Comparative Effectiveness Research on Localized Prostate Cancer Treatments

Mónica Marcela Ávila Pacheco

TESI DOCTORAL UPF / 2017

DIRECTOR DE LA TESI

Dra. Montserrat Ferrer IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona. CIBER en Epidemiología y Salud Pública (CIBERESP), Spain. Departament de Pediatria, d'Obstetrícia i Ginecologia i de Medicina Preventiva, Universitat Autònoma de Barcelona (UAB), Bellaterra

CO-DIRECTOR

Dr. Jordi Alonso IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona. CIBER en Epidemiología y Salud Pública (CIBERESP), Spain. Universitat Pompeu Fabra (UPF), Barcelona

DEPARTAMENT DE CIÈNCIES EXPERIMENTALS I DE LA SALUT

A Dios.
A mis padres y familia.
A mis abuelitos en el cielo.
Y a quienes han sido mi familia en Barcelona.

Acknowledgements

Durante esta parte de mi camino llamado “tesis” muchas personas me han acompañado, más o menos tiempo, pero todas han contribuido a mi recorrido. Primero, gracias a Dios y a mis queridos padres: Georgina y Jaime, por su apoyo incondicional y soporte, en la distancia. A Orla y Adri. A mis amados sobrinos: Pipe y Ale, por sus sonrisas y existencia. A Montse con quien estaré siempre agradecida por brindarme la oportunidad de venir a Barcelona, por ser mi formadora y guía en este mundo de la investigación, y muchas veces en la vida.

A Jordi por sus consejos y críticas constructivas. A todos mis compañeros y amigos de la URSS, estén o ya no estén presentes, que me han enseñado algo durante estos casi 6 años: Àngels, por escucharme muchísimas veces, Gime, por esos buenos mates y sensatas conversaciones; Marc, por su linda y buena energía; Yolanda, por animarme; Olatz y Gemma, por su disposición de ayuda; Carme, Áurea y Puri por sus gestiones, tips, correcciones, y su inmensa colaboración; Carlos y Antonia por sus experimentados y acertados comentarios. A Pere, Susa, Víctor, Karina y Anne H., por su compañerismo. Gracias también al Cuni, a Gabi y a Eli. Especialmente a Elena y Ben por su amistad y apoyo. A las chicas IMIM: Laila y Noelle, por hacer del 2015 uno de mis mejores años. A Laura por ser mi amiga, familia y confidente.

A las queridas chicas del “Spring days” y “Únicas”. Mireia, Gemma y Nuria. A las rioplatenses: Bea, Andre, Maggie y Flor. A Abir. A Dali por su incondicional amistad. A Zonya, Dime, Marga, Luquillas y Moni B por su compañía desde el MSP. A Dinora y Monic. A Nurieta C. A los siempre queridos: Cami, Ori y Ville. A mis amigos de Colombia: Anita María, Héctor, Yira, Ana y Sensei, Yoli y Juan. A Ana Lu por sus advices. A mis compañeros de la UICEC por su apoyo en esta intensa última etapa. En general, a todas las personas que se han cruzado en mi camino durante estos cinco años y han contribuido a cumplir este sueño que un día, hace ya una década atrás en mi natal Bogotá, se cruzó por mi cabeza y corazón: Muchas gracias!

Abstract

The general aim of this doctoral thesis was to compare the effectiveness of the three most established primary treatments for localized prostate cancer, focusing on the patient's perspective: open radical prostatectomy, 3D-external conformal radiotherapy, and brachytherapy.

The "Spanish Multicentric Study of Clinically Localized Prostate Cancer" is a prospective cohort with consecutive patient recruitment at diagnosis (2003-2005) in 10 hospitals. Patients were followed yearly during 5 years. The Patient-Reported Outcomes measured included generic and prostate cancer-specific health-related quality of life (HRQoL) profiles, and direct and indirect utilities. The Patient-Oriented Prostate Utility Scale (PORPUS) was adapted into Spanish to measure indirect utilities. Also mortality and biochemical disease-free survival were assessed.

Our study finds late changes which attenuated differences between treatments, but the distinctive HRQoL impact patterns remained until the 5th year, supporting brachytherapy as the option causing the least impact, except for moderate urinary irritative-obstructive symptoms. Brachytherapy and external radiotherapy are more highly valued than radical prostatectomy, and urinary incontinence is the side effect with highest impact on preferences. The Spanish PORPUS showed appropriate metric properties to measure indirect utilities, allowing economic evaluation with cost-utility analysis.

Resumen

El objetivo general de esta tesis doctoral fue comparar la efectividad de los tres tratamientos más establecidos para cáncer de próstata localizado, desde la perspectiva del paciente: prostatectomía radical, radioterapia externa o braquiterapia

El "Estudio Multicéntrico Español de Cáncer de Próstata Localizado" es una cohorte prospectiva de pacientes reclutados en 10 centros hospitalarios (2003-2005), y seguidos anualmente durante 5 años. Los Resultados Percibidos por los Pacientes evaluados incluyeron: perfiles genéricos y específicos de Calidad de Vida Relacionada con la Salud (CVRS), y utilidades directas e indirectas. El "Patient-Oriented Prostate Utility Scale" (PORPUS) fue adaptado al español para la estimación de utilidades por el método indirecto. También se evaluaron la mortalidad, y la supervivencia libre de recidiva.

Nuestro estudio encontró cambios tardíos que atenuaban las diferencias entre los tratamientos, pero los patrones distintivos del impacto de cada tratamiento sobre la CVRS permanecieron hasta el quinto año de seguimiento, apoyando la braquiterapia como la opción con menor impacto, excepto por los moderados problemas urinarios irritativos-obstructivos. La braquiterapia y la radioterapia externa son mejor valoradas que la prostatectomía radical y la incontinencia urinaria es el efecto secundario con mayor impacto en las preferencias de los pacientes. La versión española del PORPUS mostró apropiadas propiedades psicométricas para medir utilidades indirectas, permitiendo la realización de evaluaciones económicas a través de análisis coste-utilidad.

Preface

This doctoral thesis is presented according to the instructions provided by the Department of Experimental and Health Sciences of the Universitat Pompeu Fabra. It is a compendium of scientific manuscripts published in indexed peer reviewed journals.

All of these manuscripts have been produced within the "Spanish Multicentric Study of Clinically Localized Prostate Cancer", which is an observational, prospective study that recruited patients in 10 hospitals in Spain between 2003 and 2005 consecutively, treated either with radical prostatectomy, brachytherapy or external 3D-external conformal radiotherapy. Patients were followed intensively during the first twelve months and yearly thereafter until the 5-year post-treatment point.

In the first part of this document, a narrative review summarizes background information relevant to this work. It describes the epidemiology of prostate cancer, the available treatment options for men with localized disease, and outcomes such as health-related quality of life (HRQoL), survival, and disease control measures in localized prostate cancer, as well as a general description of available comparative effectiveness research of the treatment strategies.

The first paper presents the impact of the treatments on HRQoL on localized prostate cancer patients in a 5-year follow-up. It also describes measures of cancer control such as overall survival, and biochemical disease-free survival of patients of the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort.

> *Ferrer M., Guedea F., Suárez J.F., de Paula, B., Macías V., Mariño V., Hervás A., Herruzo I., Ortiz M.J., Ponce de León J., Sancho G., Boladeras A.; Ayala A; Craven-Bratle J;* ***Ávila M;*** *Cunillera O; Pardo Y.; Alonso J; Aguiló F.* **Quality of Life Impact of Treatments for Localized Prostate Cancer: Cohort Study with a 5 Year Follow-up.** *Radiotherapy and Oncology. 2013; 108(2): 306-313.*

The second paper presents the patients' preferences and willingness to pay for the treatment options in the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort, until 5 years after treatment.

> ***Ávila M.,*** *Becerra V., Guedea F., Suárez J.F., Fernández P., Macías V., Mariño A., Hervás A., Herruzo I., Ortiz M.J., Ponce de León J., Sancho G., Cunillera O., Pardo Y., Cots F., Ferrer M. and the Group of Clinically Localized Prostate Cancer.* **Estimating Preferences for Economic Evaluation in Patients with Localized Prostate Cancer.** *Int J Radiat Oncol 2015; 91(2): 277-287.*

The third paper shows the results on the adaptation and evaluation of the psychometric properties of the Spanish version of Patient-Oriented Prostate Utility Scale (PORPUS), a specific questionnaire to measure health-related quality of life in patients with prostate cancer that was developed originally for another language and culture. It gives the reader of this thesis an overview of the process and methods followed in order to maintain the equivalence with the original instrument.

> ***Ávila M.,*** *Pardo Y., Castells M., Ferrer F., Boladeras A., Pera J., Prada P., Guix B., de Paula B., Hernandez H., Pont A., Alonso J., Garin O., Bremner K., Krahn M., Ferrer M. and the Group of Clinically Localized Prostate Cancer.* **Adaptation and Validation of the Spanish Version of the Patient-Oriented Prostate Utility Scale (PORPUS).** *Qual Life Res 2014; 23(9):2481-2487.*

Finally, a fourth manuscript describing a systematic review and meta-analysis conducted to synthesize the evidence currently available on the impact of primary treatments on HRQoL in patients with low-intermediate risk localized prostate cancer has been annexed, since it is still under revision.

> ***Ávila M.,*** *Patel L., Garin O, López S., Cortés-Sanabria L., Pont A., Ferrer F., Boladeras A., Storås AH., Fosså SD., Sanda M., Ferrer M.* **Disease-Specific Patient Reported Outcomes After Treatment for Localized Prostate Cancer: A Systematic Review and Meta-analysis.**

I hope the results of this doctoral thesis contribute to generate quality evidence for patients and clinicians to best proceed after a diagnosis of localized prostate cancer, and to inform them of the trade-offs between benefits and side effects to improve the treatment shared decision-making process.

This doctoral thesis was conducted at the Health Services Research Group at IMIM (Hospital del Mar Medical Research Institute), and with the collaboration of the National Advisory Unit on Late Effects after Cancer Treatment at Oslo University Hospital, Radiumhospitalet. It was supported by grants from Instituto de Salud Carlos III FEDER: Fondo Europeo de Desarrollo Regional» (PI13/00412), Agència d'Informació, Avaluació I Qualitat en Salut (AIAQS), 436/05/2008, and Suport del Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya (2014 SGR 748; 2009 SGR 1095). Scholarships were also granted from IMIM (Hospital del Mar Medical Research Institute): Ajuts per a la finalització de tesis doctorals 2017, and from the CIBER of Epidemiology and Public Health of Spain–CIBERESP: Ayuda para estancias breves en el extranjero para el doctorado con mención internacional.

Table of contents

1 INTRODUCTION

1.1 Clinically Localized Prostate Cancer

a Epidemiology

Prostate cancer (PCa) is the second most common cancer diagnosed for men in the world with an estimated 1.1 million new cases diagnosed in 2012 (accounting for 15% of all incident cancer cases in men),(1) almost 70% of them (759,000) occurring in more developed regions.(2) Also, it is the fifth leading cause of death from cancer in men with 307,000 deaths (6.6% of all cancer deaths in men),(1) with a number of deaths larger in less developed regions than in developed areas (165,000 and 142,000, respectively).(2) In the European Union and Spain, it was the first most frequently diagnosis in men from all incident cancer cases in 2012 with 345,195 (32.1%) and 27,853 cases (20.7%), respectively. Also, it was the third leading cause of death of all cancer deaths(3,4) with 71,789 deaths(13.7%) and 5,481 deaths (11.3%), after lung and colorectum cancer.

In general, PCa incidence has increased, while its mortality has decreased in most countries. The incidence is higher in countries with higher socioeconomic development and has shown high variations geographically and over time, whereas the mortality has shown smaller variations.(5) The incidence of PCa varies across countries; a recent analysis from 43 populations identified five temporal patterns of the incidence rates (continual, step-wise, slow rise then rapid, moderate then slower, rapid increase then a pronounced peak).(6) According to these patterns, Spain belongs to the group of populations where the overall incidence rates have risen almost continually over the past several decades, showing that the rates at the younger ages generally increased more rapidly than those at older ages.(6)

The variation in incidence rates across regions is affected by differences in screening and diagnostic practices of PCa, especially by the wide use of prostatic-specific antigen (PSA) testing in high-income countries since the mid- to late-1980s. The PSA has led to

rapid increases in population-level incidence rates and an early detection of the disease among asymptomatic and younger men. Most of the patients are diagnosed (94%) with a cancer confined to the prostate gland, which is the definition of clinically localized prostate cancer.(7) A Cochrane review published in 2013(8) showed the association of screening with increased diagnosis (RR: 1.3; 95% CI: 1.02-1.65), with more localized disease (RR: 1.79; 95% CI: 1.19-2.70), less advanced PCa (RR: 0.80; 95% CI: 0.73-0.87), and no association with overall survival benefit (RR: 1.00; 95% CI: 0.96-1.03).

PCa patients present high relative survival rates which have increased over time. The study EUROCARE-V(9) showed that in Europe the age-standardised 5-year relative survival changed from 73% for the period between 1999–2001 to 82% in 2005–2007. Patients aged 55–64 years had higher relative survival (90%), than older patients: 75–84 years (77%) and 85+ (54%).

b Risk factors

The factors causing development of PCa are largely unknown, but the association between age, race, and family history with risk of developing PCa is well established. The disease is rarely seen in men younger than 40 years and incidence rises rapidly with each decade thereafter. Men with advanced age (≥ 75 years) in many populations have peaked incidence.(6) The black populations in Africa and the Caribbean have the highest incidence.(6)(10), while the lowest is among the Japanese(6), and the inherited risk has been estimated to be as high as 60%.(11,12)

Recently dietary factors including intakes of total dairy, milk, cheese, low fat and skim milk combined, total calcium, dietary calcium, and dairy calcium have been associated with an increased risk of prostate cancer. However, diverging results for types of dairy products and sources of calcium suggest that components of dairy other than fat and calcium may increase prostate cancer risk.(13)

c Diagnosis and staging of prostate cancer

PCa is usually suspected on the basis of PSA and digital rectal examination. Definitive diagnosis depends on the histopathological verification of adenocarcinoma in prostate biopsy cores or operative specimens.(14) PSA is a glycoprotein produced, almost exclusively, by the epithelial cells in the prostate. The serine protease is secreted from the prostate glands and into the seminal fluid. PSA is organ- but not cancer-specific; therefore, it may be elevated in benign prostatic hypertrophy, prostatitis and other non-malignant conditions.(15) The level measured in ng/mL is a continuous parameter: the higher the value, the more likely the existence of PCa.(14) The clinical state is mainly based on digital rectal examination and a suspect finding is recognised as an indication for PCa biopsy. Most prostate cancers are located in the peripheral zone and may be detected by digital rectal examination, when the volume is >0.2mL.(14)

The need for prostate biopsy is based on PSA levels and/or suspicious finding at digital rectal examination. Limited PSA elevation alone should not prompt immediate biopsy, PSA levels should be verified after a few weeks using the same assay under standardised conditions. Transrectal or transperineal core biopsies are recommended to obtain material for histopatological examination.(14)

Tissue from adenocarcinoma of the prostate is graded microscopically using the Gleason grading system. This method uses histologic patterns that consider the extent of glandular differentiation and the pattern of growth of the tumour. It generates scores adding the primary grade pattern (the one that is predominant in area, by simple visual inspection) and the secondary grade pattern (the second most common pattern), which can range from 2 to 10. Gleason 8–10 tumours are considered the most aggressive, Gleason 7 tumours are considered somewhat less aggressive, and Gleason 6 or lower tumours are considered potentially indolent.(16)

i. Staging (TNM classification)

Staging is the process of assessing whether the cancer is confined within the prostate gland or has spread beyond and, if so, to what extent it has spread. The staging system has been recently updated in the 8th edition of the American Joint Committee on Cancer.

The TNM classification is based on the extent of primary tumour (T stages), whether cancer has spread to the adjacent lymph nodes (N stages), and any metastasis (M stages) (see Table 1).(17)(18)

Table 1. TNM classification

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 PSA)

T2 Tumour confined within 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 beyond the prostate[2]
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles [3]

N – Regional lymph nodes[4]

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

Staging group

Stage	T	N	M
Stage I	T1a,T2a	N0	M0
Stage II	T2b,T2c	N0	M0
Stage III	T3,T4	N0	M0
Stage IV	Any T	N1	M0

Notes:
1. Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex yet not beyond the prostate is not classified as T3, but as T2.
3. Microscopic bladder neck involvement at radical prostatectomy should be classified as T3a.
4. Metastasis no larger than 0.2cm can be designated pN1

ii. Tumour risk groups of localized prostate cancer

The definition of D'Amico et al.(19) is a categorization of the tumours localized in the prostate which incorporates the pre-treatment prognostic factors, PSA levels, Gleason histologic score, and TNM stage, to classify patients with localized PCa into risk groups. The European Association of Urology proposed in 2015 a new classification (see table 2). (14)

Table 2. Defined risk groups of localized prostate cancer

	Low risk	Intermediate risk	High risk	Locally advanced
D'Amico (19).	PSA ≤10 ng/ml and GS <7 and cT1-2a	PSA 11-20 ng/ml or GS≤7, or cT2b	PSA >20 ng/ml, or GS>7 or cT2c-3a	
EAU	PSA < 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/ml or GS 7, or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS c**T3**-4 or cN+

Modified: Mottet 2015 (14) and Mottet 2014.(20)

d Management strategies of patients with localized prostate cancer

The most commonly used management options for localized PCa identified by Agency for Healthcare Research and Quality are shown in Table 3, below.(21)

Table 3. Management Strategies for Localized Prostate Cancer (21)

Treatment option	Treatment description
Active surveillance	Active plan to postpone intervention. Decision to proceed with radical treatment based on rate of rise of prostate-specific antigen level and results of repeat biopsies.
Watchful waiting	Active plan to postpone intervention. Palliative treatment given to patients exhibiting symptoms of disease progression.
Laparoscopic radical prostatectomy and robotic-assisted radical prostatectomy	Video-assisted, minimally invasive surgical method to remove the prostate.
Radical retropubic or perineal prostatectomy	Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes. Sometimes done laparoscopically or with robotic assistance and attempt to preserve nerves for erectile function.
External beam radiotherapy	Multiple doses of radiation from an external source applied over several weeks. Dose and physical characteristics of beam may vary. *Conformal radiotherapy uses three-dimensional* planning systems to maximize dose to prostate cancer and attempt to spare normal tissue. *Intensity modulated* radiation therapy provides the precise adjusted dose of radiation to target organs, with less irradiation of healthy tissues than conformal radiation therapy. *Proton radiation therapy* is a form of EBRT in which protons rather than photons are directed in a conformal fashion to a tumour site. The use of the heavier single proton beam (vs. photon therapy) allows for a low entrance dose and maximal dose at the desired tumour location with no exit dose. This theoretically permits improved dose distribution (delivering higher dose to the tumour with lower dose to normal tissue) than other EBRT techniques. May be used alone or in combination with proton and photon-beam radiation therapy. *Stereotactic beam radiation therapy* is a newer treatment that comprises the delivery of highly conformal hypofractionated radiation to a well-defined target, using advanced imaging technology.
Brachytherapy	Radioactive implants placed under anesthesia using radiologic guidance. Lower dose/permanent implants typically used. External beam "boost" radiotherapy and/or androgen deprivation sometimes recommended.
Cryoablation	Destruction of cells through rapid freezing and thawing using transrectal guided placement of probes and injection of freezing/thawing gases
High-intensity focused ultrasonography therapy	High-intensity focused ultrasonography therapy has been used as a primary therapy in patients with localized prostate cancer not suitable for radical prostatectomy. Tissue ablation of the prostate is achieved by intense heat focused on the identified cancerous area.
Androgen deprivation therapy	Oral or injection medications or surgical removal of testicles to lower or block circulating androgens.

From: Chou 2011.(21)

i. Deferred treatment (active surveillance/watchful waiting)

Treatment of localized PCa may be deferred to avoid loss of health-related quality of life. There are two distinct strategies for conservative management that aim to reduce overtreatment: active surveillance and watchful waiting (see Table 4).

Active surveillance (AS)

This management strategy involves close monitoring of the disease course with the expectation to intervene if cancer progresses. By delaying intervention for indolent tumours and treating only when more clinically-significant PCa is detected, AS has the following advantages: (a) avoiding the side effects of definitive therapy that may not be necessary; (b) maintaining health-related quality of life and normal activities; (c) minimizing the risk of unnecessary treatment for small, indolent cancers; and (d) low initial costs.(22)

However, AS has some potential disadvantages: (a) possibility of missing an opportunity for cure; (b) possibility of progression or metastasis of the cancer before treatment; (c) increased difficulty in the treatment of more aggressive cancer with greater side effects; (d) increased difficulty of the nerve-sparing technique during radical prostatectomy; (e) increased anxiety of living with untreated cancer; (f) need to examine and undergo frequent prostate biopsies; (g) uncertain long-term natural history of untreated PCa; and (h) undetermined timing and value of periodic imaging studies.(22) AS might mean no treatment at all for patients older than 70 years, while in younger patients it might mean delaying treatment by possibly as long as years.(14) Currently, there are some protocols but they vary in the criteria used of AS. Therefore, there is an urgent need for further clinical studies regarding the criteria for recommending, following-up and assessing schedule for AS, in order to propose it to the most adequate low-risk patients.(14)(22)

Watchful waiting (WW)

WW refers to conservative management, which involves monitoring the course of PCa with the expectation of delivering palliative therapy in case of symptoms and/or changes in PSA values. WW is possible in patients with localized disease and limited life expectancy, or in older patients with less aggressive cancer.(14)(22)

Table 4 Active surveillance versus watchful waiting(14)

	Active Surveillance	**Watchful waiting**
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	Digital rectal examination, PSA, rebiopsy, optional Magnetic resonance imaging.	Not predefined
Life-expectancy	> 10 years	< 10 years
Aim	Minimize treatment-related toxicity without compromising survival	Minimize treatment-related toxicity
Comments	Only for low-risk patients	Can apply to patients with all stages

From:Mottet 2015.(14)

ii. Radical Prostatectomy (RP)

This surgical treatment is an operation that removes the entire prostate gland between the urethra and bladder, and resects both seminal vesicles with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP in any approach must be disease eradication, while preserving continence and possibly potency. There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone. However, patients with a life expectancy of > 10 years are more likely to benefit from this procedure. There are four main types of radical prostatectomy which are described in the subsequent sections.(14)

Open retropubic prostatectomy (ORRP). This procedure removes tissue through a cut that runs from the belly button down to the base of the penis. After removing the prostate, the urethra is reattached to the bladder. When the cavernous nerve bundlers, necessary to natural erections, are maintained, the procedure is considered a nerve-sparing surgery. If the cancer involves them, however, one or both bundles are removed; this is considered a non-nerve sparing procedure.

Open perineal prostatectomy (ORPP). This procedure removes tissue through a cut in the perineum. The perineum is the area between the scrotum and anus. In this technique, the nerve sparing is possible but more difficult.

Laparoscopic prostatectomy (LRP). This procedure makes five small cuts, called ports, in the pelvis. Tools are inserted into these cuts to see and remove tissue. This technique was used initially in Europe in 1997 with the intent of reducing the invasiveness of traditional open surgery and improving functional results. Since then, there has been a slow but consistent increase in its popularity in many countries worldwide. The open approach has not been completely supplanted because laparoscopic surgery represents a difficult task for surgeons,(23) mainly due to the long learning curve associated to the procedure and the surgical tools.(24)

Robotic-assisted laparoscopic prostatectomy (RALP). This procedure is a laparoscopic prostatectomy performed with the help of a robot. During this surgery, the surgeon uses a computer system that allows moving robotic arms, which hold the surgical tools, and making more precise cuts compared to a surgeon's hand. This technique began in 2000, with the first cases performed in Germany and France. It was introduced in an attempt to reduce the difficulty in performing procedures, particularly for non-laparoscopic surgeons, yielding shorter learning curves, and also improving functional results.(23) However, its most important disadvantage is the high cost of the Da Vinci® robot, which is available at few institutions.(24)

iii. External Beam Radiotherapy (EBRT)

Three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated external-beam radiotherapy (IMRT). These deliver dose escalation and use high-energy rays to treat a patient's tumour. Anatomical data is acquired by scanning the patient, then data is transferred to the three-dimensional (3D) treatment planning system, which visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field using portal imaging allows comparison of the treated and simulated fields and correction of deviations. At the time of irradiation, a multileaf collimator adapts to the contours of the target volume seen by each beam.(14)

IMRT divides the radiation beam into smaller beams. This technique combines two advanced concepts to deliver 3D-CRT: (a) inverse treatment planning with optimization

by computer and (b) computer-controlled intensity modulation of the radiation beam during treatment. This allows for a more complex distribution of the dose to be delivered within the treatment field and reduce the dose to organs at risk. The main advantage of IMRT is referring lower doses to the rectum than 3D-CRT.(25).

Stereotactic body radiotherapy (SBRT). Several studies support the concept that PCa tumours are sensitive to changes in radiation therapy fraction size.(25) SBRT is based on hypofractionation (increasing dose per fraction): a single 3.5-15 Gy fraction, lasting up to 45 min/day, five days per week, for about two weeks. This provides tumour control without additional normal tissue toxicity, and decreases the overall duration of treatment compared with traditional external beam approaches (a single 1.8-2.0 Gy fraction lasting 15 min/day, five days per week, for about eight weeks).(26)(27)

Proton therapy. Most types of cancer radiotherapy use ionizing photon beams (i.e. conventional radiotherapy, IMRT; stereotactic, brachytherapy). Proton therapy deposits almost all their radiation dose at the end of the particle's path in tissue, increasing the ability to regulate the range the radiation penetrates within the tissue, being dosimetrically advantageous in comparison to photons which deposit radiation along their path. There is also a sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.(14)(25)

iv. Brachytherapy (BT)

This treatment, also called interstitial radiation, involves placing radioactive seeds (Iodine-125, Palladium-103, and echnogenic Iodine-125) inside the prostate. The seeds are about the size of a grain of rice and are inserted through the perineum by ultrasound-guided needle, catheter or any other delivery device. Its goal is to achieve an ablative tumour dose to the prostate while sparing surrounding organs, using a computerized treatment planning and image-guided delivery system. Two different brachytherapy techniques can be used to treat prostate cancer: **low-dose rate (LDR) brachytherapy**, in which radioactive seeds are permanently implanted into prostate tissue, or **high-dose**

rate (HDR) brachytherapy, in which the radioactive source is temporarily placed into the prostate via implanted needles.(28)

v. Cryotherapy (CT)

CT uses freezing techniques to induce cell death by (a) dehydration, (b) direct rupture of cellular membranes by ice crystals, and (c) apoptosis. Freezing of the prostate is ensured by the placement of cryoneedles under transrectal ultrasound guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Patients who are potential candidates for this procedure are those who have organ-confined PCa and those identified as having minimal tumour extension beyond the prostate.(14)

vi. High-intensity focused ultrasonography therapy (HIFU)

HIFU consists of focused ultrasound waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation. The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis. HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position. The procedure is time-consuming, with about 10g prostate tissue treated per hour.(14)

vii. Androgen deprivation therapy

Androgen deprivation therapy can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor using competing compounds known as anti-androgens. In addition, these two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB).(14)

Surgical castration or orchiectomy. Still considered the ‘gold standard’ for androgen deprivation therapy, it leads to a considerable decline in testosterone levels and induces a hypogonadal status, known as the ‘castration level’. The standard castration level is

<50ng/dL (1.7nmol/L).(14) It is considered bilateral when both testicles are removed, and is the quickest way to achieve a castration level, usually within less than 12 hours. It is irreversible and does not allow for intermittent treatment.(14)

Oestrogens. These reduce the production of testosterone and are not associated with bone loss. The most commonly used is diesthylstilboesterol at doses of 1 mg/day and 3 mg/day.(14)

Luteinising-hormone-releasing hormone analogues (agonists and antagonists). These are currently the main forms of androgen deprivation therapy. These synthetic analogues prevent the production of luteinizing hormone in the pituitary gland which subsequently leads to a drop in testosterone. The agonists are delivered generally as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. The castration level is usually obtained within 2-4 weeks.(14)

Anti-androgens. These oral compounds are classified according to their chemical structure as: (a) steroidal, e.g. cyproterone acetate, megestrol acetate and medroxyprogesterone acetate, and (b) non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide. Both classes compete with androgens at the receptor level, blocking the action of male hormones.(14)

1.2 Definitions of Outcomes in Localized Prostate Cancer

The International Consortium for Health Outcomes Measurement (ICHOM) is a non-profit organization with the purpose to transform health care systems worldwide by measuring and reporting patient outcomes in a standardized way. In 2015, it defined a standard set of outcomes integrating both established disease control measures and Patient-Reported Outcomes for men with localized PCa.(29)

a Survival and Disease Control Measures

The overall survival, cause-specific survival, metastasis-free survival, and biochemical recurrence-free survival are considered measures of cancer eradication for the standard set of outcomes.(29)

i. Overall survival

Overall Survival (OS) is defined as the percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed or started treatment for PCa. The overall survival rate is often stated as a five-year survival rate, which is the percentage of people who live at least 5 years after being diagnosed with prostate cancer or the start of treatment.(30)

ii. Cause-specific Survival

Prostate- cancer-specific survival is defined as the length of time from either the date of diagnosis or the start of treatment of PCa, to the date of death from PCa. Patients who die from causes unrelated to the disease are not counted in this measure.(30)

iii. Metastasis-free survival

Metastatic disease is defined as the presence of osseous metastases visualized on a bone scan (or Magnetic resonance imaging); and/or visceral (liver, lung, brain) or extrapelvic nodal metastases visualized on computed tomography scans. Metastasis-free survival is defined as the interval from PSA recurrence to initial metastasis.(31)

iv. Biochemical recurrence-free survival (bRFS)

The PSA level that defines treatment failure differs between men who have undergone radical prostatectomy from those who have received radiotherapy. In patients that are following RP, the recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL and rising.(32) After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA

failure (with an accuracy of > 80%) is any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the nadir's serum concentration.(33)

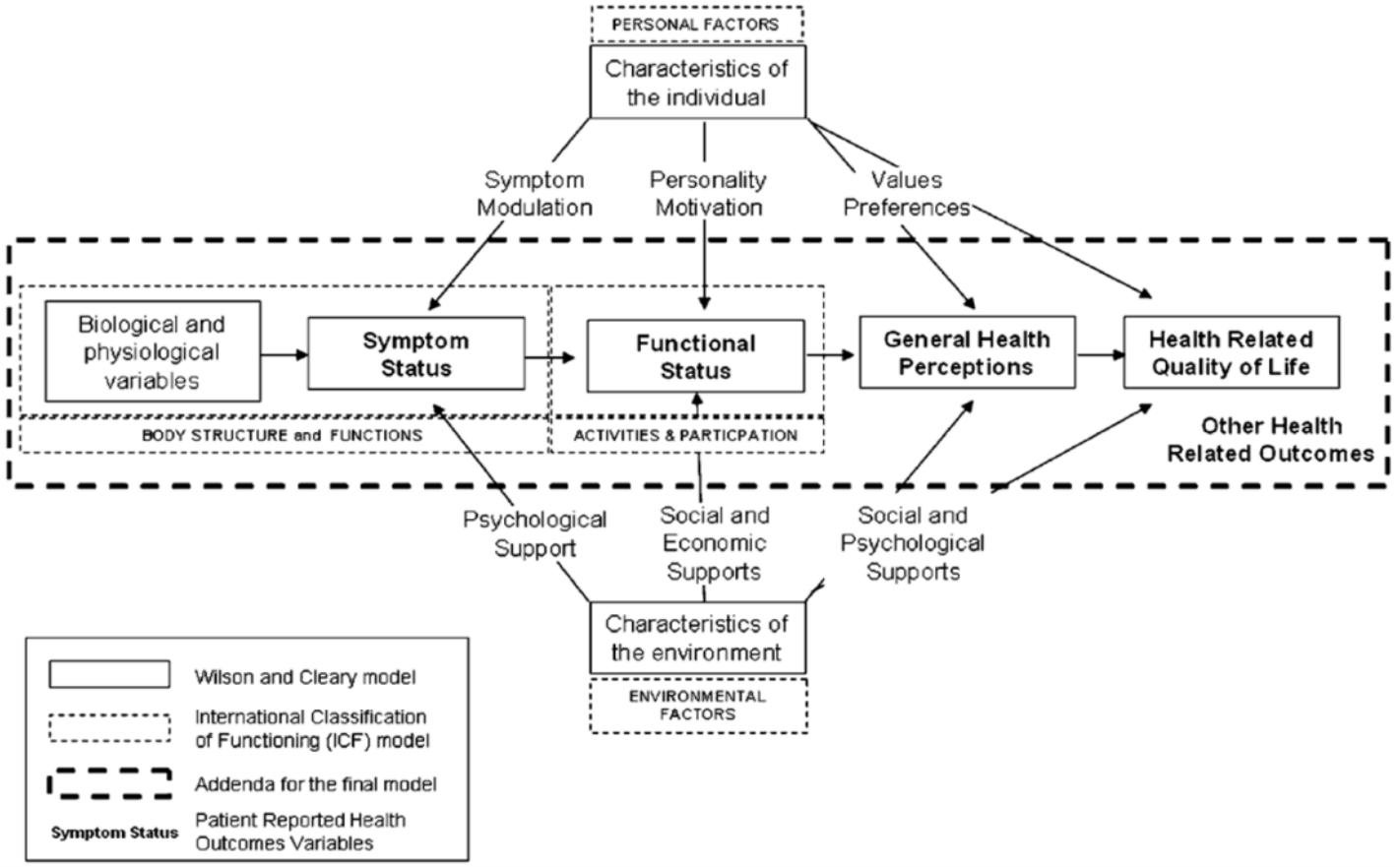
b Patient-Reported Outcomes

According to European Medicines Agency (EMEA), Patient-Reported Outcomes (PROs) include any outcome evaluated directly by the patient himself or herself and it is based on patient's perception of a disease and its treatment(s). PROs cover both single dimension and multi-dimension measures (Figure 1),(34) from symptoms to Health-Related Quality of Life (HRQoL). PROs are instruments that have been developed to ensure both a valid and reliable measurement of a specific concept (that is a construct) in a standardised way.(35) PROs provide a unique mean of capturing the personal and social context of the disease and treatment experience, in a way than other measures such as overall survival; progression free survival, biomarker measures or adverse events may not capture, and complement them. But in addition to be used at the individual level for clinical management, it can be used to help in decision making, and in clinical trials to evaluate an intervention's efficacy and effectiveness. Most PROs administered nowadays assess health-related quality of life.(36)

i. Health-Related Quality of Life

HRQoL is a concept that includes the individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations and concerns. There are different theoretical models that try to explain the concept but there is a lack of consensus in the definition.(37,38) However, there is a general agreement that HRQoL (a) is subjective, given that it considers the person's global evaluations of behaviours, states and capacities and satisfaction/dissatisfaction with them; (b) is multidimensional, given that includes physical, psychological, social and spiritual domains; and (c) covers both positive (i.e. role functioning, contentment and mobility) and negative dimensions (i.e. negative feelings, fatigue, pain).(39)

Figure 1. An integrate model for health outcomes.(34)



From: Valderas 2008.(34)

HRQoL instruments must have adequate measurement properties to be useful in their ample potential applications. Table 5 shows a modified version of the eight attributes and main criteria for each of them proposed by the Scientific Advisory Committee of the Medical Outcome Trust(40): conceptual and measurement model, reliability, validity, responsiveness, interpretability, respondent and administrative burden, alternative forms, and cultural and language adaptations.

