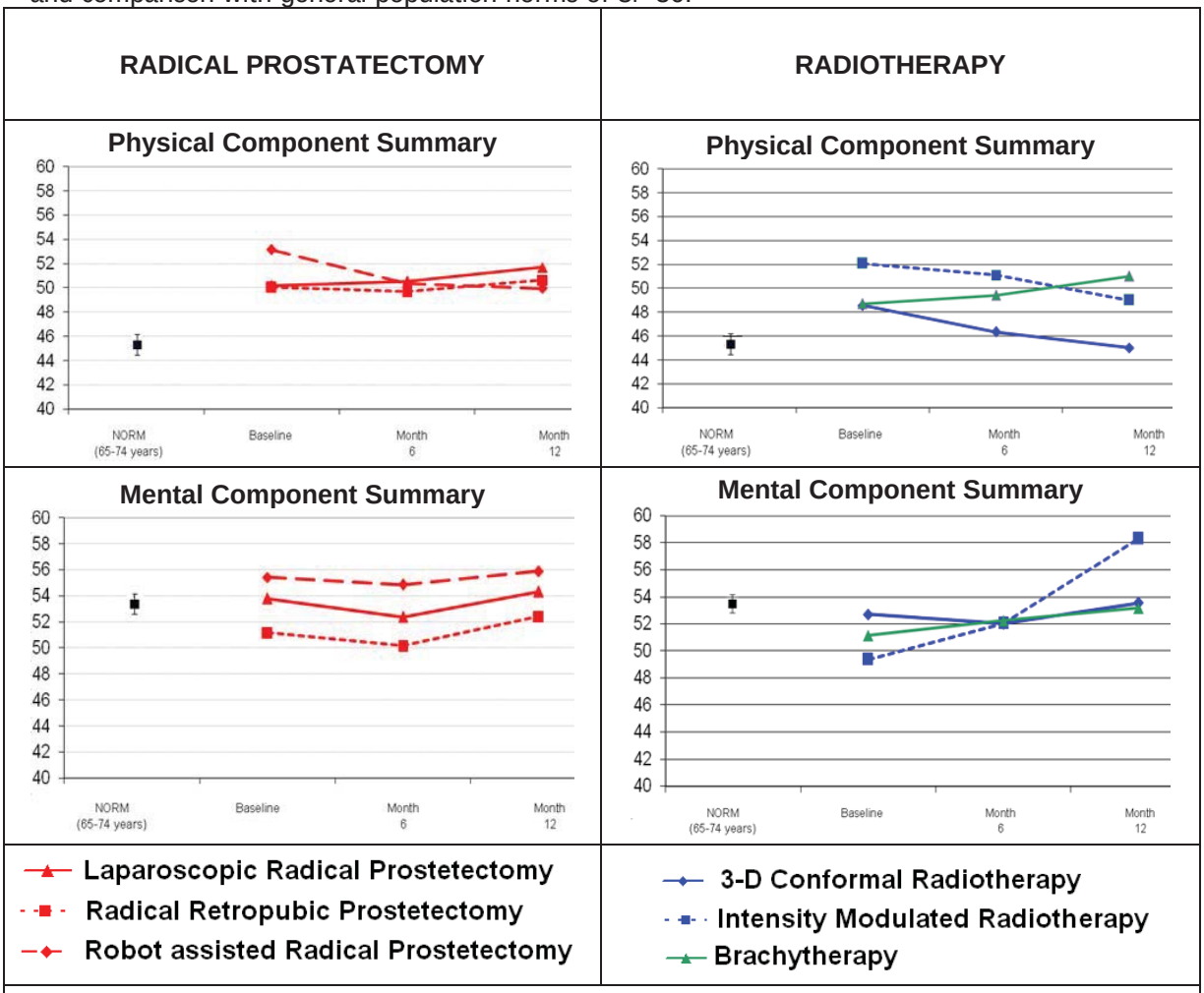
‡ Excluding any urologic cancer.