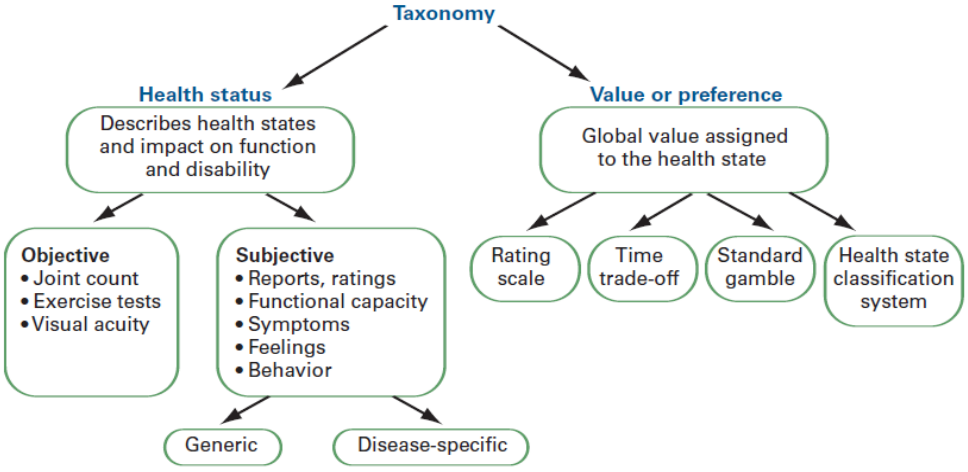
Table 5. Attributes and criteria for evaluating PROs(40)

1. **Conceptual and measurement model:** The rationale for, and description of, the concept and populations that a measure is intended to assess and the relationship between these concepts.
2. **Reliability:** The degree in which an instrument is free from random error.
   a) *Internal consistency*: The precision of a scale, based on the homogeneity (inter-correlations) of the scale's items at one point in time (using Cronbach's coefficient: the degree to which items within a single scale are associated with one another(41))
   b) *Reproducibility:* Stability of an instrument over time (test–retest) and inter-rater agreement at one point in time.
3. **Validity:** The degree to which the instrument measures what it tries to measure.
   a) *Content-related*: Evidence that the domain of an instrument is appropriate regarding its intended use.
   b) *Construct-related*: Evidence that supports a proposed interpretation of scores based on theoretical implications associated with the constructs being measured.
   c) *Criterion-related*: Evidence that shows the extent to which scores of the instrument are related to a criterion measure.
4. **Responsiveness:** An instrument's ability to detect change over time.
5. **Interpretability:** The degree to which one can assign easily understood meaning to an instrument's quantitative scores.
6. **Respondent and administrative burden:** The time, effort, and other demands placed on those to whom the instrument is administered (respondent burden) or on those who administer the instrument (administrative burden).
7. **Alternative forms:** These include self-report, interviewer-administered, trained observer rating, computer-assisted interviewer-administered, evidence on reliability, validity, responsiveness, interpretability, and burden for each mode of administration performance-based measures.
8. **Cultural and language adaptations**: This refers to the assessment of conceptual and linguistic equivalence, as well as to the evaluation of measurement properties

ii. Psychometrics vs Econometric Instruments

The growing interest in HRQoL resulted in the development of many instruments to assess a person's interpretation of their health status in comparison to how they might hope to be.(42)(43) It has originated from two fundamentally different approaches: Health status and value/preference (Figure 2). In general, health status measures provide information on several concepts describing a person's functioning by a profile of interrelated scores or domains (e.g., physical functioning or mental wellbeing). In contrast, health value/preference/utility measures assess the value or desirability of a state of health against an external metric and summarize HRQoL as a single index value(utility).(44)

Figure 2. Health-Related Quality of Life Taxonomy.



From: Khanna 2007.(44)

Most health status profiles are developed based on psychometric theory or unobservable constructs (HRQoL domains like physical functioning or emotions); it is assumed that these variables can be measured by the response on some specific questions. In practice the respondents are asked to indicate the presence, frequency or intensity of symptoms, feelings or behaviours. The responses to individual questions are aggregated to form scales, measuring a particular construct or HRQoL domain. Econometric instruments, on the other hand, are instruments based on patient's values or preferences (utilities) for different health states that use mathematical decision theory to characterise how a rational individual should make decisions when faced with uncertain outcomes.

Utilities are numbers that represent the strength of an individual's preference for a particular health state under conditions of uncertainty, and are generally between 0 and 1, with 0 associated with death and 1 with perfect health, although some states have been identified to be considered worse than death. These preferences measures are used to evaluate the trade-off between the quality and quantity of life(45), and to describe the usefulness of health gains or losses which result when medical interventions prolong the life and/or influence the quality of life.(46)

To estimate utilities, imaginable health states are presented to people with the purpose to elicit their preferences comparing these states with others.(46) There are two major families of utility measures classified according to the method used to their elicitation. These are direct and indirect methods, the latter also known as multi-attribute utilities or health state classification systems.(44)

Direct health utilities. They are usually ascertained via face-to-face interviews with patients, using computer-assisted administration. The most common methods used to calculate utilities are standard gamble, time-trade-off, and rating scale (See Table 6).(47)

Standard gamble determines the risk of death that a person would be willing to take to improve a state of health. Time-trade-off technique asks how many days, months, or years of life a person would be willing to give up in exchange for a better health state. A score of 0.7, for example, indicates a willingness to accept up to a 30% risk of immediate death ([1.0–0.7] × 100) in exchange for perfect health on the standard

gamble, while the same score on the time-trade-off indicates a willingness to give up 30% of one's life expectancy in exchange for perfect health. Rating scale is perhaps the simplest of the 3 methods; although it is not considered a true measure of utility in a strict sense because it does not involve comparison against an external metric such as risk or time, but asks the subject to rate his or her health on a scale (i.e., from 0 to 100) where 0 usually represents dead and 100 is perfect health.(44)

Finally, willingness to pay measures the value of health improvement or health risk decrease by determining the maximum amount of money a person would willingly exchange for such change. Willingness to pay is contingent on ability to pay and individual's wealth.(44)

Table 6. Direct methods to elicit preferences.(47)

Answer Method	**Question formulation**	
	Certainty (Values)	**Uncertainty (Utilities)**
Rating scale	Rating scale Visual Analogue Scale(VAS)	
Choose	TTO- Time-trade-off	SG- Standard Gamble

From: Drummond 2005.(47)

The overall limitation of the aforementioned direct methods (elicitation from patients) is that they violate the utility theory assumption that a utility assessment should be performed in the general population who pay for health care. However, many clinicians and researchers support that patients who have undergone the experience of a specific health condition are the best evaluators. Other limitations include: the need for face-to-face interviews, questions may be difficult for some subjects to comprehend, and responses may vary upon patients' attitudes toward risk (standard gamble) or survival (time-trade-off).(44)

Indirect health utilities. They are estimated from health status instruments that use previously population-assigned values of utilities to particular health states. The ease of administration (self-administered) of these indirect measures enables them to be used in national surveys, and they are commonly used as the source of utilities in economic evaluations (cost-utility analyses). Within the econometric instruments are the EuroQol-5D (EQ-5D), the Medical Outcomes Study 6-Item Short Form (SF- 6D), and the Health

Utilities Index (HUI). They have different numbers of domains and use population-assigned values to different health states, and may not require face-to-face interviews (see Table 7).(44)

Health utility measures, combined with the time course of disease, generate an outcome expressed as Quality-Adjusted-Life-Years (QALYs). QALYs are indicators of effectiveness that combine the impact of morbidity and mortality. A single Quality-Adjusted-Life-Year (QALY) is 1 year of life in a health state with utility 1.0, or 2 years on a state with utility 0.5, 10 years at 0.1, etc. Combining QALYs with the cost of medical interventions yields cost-utility analysis.(44)

Table 7. Main characteristics of indirect preference-based measures(48)

Instrument	Domains	Potential health states	Valuation method	Original population preferences are based on
EQ-5D	5	245	TTO	Random sample of approximately 3,000 adults in the UK
HUI	8	972,000	SG y VAS	Random sample of general population adults in Canada
SF-6D	6	18,000	SG	Random sample of 836 members of general population in the UK

From: Whitehead 2010(48)

iii. Generic vs Specific Instruments

HRQoL measures can be also classified as generic or specific according to the target population (see Table 8). **Generic measures** are applicable to multiple types and severities of disease, patients, and populations.(49) Their broad applicability is derived from their coverage of the complete spectrum of function, disability and distress relevant to HRQoL (symptoms, emotional function, or social relations).

One of the most popular generic profiles is the Medical Outcomes Study 36-Item Short Form (SF-36). It includes 36 questions and 8 domains (physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain, and general health perception), which can be summarized into physical component summary and mental component summary scores. Major advantages of these profiles include dealing with a variety of areas, its

potential use in any population regardless of their underlying condition, and that it allows comparisons to reference norms.(44)

Specific measures are those designed to assess specific populations. Disease-specific instruments focus on how a dysfunction in a single organ or disease affects overall HRQoL. Other instruments may be specific to a patient population, to a certain function, or to a given condition or problem.(50) The disadvantages of specific measures are that they are not comprehensive and cannot be used to compare across sub-populations or conditions. Nevertheless, as specific instruments are designed to focus on elements of a specific condition, they may be more responsive to the effects of health care, and relate more closely to clinical symptoms.(51)

Table 8. Generic vs Specific instruments.(44)

	Clinical Uses	Advantages	Disadvantages
Generic	Informing and monitoring outcomes in clinical encounters	Can be used across diseases and populations	May not be as sensitive to change as disease-specific measures
	Monitoring population health Estimating the burden of different conditions	Allows comparison on the same metric across diseases, levels of health and age ranges	Often does not provide a single summary HRQoL score
	As end points in clinical trials		
Specific		More sensitive to smaller differences and smaller changes over time	Only applicable to certain diseases or conditions
		Better face validity for the population under study	
		Can be self-administered	

From: Khanna 2007.(44)

iv. Health-related quality of life instruments in localized prostate cancer

With the increased survival rates in patients with localized prostate cancer and the development of different strategies for its management, health-related quality of life has become an important outcome in these patients. The National Cancer Institute conducted a systematic review to determine the prevalence and severity of symptoms in PCa patients(52), and defined five domains for studies of localized PCa patients who experience different types of HRQoL impact from their treatment (urinary incontinence, urinary obstruction and irritation, bowel-related symptoms, sexual dysfunction, and hormonal symptoms):

- **Urinary incontinence** is measured as presence/ absence of incontinence, incontinence frequency, and pad use.
- **Urinary obstruction and irritation** occur and change independently from incontinence. It is measured as ease/strength of urinary flow, nocturia, urinary frequency, urgency and dysuria.
- **Bowel-related symptoms** included diarrhoea, bowel urgency, incontinence, frequency, pain with bowel movements, haematochezia, abdominal cramping, and tenesmus.
- **Sexual dysfunction** is measured as libido, sexual activity frequency, quality of erection, ability to get and keep an erection, and ability to achieve orgasm and ejaculation.
- **Hormonal-related symptoms** include hot flashes, breast tenderness or enlargement, depression, fatigue, and weight change.

A systematic review addressed to study the psychometric properties of the most used HRQoL instruments in prostate cancer was published by Hamoen et al.,(53) including (a) generic measures of HRQoL that have been used for non-cancer medical patients, (b) instruments that have been especially developed for general cancer populations (cancer-specific), and (c) prostate-cancer-specific questionnaires.

Among generics, they identified the SF-36(54)(55) as the most commonly used tool for men with prostate cancer.(53) Other generic instruments used in these patients includes Ferrans and Powers Quality of Life Index (QLI),(56) World Health Organization Quality of Life,(59) Padilla QLI,(58) 20-Item short form health survey,(59) and Satisfaction with Life Scale.(60) Regarding cancer-specific instruments, the most commonly used are The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30),(61) and the Functional Assessment of Cancer Therapy (FACT-G).(62) Both instruments have a specific module for PCa.

The FACT-Prostate is a 12-item supplementary prostate module to the FACT-G that focuses on concerns such as pain, erectile dysfunction, and urinary habit. It is available in more than 50 languages.(63) The EORTC QLQ-PR25(64) is a 25-item supplementary

module to the EORTC QLQ-30. It has four domains focusing on sexual activity and functioning, urinary symptoms, bowel symptom, and treatment-related symptoms during the past 1 and 4 weeks.

Prostate-cancer-specific questionnaires identified by Hamoen et al. (53)were the same as those included in a systematic review published previously by Schmidt et al. and the EMPRO Group in 2014 focused on metric properties evaluation.(65) From the eight prostate-cancer-specific instruments evaluated, the three presenting best metric properties were the Expanded Prostate Cancer Index (EPIC) instrument, followed by the University of California Los Angeles Prostate Cancer Index (UCLA-PCI), and the Patient-Oriented Prostate Utility Scale (PORPUS).

The UCLA-PCI(66) instruments cover sexual, urinary and bowel function, and bother domains assessing the degree to which symptoms are interfering with an individual's life. The EPIC(67) was developed using UCLA-PCI content by aggregating items to assess storage and voiding symptoms, haematuria, and hormonal domains. Both instruments have validated versions in French, Spanish, Dutch, and Italian among other languages.(68)

The Patient-Oriented Prostate Utility Scale (PORPUS) is the only prostate cancer-specific PRO combining econometric and psychometric methods. It has five general dimensions and five specific ones, and two different versions of preferences obtained in the general population: the PORPUS-U_{RS} (with preferences estimated by VAS) and PORPUS-U_{SG} (with preferences estimated by SG).(69–72) The PORPUS has been used recently in multiple studies.(69,73–80)

v. Utilities in localized prostate cancer

A systematic review and meta-analysis focused on utilities,(81) including articles published between 1966 and September 2004, identified 23 studies estimating 173 utilities values. Approximately 50% (87 values) were from prostate cancer patients, either rating their own health (17.3%) or rating hypothetical scenarios (32.9%). The remainder (49.3%) was assessed by non-patients of cancer (e.g., primary care patients

without prostate cancer or patients' wives); 54.3% of these indices corresponded to not metastatic cancer and 72.3% were obtained by TTO. They found considerable heterogeneity in individuals' preferences for health states, even in similar treatments and clinical risks: severe sexual problems ranged from 0.61 to 1; severe urinary problems ranged from 0.48 to 0.96; and bowel problems from 0.85 to 0.98. These markedly different preferences for treatment outcomes could be caused by methodological factors such as sample characteristics and elicitation methods.(81)

Another more recent systematic review conducted by Torvinen et al.(82) includes 33 articles published between 2002 and 2013 about utilities obtained using direct or indirect methods. They identified nine studies focused on early/localized disease, 15 for advanced/metastatic disease and 14 including patients in different stages. Utilities for localized and early stage disease ranged from 0.63 to 0.91, and for advanced or metastatic stage disease the values varied between 0.50 and 0.87. They also observed that longitudinal studies used indirect methods, while cross-sectional studies used direct methods. The vast majority of studies elicited the patient's current health state, and only four studies elicited preferences for hypothetical health states.

The direct methods most commonly used in studies of preferences from patients with prostate cancer are the TTO(76,83–94) and VAS.(86,89,92,95–105) The SG method is not used as often.(91,92,95,106) These techniques are applied via personal or telephone interviews, on paper or computer-assisted software that facilitate their implementation. The most commonly used questionnaires to measure utilities by the indirect method are the EQ-5D(69,83,97–99,101,103,104,107–117), the 15D (used in some studies developed in Finland,(101,103,117) Norway(118) and Turkey(119)), and the Quality of Well-Being scale (QWB) which has been used is two Canadian(69,77) and one USA(120) studies. The HUI has been used in combination with the QWB.(69,77) The SF-6D is a generic preference-based measure derived from the SF-36, which has only been used in two screening studies in Finland(117) and Japan.(83)

In PCa, the limitations of the indirect method to estimate econometric preferences are particularly relevant because attributes specific to PCa, such a sexual, urinary, and bowel dysfunctions, are not covered by generic questionnaires. However, many studies have used indirect methods (generic questionnaires) in conjunction with direct methods.

Finally, it is worth to remark the development of the Patient-Oriented Prostate Utility Scale (PORPUS), the first prostate cancer-specific questionnaire developed for obtaining utilities by direct and indirect methods.(69–72)

1.3 Comparative Effectiveness Research in Localized Prostate Cancer

In the last years, systematic reviews(17,121–124) and metanalyses(121,124) have synthetized the available literature addressing comparison within (comparing different techniques of one treatment) and between (comparison between surgery, radiation therapy, brachytherapy, etc) treatments options. The results considered include mortality outcomes (overall survival, cause-specific survival), progression outcomes (biochemical recurrence free survival), and health-related quality of life, among others. Although these systematic reviews have identified a wide number of randomized controlled trials and non-randomized comparative studies, the majority of them conclude that there is no strong evidence to support one therapy over another, due to the medium to high risk of bias in most of the individual studies and to the small number of studies addressing comparison between treatments.

In 2014, the Agency for Healthcare Research and Quality (AHRQ) published an update(17) of a previous systematic review conducted in 2008.(125) One of the main objectives of this review was to evaluate the comparative risks and benefits of treatments for localized PCa. Among non-randomized trials that compared between treatments, the most commonly evaluated outcome was mortality. Five of seven studies(126–132) found that overall mortality and prostate cancer-specific mortality was significantly lower following RP than EBRT (follow-up ranging between 3 and 15 years). Also, for the comparison of RP vs observation, four studies(126,132–134) evaluating all-cause mortality reported results favouring surgery. Finally, there are a few studies(127,130,135,136) reporting results in favour of RP in comparison with BT, and in favour of BT in comparison with the EBRT regarding all-cause mortality and prostate-cancer specific mortality.

The 2014-AHRQ systematic review identified only three non-randomized studies that compared between treatment options which evaluated biochemical failure or biochemical progression free-survival. Two compared BT with radiotherapy,(137,138) and one comparing RP and EBRT with WW.(126) Men who underwent BT had lower biochemical failure rates (6%) than those treated with 3D-CRT (26%) or IMRT (13%), while no differences between RP and EBRT were found. Only one study reported higher biochemical free-survival rates for BT in comparison with IGRT.(138)

In relation to HRQoL, the 2014-AHRQ identified four non-randomized studies: Sanda et al.(139) compared HRQoL at 2 years, reporting higher urinary incontinence in the RP group, higher bowel problems in patients treated with RT, and more urinary irritative-obstructive and bowel problems in those underwent BT, while there was not between-group difference in sexual problems. Results at two years of the 'Spanish Multicentric Study of Clinically Localized Prostate Cancer'(140) showed that surgery had a considerable negative effect on sexual functioning and urinary continence, 3D-CRT had a moderate negative impact on bowel functioning, and BT caused moderate urinary irritative-obstructive problems. Malcolm et al.(141) reported that patients treated with BT had better rates of returning to baseline urinary and sexual function than robotic-assisted prostatectomy patients, while no significant differences were observed for bowel function and bother. Lastly, the Prostate Cancer Outcomes Study (PCOS)(142) did not find differences between surgery and radiotherapy groups at 15 years of follow-up.

The 2014-AHRQ also identified four randomized clinical trials in PCa. Two of them compared all-cause mortality, prostate cancer specific mortality, progression to metastasis and HRQoL outcomes between RP and WW: the Prostate Cancer Intervention Versus Observation Trial (PIVOT)(143), with a follow-up of 12 years, and the Scandinavian Prostate Cancer Group-4 trial (SPCG-4)(144–147), reporting data on these same outcomes at the end of the 12- and 15-year follow-up periods. Their main conclusions(143–147) were that progression to metastases was reduced at 12 years among patients undergoing RP, compared to those receiving WW, and urinary incontinence was lower among patients receiving WW than for those undergoing RP. A Italian trial published by Giberti et al. compared RP vs BT,(148) and did not find differences in biochemical recurrence-free survival and HRQoL outcomes at a 5-year

follow-up between treatments. Donelly et al. compared EBRT vs CT(149) in Canada, showing no significant differences in PCa-specific survival and biochemical failure at 5-year follow-up.

The ProtecT (Prostate testing for cancer and Treatment) Study was ongoing when the 2014-AHRQ review was published. Recently the first results showing survival at ten years(150) and HRQoL at six years after surgery (radical prostatectomy), radiotherapy (radical conformal) and active surveillance have been published.(151) They found that all three treatment groups had similar and very high rates of survival after treatment. The active monitoring group, however, had higher rates of disease progression and metastases at ten years of follow-up.(150) Regarding HRQoL, their findings showed that the negative effect of prostatectomy on urinary incontinence and sexual function was worse than in the other treatment groups over 6 years. At 6 months bowel function, urinary voiding and nocturia were worse in the radiotherapy group than in the other groups, but with a considerable recovery. In the active monitoring group, sexual function, urinary incontinence and urinary function worsened gradually over time, but were affected much less than in the other two groups.(151)

Other attempts to summarize the available evidence also merit a comment. Xiong et al.(121) developed a network meta-analysis of 14 randomized clinical trials evaluating all-cause mortality, cancer-related mortality at 5 years, and gastro intestinal /genitourinary toxicities between RP, EBRT, BT, observational management, CT and HIFU (six of which considered the comparison between treatments options(144,149,152–154)). They did not find evidence of superiority for any of the compared treatments regarding all-cause mortality and cancer-related mortality. Wolff et al.(122) included 36 individual randomized clinical trials comparing BT or EBRT to other management options. Most of these studies compared different dose management within the radiotherapeutic strategy, and only seven compared between treatments: two compared BT vs RP,(148,155) two compared EBRT vs CT,(149,156) two compared EBRT vs RP,(157,158) and one EBRT vs WW.(159) Review authors concluded that there is no strong evidence to support one therapy over another.

Two systematic reviews(123)(124) focusing on mortality outcomes comparison between radiation therapy and surgery have been published recently. Roach et al.(123) assessed 10-year overall survival (OS) and cause-specific survival (CSS), identifying 14 studies, from which 12 were retrospective observational studies and only two reported results for BT.(135,160) Their conclusion was that the differences in survival between RP and RT are small, and there is not enough evidence in favour of RP. On the other hand, Wallis et al.,(124) based on the meta-analysis of 19 studies, concluded that RT is associated with an increased risk of overall and prostate cancer-specific mortality compared with RP. However, this publication has caused controversy(161–163) regarding the over-interpretation of the results, mainly arguing very low quality of the observational primary studies included in the meta-analysis.

Finally, longitudinal studies using utilities as an outcome, which evaluate radical prostatectomy(73,74,104,113,120) or radiation therapy(74,104,116) showed contradictory results at 1 year of follow-up. Some of them reported higher utility values,(104,113,120) while other lower ones(73,74) than pre-treatment assessment. None of them evaluated brachytherapy, nor preferences at long-term except Korfage et al.,(104) who followed patients until 52 months. On the other hand, the few studies which elicited willingness to pay in PCa patients are focused on screening,(106,164,165) and only one evaluated patients after treatment.(166) This study showed that patients experiencing moderate to severe declines in urinary and sexual function reported slightly higher WTP values, but without statistically significant differences compared to stable patients.(166)

2 THESIS RATIONALE

Not a single treatment is considered as the preferred strategy for the management of localized prostate cancer. Randomized controlled trials comparing outcomes between different management options are scarce, mainly restricted to the SPCG-4(144–147) published in 2005, the PIVOT(143) published in 2012, and the ProtecT(150,151) in 2016. Factors such as (a) strong patients' treatment preferences; (b) a marked polarization in the counselling by oncologists/urologists; (c) patients' unwillingness to leave their treatment to chance; (d) family members or physicians preferring that the patient does not participate; have made treatment randomization difficult.(167) Nevertheless, good longitudinal observational studies with long-term follow-up will remain useful to characterize the effectiveness of treatments providing complementary information to randomized controlled trials.

The high rates of survival observed in localized prostate cancer patients, independently from the treatment applied(150), have made patient-reported outcomes increasingly relevant for treatment comparisons. This has yielded a wide number of studies measuring HRQoL after treatment being published in the last ten years, but there is a dearth of comparisons among treatment options. Finally, there are a very few published studies integrating all the relevant outcomes in localized PCa (mortality, cancer control and HRQoL data). Concurrent measurement of them in the same cohort allows assessing whether treatments causing less HRQoL impact are followed by worse cancer control outcomes. For these reasons, the follow-up at 5 years of the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort with evaluation of generic and prostate-specific HRQoL, biochemical disease-free survival, and mortality may contribute to improve the available evidence.

Utilities and willingness to pay indicate a preference or desire for a specific health state, and their estimation is necessary to develop an economic evaluation. Preferences should be expressed quantitatively as a utility, which is a global, composite preference-based measure of HRQoL to perform cost-utility analyses, while the willingness to pay is necessary for cost-benefit analyses. Studies using the direct methods to evaluate radical prostatectomy and radiation therapy showed that utilities decreased significantly after

both treatments, but none have assessed brachytherapy. There is only a recent study estimating the impact of treatment side effects on willingness to pay.(166) For this reason, evaluating the preferences and willingness to pay of patients by direct methods may be valuable for economic evaluations of localized prostate cancer treatments (cost-utility and cost-benefit analyses, respectively).

The limitations of the direct methods related especially to the difficult understanding of time trade-off or standard gamble by the patients, and the need for face-to-face interviews. The easy use of indirect method by incorporating community preferences to standard descriptive status has made the latter widely used, especially in longitudinal studies. The development of a prostate cancer-specific instrument such as PORPUS, that allows obtaining utilities (PORPUS-U), and also to describe the HRQoL profile (PORPUS-P), has been an advance regarding the PROs in prostate cancer. Finally, the adapted and validated Spanish version may contribute to generate new evidence about these relevant outcomes in prostate cancer patients.

3 OBJECTIVES

The general aim of this Doctoral Thesis was to compare the effectiveness of the three most established primary treatments for localized prostate cancer, focusing on the patient's perspective: open radical prostatectomy, 3D-external conformal radiotherapy, and brachytherapy.

a Specific objectives

1. The primary aim was to assess HRQoL impact of treatments' side effects after 5 years of follow-up in patients with localized prostate cancer treated with radical prostatectomy, external radiotherapy or brachytherapy. A secondary objective was to estimate biochemical disease-free survival and overall mortality after 5 years of follow-up in patients with localized prostate cancer treated with radical prostatectomy, external radiotherapy or brachytherapy, per treatment group.

2. To assess the preferences and WTP of patients with localized prostate cancer for radical prostatectomy, external radiation therapy, and brachytherapy, and the treatments' related urinary, sexual, and bowel side effects.

3. To develop a Spanish version of Patient-Oriented Prostate Utility Scale (PORPUS), to prove its conceptual equivalence with the original, and to assess its acceptability, reliability, and validity.

4 PUBLICATIONS

4.1 Article 1

It was published in the Journal of the European Society for Radiotherapy and Oncology and affiliated to the Canadian Association of Radiation Oncology: Radiotherapy and Oncology. (IF:4.363, Oncology and Radiology Q1).

Ferrer M., Guedea F., Suárez J.F., de Paula, B., Macías V., Mariño V., Hervás A., Herruzo I., Ortiz M.J., Ponce de León J., Sancho G., Boladeras A.; Ayala A; Craven-Bratle J; ***Ávila M;*** *Cunillera O; Pardo Y.; Alonso J; Aguiló F.* **Quality of Life Impact of Treatments for Localized Prostate Cancer: Cohort Study with a 5 Year Follow-up.** *Radiotherapy and Oncology. 2013; 108(2): 306-313.*

4.2 Article 2

It was published in the Official Journal of the American Society for Radiation Oncology, known in the field as the Red Journal or International Journal of Radiation Oncology Biology Physics. (IF:4.258, Oncology and Radiology Q1).

Ávila M., Becerra V., Guedea F., Suárez J.F., Fernández P., Macías V., Mariño A., Hervás A., Herruzo I., Ortiz M.J., Ponce de León J., Sancho G., Cunillera O., Pardo Y., Cots F., Ferrer M. and the Group of Clinically Localized Prostate Cancer. **Estimating Preferences for Treatments in Patients With Localized Prostate Cancer.** *Int J Radiat Oncol 2015; 91(2): 277-287.*

4.3 Article 3

It was published in the Official Journal of the International Society of Quality of Life Research (ISOQOL): Quality of Life Research. (IF:2.486, Health Care Sciences & Services Q1).

Ávila M., *Pardo Y., Castells M., Ferrer F., Boladeras A., Pera J., Prada P., Guix B., de Paula B., Hernandez H., Pont A., Alonso J., Garin O., Bremner K., Krahn M., Ferrer M. and the Group of Clinically Localized Prostate Cancer.* **Adaptation and Validation of the Spanish Version of the Patient-Oriented Prostate Utility Scale (PORPUS).** *Qual Life Res 2014; 23(9):2481-2487.*

5 DISCUSSION

Prior to our publication in 2013 describing the impact of localized prostate cancer treatments on patients' HRQoL at 5 years of follow-up, there were no existing studies which had reported evidence on HRQoL impact at long term. Just after this article, relevant studies on this issue which merit comment were rapidly published. In the same year, 2013, the Prostate Cancer Outcomes Study (PCOS) reported the results until 15 years of follow-up.(142) In 2016, two randomized controlled trials were published, the ProtecT (Prostate testing for cancer and Treatment) trial with a HRQoL follow-up of six years,(151) and Yaxley et al.,(168) who reported early outcomes at 3 months. Finally, an international study comparing results from our cohort with American and Norwegian patients was published in 2014(169) and 2016.(170)

The Spanish Multicentric Study of Clinically Localized Prostate Cancer followed for 5 years three cohorts diagnosed in 2003-2005: the radical prostatectomy group (most of the operations involved an open retropubic with non-nerve-sparing procedure), the external beam radiotherapy group (3D-CRT delivered at a mean dose of 74.03 Gy), and the brachytherapy group (^{125}I with a prescription dose of 144 Gy). We used the generic SF-36 and the prostate cancer-specific EPIC questionnaire to measure the impact of treatments on HRQoL.

The PCOS study is a population-based cohort of men whose prostate cancer had been diagnosed in 1994 and 1995,(142) who underwent either prostatectomy or radiotherapy as primary treatment (with or without androgen-deprivation therapy). They used the SF-36, and items adapted from UCLA and EPIC instruments to measure urinary, sexual and bowel function. The authors concluded that men who had undergone prostatectomy were more likely to have urinary incontinence and erectile dysfunction than those receiving radiotherapy at 5 years of follow-up, but differences were not statistically significant at 15 years.