Table 2 - Differences in HRQL score changes (from baseline to 12 months).

	SF-36			EPIC					
	PCS	MCS		EPIC Urinary	EPIC Urinary Incontinence	EPIC Urinary obstructive	EPIC Sexual	EPIC Bowel	EPIC Hormonal
Age, years									
< 60 years	-0.1 (7.6)	0.5 (9.20)		-3.9 (15.2)	-1.3 (21.1)	-1.3 (18.3)	-21.9 (26.9)	-0.2 (15.5)	-0.4 (16.1)
60– 70 years	-0.9 (8.0)	1.4 (11.1)		1.3 (20.7)	-2.6 (30.0)	3.4 (19.8)	-18.4 (29.0)	-0.2 (10.2)	-1.2 (11.4)
> 70 years	-1.8 (9.2)	0.6 (9.3)		-1.5 (17.2)	-5.4 (24.2)	1.6 (16.0)	-13.7 (25.0)	-1.5 (11.7)	-4.0 (14.5)
p-value	0.437	0.769		0.167	0.376	0.262	0.149	0.991	<0.001
Education									
Incomplete studies	-4.0 (7.3)	1.3 (10.6)		-0.1 (21.3)	-2.0 (31.6)	1.5 (18.7)	-12.1 (22.0)	-0.8 (8.1)	-4.4 (12.8)
Primary or secondary	-0.6 (8.5)	0.7 (10.8)		-0.4 (19.2)	-5.6 (28.2)	2.7 (18.2)	-18.3 (29.0)	-0.7 (11.9)	-1.7 (13.8)
University	-0.8 (8.3)	1.5 (8.4)		-0.5 (17.0)	-2.6 (21.2)	1.2 (18.4)	-17.0 (26.0)	-0.6 (11.8)	-1.8 (12.5)
p-value	0.085	0.813		0.995	0.574	0.788	0.455	0.997	0.513
Number of comorbidities									
0	-1.5 (10.3)	1.5 (10.3)		-1.6 (16.3)	-6.5 (24.5)	1.4 (16.2)	-18.1 (28.3)	-0.5 (9.5)	-2.1 (12.0)
1	-0.6 (8.4)	-0.3 (9.6)		0.5 (21.0)	-2.0 (26.8)	2.0 (20.6)	-15.9 (27.6)	-0.7 (11.7)	-1.5 (13.0)
2 or more	-1.4 (8.1)	1.5 (10.2)		1.9 (22.4)	-1.7 (33.1)	4.3 (20.3)	-18.0 (25.6)	-1.1 (17.1)	-3.7 (18.4)
p-value	0.842	0.331		0.397	0.284	0.596	0.804	0.935	0.618
T: Primary clinical tumour									
T1	0.0 (8.5)	1.5 (9.3)		0.2 (17.9)	-4.3 (29.2)	2.7 (15.2)	-16.2 (30.8)	-0.4 (8.9)	-1.0 (12.8)
T2	-1.4 (8.4)	0.3 (10.8)		-0.7 (20.8)	-5.7 (28.3)	2.4 (20.0)	-19.2 (24.5)	-0.7 (13.2)	-1.9 (13.4)
T3	-2.3 (8.0)	0.7 (9.6)		-2.3 (16.0)	-0.5 (15.0)	-1.8 (19.2)	-17.6 (28.7)	-1.0 (7.7)	-5.8 (12.5)
T4	-0.2 (9.8)	19.9 (14.3)		-4.7 (8.1)	-12.9 (12.1)	-0.7 (8.1)	1.5 (17.2)	7.3 (30.3)	10.5 (22.0)
pvalue	0. 284	0. 010		0. 855	0. 522	<0. 409	0. 367	0. 476	0. 025
N lymph nodes									
Nx	-2.4 (8.6)	0.9 (8.9)		0.9 (18.3)	-3.0 (31.2)	3.5 (15.0)	-16.1 (28.3)	-3.0 (11.2)	-4.5 (13.3)
N0	-0.6 (8.3)	0.9 (10.3)		-0.7 (18.8)	-4.6 (25.4)	1.7 (19.1)	-18.0 (27.7)	-0.2 (11.5)	-1.3 (13.2)
N1	-4.6 (6.9)	6.2(17.7)		-2.9 (22.5)	-8.6 (28.0)	0.5 (16.9)	-7.1 (17.2)	7.5 (14.7)	-6.5 (18.0)
p-value	0. 153	0. 514		0. 762	0. 821	0. 730	0. 540	0. 030	0.137
M metastasis									
Mx	-3.1 (8.6)	1.3 (8.4)		.9 (16.8)	-2.9 (25.3)	3.9 (14.8)	-18.4 (28.5)	-4.2 (11.2)	-4.7 (9.8)

M0	-0.6 (8.3)	0.7 (10.3)		-.8 (19.2)	-4.8 (27.1)	1.6 (19.0)	-17.5 (27.5)	-0.2 (11.2)	-1.7 (13.7)
M1	0.3 (8.8)	13.7 (16,2)		4.9 (20,1)	-0.4 (18.4)	6.4 (14.6)	-0.3 (24.6)	18.0 (15.6)	7.7 (24.8)
p-value	0. 105	0. 038		0. 673	0. 844	0. 573	0. 371	<0.001	0.077
Tumour stage									
I	0.9 (5.7)	2.0 (6.5)		-0.3 (21.0)	-6.8 (34.3)	3.4 (15.4)	-21.6 (19.9)	-2.2 (10.8)	-2.2 (7.9)
II	0.8 (8.8)	0.8 (10.7)		-0.1 (19.4)	-4.3 (27.8)	2.5 (18.5)	-17.2 (29.1)	-0.4 (11.6)	-1.3 (14.0)
III	1.7 (8.3)	0.7 (9.8)		-2.7 (14.8)	-1.1 (14.0)	-2.2 (18.9)	-17.2 (28.8)	-1.5 (9.6)	-4.8 (12.0)
V	3.0 (8.0)	3.0 (13.0)		-1.4 (14.7)	-9.4 (25.0)	2.5 (11.8)	-10.4 (22.1)	6.1 (13.4)	-4.0 (18.8)
p-value	0.887	0.905		0.853	0.823	0.337	0.686	0.136	0.487
Treatment									
Surgery	0.3 (7.1)	0.9 (10.3)		-2.2 (19.6)	-7.9 (32.3)	1.6 (16.7)	-21.8 (26.7)	0.3 (9.0)	-,3 (10,1)
Radiotherapy	-2,2 (8,8)	2,4 (10,4)		1,8 (16,1)	1,1 (13,7)	2,2 (19,0)	-14,4 (31,1)	-3,5 (15,3)	-2,4 (15,0)
Hormonotherapy	-3.6 (10.8)	-1.3 (9.7)		1.1 (19.4)	-1.1 (23.4)	2.4(19.7)	-9.2 (22.8)	0.9 (10.5)	-7,5 (18,1)
p-value	<0.001	0.330		0.409	0.071	0.837	<0.001	0.008	<0.001
Hormonoterapy									
No	.0 (7.2)	1.1 (9.8)		-1.1 (19.0)	-6.3 (29.7)	2.1 (17.6)	-19.3 (27.3)	.0 (9.4)	-0.6 (10.5)
Yes	-3.1 (9.9)	0.9 (10.8)		0.9 (18.2)	-.6 (19.4)	2.0 (19.5)	-13.6 (27.9)	-1.9 (14.6)	-4.8 (17.3)
p-value	0. 001	0. 900		0. 359	0. 065	0. 980	0. 071	0. 140	0.005

Figure 1. Evolution of patient's physical and mental health according to treatment modalities, and comparison with general population norms of SF-36.