The ProtecT trial assessed three arms for 6 years:(151) radical prostatectomy (most of the operations involved an open retropubic procedure with a nerve-sparing approach), external beam radiotherapy (3D-CRT delivered at a dose of 74Gy along with

neoadjuvant androgen therapy), and active monitoring (regular PSA levels with clinical review to enable change to radical treatment if disease progressed). Patients were diagnosed between 1999 and 2009. The PRO measures they administered from the beginning were the International Continence Society Male Short-Form (ICSmaleSF), SF-12, and Hospital Anxiety and Depression Scale (HADS). In 2001 they included the International consultation on Incontinence Questionnaire (ICIQ), and then the EPIC questionnaire in 2005. The authors concluded that prostatectomy had the greatest effect on urinary continence and sexual function, particularly in the early years of follow-up, and radiation results in a slow decline in urinary function, largely manifesting as irritative urinary bother rather than incontinence. Sexual and urinary function declined gradually in the active monitoring group.

The randomized controlled trial published by Yaxley et al.(168) compared robotic-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy (nerve preservation was undertaken upon individual surgeon discretion, based on clinical staging). They reported results at 6 weeks and 3 months after treatment using the SF-36 and EPIC, among other PROs. The authors concluded that the two surgical techniques yield similar outcomes at short term.

Storås et al. assessed between-country differences in the distribution of sociodemographic, clinical variables, and PROs before radical prostatectomy and external radiotherapy with results from three studies:(169) the Spanish Multicentric Study of Clinically Localized Prostate Cancer,(96,140) the PROSTAQA (Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment) Study with results from 1201 USA patients recruited from 2003 to 2006,(139) and a study conducted in the Oslo University Hospital with 627 patients diagnosed in 2008-2009.(171,172) The authors concluded that there are statistically significant between-country differences in most factors investigated before treatment. They also compared the erectile dysfunction and sexual problems reported in the same studies(170) at 2-3 years after radical prostatectomy. They concluded that, after adjusting for important pre-treatment medical and demographic variables, there are not inter-country differences.

5.1 Prostatectomy findings: comparison between studies

In line with the prostatectomy results of the ProtecT trial the first year after treatment, we observed that surgery had a notorious negative effect on EPIC urinary incontinence and EPIC urinary summary (Figure 3). No differences with the ProtecT trial (black line in the figures below) were observed at 1 year of follow-up for mean EPIC urinary scores. However, there were statistically significant differences the second year, due to the decline presented by the Spanish patients (red line). In contrast to our results, the ProtecT trial showed stability or even a slight recovery. The PCOS (blue line), which only measured function domains, reported clearly worse results than those estimated by our study in the urinary function, especially at the first and the second year of follow-up.

The three studies had a notable worsening in all the EPIC sexual scores one year after treatment that remained during all the follow-ups. Sexual function scores of the PCOS were slightly higher than those of the ProtecT trial and our cohort, but this difference is consistent from baseline in all evaluations, which indicates similar worsening. Only remarkable differences were observed in the EPIC sexual bother domain, in which our patients showed better scores than the patients of ProtecT. Our hypothesis is that many older Spanish PCa patients probably accept impaired sexual function as a common consequence of aging and comorbidity. In contrast, among the younger and healthier US patients in the RP group, impaired sexual function was more often reported as a bothersome loss.

Both the ProtecT study and our cohort showed a similar pattern of stability in mean EPIC bowel scores, showing that the surgery did not have impact on this domain. Bowel function results obtained in the PCOS were almost identical to those of ProtecT trial, while our Spanish patients had higher scores. However, it does not indicate differences in prostatectomy impact between studies, because it is consistent from baseline evaluation. Storås et al.(169) also showed that our Spanish patients had higher scores at baseline in EPIC Bowel summary than American and Norwegian patients.

Figure 3a. Mean EPIC urinary scores for prostatectomy groups at baseline and annual follow-ups

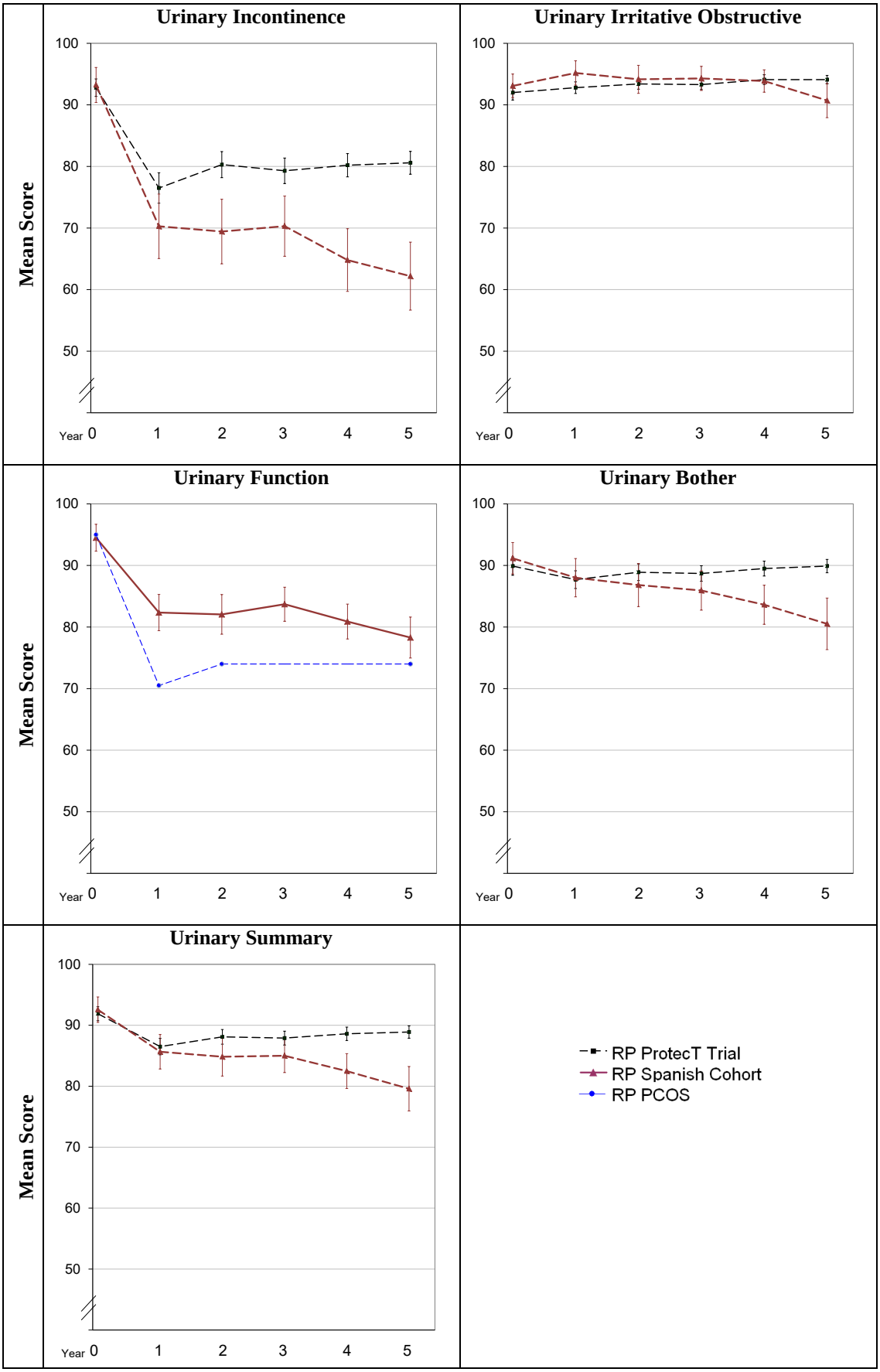


Figure 3b. Mean EPIC sexual and bowel scores for prostatectomy groups at baseline and annual follow-ups

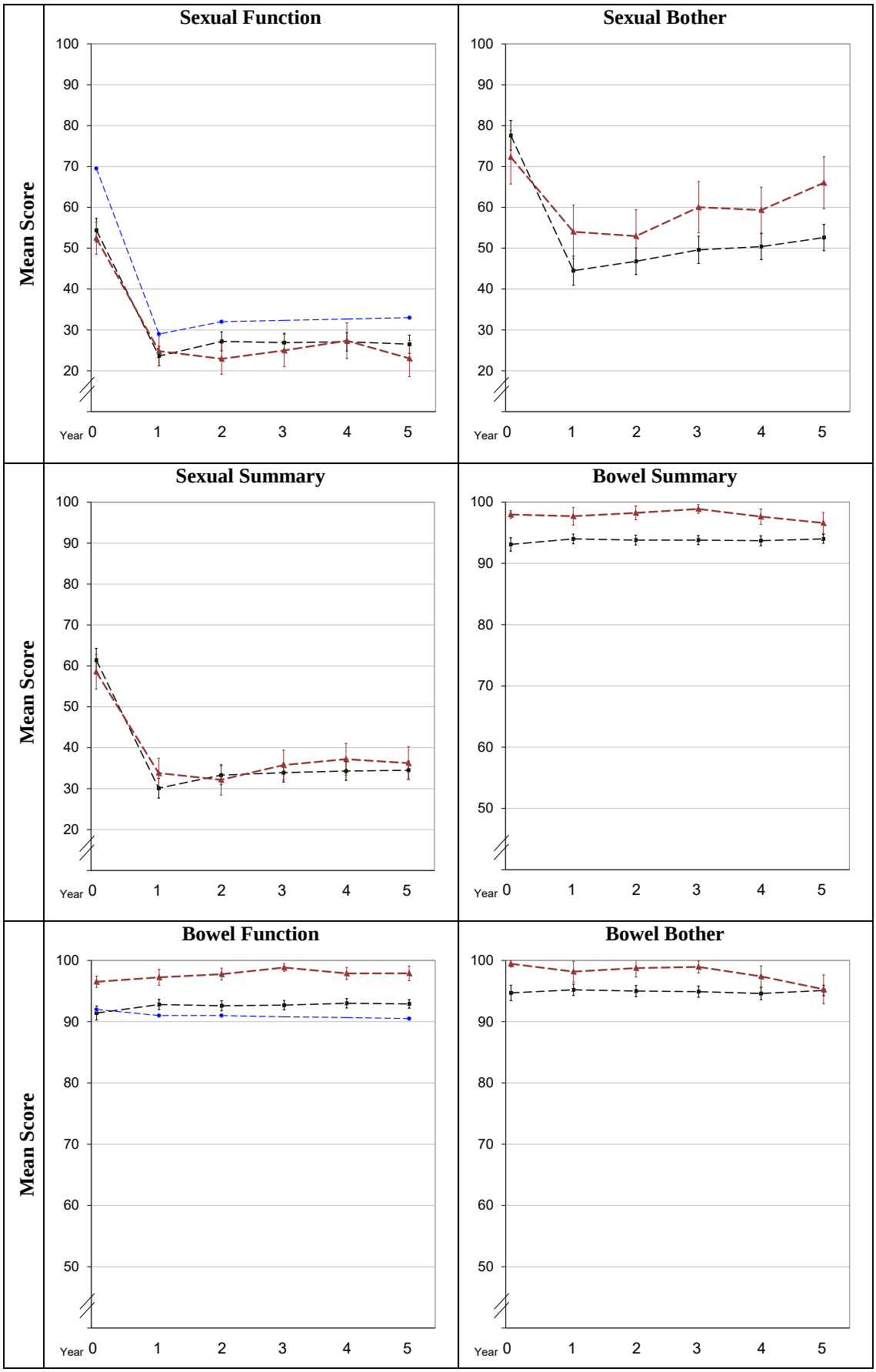
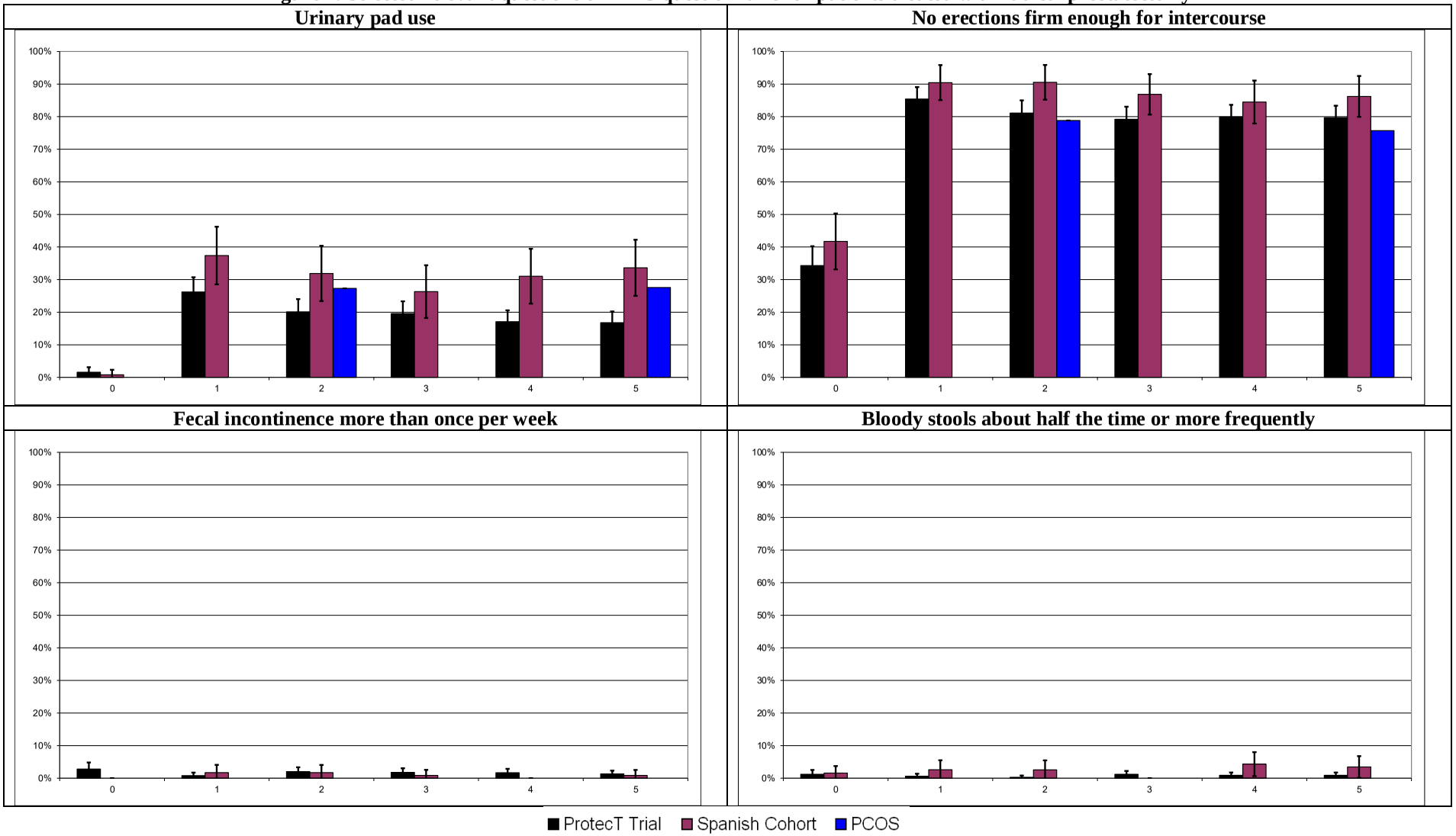


Figure 4. Selected relevant questions of EPIC questionnaire for patients treated with radical prostatectomy



In addition to EPIC domains, the ProtecT trial analysed selected relevant questions of the EPIC questionnaire, as previously done in our article,(173) to provide a direct interpretation of the treatment impact in each specific domain (Figure 4). Regarding the urinary effect of the prostatectomy, the percentage of patients who required the 'urinary pads use' was around 15-30% in the three studies from the year 1 to 5. The ProtecT trial (in black) presented statistically lower proportion of patients using pads in the majority of evaluations. At the year 5, 17% (95%CI 16.7; 16.8) used pads in ProtecT vs 34% (95%CI 33.5; 33.7) in our study (in red), and 28% (95%CI 27.5; 27.6) in PCOS (in blue). Regarding the sexual effect, around 80% of surgery patients reported 'no erections firm enough for intercourse' in the three studies at all the annual follow-ups. Regarding the bowel effect of prostatectomy, the percentage of patients who reported 'fecal incontinence more than once per week' or 'bloody stools about half the time or more frequently' was extremely low in both studies in all the follow-ups. The PCOS did not report any comparable measure for the bowel domain.

Finally, we will compare our results with those provided by the first randomized clinical trial evaluating robotic-assisted laparoscopic prostatectomy versus open surgery, published by Yiexler et al.(168) For EPIC urinary and sexual function, our surgery group showed a higher decline than open and robotic-assisted prostatectomy groups of the trial at 3 months of follow-up. In line with these results, the percentage of patients using pads in our study was higher than in the Yiexler et al. trial (61% vs 33 % and 40% for open and for robotic assisted prostatectomy, respectively).

5.2 Radiotherapy findings: comparison between studies

The ProtecT trial did not show any impact of radiotherapy on urinary domains, since all urinary scores were stable during the whole follow-up (see black lines in Figure 5). Our results (in red) were consistent with the Protect trial for the first two-three years after treatment. However, declines were observed in our radiotherapy cohort in the last follow-ups, especially for the EPIC irritative-obstructive and bother urinary domains. Regarding urinary function, our patients reported higher scores from baseline to the fifth year than those estimated by PCOS patients (in blue). Again, this inequality between studies does not indicate differences in radiotherapy impact, since lines moved along in parallel.

The ProtecT trial reported much higher (better) sexual scores at baseline than our radiotherapy cohort. Since Spanish men were older (mean of 70 years versus 62 years old in the ProtecT trial), it could be partly explained as a common consequence of aging and comorbidity. However, the three studies showed a similar notable worsening after treatment in the sexual function. The EPIC sexual bother presented important differences between studies: stability was observed on Spanish patients, while a decrease of around 20 points was reported by the ProtecT trial. A possible explanation is that many older Spanish prostate cancer patients probably accepted impaired sexual function and reported bothers less frequently. In contrast, the younger and healthier ProtecT patients reported more often bothers related to sexual dysfunction.

Similarly to the pattern mentioned above for bowel scores among radical prostatectomy patients, bowel scores of Spanish radiotherapy cohort were higher (better) than ProtecT and PCOS patients at baseline and during all the follow-up. Scores of the PCOS were even lower (worse) than those of ProtecT. This consistent difference in bowel scores between Spanish patients and those from other countries (United Kingdom, Americans and Norwegian),(169) regardless the treatment, merits a comment. Linguistic inequalities among English and Spanish versions of the questionnaire in the EPIC items of bowel could not be discarded, as well as cultural differences in the perception, expectative and/or communication regarding these scatological questions.

Figure 5a. Mean EPIC urinary scores for radiotherapy groups at baseline and annual follow-up

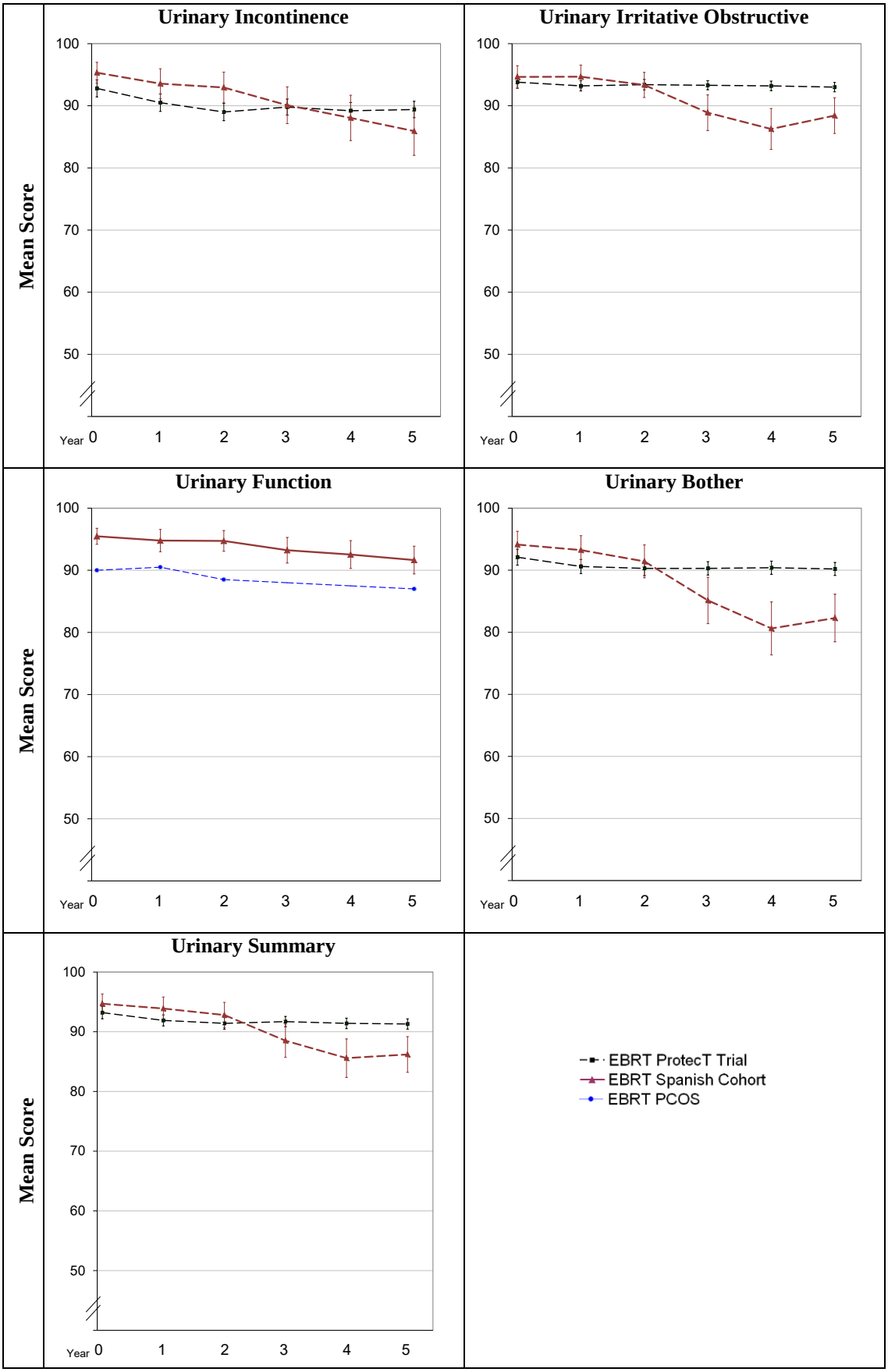


Figure 5b. Mean EPIC sexual and bowel scores for radiotherapy groups at baseline and annual follow-ups

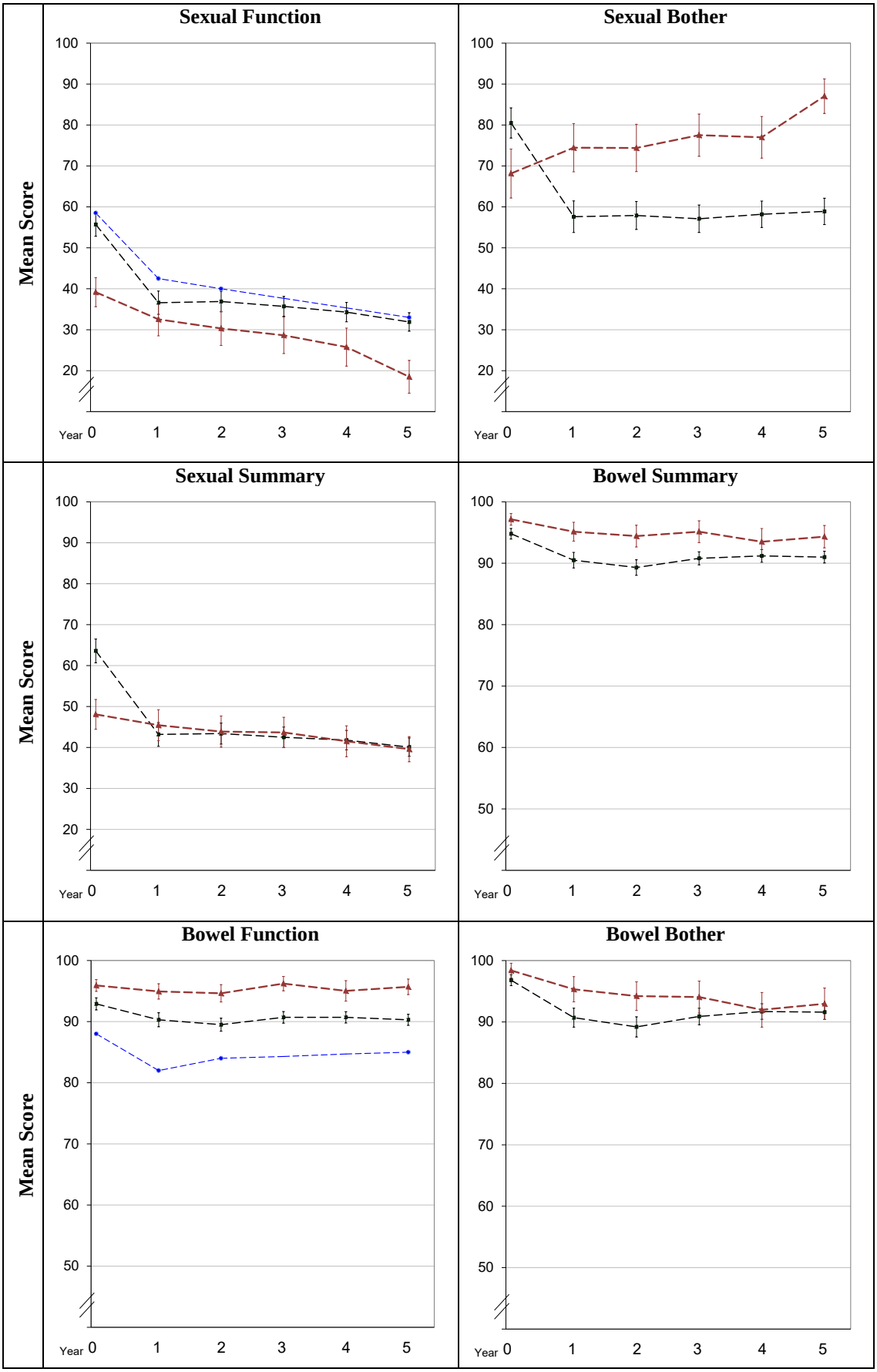
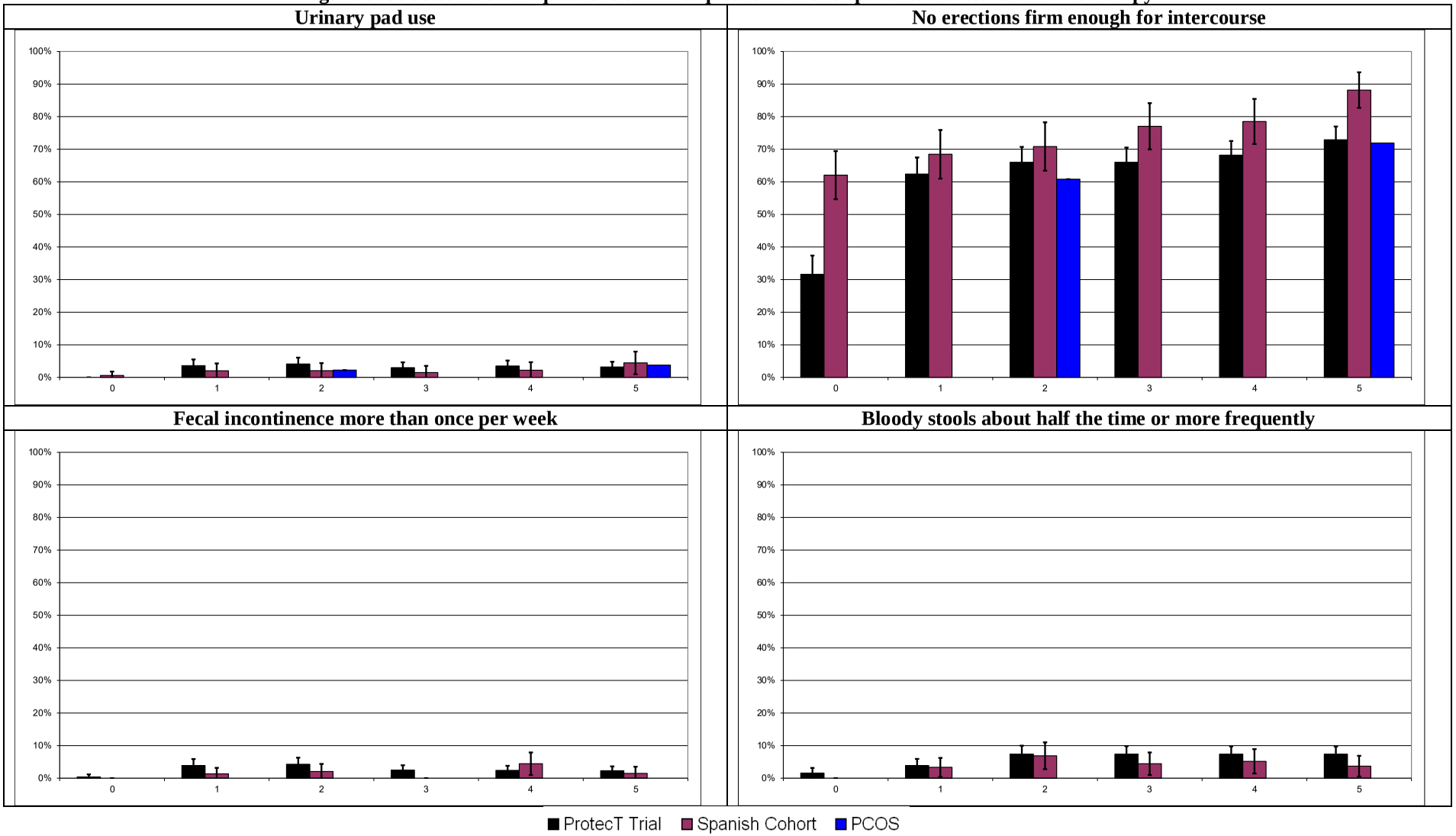


Figure 6. Selected relevant questions of EPIC questionnaire for patients treated with radiotherapy



Regarding the relevant questions selected of the EPIC questionnaire, we found very low similar percentages of patients reporting ‘urinary pads use’ (ranging 2%-4%) during the whole follow-up after radiotherapy, and high percentages of patients reporting ‘no erections firm enough for intercourse’ (50-60% the first year and 70-80% the fifth year) in the three studies. Regarding bowel items, a low percentage of patients reported ‘fecal incontinence more than once per week’ (1.3-4.4%) and ‘bloody stools about half the time or more frequently’ (3.3-7.4%). The ProtecT trial reported a statistically higher proportion of patients with bloody stools from the third year, which was maintained around 7.4% until the fifth year of follow-up. PCOS did not provide results from comparable items for bowel domain.

5.3 Brachytherapy and active monitoring findings: comparison between studies

Figure 3 shows results obtained in our study with brachytherapy treatment (in lilac) and results reported by the ProtecT trial with active monitoring (in orange). Patients treated with brachytherapy in our study presented at baseline higher (better) scores on urinary incontinence than ProtecT patients in active monitoring. After the decline observed between pre and post-brachytherapy (3.3 points), both lines totally coincided from the second to the fifth year of follow-up, indicating a small impact of brachytherapy on urinary incontinence (0.3SD). Regarding the ‘urinary pad use’, we observed extremely low percentages (< 5%) during almost all the follow-up evaluations in the brachytherapy and active monitoring groups. The EPIC urinary irritative-obstructive and bother scores showed a higher deterioration in brachytherapy patients than the active monitoring group of ProtecT, which was statistically significant at fourth and fifth year of follow-up.

EPIC bowel scores indicated stability during the five years of follow-up for both the brachytherapy and active monitoring groups. Similarly to the pattern observed before in radical prostatectomy and radiotherapy patients, the Spanish brachytherapy cohort showed higher (better) scores than ProtecT active monitoring patients, supporting cultural differences between countries and/or languages. Both groups showed an extremely low percentage of patients reporting ‘fecal incontinence more than once per

week' and 'bloody stools about half the time or more frequently' in all the evaluations. Again, results obtained with the selected EPIC relevant questions were consistent with those showed by EPIC scores.

Patients treated with brachytherapy in our study presented at baseline lower (worse) scores on sexual function and sexual summary than ProtecT patients in active monitoring. After the declines observed during the first year in active monitoring (8.8 and 9.1, respectively in sexual function and summary), the lines totally coincided in the three last years of follow-up. Baseline differences between both studies could be explained by difference in mean age (67.5 in our cohort vs 62 in the ProtecT trial) as argued regarding radiotherapy groups. For the EPIC sexual bother domain, we observed a gradual worsening in the active monitoring group of the ProtecT trial, while the Spanish brachytherapy group showed stability until the third year, and even improvement afterwards. Both groups presented similar percentages of patients reporting 'no erections firm enough for intercourse' in all the evaluations, except for baseline. Similarly to results on mean sexual scores, the ProtecT active monitoring group showed a lower proportion of patients with sexual dysfunction at baseline than the Spanish brachytherapy patients. As commented above, it could be probably explained by their younger age. The increment of patients with sexual dysfunction reported in the active monitoring group after 1 year of follow-up was consistent with the worsening observed in mean EPIC sexual scores. This sexual deterioration might be explained by patients randomized to active monitoring which switch to prostatectomy and radiotherapy during the follow-up, given that the ProtecT trial had an intention to treat analysis. The proportion of patients who underwent radical prostatectomy and radiotherapy were 9% and 4.4% at 1 year of follow-up, and it increased until 20.6% and 7.7% at 5 years of follow-up, respectively. Thus, almost 30% of the patients in the active monitoring group had undergone a radical treatment at 5 years.

Figure 7a. Mean EPIC urinary scores for brachytherapy and active monitoring groups at baseline and annual follow-ups

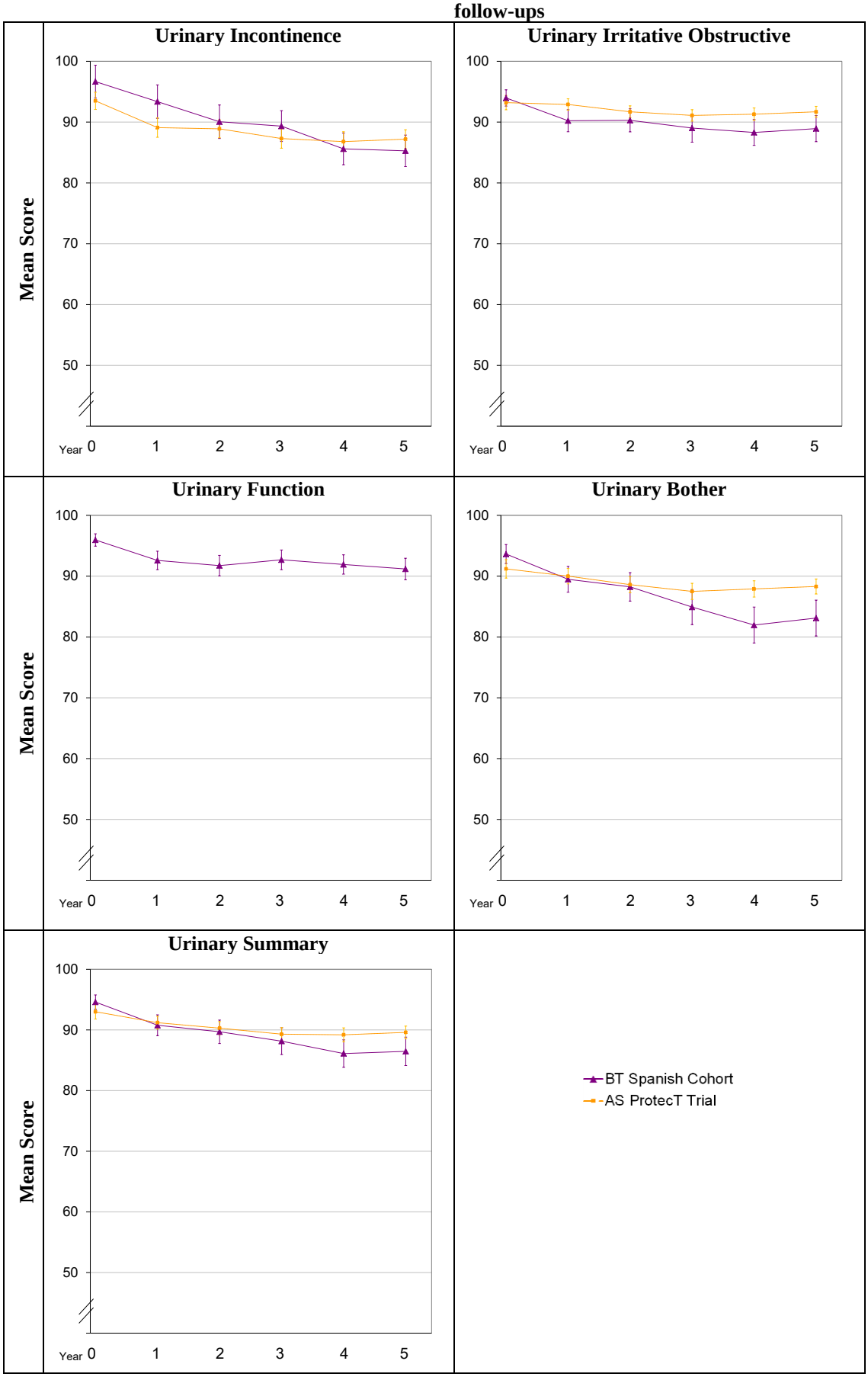


Figure 7b. Mean EPIC sexual and bother scores for brachytherapy and active monitoring groups at baseline and annual follow-ups

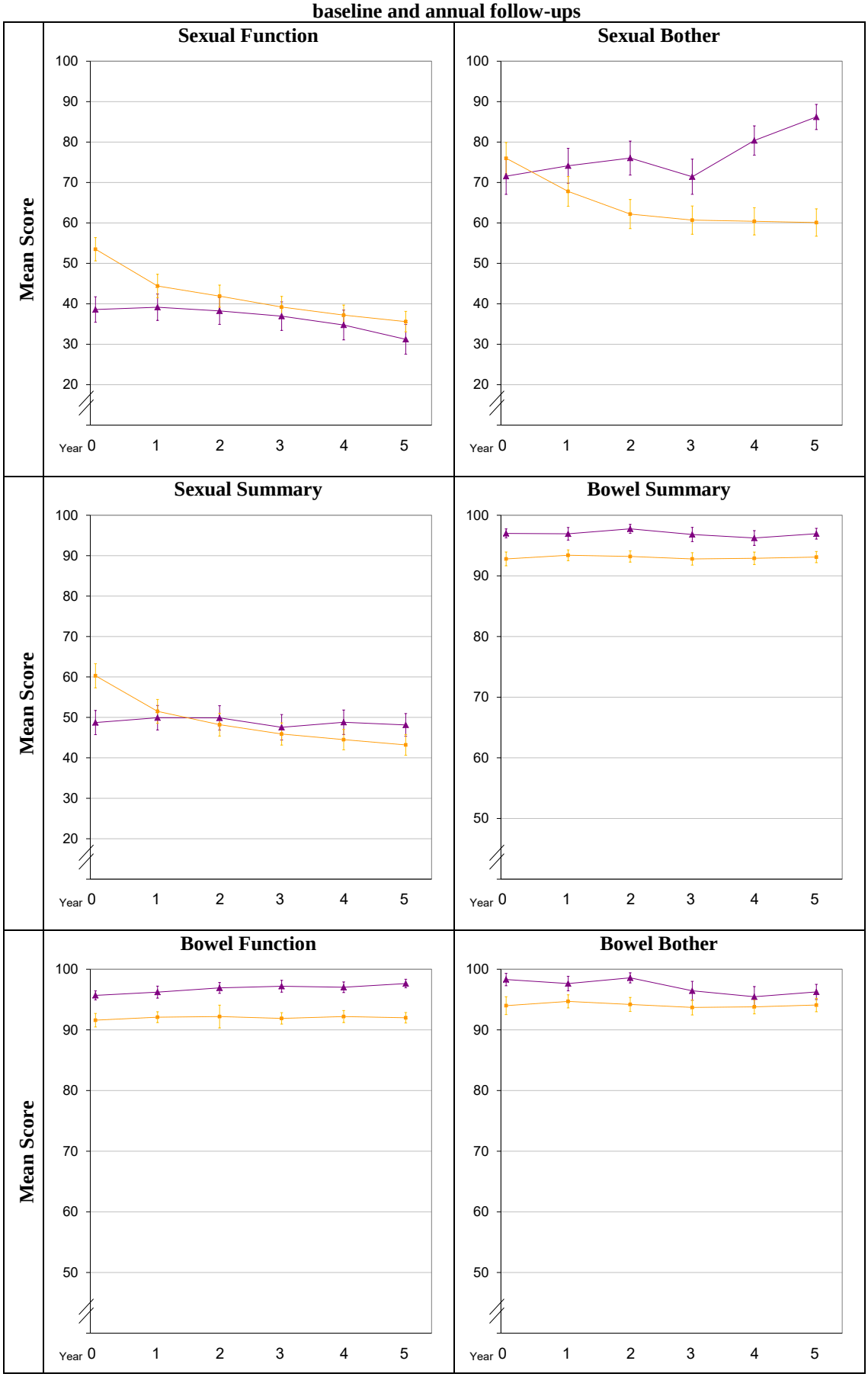
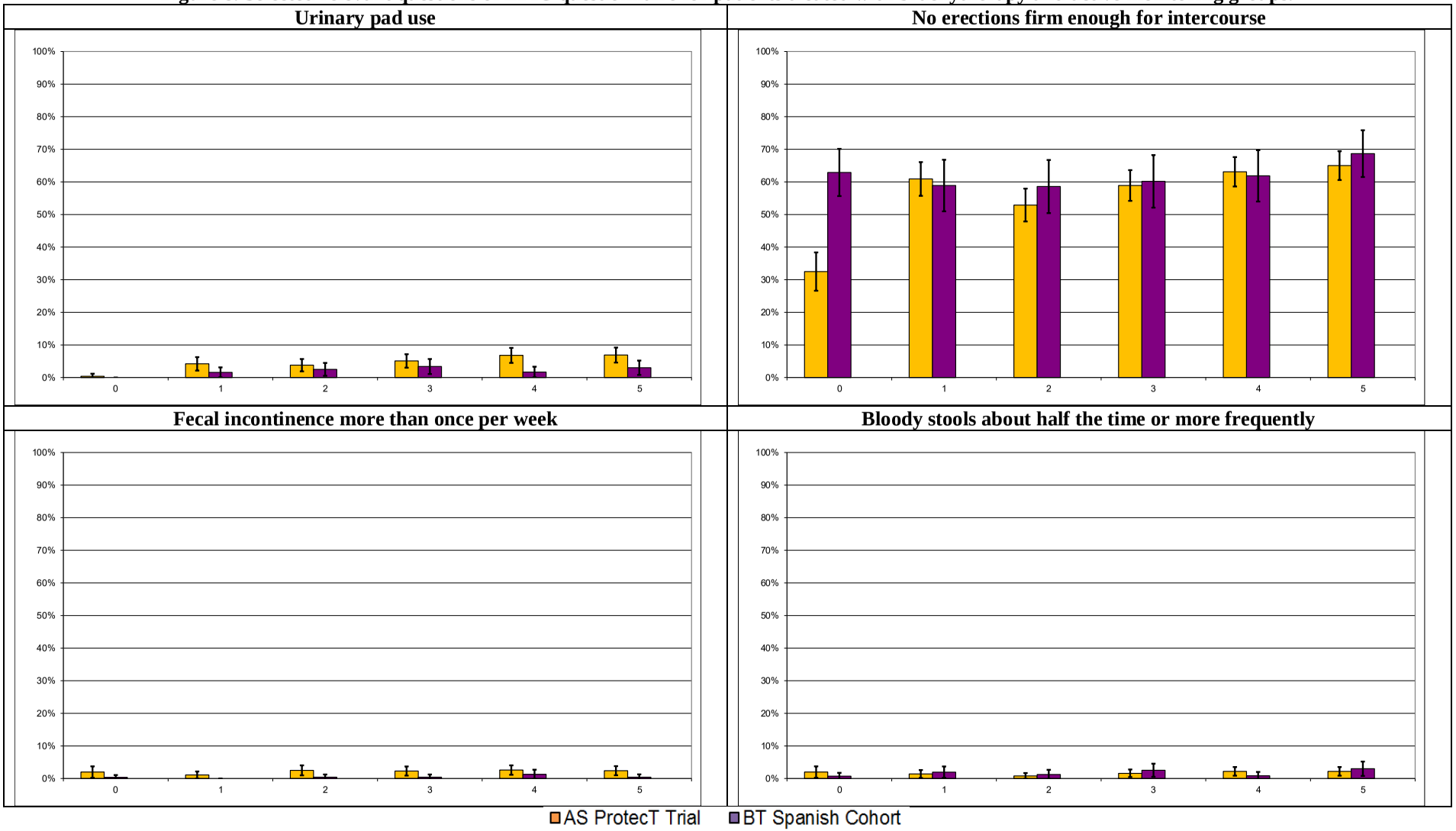


Figure 8. Selected relevant questions of EPIC questionnaire for patients treated with brachytherapy and active monitoring groups.



5.4 Overall discussion

The findings of the studies compared above consistently show that each prostate-cancer treatment has a particular short- and medium-term impact pattern: prostatectomy presents the highest negative effect on urinary incontinence and sexual function, while radiotherapy shows the highest impact on bowel domain. In our study, brachytherapy presented the highest worsening of urinary irritative-obstructive symptoms. Results of ProtecT trial indicate that active monitoring avoids or postpones adverse effects of radical treatments.

It is worth remarking the absence of brachytherapy in the ProtecT randomized clinical trial,(151) as well as the scarcity of observational longitudinal studies comparing it with the other radical treatments. Furthermore, most studies evaluating brachytherapy had only one,(174–181) two(139,182–184) or three years of follow-up.(185) Results of the majority of these studies on urinary incontinence, urinary irritative-obstructive, and sexual domains at 1-year follow-up were similar to our findings, but Sanda et al.(139) reported higher worsening than us on sexual summary. A higher heterogeneity is remarkable in bowel domain: similarly to our results, some studies reported no change,(179–181,183) while others showed moderate worsening.(174,175,178,176) Therefore, although this treatment option could offer a reduced adverse effect profile, the evidence is still lacking at medium and long term.

The English ProtecT study showed that patients allocated to the arm of active monitoring presented similar sexual dysfunction and sexual bother than those allocated to radiotherapy at the 3rd year of follow-up. These results are consistent with findings from a population-based Australian prospective cohort study,(185) and also with two articles recently published.(186,187) It is important to highlight that, since these studies evaluated treatment efficacy or effectiveness, the active monitoring arm included also patients who underwent radical prostatectomy or external radiotherapy at some point during follow-up: 14% at the 2nd year in the Australian study,(185)24% at 3rd year in the study of Barocas et al.,(186) 19% at 2nd year in the study by Chen et al.,(187) and around 20%, 40% and 55% at 2nd, 5th and 10th year, respectively, in ProtecT trial. This ‘intention to treat’ analytical strategy prevents a clear picture of patients who remained

on active monitoring, thus further studies are needed to describe long-term impact experienced by those patients without radical treatment. Although there was not much accumulated evidence about active surveillance, these important findings recently published support that it may be considered an alternative for men with localized prostate cancer who want to avoid the side effects of the active treatments during a time.

Finally, the differences observed between studies need to be debated because it is difficult to know their source. Differences in design, questionnaire administration methods, sample characteristics, or modalities within a treatment option, among others, could produce them. As the studies were developed in different countries with several languages such as British English, American English, Norwegian, and Spanish, they could reflect subtle deviations among versions of the questionnaires, or cultural differences in their perception, expectative and/or communication. As commented above, age differences could be a possible explanation for observed inequalities between function impairment and perceived bother. Regarding this aspect, it is important to remark that the recommendation for EPIC-26 scores include only summaries without breaking down into bother and function, but differences observed between studies support to maintain the distinction between them.

5.5 Directions for future research

This project has revealed areas in need of further investigation including:

a) Development of longer longitudinal follow-up studies comparing HRQoL and utilities impact of the treatments through generic and specific patient-reported outcomes measures at 10 or more years.

b) Assessment of the impact of the new therapeutic modalities of well-established treatments such as robotic-assisted radical prostatectomy, real-time prostate brachytherapy, proton therapy, or stereotactic beam radiation therapy.

c) Assessment of the efficacy and effectiveness of active surveillance, including comparisons among different follow-up protocols, and describing long-term impact experienced by those patients without radical treatment.

d) Disagreement between bother and function scores of the EPIC questionnaire observed merits a deep analysis. Although the latest recommendation of EPIC developers considered only three summaries (sexual, bowel and hormonal) and two urinary domains (incontinence and irritative-obstructive symptoms), further research is needed to evaluate the domains in bother and function that were initially proposed.

e) Establishing a model to predict PORPUS-U utility scores from EPIC scores (mapping) in order to perform economic evaluations with cost-utility analysis.

f) Joining mortality and non-mortal outcomes by estimating Quality Adjusted Life Years (QALYs) gained by each intervention, using direct and indirect methods (PORPUS).

g) Development of patient decision aids with description of risks and benefits of the treatments based on the new evidence recently published about survival, disease control measures and HRQoL to use in shared treatment decision making process.

6 CONCLUSIONS

a) The Spanish Multicentric Study of Clinically Localized Prostate Cancer showed that HRQoL impact of brachytherapy was restricted to the urinary domain; incontinence was large at five years, while irritative–obstructive symptoms were moderate during the whole follow-up. Radical prostatectomy presented no urinary irritative–obstructive side effects but led to larger and persisting urinary incontinence than brachytherapy. Sexual impact of radical prostatectomy and external radiotherapy could be qualified as large and small-moderate, respectively, at the end of follow-up. External radiotherapy also caused moderate bowel impact.

b) Our findings support that, despite minor late changes, brachytherapy is the treatment option causing the least impact on HRQoL (except for moderate urinary irritative–obstructive symptoms), with otherwise similar results to radical prostatectomy in overall survival and cancer control at five years. In the absence of multicentric randomized clinical trials, our study supports brachytherapy as a possible alternative to radical prostatectomy for patients with low or intermediate risk prostate cancer seeking an attempted curative treatment while limiting the risk for urinary incontinence and sexual impact on HRQoL.

c) Our findings indicated that urinary incontinence is the side effect with highest impact on preferences, and brachytherapy and external radiation therapy are more highly valued than radical prostatectomy. These TTO and SG preference assessments, as well as the estimation of WTP, reflect the patients' preferences according to side effects of different treatments for localized prostate cancer, and they are useful for performing cost-utility or cost-benefit analyses, which can guide health policy decisions.

d) Our results provide considerable support for the appropriate metric properties of the Spanish PORPUS. At the same time, comparison with the original Canadian version shows that it is similarly reliable and valid; suggesting that the adaptation method followed has yielded an equivalent version.

e) The PORPUS-P and PORPUS-U are appropriate and valuable tools for assessing HRQoL in Spanish prostate cancer patients and estimating utilities for cost-utility analysis.

REFERENCES

1. GLOBOCAN. Cancer fact sheets: prostate cancer [Internet]. [cited 2016 Jun 3]. Available from: http://gco.iarc.fr/today/fact-sheets-cancers?cancer=19&type=0&sex=1
2. Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132(5):1133–45.
3. GLOBOCAN. Population fact sheets: European Union (EU-28) [Internet]. [cited 2016 Jun 3]. Available from: http://gco.iarc.fr/today/fact-sheets-populations?population=990&sex=1#
4. GLOBOCAN. Population fact sheets: Spain [Internet]. [cited 2016 Jun 3]. Available from: http://gco.iarc.fr/today/fact-sheets-populations?population=724&sex=1#collapse1.
5. Wong MCS, Goggins WB, Wang HHX, Fung FDH, Leung C, Wong SYS, et al. Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries. Eur Urol. 2016 Nov 8;70(5):862–74.
6. Zhou CK, Check DP, Lortet-Tieulent J, Laversanne M, Jemal A, Ferlay J, et al. Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group. Int J Cancer. 2016;138(6):1388–400.
7. Shao Y-H, Demissie K, Shih W, Mehta AR, Stein MN, Roberts CB, et al. Contemporary risk profile of prostate cancer in the United States. J Natl Cancer Inst. 2009 Sep 16;101(18):1280–3.
8. Pron G. Prostate-Specific Antigen (PSA)-Based Population Screening for Prostate Cancer: An Evidence-Based Analysis. Ilic D, editor. Ont Health Technol Assess Ser. Chichester, UK: John Wiley & Sons, Ltd; 2015 Jan 31;15(10):1–64.
9. Trama A, Foschi R, Larrañaga N, Sant M, Fuentes-Raspall R, Serraino D, et al. Survival of male genital cancers (prostate, testis and penis) in Europe 1999-2007: Results from the EUROCARE-5 study. Eur J Cancer. 2015 Sep 6;51(15):2206–16.
10. Bunker CH, Patrick AL, Konety BR, Dhir R, Brufsky AM, Vivas CA, et al. High prevalence of screening-detected prostate cancer among Afro-Caribbeans: The Tobago prostate cancer survey. Cancer Epidemiol Biomarkers Prev. 2002 Aug;11(8):726–9.
11. Institute NC. Genetics of Prostate Cancer (PDQ®)–Health Professional Version [Internet]. [cited 2016 Jun 3]. Available from: http://www.cancer.gov/types/prostate/hp/prostate-genetics-pdq#link/_1176_toc
12. Carter BS, Steinberg GD, Beaty TH, Childs B, Walsh PC. Familial risk factors for prostate cancer. Cancer Surv. 1991;11:5–13.
13. Aune D, Navarro Rosenblatt DA, Chan DSM, Vieira AR, Vieira R, Greenwood DC, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr. 2015 Jan 1;101(1):87–117.
14. Mottet N, Bellmunt J, Briers E, van den Bergh RCN, Bolla M, van Casteren NJ, et al. Guidelines on Prostate Cancer- UPDATE MARCH 2015 [Internet]. 2015 [cited 2016 Jun 14]. Available from: https://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf.
15. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987 Oct 8;317(15):909–16.
16. Humphrey PA. Gleason grading and prognostic factors in carcinoma of the prostate. Mod Pathol. 2004 Mar;17(3):292–306.
17. Sun F, Oyesanmi O, Fontanarosa J, et al. Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review [Internet]. Rockville (MD):

Agency for Healthcare Research and Quality (US); 2014.(Comparative Effectiveness Reviews, No. 146.) Methods. [cited 2016 Jun 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK269322/.
18. Buyyounouski MK, Choyke PL, McKenney JK, Sartor O, Sandler HM, Amin MB, et al. Prostate cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 Feb 21;
19. D'Amico A V, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. J Am Med Assoc.1998 Sep 16;280(11):969–74.
20. Mottet N, Bastian P, Bellmunt J, van den Bergh R, Bolla M, van Casteren N, et al. Prostate Cancer [Internet]. 2014 [cited 2016 Jun 14]. Available from: https://uroweb.org/wp-content/uploads/1607-Prostate-Cancer_LRV3.pdf.
21. Chou R, Dana T, Bougatsos C, Fu R, Blazina I, Gleitsmann K, et al. Treatments for Localized Prostate Cancer: Systematic Review to Update the 2002 U.S. Preventive Services Task Force Recommendation. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. 2011.
22. Chung MS, Lee SH. Current status of active surveillance in prostate cancer. Investig Clin Urol. 2016;57(1):14.
23. Ficarra V, Novara G, Artibani W, Cestari A, Galfano A, Graefen M, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2009 May;55(5):1037–63.
24. De Carlo F, Celestino F, Verri C, Masedu F, Liberati E, Di Stasi SM. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: surgical, oncological, and functional outcomes: a systematic review. Urol Int. 2014;93(4):373–83.
25. Dal Pra A, Souhami L, Angelis R De, Sant M, Coleman MP, Francisci S, et al. Prostate cancer radiation therapy: A physician's perspective. Phys Medica. Elsevier; 2016 Mar;32(3):438–45.
26. Halpern JA, Sedrakyan A, Hsu W-C, Mao J, Daskivich TJ, Nguyen PL, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. Cancer. 2016 May 25;1–9.
27. Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy for organ-confined prostate cancer. BMC Urol. BioMed Central; 2010 Feb 1;10(1):1.
28. Chao MWT, Grimm P, Yaxley J, Jagavkar R, Ng M, Lawrentschuk N. Brachytherapy: State-of-the-art radiotherapy in prostate cancer. BJU Int. 2015;116:80–8.
29. Martin NE, Massey L, Stowell C, Bangma C, Briganti A, Bill-Axelson A, et al. Defining a standard set of patient-centered outcomes for men with localized prostate cancer. Eur Urol. 2015;67(3):460–7.
30. NCI Nacional Cancer Institute. No Title [Internet]. NCI Dictionary of Cancer Terms. [cited 2016 Jun 15]. Available from: http://www.cancer.gov/publications/dictionaries/cancer-terms
31. Antonarakis ES, Chen Y, Elsamanoudi SI, Brassell SA, Da Rocha M V., Eisenberger MA, et al. Long-term overall survival and metastasis-free survival for men with prostate-specific antigen-recurrent prostate cancer after prostatectomy: Analysis of the Center for Prostate Disease Research National Database. BJU Int. 2011;108(3):378–85.

32. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico A V., Dmochowski RR, et al. Variation in the Definition of Biochemical Recurrence in Patients Treated for Localized Prostate Cancer: The American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel Report and Recommendations for a Standard in the Reporting of Surgical Outcomes. J Urol. 2007 Feb;177(2):540–5.
33. Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006 Jul 15;65(4):965–74..
34. Valderas JM, Alonso J. Patient reported outcome measures: a model-based classification system for research and clinical practice. Qual Life Res. Springer Netherlands; 2008 Nov 3;17(9):1125–35.
35. Agency EM. Guideline on the evaluation of anticancer medicinal products in man. Vol. 44, European Medicines Agency. 2012.
36. Mckenna SP. Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. BMC Med. 2011;9:86.
37. Taillefer M-C, Dupuis G, Roberge M-A, LeMay S. Health-Related Quality of Life Models: Systematic Review of the Literature. Soc Indic Res. Kluwer Academic Publishers; 2003;64(2):293–323.
38. Bakas T, McLennon SM, Carpenter JS, Buelow JM, Otte JL, Hanna KM, et al. Systematic review of health-related quality of life models. Heal Qual Life Outcomes. 2012;10(1):134–45.
39. The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization. Soc Sci Med. 1995 Nov;41(10):1403–9.
40. Trust. SAC of the MO. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res. The Netherlands Cancer Institute, Amsterdam; 2002 May;11(3):193–205.
41. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297–334.
42. Fitzpatrick R, Fletcher A, Gore S, Jones D, Spiegelhalter D, Cox D. Quality of life measures in health care. I: Applications and issues in assessment. BMJ. 1992 Oct 31;305(6861):1074–7.
43. Fletcher A, Gore S, Jones D, Fitzpatrick R, Spiegelhalter D, Cox D. Quality of life measures in health care. II: Design, analysis, and interpretation. BMJ. 1992 Nov 7;305(6862):1145–8.
44. Khanna D, Tsevat J. Health-related quality of life--an introduction. Am J Manag Care. 2007 Dec;13 Suppl 9:S218-23.
45. Valderas JM, Alonso J. Medidas de calidad de vida relacionada con la salud: tipos y características. In: Martinez-Martin P, editor. Calidad de vida en neurología. Barcelona: Ars Medica XXI; 2006. p. 19–31.
46. Velikova G, Stark D, Selby P. Quality of life instruments in oncology. Eur J Cancer. 1999;35(11):1571–80.
47. Drummond MF. Methods for the economic evaluation of health care programmes. Vol. 3rd ed. Oxford: Oxford University Press; 2005.
48. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010 Dec 1;96(1):5–21.
49. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. Med Care. 1989 Mar;27(3 Suppl):S217-32.

50. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993 Apr 15;118(8):622–9.
51. Wiebe S, Guyatt G, Weaver B, Matijevic S, Sidwell C, Kantz ME, et al. Comparative responsiveness of generic and specific quality-of-life instruments. J Clin Epidemiol. Elsevier; 2003 Jan;56(1):52–60.
52. Chen RC, Chang P, Vetter RJ, Lukka H, Stokes WA, Sanda MG, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. J Natl Cancer Inst. 2014 Jul;106(7).
53. Hamoen EHJ, De Rooij M, Witjes JA, Barentsz JO, Rovers MM. Measuring health-related quality of life in men with prostate cancer: A systematic review of the most used questionnaires and their validity. Urol Oncol. 2015 Feb;33(2):69.e19-28.
54. McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247–63.
55. McHorney CA, Ware JE, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994 Jan;32(1):40–66.
56. Ferrans CE, Powers MJ. Quality of life index: development and psychometric properties. ANS Adv Nurs Sci. 1985 Oct;8(1):15–24.
57. Bonomi AE, Patrick DL, Bushnell DM, Martin M. Validation of the United States' version of the World Health Organization Quality of Life (WHOQOL) instrument. J Clin Epidemiol. 2000 Jan;53(1):1–12.
58. Padilla G V, Presant C, Grant MM, Metter G, Lipsett J, Heide F. Quality of life index for patients with cancer. Res Nurs Health. 1983 Sep;6(3):117–26.
59. Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988 Jul;26(7):724–35.
60. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. J Pers Assess. 1985 Feb;49(1):71–5.
61. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365–76.
62. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570–9.
63. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. University of Michigan, Ann Arbor, USA; 1997 Dec;50(6):920–8.
64. van Andel G, Bottomley A, Fosså SD, Efficace F, Coens C, Guerif S, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer. 2008 Nov;44(16):2418–24.
65. Schmidt S, Garin O, Pardo Y, Valderas JM, Alonso J, Rebollo P, et al. Assessing quality of life in patients with prostate cancer: a systematic and standardized comparison of available instruments. Qual Life Res. 2014 Oct 19;23(8):2169–81.
66. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998 Jul;36(7):1002–12.

67. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000 Dec 20;56(6):899–905.
68. Bergman J, Laviana A. Quality-of-life assessment tools for men with prostate cancer. Nat Rev Urol. 2014 Jun;11(6):352–9.
69. Krahn M, Bremner KE, Tomlinson G, Ritvo P, Irvine J, Naglie G. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. Qual Life Res. 2007 Apr 8;16(3):509–22.
70. Ritvo P, Irvine J, Naglie G, Tomlinson G, Bezjak A, Matthew A, et al. Reliability and validity of the PORPUS, a combined psychometric and utility-based quality-of-life instrument for prostate cancer. J Clin Epidemiol. 2005 May;58(5):466–74.
71. Tomlinson G, Bremner KE, Ritvo P, Naglie G, Krahn MD. Development and validation of a utility weighting function for the patient-oriented prostate utility scale (PORPUS). Med Decis Making. 2012 Jan 1;32(1):11–30.
72. Krahn M, Ritvo P, Irvine J, Tomlinson G, Bezjak A, Trachtenberg J, et al. Construction of the Patient-Oriented Prostate Utility Scale (PORPUS): a multiattribute health state classification system for prostate cancer. J Clin Epidemiol. 2000 Sep;53(9):920–30
73. Krahn MD, Bremner KE, Tomlinson G, Naglie G. Utility and health-related quality of life in prostate cancer patients 12 months after radical prostatectomy or radiation therapy. Prostate Cancer Prostatic Dis. 2009 Dec 1;12(4):361–8.
74. Ku J, Krahn M, Trachtenberg J, Nesbitt M, Kalnin R, Lockwood G, et al. Changes in health utilities and health-related quality of life over 12 months following radical prostatectomy. Can Urol Assoc J. 2009 Dec;3(6):445–52.
75. Krahn MD, Bremner KE, Alibhai SMH, Ni A, Tomlinson G, Laporte A, et al. A reference set of health utilities for long-term survivors of prostate cancer: population-based data from Ontario, Canada. Qual Life Res. 2013 Dec;22(10):2951–62.
76. Volk RJ, Cantor SB, Cass AR, Spann SJ, Weller SC, Krahn MD. Preferences of husbands and wives for outcomes of prostate cancer screening and treatment. J Gen Intern Med. 2004 Apr;19(4):339–48.
77. Krahn M, Ritvo P, Irvine J, Tomlinson G, Bremner KE, Bezjak A, et al. Patient and community preferences for outcomes in prostate cancer: implications for clinical policy. Med Care. 2003 Jan;41(1):153–64.
78. Matthew AG, Alibhai SMH, Davidson T, Currie KL, Jiang H, Krahn M, et al. Health-related quality of life following radical prostatectomy: long-term outcomes. Qual Life Res. 2014 Oct;23(8):2309–17.
79. Bremner KE, Tomlinson G, Krahn MD. Marker states and a health state prompt provide modest improvements in the reliability and validity of the standard gamble and rating scale in prostate cancer patients. Qual Life Res. 2007 Dec;16(10):1665–75.
80. Waldmann A, Rohde V, Bremner K, Krahn M, Kuechler T, Katalinic A. Measuring prostate-specific quality of life in prostate cancer patients scheduled for radiotherapy or radical prostatectomy and reference men in Germany and Canada using the Patient Oriented Prostate Utility Scale-Psychometric (PORPUS-P). BMC Cancer. 2009 Aug 23;9(1471–2407):295.
81. Bremner KE, Chong CAKY, Tomlinson G, Alibhai SMH, Krahn MD. A review and meta-analysis of prostate cancer utilities. Med Decis Making. 2007 May;27(3):288–98.