Black squares indicate the mean and 95% confidence interval of men aged 65-74 years from United States general population norms of SF-36. One-way analysis of variance of SF-36 scores among treatment groups for each assessment (*p<0.05)

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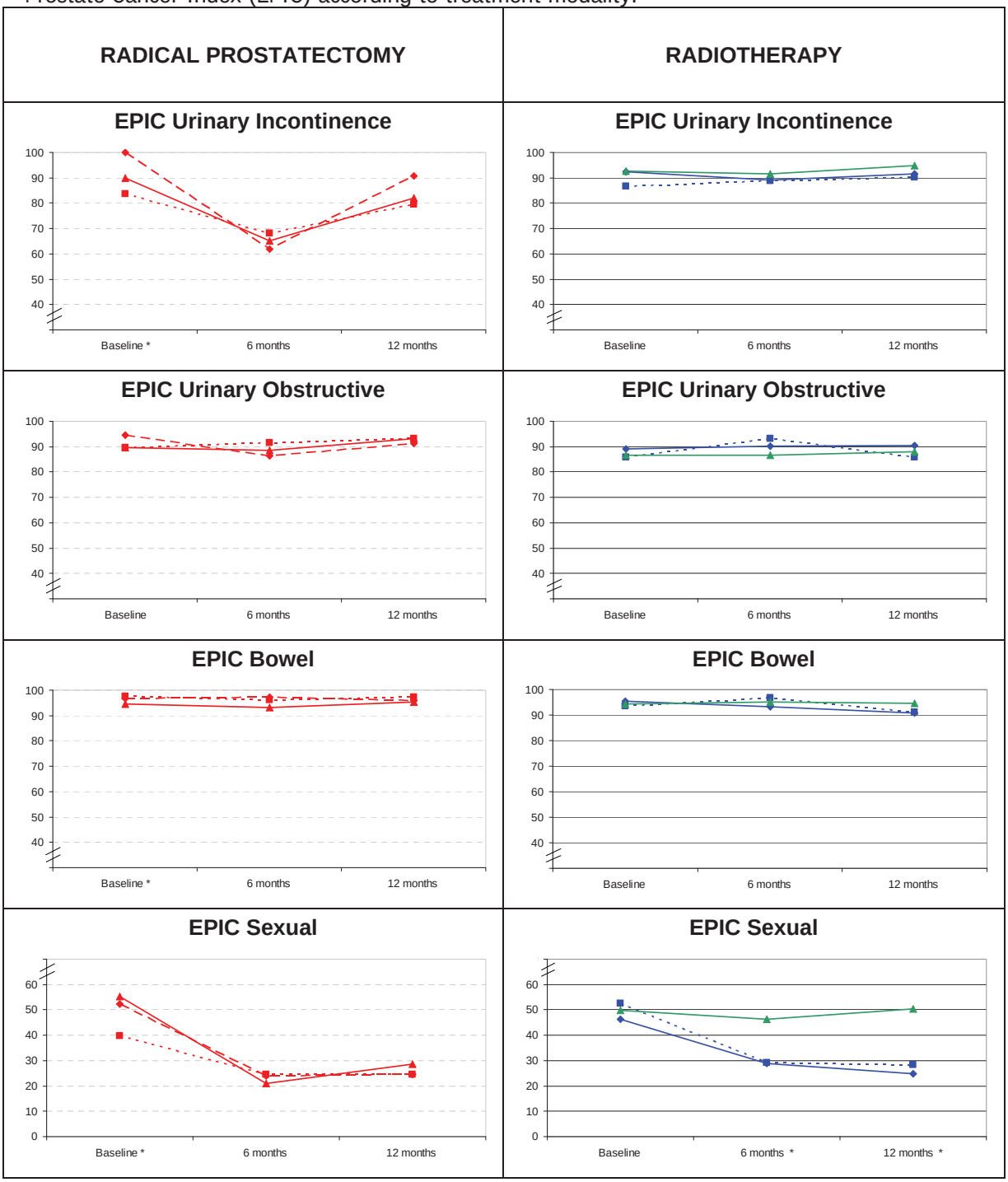
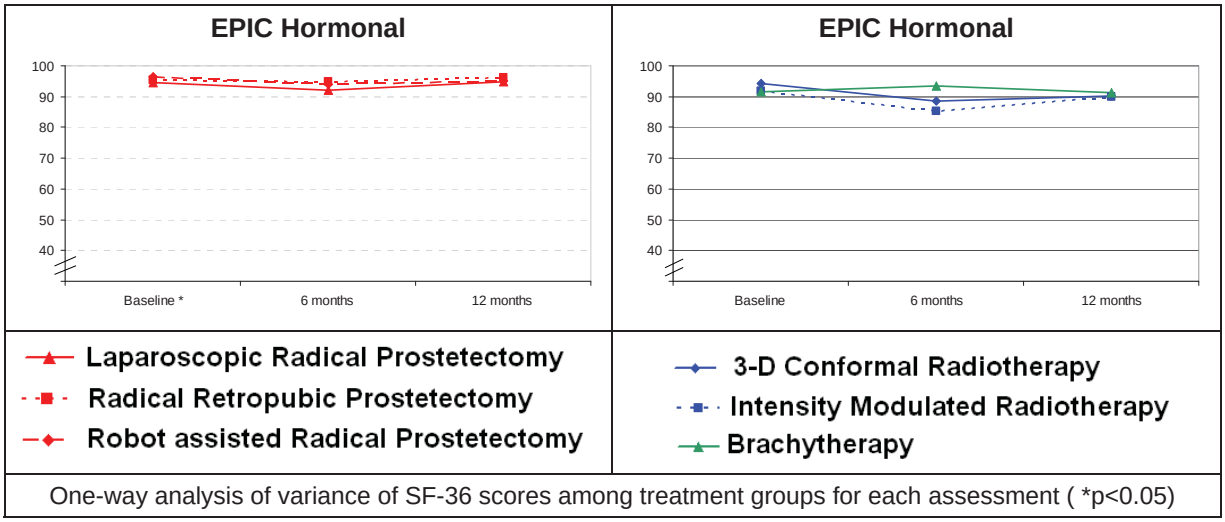