82. Torvinen S, Bergius S, Roine R, Lodenius L, Sintonen H, Taari K. Use of Patient Assessed Health-Related Quality of Life Instruments in Prostate Cancer Research: A Systematic Review of the Literature 2002-15. Int J Technol Assess Health Care. 2016 Jan;32(3):97–106.
83. Shimizu F, Fujino K, Ito YM, Fukuda T, Kawachi Y, Minowada S, et al. Factors associated with variation in utility scores among patients with prostate cancer. Value Health. 2008 Dec;11(7):1190–3.
84. Bruner DW, Hanlon A, Mazzoni S, Raysor S, Konski A, Hanks G, et al. Predictors of preferences and utilities in men treated with 3D-CRT for prostate cancer. Int J Radiat Oncol Biol Phys. 2004 Jan 1;58(1):34–42.
85. Sommers BD, Beard CJ, D'Amico A V, Kaplan I, Richie JP, Zeckhauser RJ. Predictors of patient preferences and treatment choices for localized prostate cancer. Cancer. 2008 Oct 15;113(8):2058–67.
86. Meghani SH, Lee CS, Hanlon AL, Bruner DW. Latent class cluster analysis to understand heterogeneity in prostate cancer treatment utilities. BMC Med Inform Decis Mak. 2009 Dec 27;9(1):47.
87. Dale W, Basu A, Elstein A, Meltzer D. Predicting utility ratings for joint health States from single health States in prostate cancer: empirical testing of 3 alternative theories. Med Decis Making. 2008 Jan;28(1):102–12.
88. Saigal CS, Gornbein J, Nease R, Litwin MS. Predictors of utilities for health states in early stage prostate cancer. J Urol. 2001 Sep;166(3):942–6.
89. Souchek J, Stacks JR, Brody B, Ashton CM, Giesler RB, Byrne MM, et al. A trial for comparing methods for eliciting treatment preferences from men with advanced prostate cancer: results from the initial visit. Med Care. 2000 Oct;38(10):1040–50.
90. Kattan MW, Cowen ME, Miles BJ. A decision analysis for treatment of clinically localized prostate cancer. J Gen Intern Med. 1997 May;12(5):299–305.
91. Smith DS, Krygiel J, Nease RF, Sumner W, Catalona WJ. Patient preferences for outcomes associated with surgical management of prostate cancer. J Urol. 2002 May;167(5):2117–22.
92. Kramer KM, Bennett CL, Pickard AS, Lyons EA, Wolf MS, McKoy JM, et al. Patient preferences in prostate cancer: a clinician's guide to understanding health utilities. Clin Prostate Cancer. 2005 Jun;4(1):15–23.
93. Elstein AS, Chapman GB, Knight SJ. Patients' values and clinical substituted judgments: the case of localized prostate cancer. Health Psychol. 2005 Jul;24(4S):S85-92.
94. Bennett CL, Chapman G, Elstein AS, Knight SJ, Nadler RB, Sharifi R, et al. A comparison of perspectives on prostate cancer: analysis of utility assessments of patients and physicians. Eur Urol. 1997;32 Suppl 3(0302–2838 (Print)):86–8.
95. Stewart ST, Lenert L, Bhatnagar V, Kaplan RM. Utilities for prostate cancer health states in men aged 60 and older. Med Care. 2005 Apr;43(4):347–55.
96. Pardo Y, Guedea F, Aguiló F, Fernández P, Macías V, Mariño A, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol. Institut Municipal d'Investigacions Mediques-Hospital del Mar, Barcelona, Bellaterra, Spain; 2010 Nov 1;28(31):4687–96.
97. Fernández-Arjona M, de la Cruz G, Delgado JA, Malet JM, Portillo JA. Validation in Spain of the Quality of Life questionnaire PROSQOLI in patients with advanced prostate cancer. Actas Urológicas Españolas (English Ed. 2012;36(7):410–7.
98. Cameron S, Springer C, Fox-Wasylyshyn S, El-Masri MM, Bellmunt J, Macia F, et al. A descriptive study of functions, symptoms, and perceived health state after radiotherapy for prostate cancer. Eur J Oncol Nurs. Elsevier; 2012 Jul;16(3):310–4.

99. Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005 Apr;16(4):579–84.
100. Pearcy R, Waldron D, O 'boyle C, Macdonagh R, Pearcy R. Proxy assessment of quality of life in patients with prostate cancer: how accurate are partners and urologists?
101. Torvinen S, Färkkilä N, Sintonen H, Saarto T, Roine RP, Taari K. Health-related quality of life in prostate cancer. Acta Oncol. 2013 Aug;52(6):1094–101.
102. Orsola A, Morote J. Epidemiologia de la incontinencia urinaria en el cancer de próstata: Incidencia, calidad de vida y aspectos farmacoeconómicos. Arch Españoles Urol. 2009;62:786–92.
103. Färkkilä N, Torvinen S, Roine RP, Sintonen H, Hänninen J, Taari K, et al. Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease. Qual Life Res. 2014 May;23(4):1387–94.
104. Korfage IJ, Essink-Bot M-L, Borsboom GJJM, Madalinska JB, Kirkels WJ, Habbema JDF, et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J cancer. 2005 Aug 20;116(2):291–6.
105. Mickevičienė A, Vanagas G, Jievaltas M, Ulys A. Does illness perception explain quality of life of patients with prostate cancer? Medicina (Kaunas). 2013;49(5):235–41.
106. Yasunaga H. Willingness to pay for mass screening for prostate cancer: a contingent valuation survey. Int J Urol. 2008 Jan;15(1):102–5; discussion 105.
107. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002 Oct 2;94(19):1458–68.
108. Reed SD, Radeva JI, Glendenning GA, Saad F, Schulman KA. Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. J Urol. 2004 Apr;171(4):1537–42.
109. Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. Qual Life Res. 2007 May;16(4):571–5.
110. Wu AK, Cooperberg MR, Sadetsky N, Carroll PR. Health Related Quality of Life in Patients Treated With Multimodal Therapy for Prostate Cancer. J Urol. 2008;180(6):2415–22.
111. Skaltsa K, Longworth L, Ivanescu C, Phung D, Holmstrom S. Mapping the FACT-P to the Preference-Based EQ-5D Questionnaire in Metastatic Castration-Resistant Prostate Cancer. 2014;
112. Diels J, Hamberg P, Ford D, Price PW, Spencer M, Dass RN. Mapping FACT-P to EQ-5D in a large cross-sectional study of metastatic castration-resistant prostate cancer patients. Qual Life Res. 2015 Mar;24(3):591–8.
113. Glazener C, Boachie C, Buckley B, Cochran C, Dorey G, Grant A, et al. Conservative treatment for urinary incontinence in Men After Prostate Surgery (MAPS): two parallel randomised controlled trials. Health Technol Assess. 2011 Jun;15(24):1–290, iii–iv.
114. Wang EY-H, Eriksson HG. Quality of life and functional outcomes 10 years after laparoscopic radical prostatectomy. Ups J Med Sci. 2014 Mar;119(1):32–7.
115. Pickard AS, Lin H-W, Knight SJ, Knight SL, Sharifi R, Wu Z, et al. Proxy assessment of health-related quality of life in african american and white respondents with prostate cancer: perspective matters. Med Care. 2009 Feb;47(2):176–83.

116. Freytag SO, Stricker H, Lu M, Elshaikh M, Aref I, Pradhan D, et al. Prospective randomized phase 2 trial of intensity modulated radiation therapy with or without oncolytic adenovirus-mediated cytotoxic gene therapy in intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys. Elsevier; 2014 Jun 1;89(2):268–76.
117. Booth N, Rissanen P, Tammela TLJ, Määttänen L, Taari K, Auvinen A. Health-Related Quality of Life in the Finnish Trial of Screening for Prostate Cancer. Eur Urol. 2014;65(1):39–47.
118. Ruland CM, Andersen T, Jeneson A, Moore S, Grimsbø GH, Børøsund E, et al. Effects of an internet support system to assist cancer patients in reducing symptom distress: a randomized controlled trial. Cancer Nurs. 36(1):6–17.
119. Soyupek F, Soyupek S, Perk H, Ozorak A, Society AC, Klotz L, et al. Androgen deprivation therapy for prostate cancer: effects on hand function. Urol Oncol. Elsevier; 2004;26(2):141–6.
120. Jayadevappa R, Schwartz JS, Chhatre S, Wein AJ, Malkowicz SB. Association between utility and treatment among patients with prostate cancer. Qual Life Res. 2010 Jun;19(5):711–20.
121. Xiong T, Turner RM, Wei Y, Neal DE, Lyratzopoulos G, Higgins JPT. Comparative efficacy and safety of treatments for localised prostate cancer: an application of network meta-analysis. BMJ Open. 2014;4(5):e004285.
122. Wolff RF, Ryder S, Bossi A, Briganti A, Crook J, Henry A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer. 2015 Nov;51(16):2345–67.
123. Roach M, Ceron Lizarraga TL, Lazar AA. Radical Prostatectomy Versus Radiation and Androgen Deprivation Therapy for Clinically Localized Prostate Cancer: How Good Is the Evidence? Int J Radiat Oncol Biol Phys. 2015 Dec 1;93(5):1064–70.
124. Wallis CJD, Saskin R, Choo R, Herschorn S, Kodama RT, Satkunasivam R, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016 Jul;70(1):21–30.
125. Wilt TJ, Shamliyan T, Taylor B, MacDonald R, Tacklind J, Rutks I, et al. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer. Agency for Healthcare Research and Quality (US); 2008.
126. Rice KR, Colombo ML, Wingate J, Chen Y, Cullen J, McLeod DG, et al. Low risk prostate cancer in men ≥ 70 years old: to treat or not to treat. Urol Oncol. 2013 Aug;31(6):755–60.
127. Mukherjee S, Reddy CA, Ciezki JP, Abdel-Wahab M, Tiu R V, Copelan E, et al. Risk for developing myelodysplastic syndromes in prostate cancer patients definitively treated with radiation. J Natl Cancer Inst. 2014 Mar;106(3):djt462.
128. Hoffman RM, Koyama T, Fan K-H, Albertsen PC, Barry MJ, Goodman M, et al. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. J Natl Cancer Inst. 2013 May 15;105(10):711–8.
129. Cooperberg MR, Vickers AJ, Broering JM, Carroll PR. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer. 2010 Nov 15;116(22):5226–34.
130. Nepple KG, Stephenson AJ, Kallogjeri D, Michalski J, Grubb RL, Strope SA, et al. Mortality after prostate cancer treatment with radical prostatectomy, external-beam radiation therapy, or brachytherapy in men without comorbidity. Eur Urol. 2013 Sep;64(3):372–8.

131. Degroot JM, Brundage MD, Lam M, Rohland SL, Heaton J, Mackillop WJ, et al. Prostate cancer-specific survival differences in patients treated by radical prostatectomy versus curative radiotherapy. Can Urol Assoc J. 7(5–6):E299-305.
132. Albertsen PC, Hanley JA, Penson DF, Barrows G, Fine J. 13-year outcomes following treatment for clinically localized prostate cancer in a population based cohort. J Urol. 2007 Mar;177(3):932–6.
133. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. Eur Urol. 2011 Nov;60(5):920–30.
134. Hadley J, Yabroff KR, Barrett MJ, Penson DF, Saigal CS, Potosky AL. Comparative Effectiveness of Prostate Cancer Treatments: Evaluating Statistical Adjustments for Confounding in Observational Data. JNCI J Natl Cancer Inst. Oxford University Press; 2010 Dec 1;102(23):1780–93.
135. Kibel AS, Ciezki JP, Klein E a, Reddy C a, Lubahn JD, Haslag-Minoff J, et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. J Urol. 2012;187(4):1259–65.
136. Shen X, Keith SW, Mishra M V, Dicker AP, Showalter TN. The impact of brachytherapy on prostate cancer-specific mortality for definitive radiation therapy of high-grade prostate cancer: a population-based analysis. Int J Radiat Oncol Biol Phys. 2012 Jul 15;83(4):1154–9.
137. Wong WW, Vora SA, Schild SE, Ezzell GA, Andrews PE, Ferrigni RG, et al. Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. Cancer. 2009 Dec 1;115(23):5596–606.
138. Marina O, Gustafson GS, Kestin LL, Brabbins DS, Chen PY, Ye H, et al. Comparison of dose-escalated, image-guided radiotherapy vs. dose-escalated, high-dose-rate brachytherapy boost in a modern cohort of intermediate-risk prostate cancer patients. Brachytherapy. 13(1):59–67.
139. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008 Mar 20;358(12):1250–61.
140. Ferrer M, Suárez JF, Guedea F, Fernández P, Macías V, Mariño A, et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008 Oct 1;72(2):421–32.
141. Malcolm JB, Fabrizio MD, Barone BB, Given RW, Lance RS, Lynch DF, et al. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol. 2010 May;183(5):1822–8.
142. Resnick MJ, Koyama T, Fan K-H, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368(5):436–45.
143. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012 Jul 19;367(3):203–13.
144. Bill-Axelson A, Holmberg L, Ruutu M, Häggman M, Andersson S-O, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005 May 12;352(19):1977–84.

145. Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C, et al. Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer: the Scandinavian Prostate Cancer Group-4 Randomized Trial. JNCI J Natl Cancer Inst. 2008 Aug 20;100(16):1144–54.
146. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2011 May 5;364(18):1708–17.
147. Holmberg L, Bill-Axelson A, Steineck G, Garmo H, Palmgren J, Johansson E, et al. Results from the Scandinavian Prostate Cancer Group Trial Number 4: a randomized controlled trial of radical prostatectomy versus watchful waiting. J Natl Cancer Inst Monogr. 2012 Dec 1;2012(45):230–3.
148. Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. World J Urol. 2009 Oct;27(5):607–12.
149. Donnelly BJ, Saliken JC, Brasher PMA, Ernst SD, Rewcastle JC, Lau H, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer. 2010 Jan 15;116(2):323–30.
150. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. Massachusetts Medical Society; 2016 Oct 13;375(15):1415–24.
151. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. Massachusetts Medical Society; 2016 Oct 13;375(15):1425–37.
152. Akakura K, Suzuki H, Ichikawa T, Fujimoto H, Maeda O, Usami M, et al. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: Results at median follow-up of 102 months. Jpn J Clin Oncol. 2006 Dec;36(12):789–93.
153. Chin JL, Ng C-K, Touma NJ, Pus NJ, Hardie R, Abdelhady M, et al. Randomized trial comparing cryoablation and external beam radiotherapy for T2C-T3B prostate cancer. Prostate Cancer Prostatic Dis. 2008;11(1):40–5.
154. Graversen PH, Nielsen KT, Gasser TC, Corle DK, Madsen PO. Radical prostatectomy versus expectant primary treatment in stages I and II prostatic cancer. A fifteen-year follow-up. Urology. 1990 Dec;36(6):493–8.
155. Crook JM, Gomez-Iturriaga A, Wallace K, Ma C, Fung S, Alibhai S, et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. J Clin Oncol. 2011 Feb 1;29(4):362–8.
156. Al-Zahrani A YVAAIJCJ. Long-term outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). Urology. 2012;80(3 SUPPL. 1).
157. Paulson DF, Lin GH, Hinshaw W, Stephani S. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. J Urol. 1982 Sep;128(3):502–4.
158. Di Stasi SM, Giannantoni A, Valenti M, Storti L, Attisani F, Palloni T, et al. Multicenter, randomized, phase III trial comparing radical retropubic prostatectomy with conventional external beam radiotherapy for localized prostate cancer: An interim report. J Clin Oncol. American Society of Clinical Oncology; 2006 Jun 20;24(18_suppl):4607.
159. Fransson P, Damber J-E, Widmark A. Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer. Scand J Urol Nephrol. 2009;43(2):119–26.

160. Yamamoto S, Kawakami S, Yonese J, Fujii Y, Urakami S, Kitsukawa S, et al. Long-term oncological outcome in men with T3 prostate cancer: radical prostatectomy versus external-beam radiation therapy at a single institution. Int J Clin Oncol. 2014;19(6):1085–91.
161. Parker C. Re: Christopher J.D. Wallis, Refik Saskin, Richard Choo, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;70:21–30. Eur Urol. 2016 Jul;70(1):e17.
162. Blanchard P, Briganti A, Bossi A. Re: Christopher J.D. Wallis, Refik Saskin, Richard Choo, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;70:21–30. Eur Urol. 2016 Jul;70(1):e15–6.
163. Ost P, Ghadjar P. Re: Christopher J.D. Wallis, Refik Saskin, Richard Choo, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;70:21–30. Eur Urol. 2016 Jul;70(1):e11–2.
164. Yasunaga H, Ide H, Imamura T, Ohe K. Benefit evaluation of mass screening for prostate cancer: willingness-to-pay measurement using contingent valuation. Urology. 2006 Nov;68(5):1046–50.
165. Neumann PJ, Cohen JT, Hammitt JK, Concannon TW, Auerbach HR, Fang C, et al. Willingness-to-pay for predictive tests with no immediate treatment implications: a survey of US residents. Health Econ. 2012 Mar 28;21(3):238–51.
166. Li C, Zeliadt SB, Hall IJ, Smith JL, Ekwueme DU, Moinpour CM, et al. Willingness to pay for prostate cancer treatment among patients and their family members at 1 year after diagnosis. Value Health. 2012;15(5):716–23.
167. Wilt TJ. Can randomized treatment trials in early stage prostate cancer be completed? Clin Oncol (R Coll Radiol). 1998;10(3):141–3.
168. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet. 2016;388(10049):1057–66.
169. Storås AH, Sanda MG, Ferrer M, Loge JH, Dahl AA, Steinsvik EAS, et al. Localized Prostate Cancer in Norway, the United States, and Spain: Between-Country Differences of Variables Before Treatment Among Patients Eligible for Curative Treatment. Clin Genitourin Cancer. 2014 Aug;12(4):e117–25.
170. Storås AH, Sanda MG, Boronat OG, Chang P, Patil D, Crociani C, et al. Erectile Dysfunction and Sexual Problems Two to Three Years After Prostatectomy Among American, Norwegian, and Spanish Patients. Clin Genitourin Cancer. 2016 Jun;14(3):e265–73.
171. Steinsvik EAS, Axcrona K, Angelsen A, Beisland C, Dahl A, Eri LM, et al. Does a surgeon's annual radical prostatectomy volume predict the risk of positive surgical margins and urinary incontinence at one-year follow-up? - Findings from a prospective national study. Scand J Urol. 2013 Apr 6;47(2):92–100.
172. Steinsvik EAS, Axcrona K, Dahl AA, Eri LM, Stensvold A, Fosså SD. Can sexual bother after radical prostatectomy be predicted preoperatively? Findings from a prospective national study of the relation between sexual function, activity and bother. BJU Int. 2012 May;109(9):1366–74.
173. Ferrer M, Guedea F, Suárez JF, de Paula B, Macías V, Mariño A, et al. Quality of life impact of treatments for localized prostate cancer: cohort study with a 5 year follow-up. Radiother Oncol. 2013 Aug;108(2):306–13.

174. van Tol-Geerdink JJ, Leer JWH, van Oort IM, van Lin EJNT, Weijerman PC, Vergunst H, et al. Quality of life after prostate cancer treatments in patients comparable at baseline. Br J Cancer. 2013 May 14;108(9):1784–9.
175. Dragićević S, Naumović T, Soldatović I, Mićić S, Tulić C, Pekmezović T. Evaluation of health-related quality of life in patients with prostate cancer after treatment with radical retropubic prostatectomy and permanent prostate brachytherapy. Urol Int. 2010;85(2):173–9.
176. Hashine K, Kusuhara Y, Miura N, Shirato A, Sumiyoshi Y, Kataoka M. Health-related Quality of Life using SF-8 and EPIC Questionnaires after Treatment with Radical Retropubic Prostatectomy and Permanent Prostate Brachytherapy. Jpn J Clin Oncol. 2009 Aug 1;39(8):502–8.
177. Pinkawa M, Asadpour B, Piroth MD, Gagel B, Nussen S, Kehl M, et al. Health-related quality of life after permanent I-125 brachytherapy and conformal external beam radiotherapy for prostate cancer--a matched-pair comparison. Radiother Oncol. 2009 May;91(2):225–31.
178. Rice K, Hudak J, Peay K, Elsamanoudi S, Travis J, Lockhart R, et al. Comprehensive Quality-of-life Outcomes in the Setting of a Multidisciplinary, Equal Access Prostate Cancer Clinic. Urology. 2010 Nov;76(5):1231–8.
179. Namiki S, Satoh T, Baba S, Ishiyama H, Hayakawa K, Saito S, et al. Quality of life after brachytherapy or radical prostatectomy for localized prostate cancer: A prospective longitudinal study. Urology. 2006 Dec;68(6):1230–6.
180. Maliski SL, Kwan L, Orecklin JR, Saigal CS, Litwin MS. Predictors of fatigue after treatment for prostate cancer. Urology. 2005 Jan;65(1):101–8.
181. Hashine K, Kusuhara Y, Miura N, Shirato A, Sumiyoshi Y, Kataoka M. A Prospective Longitudinal Study Comparing a Radical Retropubic Prostatectomy and Permanent Prostate Brachytherapy Regarding the Health-related Quality of Life for Localized Prostate Cancer. Jpn J Clin Oncol. 2008 Jul 11;38(7):480–5.
182. Strom TJ, Cruz AA, Figura NB, Shrinath K, Nethers K, Mellon EA, et al. Health-related quality-of-life changes due to high-dose-rate brachytherapy, low-dose-rate brachytherapy, or intensity-modulated radiation therapy for prostate cancer. Brachytherapy. 2015 Nov;14(6):818–25.
183. Ash D, Bottomley D, Al-Qaisieh B, Carey B, Gould K, Henry A. A prospective analysis of long-term quality of life after permanent I-125 brachytherapy for localised prostate cancer. Radiother Oncol. 2007 Aug;84(2):135–9.
184. Litwin MS, Gore JL, Kwan L, Brandeis JM, Lee SP, Withers HR, et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. Cancer. 2007 Jun 1;109(11):2239–47.
185. Smith DP, King MT, Egger S, Berry MP, Stricker PD, Cozzi P, et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. BMJ. 2009 Nov 27;339(1756–1833 (Electronic)):b4817.
186. Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. JAMA. 2017 Mar 21;317(11):1126.
187. Chen RC, Basak R, Meyer A-M, Kuo T-M, Carpenter WR, Agans RP, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA. 2017 Mar 21;317(11):1141.

ANNEXES

Annex 1. Manuscript.

Ávila M., Patel L., Garin O, López S., Cortés-Sanabria L., Pont A., Ferrer F., Boladeras A., Storås AH., Fosså SD., Sanda M., Ferrer M. ***Disease-Specific Patient Reported Outcomes After Treatment for Localized Prostate Cancer: A Systematic Review and Meta-analysis.***

Annex 2. EPIC Questionnaire

Annex 3. Spanish Version PORPUS Questionnaire

Annex 1. Manuscript

Ávila M., Patel L., Garin O, López S., Cortés-Sanabria L., Pont A., Ferrer F., Boladeras A., Storås AH., Fosså SD., Sanda M., Ferrer M. ***Disease-Specific Patient Reported Outcomes After Treatment for Localized Prostate Cancer: A Systematic Review and Meta-analysis.***

Disease-Specific Patient Reported Outcomes after Treatment for Localized Prostate Cancer: A Systematic Review and Meta-analysis.

Mónica Ávila. MPH 1, 2, 3, Laila Patel 4, Silvia López 1, Laura Cortés-Sanabria 5, Olatz Garin 1, 2, 3, Ferran Ferrer 6, Ana Boladeras 6, Victor Zamora 1, Sophie Fosså 7, Anne H. Storås 7, Martin Sanda 8, Montse Ferrer M.D, Ph.D 1, 2,9.

1. Health Services Research Unit, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
2. CIBER en Epidemiología y Salud Pública, CIBERESP, Spain
3. Universitat Pompeu Fabra, Barcelona, Spain.
4. James Cook University, Cairns, Australia.
5. Unidad de Investigación Médica en Enfermedades Renales. Hospital de Especialidades, CMNO, IMSS, Guadalajara, Mexico.
6. ICO
7. The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway.
8. Department of Urology, Emory University School of Medicine, United States.
9. Universitat Autònoma de Barcelona, Bellaterra, Spain

Correspondence Author
Montse Ferrer M.D., Ph.D.
Health Services Research Unit, IMIM (Hospital del Mar Research Institute)
Doctor Aiguader 88. 08003. Barcelona, Spain.
Phone: +34 93 3160 740; Fax: +34 93 3160 797; e-mail address*:* mferrer@imim.es
Keywords: Prostate cancer, quality of life, meta-analysis.

Running title: Prostate Cancer Patients' Health-Related Quality of Life

Acknowledgements: This study was supported by Instituto de Salud Carlos III FEDER (FIS PI11/01191); DIUE of Generalitat de Catalunya (2014 SGR 748); Ayuda económica "Doctorado con mención internacional al título" CIBERESP.

INTRODUCTION

Prostate cancer is currently the most common male tumor in the United States and second in the European Union (1;2). Usually diagnosed at localized stages, with low mortality rates(3), there are many available treatments with good cancer control, from radical prostatectomy to active surveillance, also including various techniques of radiotherapy. Unfortunately, due to the location of the prostate, men receiving treatment could suffer side-effects which can have a long impact on their health-related quality of life (HRQoL).

The growing interest in the use of patient-reported outcomes (PRO) for treatment decision-making led to the development of instruments designed specifically to measure the impact of localized prostate cancer, which appeared around 2000 (4) (5) (6). Meanwhile, in parallel with emergence of validated PRO instruments (7), first years of twenty one century has been critical in terms of treatment development for localized prostate cancer, both producing a great number of primary studies(8;9), and of the first systematic reviews trying to synthesize the generated knowledge (10-12).

The Agency for Healthcare Research and Quality published in 2014 an update(10)of a previous systematic review centered on patients with localized prostate cancer, including 21 studies with HRQoL data. A systematic review on major treatments HRQoL impact (11) in these patients conducted by Whiting et al. identified 64 studies (80 treatment cohorts). Baker et al.(12) performed a qualitative synthesis on the HRQoL effects of traditional treatments reported by 24 studies. These three systematic reviews (11-13) were published in the last 3 years (2014-2016), but none of them include a quantitative synthesis by meta-analysis. For this reason, our principal objective was to assess the HRQoL impact of primary treatments in patients with localized prostate cancer, measured with disease-specific instruments, by synthesizing results from longitudinal studies through a systematic review and meta-analysis. A secondary aim was to examine differences between modalities within each treatment on the patients' HRQoL.

METHODS

Protocol and Registration

The protocol for this review was registered on PROSPERO with the number CRD42015019747 (http://www.crd.york.ac.uk/Prospero). We used Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)(14) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines(15) for the reporting of this systematic review and meta-analysis.

Information Sources and Search

Search for eligible articles was undertaken in MEDLINE database from January 2005, when the first prospective studies measuring HRQoL with specific instruments for localized prostate cancer were published, to March 2017. The detailed search strategy used in PubMed can be found in the supplementary material. We used both subject headings and text-word terms for 'Prostate Cancer' AND 'Quality of Life'. The reference lists of previous systematic reviews were checked to identify other possible studies that could be included. Authors were contacted via email to obtain additional information when data were missing or unclear.

Eligibility Criteria

We looked for longitudinal studies in all languages measuring HRQoL of patients with localized prostate cancer. Inclusion criteria were: participants with localized prostate cancer; primary treatments with curative intention (radical prostatectomy, radiation therapy, interstitial brachytherapy, cryotherapy, high-intensity focused ultrasound

(HIFU), and active surveillance); prospective observational studies and clinical trials; follow-up of patients from pre-treatment to 1 year post-treatment or longer; and measuring HRQoL with a disease-specific instrument. Studies with cross-sectional design, without HRQoL assessment before treatment, evaluating secondary treatments, and/or those including >25% of participants with high risk or advanced prostate cancer were excluded.

Study Selection
Two members of the study team (LP and SL) independently reviewed articles found in the literature search by examining them in three consecutive phases: titles, abstracts, and full-text revision. A pilot test was performed to homogenize criteria between reviewers. Discrepancies were resolved with the assistance of an independent third party (OG).

Data Collection Process
Data were extracted using a standardized, predefined collection form. Completion of the data extraction was carried out by one author (LP or MA) with independent verification performed by other authors (AP or LS). Neither authors nor journals were blinded to reviewers. Coding for inclusion and exclusion criteria was defined and recorded for each phase.

Data Items
The information extracted was: study design, primary treatments, number of patients in each treatment cohort, patient characteristics, adjuvant hormonotherapy, HRQoL instrument used, and the following HRQoL data: mean of change with standard deviation (SD), as well as mean, SD, and number of patients at baseline and at each point of follow-up.

Summary Measures
The primary outcome to assess the impact of each treatment on patients' HRQoL was defined as the standardized difference of means between baseline and follow-up points. As proposed by Cohen's effect size(17) difference of means was standardized dividing it by the pooled SD (considering SD pre-treatment and at the follow-up). Effect size magnitude was considered small for 0.2 SD, moderate for 0.5 SD, and large for >0.8 SD.

Mean of change was considered the best estimator of this difference of means, and was extracted when available. Otherwise, we calculated the difference of means by the basic subtraction of the scores' mean at baseline and follow-up evaluations. As longitudinal studies present differences in the number of participants among evaluations due to withdrawals, the estimator was not calculated when participation rate was <75% at year 1, <65% at years 2 and 3, or <60% at years 4 and 5 of follow-up.

Synthesis of Results
We employed a random effect model (DerSimonian-Laird method) for all meta-analyses, as we expected variation in effects due to differences in study populations, questionnaires, and methods. Meta-analyses were carried out always stratifying by curative treatment group: radical prostatectomy, radiation therapy, interstitial brachytherapy, cryotherapy, HIFU, and active surveillance. Chi square test by cohort subgroups was performed according to the treatment modalities or techniques, since it could be a relevant source of heterogeneity (for example open, laparoscopic and robotic assisted modalities for radical prostatectomy).

Heterogeneity among studies was evaluated using I^2 statistic categorized as follows: <30% not important; 30%-50% moderate; 50%-75% substantial; and 75%-100% considerable (16). Forest plots were constructed showing the summary and 95% Confidence Interval (CI) estimated in the meta-analyses, together with results from individual studies. The forest plot was examined if I^2 >75% to identify which trials were the possible sources of heterogeneity. The meta-analytic software program used was STATA12.

A priori the results of studies which measured HRQoL using PORPUS, EORTC-PR25, or FACT-P were considered not possible to merge as they measured different domains, while results obtained with EPIC, UCLA-PCI, PC-QoL and PCSI were merged because they measured the same domains(7).

RESULTS

Study Selection

The literature search identified 5,001 articles (Figure 1- Flow Diagram of Review Process). After screening titles and abstracts, 503 were reviewed in full text and 311 were excluded. During full-text review, the most common reason for exclusion was that the study design, methods or instruments were not meeting inclusion criteria (39%), studies measuring other outcomes (20%), or that the sample included >25% of patients with high risk or locally advanced cancer (17%). All studies included in the systematic review had been approved by their Ethics Committee.

Of the 192 articles that met the inclusion criteria, 87 were selected for meta-analysis. (9;18-66) (67-103) Of the remaining 105 articles (92 studies), 2/3 were not included because they did not provide the necessary data (mean and/or SD in 59 studies, and number of patients in five). The other third included mainly studies with HRQoL instruments or treatments evaluated without enough common estimators to construct any meta-analyses: nine which administered the QLQ-PR25; five which used a questionnaire developed ad-hoc; two with the FACT-P, one with the PORPUS; three evaluating active surveillance; one evaluating combined treatment of brachytherapy and external radiotherapy; and one assessing High Intensity Focused Ultrasound (HIFU) treatment.

Study Characteristics

The 87 articles included describe the results from 55 studies, as 14 studies published more than one article due to reporting different follow-ups. The characteristics of the studies included and of those not included in meta-analyses are detailed in supplementary materials 2 and 3, respectively.

Table 1 summarizes the characteristics of the cohorts included and not included in the meta-analyses grouped by treatments. Of 93 cohorts of patients treated with radical prostatectomy, 40 were included in meta-analysis and 53 were not (in both cases open surgery was the main technique evaluated); of 87 cohorts with radiotherapy, half were included (11 SBRT, 9 IMRT, 8 external beam, 7 conformational 3D, 6 Proton Therapy, and 3 with various techniques); of 44 cohorts with Brachytherapy, 18 were included in meta-analysis, and 26 were not; while no meta-analysis was constructed with the 11 cohorts of Active Surveillance, the 6 cohorts of HIFU, and the 2 cohorts of cryotherapy. Regarding sample size, number of participants in each treatment cohort included in meta-analysis varies from 16 in IMRT to 1,806 in open radical prostatectomy(67;78), and it also varies substantially among those cohorts not included in meta-analysis.