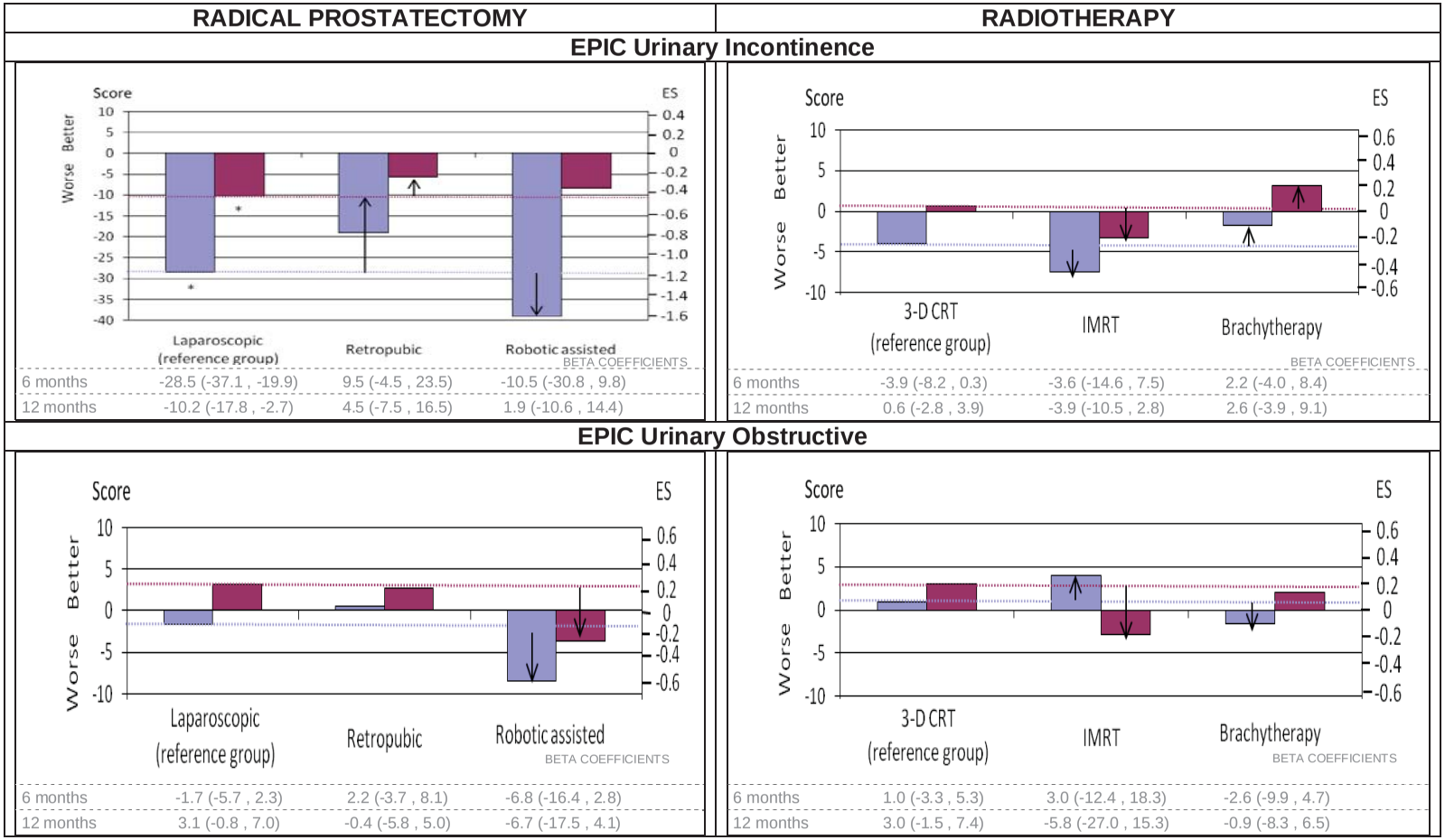
Figure 2. Evolution of patients' health-related quality of life, measured with the Expanded Prostate Cancer Index (EPIC) according to treatment modality.



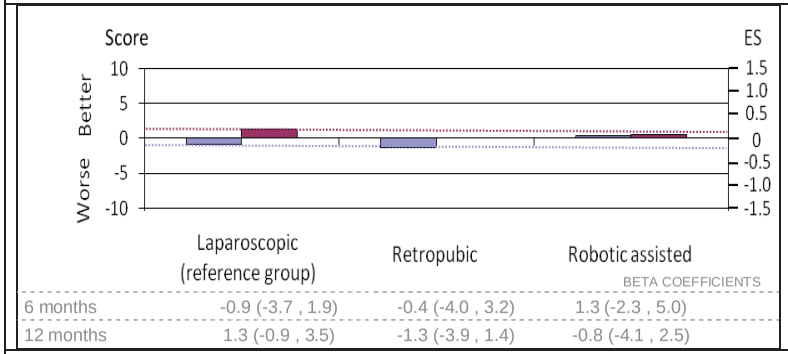


One-way analysis of variance of SF-36 scores among treatment groups for each assessment (*p<0.05)

Figure 3 – Adjusted Expanded Prostate Cancer Index (EPIC) score changes over time according to treatment modalities.

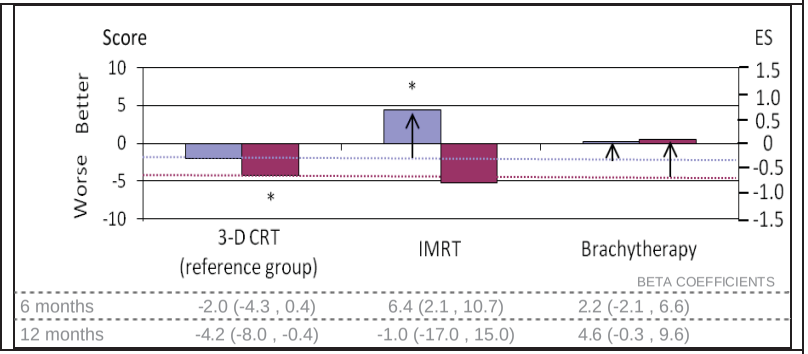


EPIC Bowel



BETA COEFFICIENTS

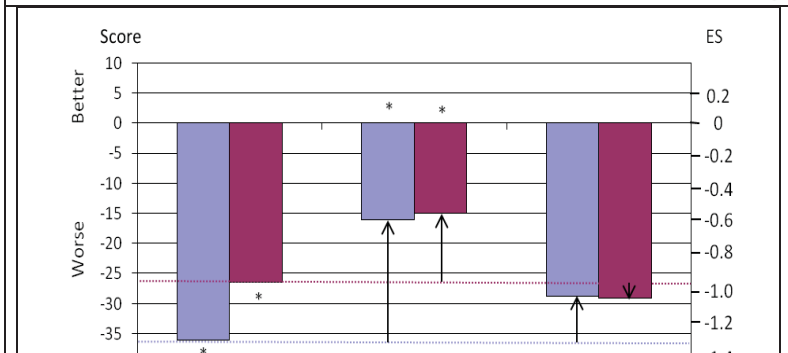
6 months	-0.9 (-3.7 , 1.9)	-0.4 (-4.0 , 3.2)	1.3 (-2.3 , 5.0)
12 months	1.3 (-0.9 , 3.5)	-1.3 (-3.9 , 1.4)	-0.8 (-4.1 , 2.5)



BETA COEFFICIENTS

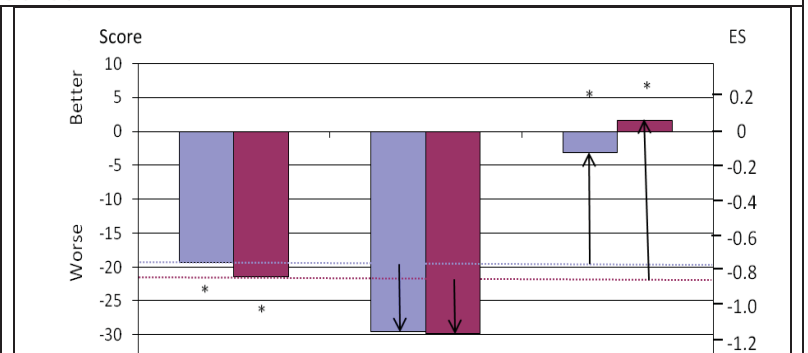
6 months	-2.0 (-4.3 , 0.4)	6.4 (2.1 , 10.7)	2.2 (-2.1 , 6.6)
12 months	-4.2 (-8.0 , -0.4)	-1.0 (-17.0 , 15.0)	4.6 (-0.3 , 9.6)

EPIC Sexual



BETA COEFFICIENTS

6 months	-36.1 (-42.0 , -30.2)	20.1 (11.1 , 29.1)	7.3 (-6.6 , 21.2)
12 months	-26.4 (-32.3 , -20.6)	11.4 (2.5 , 20.2)	-2.7 (-15.5 , 10.1)



BETA COEFFICIENTS

6 months	-19.3 (-27.9 , -10.8)	-10.2 (-30.1 , 9.7)	16.2 (3.4 , 29.1)
12 months	-21.4 (-29.8 , -13.1)	-8.3 (-25.8 , 9.2)	23.1 (9.0 , 37.2)

Bars indicate the change from baseline to 6 months (blue bar) and 12 months follow-up (purple bar) as estimated by GEE models adjusted for hospital, age, TNM, and hormonotherapy. The arrows indicate the direction and magnitude of the difference when compared with the reference group (indicated with the dot line). *p-value <0.05.