The maximum follow-up for most of the cohorts included in meta-analysis is 12-24 months, four cohorts followed patients for 5 years (45;52;82) and 2 cohorts during 6 years. The maximum follow-up was similar in cohorts not included in meta-analysis, except for the Prostate Cancer Outcomes Study (PCOS) (104-106) and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE),(107;108) which followed patients for 15 and 10 years, respectively. Among cohorts included in meta-analysis, the age ranges between 58 and 70 years for RP, 56–75 years for RT, and 62–70 years for BT, the minimum PSA mean is 3.1 ng/mL(33), and the maximum is 29.4 ng/mL(78). Ranges of age and PSA mean are similar among cohorts not included in meta-analysis. Finally, regarding the HRQoL instrument applied, all estimators included in meta-analysis are measured with EPIC (67 cohorts) and UCLA-PCI (37 cohorts), except for 4 cohorts which used the PCSI (59;62). In contrast, the variety of HRQoL instruments increased in cohorts not included in meta-analysis, mainly with QLQ-PR25, PCSI, and FACT-P (26, 8, and 5 cohorts, respectively).

Synthesis of Results

Subgroup and global pooled estimators obtained by meta-analysis (with the 95% confidence interval), the minimum and the maximum estimator included, as well as heterogeneity data, are shown in figures. Meta-analyses were constructed with results obtained using EPIC, UCLA-PCI, and PCSI. Although PC-QoL was considered suitable for merging because it measured the same domains, the only study with estimators required for meta-analyses (109) was excluded due to 62% of loss of follow-up at 12 months after treatment.

It is necessary to comment about outcomes measured in meta-analyses constructed. The EPIC questionnaire, originally developed following UCLA-PCI conceptual model, included a summary score as well as function and bother scores for each urinary, sexual, bowel and hormonal domain, and two additional specific urinary dimensions: incontinence and irritative-obstructive. However, as the derived short version EPIC-26 does not provide summary scores, meta-analyses constructed with these estimators contained a lower number of studies and for this reason were included as supplementary material 4, and the meta-analyses constructed with the other scores were selected to comment here. Figures 2, 3, and 4 show results from meta-analyses of cohorts treated with radical prostatectomy, radiotherapy, and brachytherapy, respectively, for: A) urinary incontinence and irritative-obstructive; B) urinary function and bother; C) sexual function and bother; D) bowel function and bother.

Meta-analyses of cohorts treated with radical prostatectomy

Supplementary material 4 shows changes in urinary, sexual and bowel summaries. Urinary summary showed small-moderate worsening at 1st year of follow-up (-0.39; 95%CI -0.50, -0.28) without differences among subgroups of surgery techniques (p=0.942). Pooled data from two cohorts treated with ORP also indicated small-moderate worsening for follow-ups from the 2nd to the 5th year, with considerable heterogeneity the last two years (I^2 87% and 91%). Sexual summary showed large worsening at 1st year of follow-up (-1.42; 95%CI -1.62, -1.22) with statistically significant differences among subgroups of surgery techniques (p=0.001). Pooled data mainly from two ORP cohorts indicated large worsening from the 2nd to the 5th year follow-ups. Bowel summary showed negligible changes throughout all evaluations.

Meta-analysis of urinary scores (Figure 2A) presents a large worsening for incontinence without statistically significant differences among subgroups of surgery techniques at 1st year (p=0.223), but with considerable heterogeneity (I^2>75%). In contrast, the urinary irritative-obstructive score showed a small increase (improvement). These results are similar throughout all evaluations, but only supported by data from ORP cohorts with considerable heterogeneity. Meta-analysis of urinary

function (Figure 2B) showed moderate-large worsening without statistically significant differences among subgroups at 1st year (p=0.216), while urinary bother presented stability. Heterogeneity was also considerable in several meta-analyses.

Figure 2C shows large and moderate worsening for sexual function and bother, respectively. Both presented statistically significant differences among surgery technique subgroups at 1st year and considerable heterogeneity. Again, from this period on, only data from mainly ORP cohorts were obtained. Changes in bowel function and bother were negligible (Figure 2D).

Meta-analyses of cohorts treated with external radiotherapy

Supplementary material 4 showed stability in urinary summary at the two first years of follow-up, with differences among subgroups of radiotherapy modalities (p<0.001). From the 3rd year worsening was small-moderate but with considerable heterogeneity. Almost all sexual summaries showed moderate worsening with considerable heterogeneity (I^2 for the global 82%-92%), and statistical differences among modalities. Bowel summary also showed statistically significant differences among modalities. Worsening was small-moderate, except for SBRT with negligible changes at first (-0.20), second (-0.11) and third year (-0.15). Pooled data of PT was obtained only at first year, with considerable heterogeneity (I^2=96%).

Most of the meta-analyses of urinary incontinence (Figure 3A) showed small worsening without statistically significant differences among subgroups. Almost all irritative-obstructive meta-analyses showed no change, but heterogeneity was considerable (I^2 for the global 76%-94%). Worsening of urinary function and bother were negligible in most meta-analyses (Figure 3B).

Figure 3C showed moderate worsening of sexual function at the first and second year, except for SBRT with no change. Similarly to sexual summary meta-analysis, considerable heterogeneity for sexual function and bother was found. Changes in bowel function and bother were small in the majority of meta-analyses (Figure 3D). Moderate worsening on bowel bother was observed only for the modalities of EBRT and 3DCRT.

Meta-analyses of cohorts treated with brachytherapy

Supplementary material 4 shows small changes in urinary, sexual and bowel summaries, which were synthesized from one to five cohorts, with considerable heterogeneity in certain evaluations. All meta-analyses of urinary scores (Figure 4A) presented small worsening at 1st year (ranging between -0.17 and -0.35). Most pooled estimators of the other follow-ups presented considerable heterogeneity. Figure 4B shows small worsening for sexual function and bother in the majority of evaluations. Also small worsening for almost all bowel bother evaluations were estimated, while changes in bowel function were mainly negligible.

Meta-analyses of cohorts with other treatments

There were not sufficient estimators on Active Surveillance, HIFU and cryotherapy to perform meta-analyses. It was not possible to construct meta-analyses with the 11 cohorts of patients who underwent active surveillance due to differences on time of evaluations, questionnaires administered and domains reported. In general, these studies showed that although patients treated with active surveillance presented sexual worsening at the first years (110-112), they showed better urinary and sexual results than prostatectomy, and better bowel outcomes than radiotherapy.(9;18;31;78;113;114) However, these differences were attenuated through follow-up, mainly due to patients switching to active treatment with prostatectomy or radiotherapy.(9;18;31;114)

Of the 6 cohorts identified with HIFU, only one had complete information to perform meta-analyses after 1 year. Four HIFU studies with FACT-P showed HRQoL worsening at three months after treatment (115;116), but contradictory results at 1st year of follow-up: two studies reported no change between pre- and post-treatment (115-117) , and one study with a small sample size showed improvement.(118) Finally, the two studies evaluating cryotherapy reported patients recovering back to their baseline levels of urinary and bowel function, but without recovering sexual function at 3rd year follow-up.(119;120)

Studies meeting systematic review inclusion criteria but not included in meta-analyses

Of 105 publications (92 studies) not included in meta-analyses, some of them representing especially relevant research projects on this issue merit a comment. The PCOS is a population-based cohort of men diagnosed in 1994 and 1995, (142) who underwent either prostatectomy or radiotherapy as primary treatment. They used items adapted from UCLA and EPIC instruments to measure urinary, sexual and bowel function. The authors concluded that men who had undergone prostatectomy were more likely to have urinary incontinence and erectile dysfunction than those receiving radiotherapy at 5 years of follow-up, but differences were not statistically significant at 15 years. Means were reported in publications, but as no standard deviation was provided their estimators could not be included in meta-analyses.

The CaPSURE study is based on a prospective prostate cancer patient's registry that, since its inception in 1995, has included the UCLA-PCI to measure HRQoL impact.(107) Its results at short and medium follow-ups are in line with the PCOS, showing also attenuated differences between treatments at 10 years after treatment. Results on radical prostatectomy at 2 years were included in our meta-analyses (36;42) but not radiotherapy, brachytherapy and active surveillance cohorts because the principal CaPSURE publication (107) reported UCLA-PCI score means only at baseline. On the other hand, a lot of studies with a large sample size which were not included in meta-analyses presented specific research questions out of treatments' evaluation, such as the impact of body mass index in treatment effectiveness,(121) or the influence of pre-operative urinary bother on urinary symptoms after treatment.(122)

DISCUSSION

This systematic review identified 147 studies which met the inclusion criteria. Of them, the 55 studies finally included in the meta-analysis allowed to construct summary estimators for radical prostatectomy, external radiotherapy and brachytherapy from 1st to 5th year of follow-up. According to the treatment and outcome considered, the number of patients range included in meta-analyses was 851-6314 in radical prostatectomy, 1602-3979 in radiotherapy, 469-979 in brachytherapy at 1st year. At the 5th year the number of patients diminished substantially, with 321-577, 166-607, and 392 in radical prostatectomy, radiotherapy and brachytherapy, respectively. Radical prostatectomy meta-analyses showed large deterioration for sexual function and incontinence but a small urinary irritative-obstructive improvement. Meta-analyses of external radiotherapy indicate moderate worsening of sexual function (except for SBRT with no change until the 2nd year), and a small worsening on urinary incontinence and bowel function and bother. For brachytherapy, a small deterioration in urinary incontinence, irritative obstructive symptoms, sexual function, and bowel bother was observed in meta-analyses.

There is quite a lot of evidence on radical prostatectomy at short term, but it is scarce at medium-long term. Meta-analyses included 6-25 studies at 1st year of follow-up, but

only 2-3 studies at 4th and 5th year. Radical prostatectomy is the only treatment with side effects producing impacts of large magnitude in patients' HRQoL: sexual dysfunction and urinary incontinence. Although the meta-analyses of sexual function presented a considerable heterogeneity and statistical significant differences among technique subgroups, all the study estimators, except in Maliski et al. study (103), and all pooled estimators showed a large deterioration. Urinary incontinence meta-analyses also presented considerable heterogeneity, with study estimators ranging from -0.41 to -1.33, indicating that the HRQoL impact was between moderate and large. No robotic cohort was included in this meta-analysis, but two cohorts included in urinary function meta-analysis showed a large worsening (51;97), suggesting urinary side effects similar to the other surgery techniques. On the other hand, it is important to mention the small improvement observed on urinary irritative-obstructive symptoms, which could be an important factor to be considered in patients who already presented obstructive symptoms at diagnosis before treatment. Findings of our systematic review are consistent with results from the PCOS (104-106) and CAPSURE (107;108), which showed that patients who underwent radical prostatectomy had the largest sexual and urinary impact until 2 years after treatment, and a small urinary irritative-obstructive improvement. (114)

We found also quite a lot of evidence at short term, but scarce at medium-long term on external radiotherapy. Meta-analyses included 14-24 studies at 1st year of follow-up, but only 1-3 studies at 4th and 5th year. Meta-analyses without considerable heterogeneity showed moderate worsening on sexual function at the two first years. Statistical significant differences among subgroups suggest that SBRT is the only modality producing no deterioration of sexual function, but evidence came from three studies at the 1st year (29;30;45;49) and only one study at the 2nd year of follow-up.(45) Available evidence from several studies quite homogenously from 1st to 4th year after treatment shows that external radiotherapy produces urinary incontinence side effects, with small impact on patients' HRQoL. In general, the heterogeneity among external radiotherapy studies included in meta-analyses of bowel domains was slightly higher for function than for bother. Evidence is quite consistent to show bowel worsening of small magnitude for all modalities except for external beam radiotherapy at the 1st year after treatment, which magnitude was moderate. The same pattern was observed in both domains, function and bother. It is worth remarking that results of IMRT studies are very similar to those evaluating 3D-CRT, also producing moderate sexual dysfunction, and small urinary and bowel impact on patients' HRQoL until the 2nd year of follow-up. There is only one study of IMRT at longer-term which could not be included in meta-analyses since an ad-hoc HRQoL instrument was applied.(123)

We found a minor number of studies on brachytherapy, and meta-analyses included 4-10 studies at 1st year of follow-up, and 1-2 studies at 4th and 5th year. In general, all urinary estimators (incontinence, irritative-obstructive, function and bother) both pooled and from individual studies indicated small HRQoL impact. However, it is important to remark the variability observed, with some studies that reported no deterioration (61;84;91), a few that showed moderate worsening (52;73;80;103), and the study of Rice et al. (74) reporting large impact. Results of brachytherapy cohorts were really consistent, showing very small worsening on sexual function and bowel bother. Bowel function at 1st year also showed a small worsening, but no deterioration was observed at the following yearly evaluations. It is important to embark on further research to identify the sources of the heterogeneity on urinary side effects, because it prevents from providing reliable information to patients about this option of treatment which did not present almost any HRQoL impact in sexual and bowel domains.

Unfortunately, no meta-analyses could be constructed with studies utilizing EORTC-QLQ PR25, FACT-P, and PORPUS, as there were no 3 estimators of the same

treatment and follow-up time with these instruments. We only identified one study using PORPUS, which evaluated radical prostatectomy, (124) and two administering FACT-P to assess brachytherapy (125) and radiotherapy.(126) The EORTC-QLQ PR25 has been applied more often, and we identified nine studies which administered it to evaluate several treatments: brachytherapy (111;127-130), radical prostatectomy (131;132), SBRT(133;134), IMRT (133;134), 3D-CRT (135), active surveillance (111), and robot-assisted radical prostatectomy.(111) Despite covering urinary, sexual and bowel domains, EORTC-QLQ PR25 is more centered on symptoms without measuring function and bother like EPIC and UCLA-PCI. No meta-analysis could be constructed with the four studies evaluating brachytherapy because one was excluded due to 69% lost to follow-up rate (127), Acar et al. (111) evaluated patients only at 4 years after treatment and Roeloffezen et al. (128;129) only at 6 years. Taking into account that EORTC QLQ-PR25 was the newest specific instrument for localized prostate cancer (136), as more studies will be published in the next years it may be feasible to make a quantitative synthesis of their results in the future.

Heterogeneity was considerable (I^2>75%) in six meta-analyses constructed with radical prostatectomy cohorts (urinary incontinence, function and bother, sexual function and bother, and bowel function), in five of the radiotherapy cohorts (urinary irritative-obstructive and bother, sexual function and bother, and bowel function), but only in three of those constructed with brachytherapy cohorts (urinary incontinence and irritative obstructive, and sexual bother). This pattern suggests that heterogeneity is associated to differences among surgical and radiotherapy modalities of treatment. This is reasonable attending to radiotherapy findings, where high heterogeneity coincided with statistical significant differences among modalities. Nevertheless, in some radical prostatectomy meta-analyses with considerable heterogeneity the differences among surgical techniques were not statistically significant, such as urinary incontinence, function and bother, and bowel function at 1st year after treatment. It is necessary to highlight that, despite this considerable heterogeneity in radical prostatectomy outcomes, estimators from all individual studies were consistent supporting its side effect pattern of large incontinence, sexual dysfunction and bother.

We identified several limitations in our review process. Firstly, 63 studies could not be included in meta-analyses due to the lack of some specific estimator needed for their construction. However, most of their results were consistent with our findings, and some of them have been commented above for each treatment option. Secondly, we merged results measured with different questionnaires. This was only done for those covering similar domains, as described previously by a systematic review of prostate cancer-specific HRQoL instruments.(7) Furthermore, the use of the standardized mean of change for meta-analyses allowed us to solve differences among HRQoL instrument score units. This standardization translates results from different scales into SD units which present the advantage of being directly comparable and interpretable as magnitude of change (0.2 small, 0.5 moderate, and 0.8 large). Third, estimators incorporated in the meta-analysis were unadjusted. Although regression models and propensity scores can assist in adjusting for selection bias, since meta-analysis purpose was not comparing between treatments just to describe each one and compare between modalities, adjustment is less important. It is reasonable that patients were allocated to different modalities within a treatment option by reasons related to practical aspects such as the availability of a radiotherapy technique, and therefore, presented no major differences on clinical characteristics. Stage of cancer was a variable which we attempted to control by exclusion criteria applied to those studies with more than 25% of patients with high risk localized prostate cancer or

advanced cancer. Finally, secondary treatments or interventions such as salvage radiotherapy after prostatectomy or hormonotherapy were not considered.

In conclusion, this systematic review characterizes the impact on patients' HRQoL of the most accepted primary treatments with curative intention for patients with localized prostate cancer. Radical prostatectomy produces large sexual and incontinence deterioration but small improvement on urinary irritative obstructive symptoms; radiotherapy techniques cause moderate sexual dysfunction, and small impact on incontinence, bowel function and bother; and brachytherapy produces incontinence, irritative obstructive symptoms, sexual dysfunction and bowel bother of small HRQoL impact. Our findings suggest that there are no major differences between treatment modalities on their impact on patients' HRQoL, except for SBRT. Nowadays available evidence supports SBRT or brachytherapy as a possible alternative to radical prostatectomy for patients with localized prostate cancer seeking an attempted curative treatment while limiting the risk for urinary incontinence and sexual impact on HRQoL.

CONFLICT OF INTEREST: The authors declare no conflict of interest

REFERENCES

(1) Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015 Mar 1;136(5):E359-E386.

(2) Trama A, Foschi R, Larranaga N, Sant M, Fuentes-Raspall R, Serraino D, et al. Survival of male genital cancers (prostate, testis and penis) in Europe 1999-2007: Results from the EUROCARE-5 study. Eur J Cancer 2015 Sep 6.

(3) Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med 2016 Oct 13;375(15):1415-24.

(4) Giesler RB, Miles BJ, Cowen ME, Kattan MW. Assessing quality of life in men with clinically localized prostate cancer: development of a new instrument for use in multiple settings. Qual Life Res 2000;9(6):645-65.

(5) Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care 1998 Jul;36(7):1002-12.

(6) Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000 Dec 20;56(6):899-905.

(7) Schmidt S, Garin O, Pardo Y, Valderas JM, Alonso J, Rebollo P, et al. 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.

(8) Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet 2016 Sep 10;388(10049):1057-66.

(9) Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med 2016 Oct 13;375(15):1425-37.

(10) Sun F, Oyesanmi O, Fontanarosa J, . Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review.(Comparative Effectiveness Reviews, No. 146.). Rockville (MD): Agency for Healthcare Research and Quality (US) 2014 December 1Available from: URL: https://www.ncbi.nlm.nih.gov/books/NBK269320/

(11) Whiting PF, Moore TH, Jameson CM, Davies P, Rowlands MA, Burke M, et al. Symptomatic and quality-of-life outcomes after treatment for clinically localised prostate cancer: a systematic review. BJU Int 2016 Aug;118(2):193-204.

(12) Baker H, Wellman S, Lavender V. Functional Quality-of-Life Outcomes Reported by Men Treated for Localized Prostate Cancer: A Systematic Literature Review. Oncol Nurs Forum 2016 Mar;43(2):199-218.

(13) Bellardita L, Valdagni R, van den Bergh R, Randsdorp H, Repetto C, Venderbos LD, et al. How does active surveillance for prostate cancer affect quality of life? A systematic review. Eur Urol 2015 Apr;67(4):637-45.

(14) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009 Aug 18;151(4):264-9, W64.

(15) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000 Apr 19;283(15):2008-12.

(16) Higgins JPT GSe. C*ochrane Handbook for Systematic Reviews of Interventions*Version 5.1.0 [updated March 2011]. 2016. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

(17) Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Effect Sizes Based on Means. Introduction to Meta-Analysis. John Wiley & Sons, Ltd; 2009. p. 21-32.

(18) Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. JAMA 2017 Mar 21;317(11):1126-40.

(19) Tyson MD, Alvarez J, Koyama T, Hoffman KE, Resnick MJ, Wu XC, et al. Racial Variation in Patient-Reported Outcomes Following Treatment for Localized Prostate Cancer: Results from the CEASAR Study. Eur Urol 2016 Nov 2.

(20) Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Int J Radiat Oncol Biol Phys 2017 Apr 1;97(5):976-85.

(21) Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, Beyer D, et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. Int J Radiat Oncol Biol Phys 2015 Aug 1;92(5):971-7.

(22) Quon HC, Musunuru HB, Cheung P, Pang G, Mamedov A, D'Alimonte L, et al. Dose-Escalated Stereotactic Body Radiation Therapy for Prostate Cancer: Quality-of-Life Comparison of Two Prospective Trials. Front Oncol 2016;6:185.

(23) Bryant C, Smith TL, Henderson RH, Hoppe BS, Mendenhall WM, Nichols RC, et al. Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer. Int J Radiat Oncol Biol Phys 2016 May 1;95(1):422-34.

(24) Mendenhall NP, Hoppe BS, Nichols RC, Mendenhall WM, Morris CG, Li Z, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2014 Mar 1;88(3):596-602.

(25) Bryant C, Mendenhall NP, Henderson RH, Nichols RC, Mendenhall WM, Morris CG, et al. Does Race Influence Health-related Quality of Life and Toxicity Following Proton Therapy for Prostate Cancer? Am J Clin Oncol 2016 Jun;39(3):261-5.

(26) Morton G, Chung HT, McGuffin M, Helou J, D'Alimonte L, Ravi A, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19Gy or two fractions of 13.5Gy. Radiother Oncol 2017 Jan;122(1):87-92.

(27) Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016 Aug;17(8):1047-60.

(28) Wilkins A, Mossop H, Syndikus I, Khoo V, Bloomfield D, Parker C, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2015 Dec;16(16):1605-16.

(29) Hannan R, Tumati V, Xie XJ, Cho LC, Kavanagh BD, Brindle J, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. Eur J Cancer 2016 May;59:142-51.

(29) Hannan R, Tumati V, Xie XJ, Cho LC, Kavanagh BD, Brindle J, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. Eur J Cancer 2016 May;59:142-51.

(30) Kim DW, Straka C, Cho LC, Timmerman RD. Stereotactic Body Radiation Therapy for Prostate Cancer: Review of Experience of a Multicenter Phase I/II Dose-Escalation Study. Front Oncol 2014;4:319.

(31) Jeldres C, Cullen J, Hurwitz LM, Wolff EM, Levie KE, Odem-Davis K, et al. Prospective quality-of-life outcomes for low-risk prostate cancer: Active surveillance versus radical prostatectomy. Cancer 2015 Jul 15;121(14):2465-73.

(32) Pham KN, Cullen J, Hurwitz LM, Wolff EM, Levie KE, Odem-Davis K, et al. Prospective Quality of Life in Men Choosing Active Surveillance Compared to Those Biopsied but not Diagnosed with Prostate Cancer. J Urol 2016 Mar 11.

(33) Strom TJ, Cruz AA, Figura NB, Shrinath K, Nethers K, Mellon EA, et al. Health-related quality-of-life changes due to high-dose-rate brachytherapy, low-dose-rate brachytherapy, or intensity-modulated radiation therapy for prostate cancer. Brachytherapy 2015 Nov;14(6):818-25.

(34) Vargas CE, Hartsell WF, Dunn M, Keole SR, Doh L, Eisenbeisz E, et al. Hypofractionated Versus Standard Fractionated Proton-beam Therapy for Low-risk Prostate Cancer: Interim Results of a Randomized Trial PCG GU 002. Am J Clin Oncol 2015 Oct 29.

(35) Woo JA, Chen LN, Wang H, Cyr RA, Bhattasali O, Kim JS, et al. Stereotactic Body Radiation Therapy for Prostate Cancer: What is the Appropriate Patient-Reported Outcome for Clinical Trial Design? Front Oncol 2015;5:77.

(36) Brajtbord JS, Punnen S, Cowan JE, Welty CJ, Carroll PR. Age and baseline quality of life at radical prostatectomy--who has the most to lose? J Urol 2014 Aug;192(2):396-401.

(37) Daskivich TJ, van de Poll-Franse LV, Kwan L, Sadetsky N, Stein DM, Litwin MS. From bad to worse: comorbidity severity and quality of life after treatment for early-stage prostate cancer. Prostate Cancer Prostatic Dis 2010 Dec;13(4):320-7.

(38) Bellizzi KM, Latini DM, Cowan JE, DuChane J, Carroll PR. Fear of recurrence, symptom burden, and health-related quality of life in men with prostate cancer. Urology 2008 Dec;72(6):1269-73.

(39) van de Poll-Franse LV, Sadetsky N, Kwan L, Litwin MS. Severity of cardiovascular disease and health-related quality of life in men with prostate cancer: a longitudinal analysis from CaPSURE. Qual Life Res 2008 Aug;17(6):845-55.

(40) Wright JL, Lin DW, Cowan JE, Carroll PR, Litwin MS. Quality of life in young men after radical prostatectomy. Prostate Cancer Prostatic Dis 2008;11(1):67-73.

(41) Latini DM, Chan JM, Cowan JE, Arredondo SA, Kane CJ, Penson DF, et al. Health-related quality of life for men with prostate cancer and diabetes: a longitudinal analysis from CaPSURE. Urology 2006 Dec;68(6):1242-7.

(42) Hu JC, Elkin EP, Krupski TL, Gore J, Litwin MS. The effect of postprostatectomy external beam radiotherapy on quality of life: results from the Cancer of the Prostate Strategic Urologic Research Endeavor. Cancer 2006 Jul 15;107(2):281-8.

(43) Arredondo SA, Elkin EP, Marr PL, Latini DM, DuChane J, Litwin MS, et al. Impact of comorbidity on health-related quality of life in men undergoing radical prostatectomy: data from CaPSURE. Urology 2006 Mar;67(3):559-65.

(44) Anast JW, Sadetsky N, Pasta DJ, Bassett WW, Latini D, DuChane J, et al. The impact of obesity on health related quality of life before and after radical prostatectomy (data from CaPSURE). J Urol 2005 Apr;173(4):1132-8.

(45) Mantz C. A Phase II Trial of Stereotactic Ablative Body Radiotherapy for Low-Risk Prostate Cancer Using a Non-Robotic Linear Accelerator and Real-Time Target Tracking: Report of Toxicity, Quality of Life, and Disease Control Outcomes with 5-Year Minimum Follow-Up. Front Oncol 2014;4:279.

(46) Bhattasali O, Chen LN, Woo J, Park JW, Kim JS, Moures R, et al. Patient-reported outcomes following stereotactic body radiation therapy for clinically localized prostate cancer. Radiat Oncol 2014;9:52.

(47) Davison BJ, Matthew A, Gardner AM. Prospective comparison of the impact of robotic-assisted laparoscopic radical prostatectomy versus open radical prostatectomy on health-related quality of life and decision regret. Can Urol Assoc J 2014 Jan;8(1-2):E68-E72.

(48) Hashine K, Nakashima T, Iio H, Ueno Y, Shimizu S, Ninomiya I. Health-related quality of life in the first year after laparoscopic radical prostatectomy compared with open radical prostatectomy. Jpn J Clin Oncol 2014 Jul;44(7):686-91.

(49) Scorsetti M, Alongi F, Clerici E, Comito T, Fogliata A, Iftode C, et al. Stereotactic body radiotherapy with flattening filter-free beams for prostate cancer: assessment of patient-reported quality of life. J Cancer Res Clin Oncol 2014 Oct;140(10):1795-800.

(50) Yamamoto S, Fujii Y, Masuda H, Urakami S, Saito K, Kozuka T, et al. Longitudinal change in health-related quality of life after intensity-modulated radiation monotherapy for clinically localized prostate cancer. Qual Life Res 2014 Jun;23(5):1641-50.

(51) Berge V, Berg RE, Hoff JR, Wessel N, Diep LM, Karlsen SJ, et al. A prospective study of transition from laparoscopic to robot-assisted radical prostatectomy: quality of life outcomes after 36-month follow-up. Urology 2013 Apr;81(4):781-6.

(52) Ferrer M, Guedea F, Suarez JF, de PB, Macias V, Marino A, et al. Quality of life impact of treatments for localized prostate cancer: cohort study with a 5 year follow-up. Radiother Oncol 2013 Aug;108(2):306-13.

(53) Chang P, Regan MM, Ferrer M, Guedea F, Patil D, Wei JT, et al. Relief of Urinary Symptom Burden after Primary Prostate Cancer Treatment. J Urol 2017 Feb;197(2):376-84.

(54) Lee JY, Daignault-Newton S, Heath G, Scarlett S, Sanda MG, Chang P, et al. Multinational Prospective Study of Patient-Reported Outcomes After Prostate Radiation Therapy: Detailed Assessment of Rectal Bleeding. Int J Radiat Oncol Biol Phys 2016 Nov 15;96(4):770-7.

(55) Pardo Y, Guedea F, Aguilo F, Fernandez P, Macias V, Marino A, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. J Clin Oncol 2010 Nov 1;28(31):4687-96.

(56) Guedea F, Ferrer M, Pera J, Aguilo F, Boladeras A, Suarez JF, et al. Quality of life two years after radical prostatectomy, prostate brachytherapy or external beam radiotherapy for clinically localised prostate cancer: the Catalan Institute of Oncology/Bellvitge Hospital experience. Clin Transl Oncol 2009 Jul;11(7):470-8.

(57) Ferrer M, Suarez JF, Guedea F, Fernandez P, Macias V, Marino A, et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2008 Oct 1;72(2):421-32.

(58) Katz A, Ferrer M, Suarez JF. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. Radiat Oncol 2012;7:194.

(59) Gray PJ, Paly JJ, Yeap BY, Sanda MG, Sandler HM, Michalski JM, et al. Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. Cancer 2013 May 1;119(9):1729-35.

(60) King CR, Collins S, Fuller D, Wang PC, Kupelian P, Steinberg M, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys 2013 Dec 1;87(5):939-45.

(61) van Tol-Geerdink JJ, Leer JW, van Oort IM, van Lin EJ, Weijerman PC, Vergunst H, et al. Quality of life after prostate cancer treatments in patients comparable at baseline. Br J Cancer 2013 May 14;108(9):1784-9.

(62) Coen JJ, Paly JJ, Niemierko A, Weyman E, Rodrigues A, Shipley WU, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2012 Feb 1;82(2):e201-e209.

(63) Hoppe BS, Nichols RC, Henderson RH, Morris CG, Williams CR, Costa J, et al. Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger. Cancer 2012 Sep 15;118(18):4619-26.

(64) McBride SM, Wong DS, Dombrowski JJ, Harkins B, Tapella P, Hanscom HN, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. Cancer 2012 Aug 1;118(15):3681-90.

(65) Steinsvik EA, Axcrona K, Dahl AA, Eri LM, Stensvold A, Fossa SD. Can sexual bother after radical prostatectomy be predicted preoperatively? Findings from a prospective national study of the relation between sexual function, activity and bother. BJU Int 2012 May;109(9):1366-74.

(66) Storas AH, Sanda MG, Boronat OG, Chang P, Patil D, Crociani C, et al. Erectile Dysfunction and Sexual Problems Two to Three Years After Prostatectomy Among American, Norwegian, and Spanish Patients. Clin Genitourin Cancer 2016 Jun;14(3):e265-e273.

(67) Vainshtein J, Abu-Isa E, Olson KB, Ray ME, Sandler HM, Normolle D, et al. Randomized phase II trial of urethral sparing intensity modulated radiation therapy in low-risk prostate cancer: implications for focal therapy. Radiat Oncol 2012;7:82.

(68) Willis DL, Gonzalgo ML, Brotzman M, Feng Z, Trock B, Su LM. Comparison of outcomes between pure laparoscopic vs robot-assisted laparoscopic radical prostatectomy: a study of comparative effectiveness based upon validated quality of life outcomes. BJU Int 2012 Mar;109(6):898-905.

(69) Dragicevic SM, Krejovic-Maric SP, Hasani BH. Evaluation of quality of life after radical prostatectomy-experience in Serbia. Med Glas (Zenica) 2012 Aug;9(2):388-92.

(70) Wang R, Wood DP, Jr., Hollenbeck BK, Li AY, He C, Montie JE, et al. Risk factors and quality of life for post-prostatectomy vesicourethral anastomotic stenoses. Urology 2012 Feb;79(2):449-57.

(71) Pinkawa M, Piroth MD, Holy R, Fischedick K, Klotz J, Szekely-Orban D, et al. Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: a matched-pair comparison. Int J Radiat Oncol Biol Phys 2011 Sep 1;81(1):23-8.

(72) Pinkawa M, Piroth MD, Fischedick K, Holy R, Klotz J, Nussen S, et al. Impact of the target volume (prostate alone vs. prostate with seminal vesicles) and fraction dose (1.8 Gy vs. 2.0 Gy) on quality of life changes after external-beam radiotherapy for prostate cancer. Strahlenther Onkol 2009 Nov;185(11):724-30.

(73) Pinkawa M, Asadpour B, Piroth MD, Gagel B, Nussen S, Kehl M, et al. Health-related quality of life after permanent I-125 brachytherapy and conformal external beam radiotherapy for prostate cancer--a matched-pair comparison. Radiother Oncol 2009 May;91(2):225-31.

(74) Rice K, Hudak J, Peay K, Elsamanoudi S, Travis J, Lockhart R, et al. Comprehensive quality-of-life outcomes in the setting of a multidisciplinary, equal access prostate cancer clinic. Urology 2010 Nov;76(5):1231-8.

(75) Dragicevic S. Evaluation of health-related quality of life in patients with prostate cancer after treatment with radical retropubic prostatectomy and permanent prostate brachytherapy. Urol Int 2010;85(2):173-9.

(76) Hashine K, Kusuhara Y, Miura N, Shirato A, Sumiyoshi Y, Kataoka M. Health-related quality of life using SF-8 and EPIC questionnaires after treatment with radical retropubic prostatectomy and permanent prostate brachytherapy. Jpn J Clin Oncol 2009 Aug;39(8):502-8.

(77) Krahn MD, Bremner KE, Tomlinson G, Naglie G. Utility and health-related quality of life in prostate cancer patients 12 months after radical prostatectomy or radiation therapy. Prostate Cancer Prostatic Dis 2009;12(4):361-8.

(78) Smith DP, King MT, Egger S, Berry MP, Stricker PD, Cozzi P, et al. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. BMJ 2009;339:b4817.

(79) Hashine K, Kusuhara Y, Miura N, Shirato A, Sumiyoshi Y, Kataoka M. A prospective longitudinal study comparing a radical retropubic prostatectomy and permanent prostate brachytherapy regarding the health-related quality of life for localized prostate cancer. Jpn J Clin Oncol 2008 Jul;38(7):480-5.

(80) Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008 Mar 20;358(12):1250-61.

(81) Evans JR, Zhao S, Daignault S, Sanda MG, Michalski J, Sandler HM, et al. Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy. Radiother Oncol 2015 Aug;116(2):179-84.

(82) Inoue S, Shiina H, Hiraoka T, Wake K, Sumura M, Honda S, et al. Five-year longitudinal effect of radical perineal prostatectomy on health-related quality of life in Japanese men, using general and disease-specific measures. BJU Int 2009 Oct;104(8):1077-84.

(83) Shikanov SA, Eng MK, Bernstein AJ, Katz M, Zagaja GP, Shalhav AL, et al. Urinary and sexual quality of life 1 year following robotic assisted laparoscopic radical prostatectomy. J Urol 2008 Aug;180(2):663-7.

(84) Ash D, Bottomley D, Al-Qaisieh B, Carey B, Gould K, Henry A. A prospective analysis of long-term quality of life after permanent I-125 brachytherapy for localised prostate cancer. Radiother Oncol 2007 Aug;84(2):135-9.

(85) Litwin MS, Gore JL, Kwan L, Brandeis JM, Lee SP, Withers HR, et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. Cancer 2007 Jun 1;109(11):2239-47.

(86) Namiki S, Saito S, Nakagawa H, Sanada T, Yamada A, Arai Y. Impact of unilateral sural nerve graft on recovery of potency and continence following radical prostatectomy: 3-year longitudinal study. J Urol 2007 Jul;178(1):212-6.

(87) Namiki S, Egawa S, Baba S, Terachi T, Usui Y, Terai A, et al. Recovery of quality of life in year after laparoscopic or retropubic radical prostatectomy: a multi-institutional longitudinal study. Urology 2005 Mar;65(3):517-23.

(88) Namiki S, Ishidoya S, Tochigi T, Ito A, Arai Y. Quality of life after radical prostatectomy in elderly men. Int J Urol 2009 Oct;16(10):813-9.

(89) Namiki S, Ishidoya S, Kawamura S, Tochigi T, Arai Y. Quality of life among elderly men treated for prostate cancer with either radical prostatectomy or external beam radiation therapy. J Cancer Res Clin Oncol 2010 Mar;136(3):379-86.

(90) Kubler HR, Tseng TY, Sun L, Vieweg J, Harris MJ, Dahm P. Impact of nerve sparing technique on patient self-assessed outcomes after radical perineal prostatectomy. J Urol 2007 Aug;178(2):488-92.

(91) Namiki S, Satoh T, Baba S, Ishiyama H, Hayakawa K, Saito S, et al. Quality of life after brachytherapy or radical prostatectomy for localized prostate cancer: a prospective longitudinal study. Urology 2006 Dec;68(6):1230-6.

(92) Symon Z, Daignault S, Symon R, Dunn RL, Sanda MG, Sandler HM. Measuring patients' expectations regarding health-related quality-of-life outcomes associated with prostate cancer surgery or radiotherapy. Urology 2006 Dec;68(6):1224-9.

(93) Tseng TY, Kuebler HR, Cancel QV, Sun L, Springhart WP, Murphy BC, et al. Prospective health-related quality-of-life assessment in an initial cohort of patients undergoing robotic radical prostatectomy. Urology 2006 Nov;68(5):1061-6.

(94) Korfage IJ, Essink-Bot ML, Borsboom GJ, Madalinska JB, Kirkels WJ, Habbema JD, et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005 Aug 20;116(2):291-6.

(95) Matsubara A, Yasumoto H, Mutaguchi K, Mita K, Teishima J, Seki M, et al. Impact of radical perineal prostatectomy on urinary continence and quality of life: a longitudinal study of Japanese patients. Int J Urol 2005 Nov;12(11):953-8.

(96) Haffner MC, Landis PK, Saigal CS, Carter HB, Freedland SJ. Health-related quality-of-life outcomes after anatomic retropubic radical prostatectomy in the phosphodiesterase type 5 ERA: impact of neurovascular bundle preservation. Urology 2005 Aug;66(2):371-6.

(97) Namiki S, Saito S, Satoh M, Ishidoya S, Kawamura S, Tochigi T, et al. Quality of life after radical prostatectomy in Japanese men: 2 year longitudinal study. Jpn J Clin Oncol 2005 Sep;35(9):551-8.

(98) Namiki S, Kwan L, Kagawa-Singer M, Tochigi T, Ioritani N, Terai A, et al. Sexual function following radical prostatectomy: a prospective longitudinal study of cultural differences between Japanese and American men. Prostate Cancer Prostatic Dis 2008;11(3):298-302.

(99) Namiki S, Ishidoya S, Ito A, Kawamura S, Tochigi T, Saito S, et al. Quality of life after radical prostatectomy in Japanese men: a 5-Year follow up study. Int J Urol 2009 Jan;16(1):75-81.

(100) Namiki S, Saito S, Tochigi T, Ioritani N, Terai A, Arai Y. Impact of salvage therapy for biochemical recurrence on health-related quality of life following radical prostatectomy. Int J Urol 2007 Mar;14(3):186-91.

(101) Namiki S, Saito S, Tochigi T, Kuwahara M, Ioritani N, Yoshimura K, et al. Impact of hormonal therapy prior to radical prostatectomy on the recovery of quality of life. Int J Urol 2005 Feb;12(2):173-81.

(102) Namiki S, Kuwahara M, Ioritani N, Akito T, Arai Y. An evaluation of urinary function after radical prostatectomy in Japanese men: concordance with definitions of urinary continence. BJU Int 2005 Mar;95(4):530-3.

(103) Maliski SL, Kwan L, Orecklin JR, Saigal CS, Litwin MS. Predictors of fatigue after treatment for prostate cancer. Urology 2005 Jan;65(1):101-8.

(104) Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013 Jan 31;368(5):436-45.

(105) O'Neil B, Koyama T, Alvarez J, Conwill RM, Albertsen PC, Cooperberg MR, et al. The Comparative Harms of Open and Robotic Prostatectomy in Population Based Samples. J Urol 2016 Feb;195(2):321-9.

(106) Hoffman RM, Barry MJ, Stanford JL, Hamilton AS, Hunt WC, Collins MM. Health outcomes in older men with localized prostate cancer: results from the Prostate Cancer Outcomes Study. Am J Med 2006 May;119(5):418-25.

(107) Punnen S, Cowan JE, Chan JM, Carroll PR, Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. Eur Urol 2015 Oct;68(4):600-8.

(108) Huang GJ, Sadetsky N, Penson DF. Health related quality of life for men treated for localized prostate cancer with long-term followup. J Urol 2010 Jun;183(6):2206-12.

(109) Ratcliff CG, Cohen L, Pettaway CA, Parker PA. Treatment regret and quality of life following radical prostatectomy. Support Care Cancer 2013 Dec;21(12):3337-43.

(110) Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al. Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. BJU Int 2016 Mar;117(3):469-77.

(111) Acar C, Schoffelmeer CC, Tillier C, de BW, van ME, van der Poel HG. Quality of life in patients with low-risk prostate cancer. A comparative retrospective study: brachytherapy versus robot-assisted laparoscopic prostatectomy versus active surveillance. J Endourol 2014 Jan;28(1):117-24.

(112) Pearce SM, Wang CH, Victorson DE, Helfand BT, Novakovic KR, Brendler CB, et al. A Longitudinal Study of Predictors of Sexual Dysfunction in Men on Active Surveillance for Prostate Cancer. Sex Med 2015 Sep;3(3):156-64.

(113) Banerji JS, Hurwitz LM, Cullen J, Wolff EM, Levie KE, Rosner IL, et al. A prospective study of health-related quality-of-life outcomes for patients with low-risk prostate cancer managed by active surveillance or radiation therapy. Urol Oncol 2017 Jan 19.

(114) Chen RC, Basak R, Meyer AM, Kuo TM, Carpenter WR, Agans RP, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA 2017 Mar 21;317(11):1141-50.

(115) Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011 Apr;185(4):1246-54.

(116) Shoji S, Nakano M, Fujikawa H, Endo K, Hashimoto A, Tomonaga T, et al. Urethra-sparing high-intensity focused ultrasound for localized prostate cancer: Functional and oncological outcomes. Int J Urol 2015 Nov;22(11):1043-9.

(117) Shoji S, Nakano M, Nagata Y, Usui Y, Terachi T, Uchida T. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: a prospective study. Int J Urol 2010 Aug;17(8):715-9.

(118) Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 2012 Jun;13(6):622-32.

(119) Malcolm JB, Fabrizio MD, Barone BB, Given RW, Lance RS, Lynch DF, et al. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol 2010 May;183(5):1822-8.

(120) Robinson JW, Donnelly BJ, Siever JE, Saliken JC, Ernst SD, Rewcastle JC, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer 2009 Oct 15;115(20):4695-704.

(121) Wiltz AL, Shikanov S, Eggener SE, Katz MH, Thong AE, Steinberg GD, et al. Robotic radical prostatectomy in overweight and obese patients: oncological and validated-functional outcomes. Urology 2009 Feb;73(2):316-22.

(122) Murphy G, Haddock P, Doak H, Jackson M, Dorin R, Meraney A, et al. Urinary Bother as a Predictor of Postsurgical Changes in Urinary Function After Robotic Radical Prostatectomy. Urology 2015 Oct;86(4):817-23.

(123) Hoffman KE, Skinner H, Pugh TJ, Voong KR, Levy LB, Choi S, et al. Patient-reported Urinary, Bowel, and Sexual Function After Hypofractionated Intensity-modulated Radiation Therapy for Prostate Cancer: Results From a Randomized Trial. Am J Clin Oncol 2016 Sep 15.

(124) Ku J, Krahn M, Trachtenberg J, Nesbitt M, Kalnin R, Lockwood G, et al. Changes in health utilities and health-related quality of life over 12 months following radical prostatectomy. Can Urol Assoc J 2009 Dec;3(6):445-52.

(125) Komiya A, Fujiuchi Y, Ito T, Morii A, Yasuda K, Watanabe A, et al. Early quality of life outcomes in patients with prostate cancer managed by high-dose-rate brachytherapy as monotherapy. Int J Urol 2013 Feb;20(2):185-92.

(126) Monga U, Kerrigan AJ, Thornby J, Monga TN, Zimmermann KP. Longitudinal study of quality of life in patients with localized prostate cancer undergoing radiotherapy. J Rehabil Res Dev 2005 May;42(3):391-9.

(127) Jongkamp VG, Roeloffzen EM, Monninkhof EM, de Leeuw JR, Nijeholt AA, van VM. Brachytherapy for prostate cancer does not influence long-term depression rate. Brachytherapy 2012 Nov;11(6):495-501.

(128) Roeloffzen EM, Hinnen KA, Battermann JJ, Monninkhof EM, van Roermund JG, van Gellekom MP, et al. The impact of acute urinary retention after iodine-125 prostate brachytherapy on health-related quality of life. Int J Radiat Oncol Biol Phys 2010 Aug 1;77(5):1322-8.

(129) Roeloffzen EM, Lips IM, van Gellekom MP, van RJ, Frank SJ, Battermann JJ, et al. Health-related quality of life up to six years after (125)I brachytherapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys 2010 Mar 15;76(4):1054-60.

(130) Vordermark D, Noe M, Markert K, Wulf J, Muller G, Bratengeier K, et al. Prospective evaluation of quality of life after permanent prostate brachytherapy with I-125: importance of baseline symptoms and of prostate-V150. Radiother Oncol 2009 May;91(2):217-24.

(131) Jakobsson L, Fransson P. Patient Reported Outcome Measure (PROM) of Quality of Life After Prostatectomy - Results from a 5-Year Study. Open Nurs J 2013 Dec 27;7:165-73.

(132) Davison BJ, So AI, Goldenberg SL. Quality of life, sexual function and decisional regret at 1 year after surgical treatment for localized prostate cancer. BJU Int 2007 Oct;100(4):780-5.

(133) Tambas M, Agaoglu F, Iribas A, Guveli M, Dizdar Y, Okutan M, et al. Conventionally Fractionationed Volumetric Arc Therapy versus Hypofractionated Stereotactic Body Radiotherapy: Quality of Life, Side Effects, and Prostate-Specific Antigen Kinetics in Localized Prostate Cancer. Value Health Reg Issues 2016 Sep;10:91-9.

(134) Dixit A, Tang C, Bydder S, Kedda MA, Vosikova E, Bharat C, et al. First Australian experience of treating localised prostate cancer patients with CyberKnife stereotactic radiotherapy: early PSA response, acute toxicity and quality of life. J Med Radiat Sci 2017 Mar 8.

(135) Mc CE, Mc SO, Prue G, Parahoo K, Bunting B, Sullivan JO, et al. Quality of life in men receiving radiotherapy and neo-adjuvant androgen deprivation for prostate cancer: results from a prospective longitudinal study. J Adv Nurs 2013 Jan;69(1):53-65.

(136) van AG, Bottomley A, Fossa SD, Efficace F, Coens C, Guerif S, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008 Nov;44(16):2418-24.

Figure 1. Flow chart.

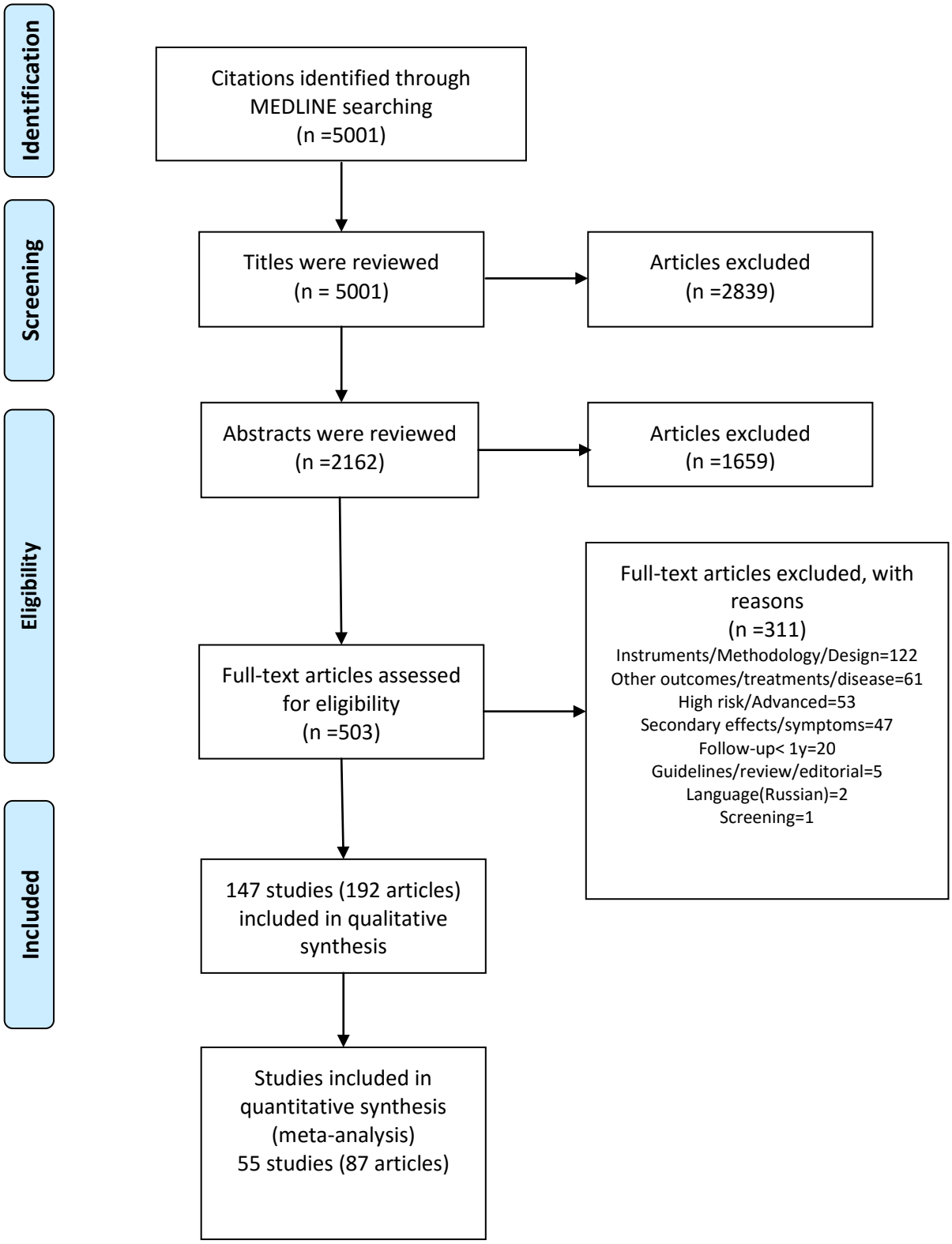
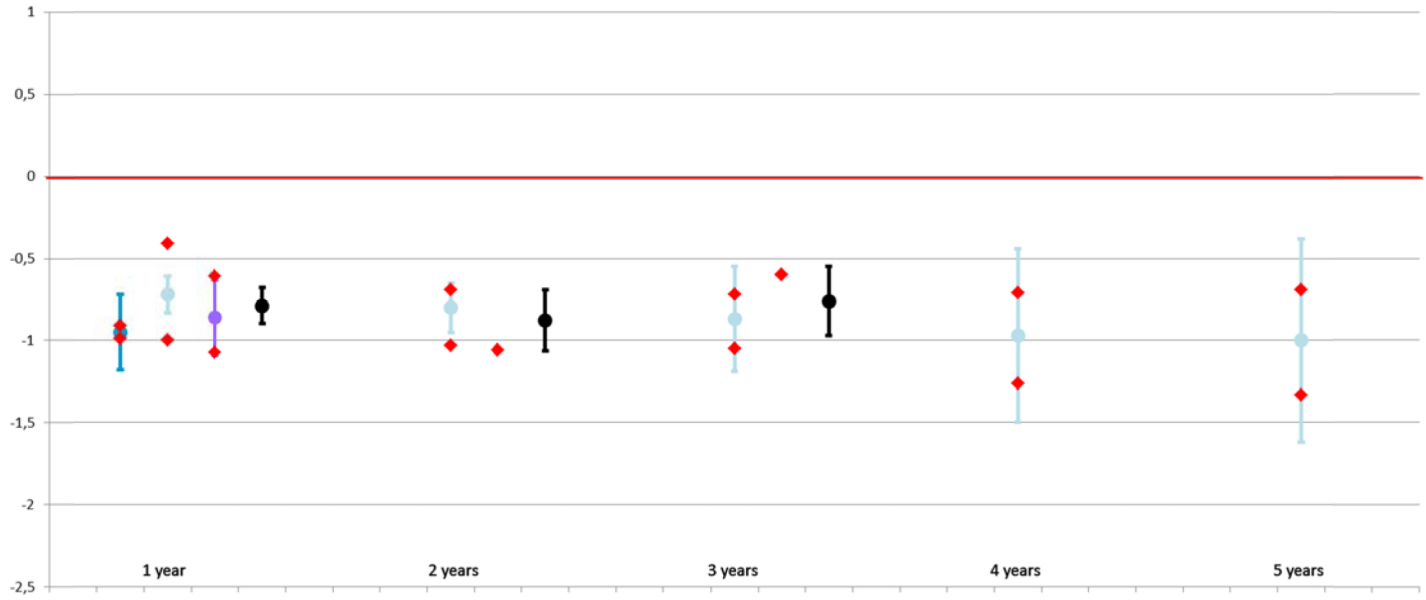


Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continues in next pages). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

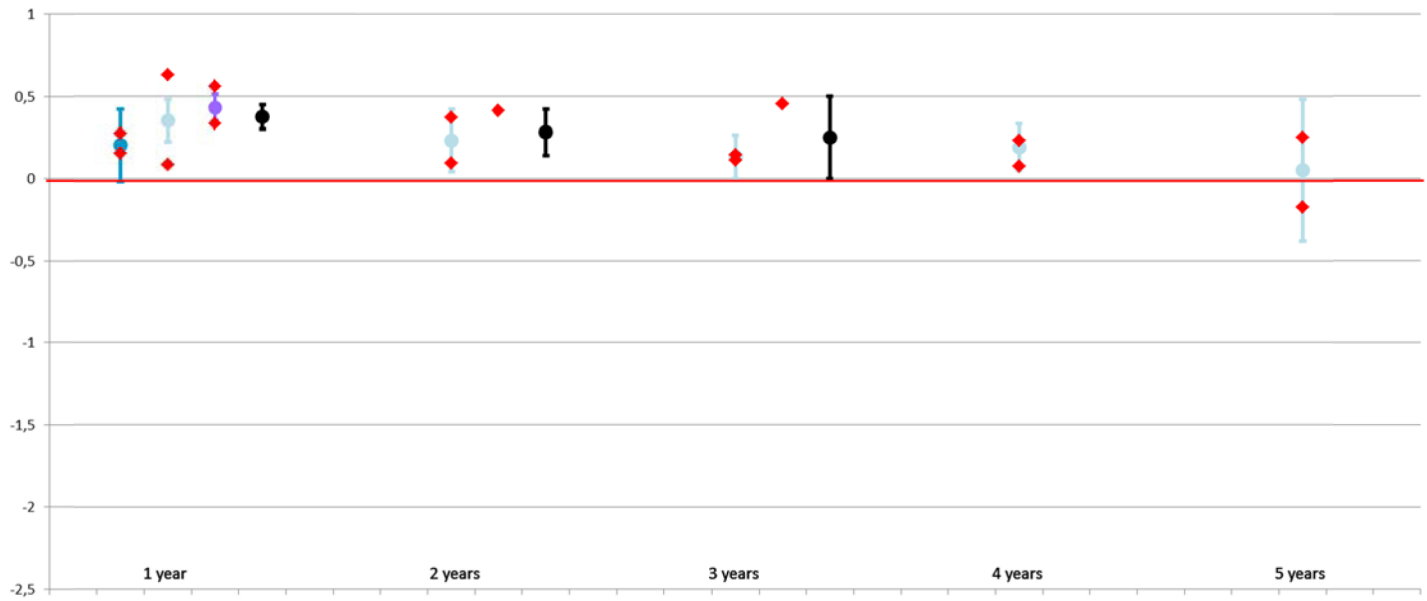
2.A URINARY INCONTINENCE



	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN		**2**	**8**	**5**	**15**			**3**	**1**	**4**			**2**	**1**	**3**			**2**					**2**		
PN		182	1443	2611	4236			968	518	1486			382	1523	1905			382					382		
I²		.0	43.0	91.0	77.3			56.0		81.4			76.0		82.0			91.0					93.0		
p		.740	.090	<.001	.001			.100		.001			.040		<.001			<.001					<.001		
χ²					3.0					11.6					6.8										
p					.223					.001					.010										

- RA (Robot Assisted Laparoscopic Prostatectomy
- LP (Laparoscopic Prostatectomy)
- ORP (Open Radical Prostatectomy)
- VT (Various Techniques of Prostatectomy)
- All (Global Estimator)

2.A URINARY IRRITATIVE-OBSTRUCTIVE

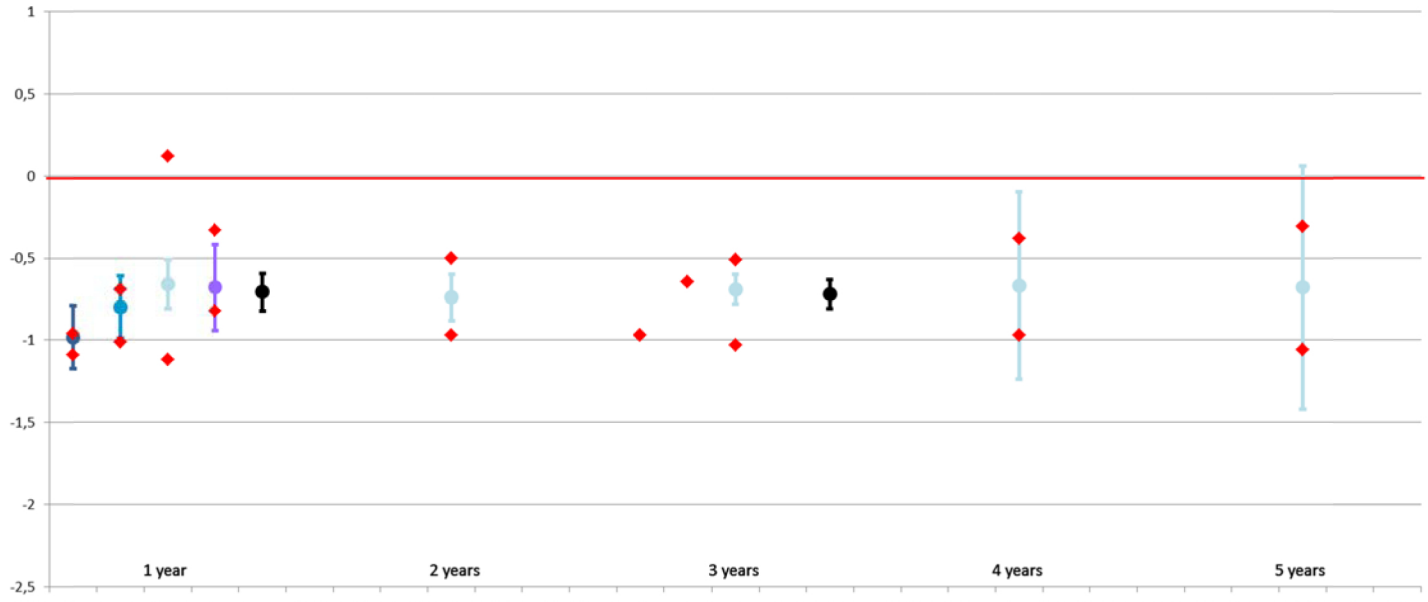


	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN		**2**	**8**	**5**	**15**			**3**	**1**	**4**			**2**	**1**	**3**			**2**					**2**		
PN		182	1461	2585	4228			986	505	1491			384	1523	1907			384					384		
I²		.0	61.0	36.0	54.0			71.0		7.5			.0		88.0			7.0					88.0		
p		.590	.010	.180	.007			.030		.017			.840		<.001			.300					.010		
χ²					6.2					3.2					16.6										
p					.046					.075					<.001										

SN Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ²** and **p-value** test by studies' subgroups;
RA Robot Assisted Laparoscopic Prostatectomy; **LP** Laparoscopic Prostatectomy; **ORP** Open Radical Prostatectomy;
VT Various Techniques of Radical Prostatectomy; **All** Global estimator

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

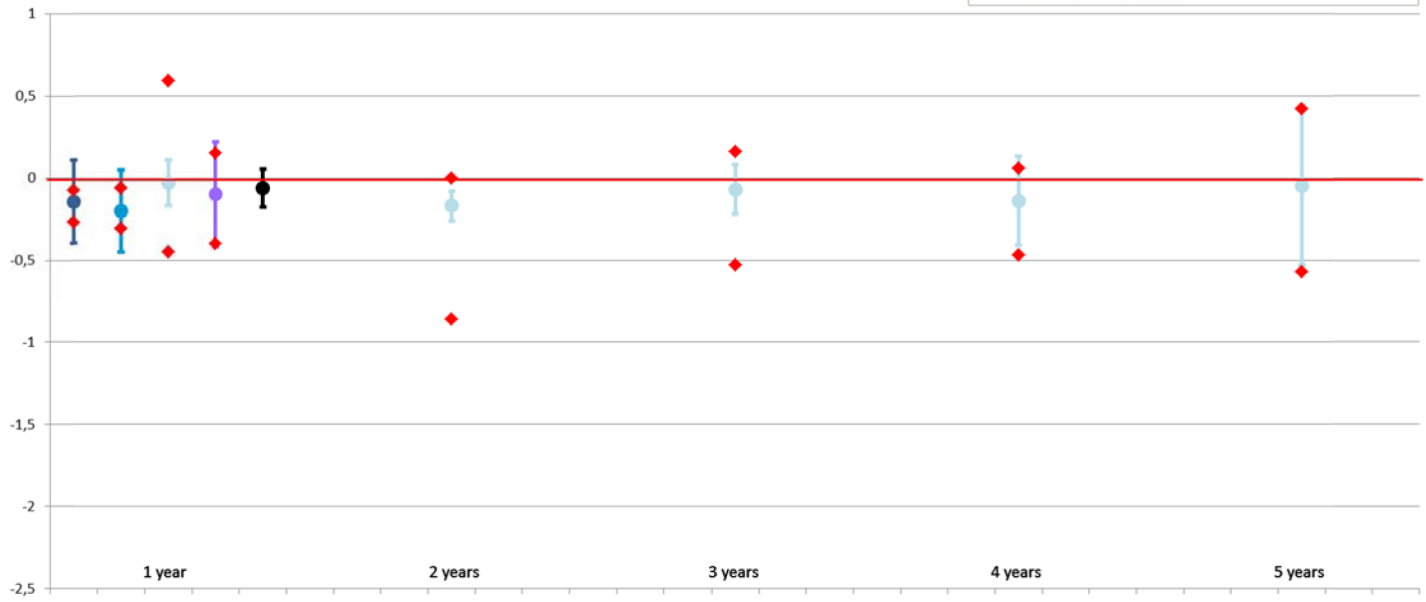
2.B URINARY FUNCTION



	1 year					2 years					3 years					4 years					5 years				
	RA	**LP**	**ORP**	**VT**	**All**	RA	LP	**ORP**	VT	All	**RA**	**LP**	**ORP**	VT	All	RA	LP	**ORP**	VT	All	RA	LP	**ORP**	VT	All
SN	**2**	**3**	**16**	**3**	**24**			**9**			**1**	**1**	**7**		**9**			**2**					**2**		
PN	239	369	3857	343	4808			3071			194	187	1404		1785			321					321		
I²	99.0	27.0	88.0	61.0	83.3			78.3					15.0		39.0			91.0					95.0		
p	<.001	.250	<.001	.080	.001			.001					.320		.110			<.001					<.001		
χ^2					4.5										6.1										
p					.216										.050										

- RA (Robot Assisted Laparoscopic Prostatectomy
- LP (Laparoscopic Prostatectomy)
- ORP (Open Radical Prostatectomy)
- VT (Various Techniques of Prostatectomy)
- All (Global Estimator)