5. CONCLUSIONS

Available evidence on prostate cancer-specific Health-Related Quality of Life instruments applicable to patients with early-stage disease would currently support a preference for the use of Expanded Prostate Index Composite (EPIC), Patient-Oriented Prostate Utility Scale (PORPUS) and Prostate Cancer Quality of Life Instrument (PC-QoL). Choosing among them will mainly depend on particular study requirements.

For longitudinal studies or clinical trials, where responsiveness and reproducibility are the maximum priority, PC-QoL or EPIC would be recommended. For economic evaluations, PORPUS would be chosen as it allows cost-utility analysis. The brief versions, such as EPIC short, EPIC-Clinical Practice or short UCLA-PCI might be preferred to minimize administration burden. Our results facilitate the decision-making process regarding the correct instrument selection for prostate cancer patients diagnosed at early-stage disease, and its use and interpretation for a certain study purpose or setting.

Researchers and clinicians now have at their disposal a bladder cancer-specific Health-Related Quality of Life instrument for use in Spanish patients that is applicable across the wide spectrum of this disease. Our results suggest the multidimensionality of the Spanish Bladder Cancer Index (BCI) version, and provide considerable evidence about its appropriate metric properties, including responsiveness to health changes over time even in patients treated with non-invasive techniques.

Comparison with the original U.S. BCI version shows that it is similar in reliability and validity, suggesting that the cross-cultural adaptation method followed has yielded an equivalent Spanish version. Moreover, proofs supporting the BCI as a valuable tool for assessing Health-Related Quality of Life in patients within the whole bladder cancer spectrum are strengthened by the demonstration of its appropriateness in a different language and culture, and reinforce its usefulness for international studies.

Our study provides novel multicentre, prospective one year follow-up results mainly for patients with bladder cancer diagnosed at non-muscle invasive stages, using generic and disease-specific validated Health-Related Quality of Life instruments. Comparing general health with population norms, our results highlight a considerable impact of bladder cancer on mental health at diagnosis that clinicians should be aware of.

A distinctive bladder cancer treatment pattern of benefits has emerged for the first time from our study. While urinary symptoms improved after transurethral resection with or without intravesical therapy, small bowel and sexual improvements were found for the combination of transurethral resection with Bacillus Calmette-Guérin and mitomycin, respectively. Since this is not a comparative effectiveness study, treatment differences should not be interpreted in terms of efficacy, but can be useful to generate hypotheses to test in future studies. Our findings contribute to the understanding of patients' burden of disease and to their clinical management.

For prostate cancer patients, Health-Related Quality of Life evolution did not support the expected better results for new modalities of surgery. Similarly, they did not show any advantage in favour of intensity modulated radiotherapy when compared to 3-D conformal radiotherapy. Therefore, it is unlikely that variations in the incorporation of these new technologies could have a major impact on the Health-Related Quality of Life of Spanish patients. Obviously, there are other relevant outcomes, such as perioperative complications, hospital stay, lost of working days, and oncologic control which also merit attention when evaluating updated modalities.

Finally, we would like to highlight that brachytherapy differs from external radiotherapy modalities in its better sexual results on prostate cancer patients. This finding supports the relevance of offering brachytherapy as an alternative to external radiation (when indicated by clinical and tumour characteristics) to patients who were seeking to limit the risk of sexual deterioration and its impact on Health-Related Quality of Life.

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7. ANNEX

7.1 **Book chapter:** Encyclopedia of Quality of Life and Well-Being Research: Normative Data

7.2 **Article:** [Reference guidelines for the 12-Item Short-Form Health Survey version 2 based on the Catalan general population].

Schmidt S, Pardo Y. Normative data. Dins: Encyclopedia of quality of life and well-being. Michalos (ed.). 4375-4379. ISBN 9789400707535

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