2.B URINARY BOTHER

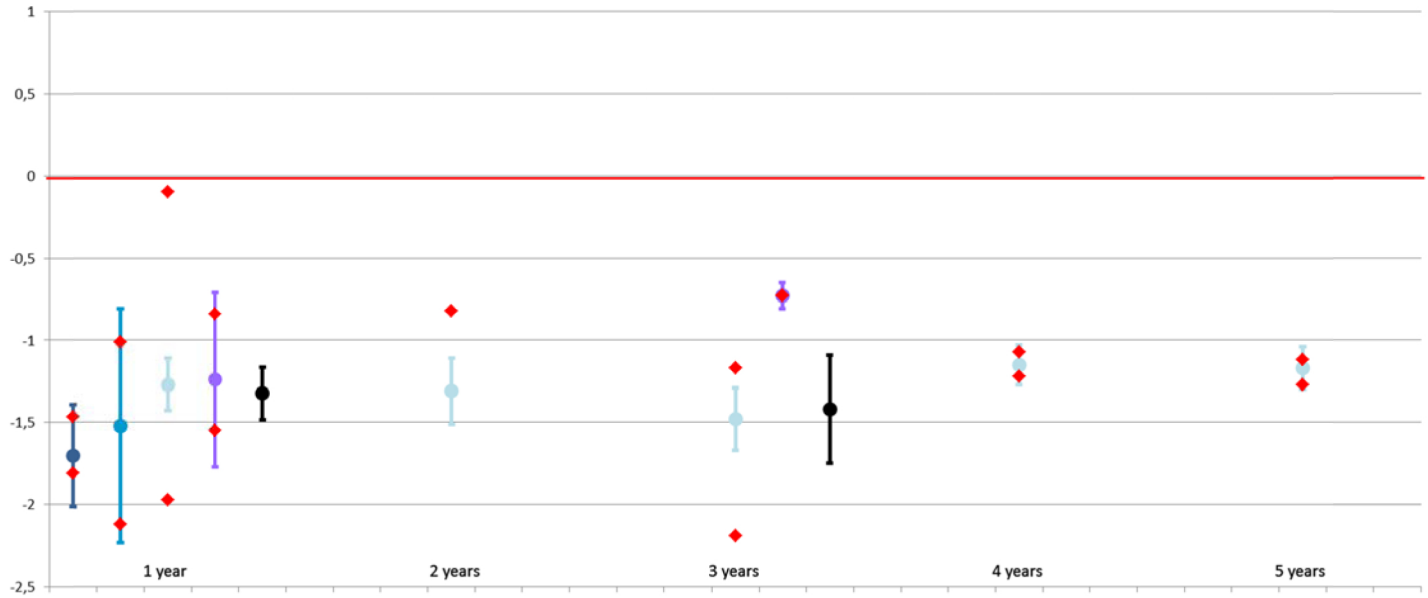


	1 year					2 years					3 years					4 years					5 years				
	RA	**LP**	**ORP**	**VT**	**All**	RA	LP	**ORP**	VT	All	RA	LP	**ORP**	VT	All	RA	LP	**ORP**	VT	All	RA	LP	**ORP**	VT	All
SN	**2**	**2**	**17**	**3**	**24**			**10**					**8**					**3**					**3**		
PN	123	182	4117	343	4855			3328					1660					577					577		
I²	75.0	23.0	88.0	75.0	84.4			6.2					73.0					82.0					94.0		
p	.020	.250	<.001	.020	.001			.007					<.001					<.001					<.001		
χ^2					.8																				
p					.847																				

SN Studies Number; **PN** Patients Number; **I^2** and **p-value** testing heterogeneity; **χ^2** and **p-value** test by studies' subgroups;
RA Robot Assisted Laparoscopic Prostatectomy; **LP** Laparoscopic Prostatectomy; **ORP** Open Radical Prostatectomy;
VT Various Techniques of Radical Prostatectomy; **All** Global estimator

Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

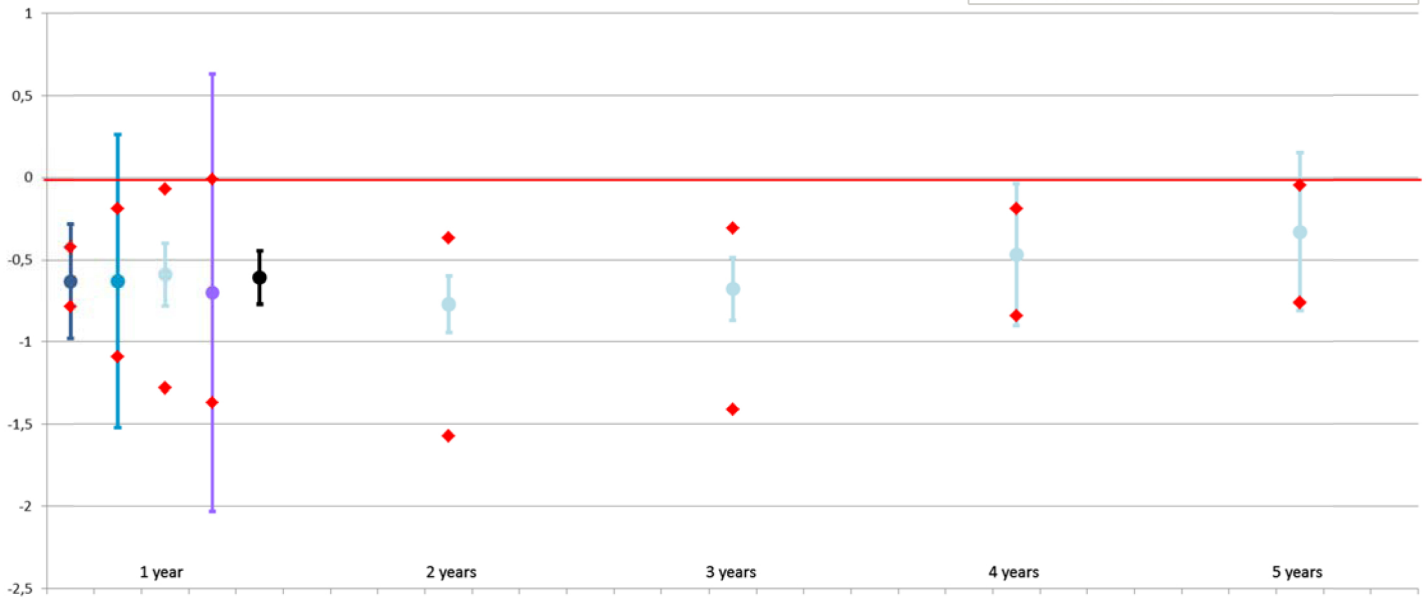
2.C SEXUAL FUNCTION



	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN	**2**	**3**	**17**	**3**	**25**			**10**					**8**	**1**	**9**			**3**					**3**		
PN	239	369	3967	1739	6314			3311					1644	1523	3167			561					561		
I²	72.0	94.0	89.0	93.0	92.9			89.6					78.0		96.0			.0					.0		
p	.030	<.001	<.001	<.001	.001			.001					<.001		<.001			.730					.700		
χ²					125.1										172.1										
p					.001										<.001										

RA (Robot Assisted Laparoscopic Prostatectomy
LP (Laparoscopic Prostatectomy)
ORP (Open Radical Prostatectomy)
VT (Various Techniques of Prostatectomy)
All (Global Estimator)

2.C SEXUAL BOTHER

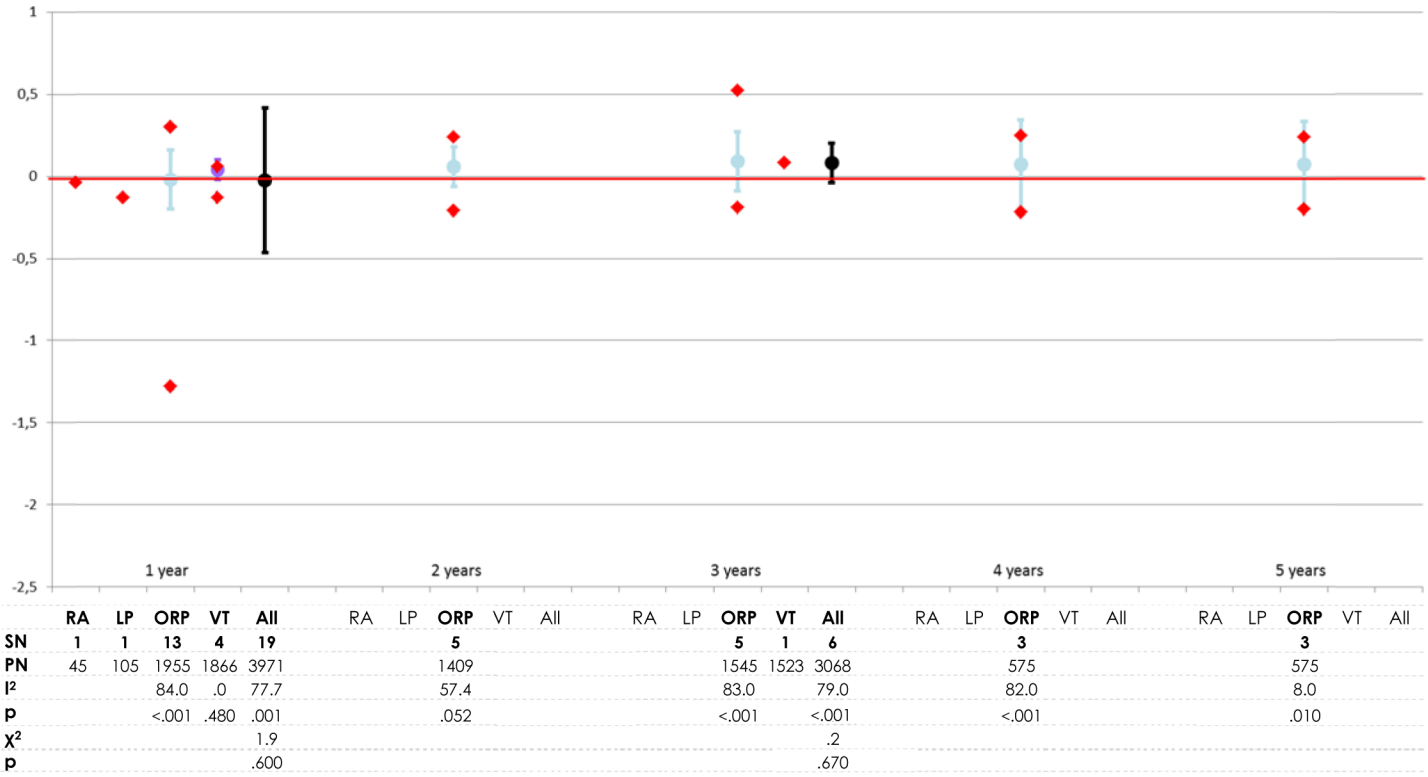


	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN	**2**	**2**	**17**	**2**	**23**			**10**					**8**					**3**					**3**		
PN	123	182	3965	216	4486			3310					1646					563					563		
I²	65.0	93.0	92.0	97.0	91.6			88.0					84.0					92.0					94.0		
p	.060	<.001	<.001	<.001	.001			<.001					<.001					<.001					<.001		
χ²					7.9																				
p					.048																				

SN Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ²** and **p-value** test by studies' subgroups;
RA Robot Assisted Laparoscopic Prostatectomy; **LP** Laparoscopic Prostatectomy; **ORP** Open Radical Prostatectomy;
VT Various Techniques of Radical Prostatectomy; **All** Global estimator

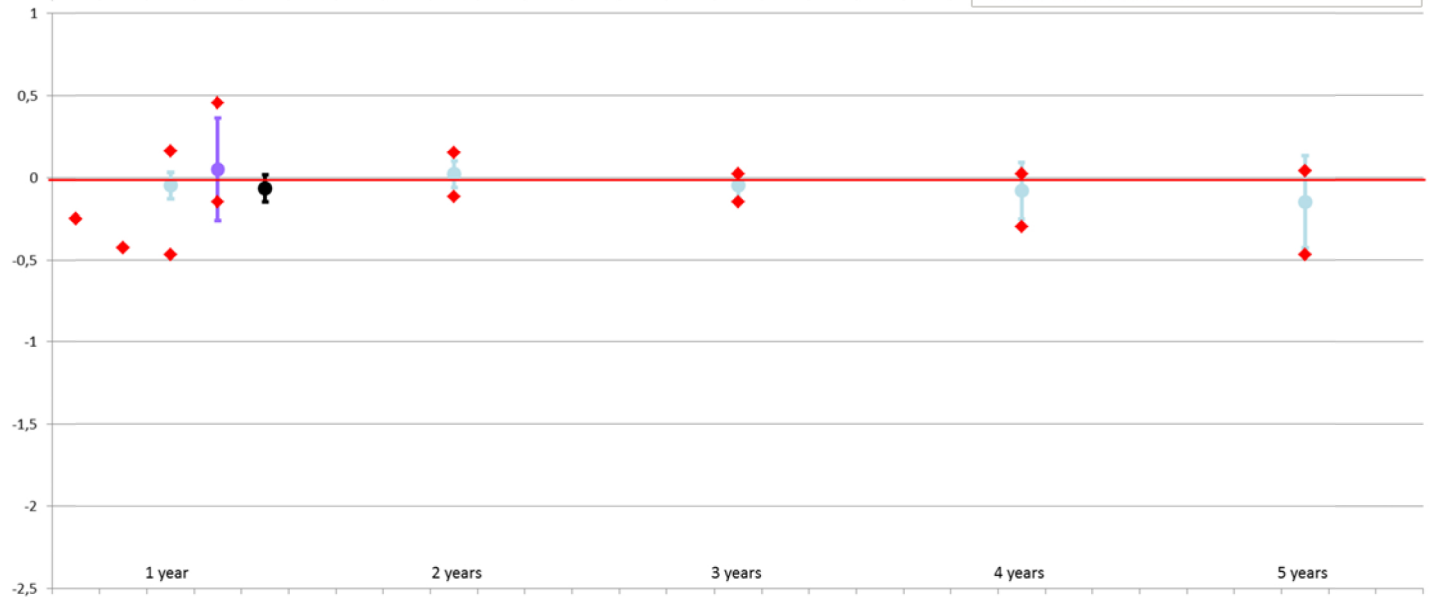
Figure 2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

2.D BOWEL FUNCTION



	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN	**1**	**1**	**13**	**4**	**19**			**5**					**5**	**1**	**6**			**3**					**3**		
PN	45	105	1955	1866	3971			1409					1545	1523	3068			575					575		
I²			84.0	.0	77.7			57.4					83.0		79.0			82.0					8.0		
p			<.001	.480	.001			.052					<.001		<.001			<.001					.010		
χ²					1.9										.2										
p					.600										.670										

2.D BOWEL BOTHER

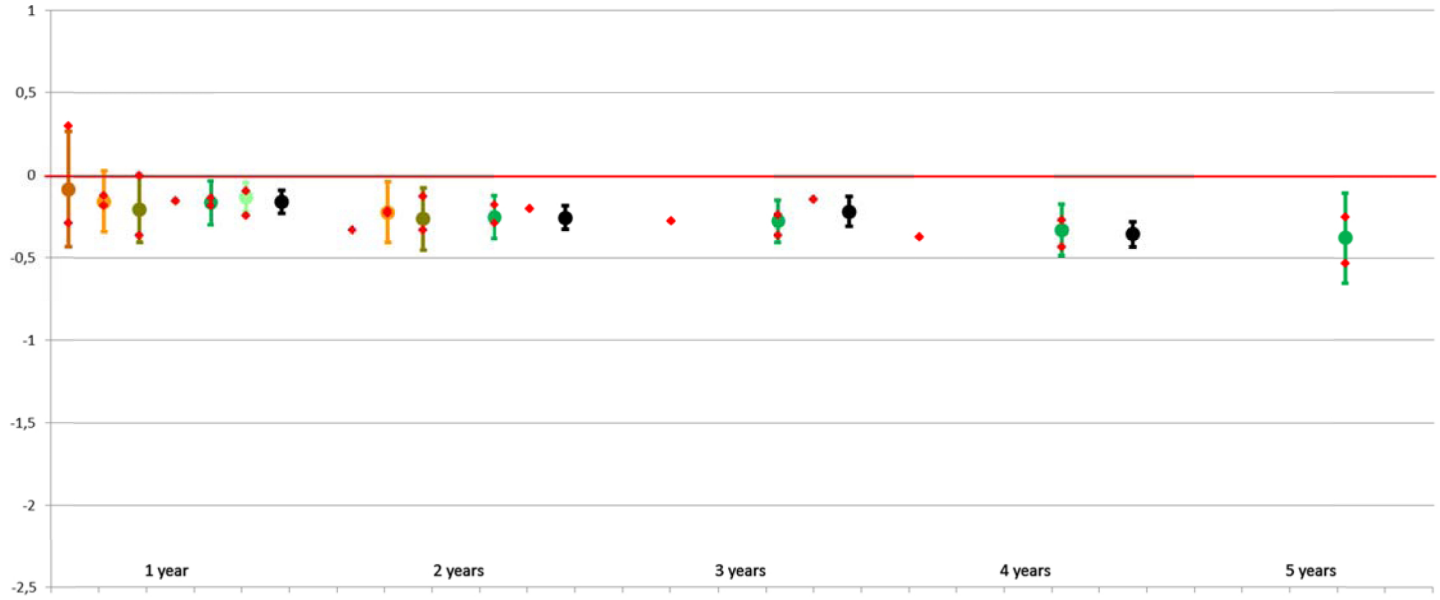


	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN	**1**	**1**	**14**	**3**	**19**			**5**					**5**					**3**					**3**		
PN	45	105	2029	343	2522			1411					1547					577					577		
I²	87.0		28.0	73.0	46.6			1.3					9.0					55.0					82.0		
p	.010		.160	.020	.014			.348					.360					.110					<.001		
χ²					8.1																				
p					.044																				

SN Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ²** and **p-value** test by studies' subgroups;
RA Robot Assisted Laparoscopic Prostatectomy; **LP** Laparoscopic Prostatectomy; **ORP** Open Radical Prostatectomy;
VT Various Techniques of Radical Prostatectomy; **All** Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continues in next pages). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

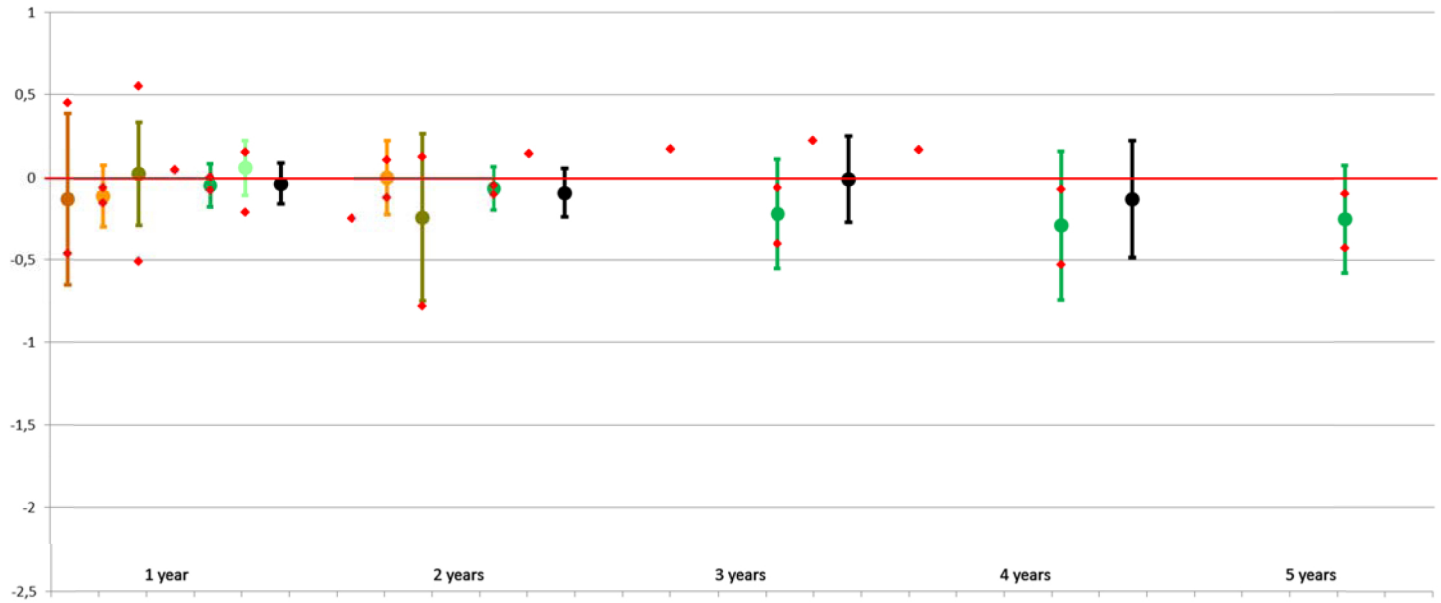
3.A URINARY INCONTINENCE



	1 year							2 years							3 years							4 years							5 years						
	PT	**SB**	**IM**	**EB**	**3D**	**VT**	**All**	**PT**	**SB**	**IM**	EB	**3D**	**VT**	**All**	PT	**SB**	IM	EB	**3D**	**VT**	**All**	**PT**	SB	IM	EB	**3D**	VT	**All**	PT	SB	IM	EB	**3D**	VT	All
SN	3	2	3	1	2	3	14	1	2	2		2	1	8		1			2	1	4	1				2		3					2		
PN	442	232	286	26	412	968	2366	255	232	244		412	282	1425		130			412	598	1140	1139				412		1551					412		
I²	82.4	.0	34.8		.0	.0	23.1		.0	25.1		.0		.0					.0		8.4					26.1		.0					74.0		
p	.003	.750	.216		.731	.552	.204		.944	.248		.425		.874					.366		.351					.245		.415					.050		
χ^2							1.1							1.1							2.5							.4							
p							.956							.888							.293							.523							

- PT (Proton Therapy)
- SB (Stereotactic Body Radiotherapy)
- IM (Intensity Modulated Radiotherapy)
- EB (External Beam Radiotherapy)
- 3D (3-Dimensional Conformational Radiotherapy)
- VT (Various Techniques of Radiotherapy)
- All (Global Estimator)

3.A URINARY OBSTRUCTIVE

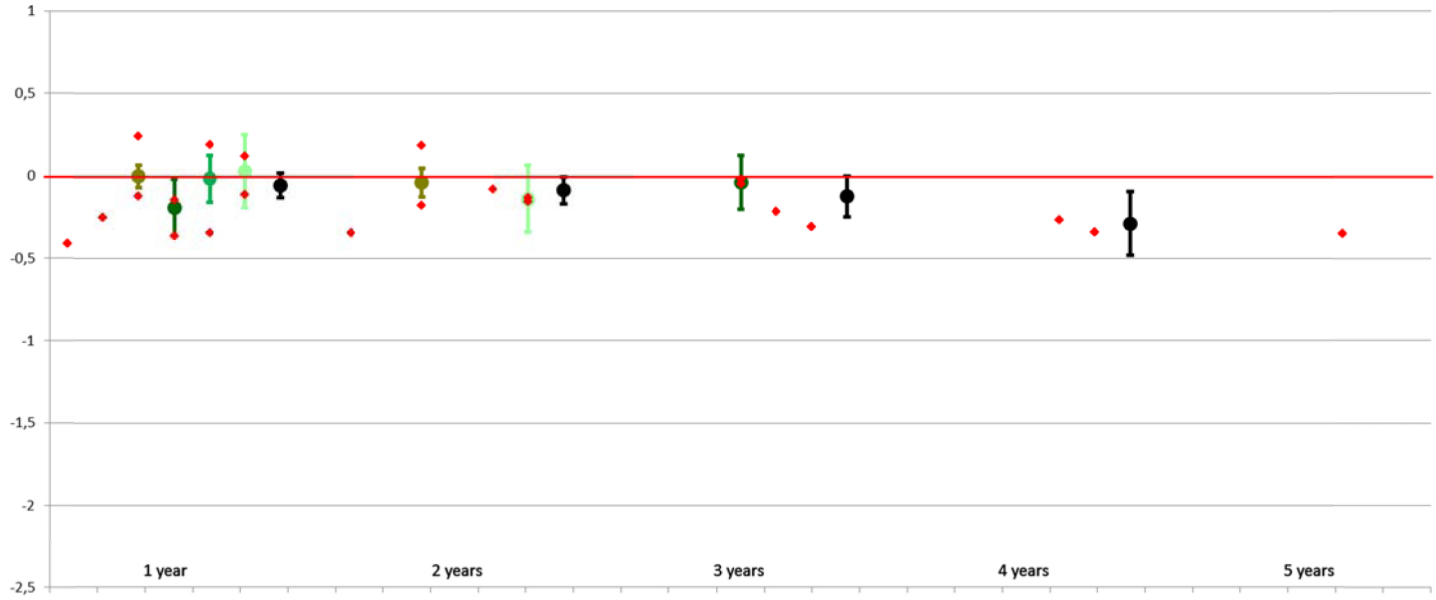


	1 year							2 years							3 years							4 years							5 years						
	PT	**SB**	**IM**	**EB**	**3D**	**VT**	**All**	**PT**	**SB**	**IM**	EB	**3D**	**VT**	**All**	PT	**SB**	IM	EB	**3D**	**VT**	**All**	**PT**	SB	IM	EB	**3D**	VT	**All**	PT	SB	IM	EB	**3D**	VT	All
SN	3	2	4	1	2	3	15	1	2	3		2	1	9		1			2	1	4	1				2		3					2		
PN	442	232	344	26	413	977	2434	255	232	298		413	289	1487		130			413	598	1141	1122				413		1535					413		
I²	92.0	.0	77.4		.0	6.4	76.8		32.0	91.0		.0		75.9					82.3		88.3					9.4		93.8					82.1		
p	<.001	.614	.004		.572	.080	<.001		.225	<.001		.676		<.001					.018		<.001					.001		<.001					.018		
χ^2							16.6							9.3							19.9							22.0							
p							.005							.055							<.001							<.001							

SN Studies Number; **PN** Patients Number; **I^2** and **p-value** testing heterogeneity; **χ^2** and **p-value** test by studies' subgroups;
PT Proton Therapy; **ST** Stereotactic Body Radiotherapy; **IM** Intensity Modulated Radiotherapy; **EB** External Beam Radiotherapy;
3D 3-Dimensional Conformational Radiotherapy; **VT** Various Techniques of Radiotherapy; **All** Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

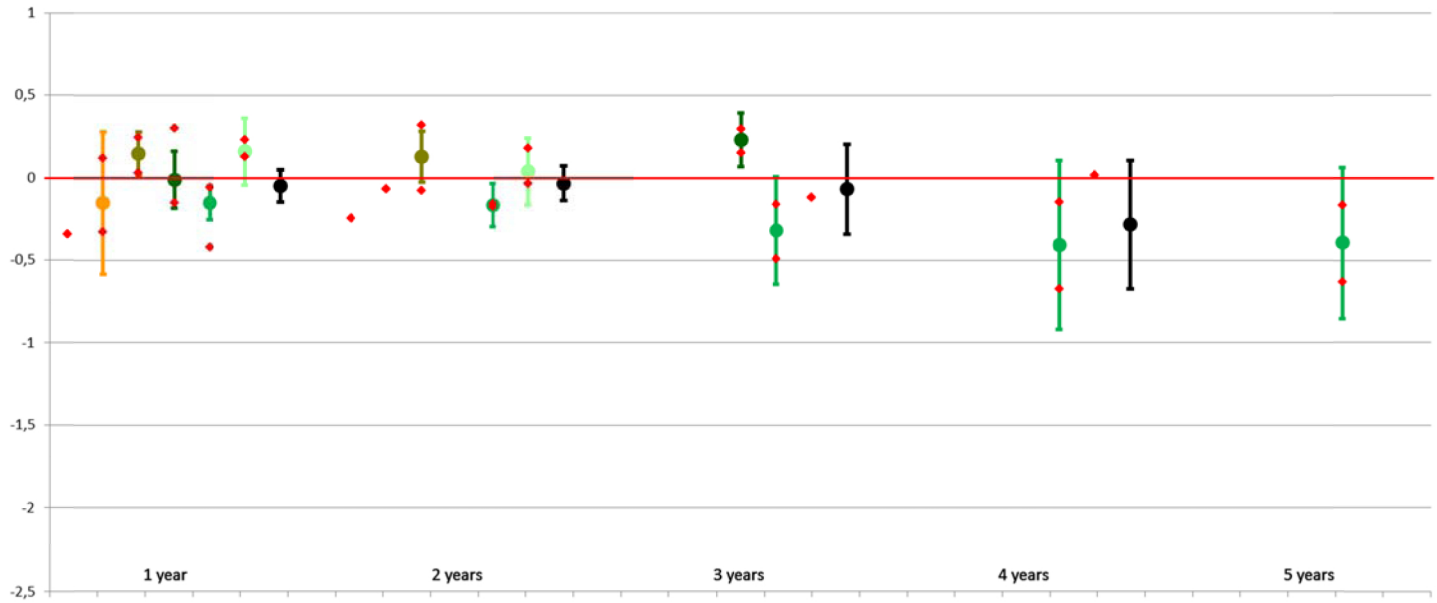
3.B URINARY FUNCTION



	1 year							2 years							3 years							4 years							5 years						
	PT	**SB**	**IM**	**EB**	**3D**	**VT**	**All**	**PT**	**SB**	**IM**	EB	**3D**	**VT**	**All**	PT	SB	IM	**EB**	**3D**	**VT**	**All**	PT	SB	IM	EB	**3D**	**VT**	**All**	PT	SB	IM	EB	**3D**	VT	All
SN	1	1	8	3	6	2	21	1		7		1	2	11				2	1	1	4					1	1	2					1		
PN	255	46	1842	259	535	196	3133	255		1800		166	196	2417				289	166	78	533					166	78	244					166		
I²			.0	.0	23.3	14.6	44.2			23.9			.0	39.0				.0			.0							.0							
p			.663	.611	.259	.279	.016			.247			.917	.089				.859			.418							.741							
χ^2							22.2							8.5							2.8							.1							
p							<.001							.037							.246							.741							

- PT (Proton Therapy)
- SB (Stereotactic Body Radiotherapy)
- IM (Intensity Modulated Radiotherapy)
- EB (External Beam Radiotherapy)
- 3D (3-Dimensional Conformational Radiotherapy)
- VT (Various Techniques of Radiotherapy)
- All (Global Estimator)

3.B URINARY BOTHER

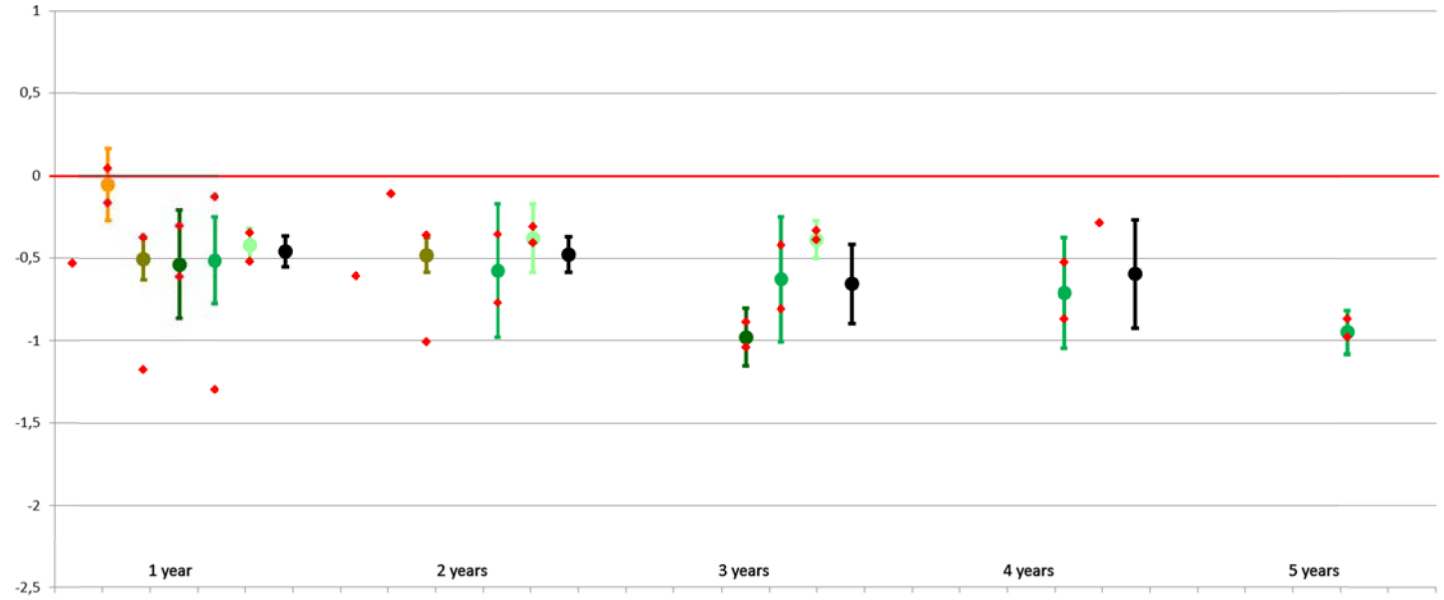


	1 year							2 years							3 years							4 years							5 years						
	PT	**SB**	**IM**	**EB**	**3D**	**VT**	**All**	**PT**	**SB**	**IM**	EB	**3D**	**VT**	**All**	PT	SB	IM	**EB**	**3D**	**VT**	**All**	PT	SB	IM	EB	**3D**	**VT**	**All**	PT	SB	IM	EB	**3D**	VT	All
SN	1	2	5	3	6	2	19	1	1	4		2	2	10				2	2	1	5					2	1	3					2		
PN	255	274	464	260	681	196	2130	255	228	422		412	196	1513				289	412	78	779					412	78	490					412		
I²		75.3	.0	.0	.0	.0	59.6			16.3		.0	.0	51.9				.0	81.7		85.8					92.5		87.6					9.7		
p		.044	.882	.484	.777	.632	<.001			.310		.900	.326	.028				.381	.019		<.001					<.001		<.001					.001		
χ^2							35.2							14.1							21.9							2.8							
p							<.001							.007							<.001							.098							

SN Studies Number; **PN** Patients Number; **I^2** and **p-value** testing heterogeneity; **χ^2** and **p-value** test by studies' subgroups;
PT Proton Therapy; **ST** Stereotactic Body Radiotherapy; **IM** Intensity Modulated Radiotherapy; **EB** External Beam Radiotherapy;
3D 3-Dimensional Conformational Radiotherapy; **VT** Various Techniques of Radiotherapy; **All** Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

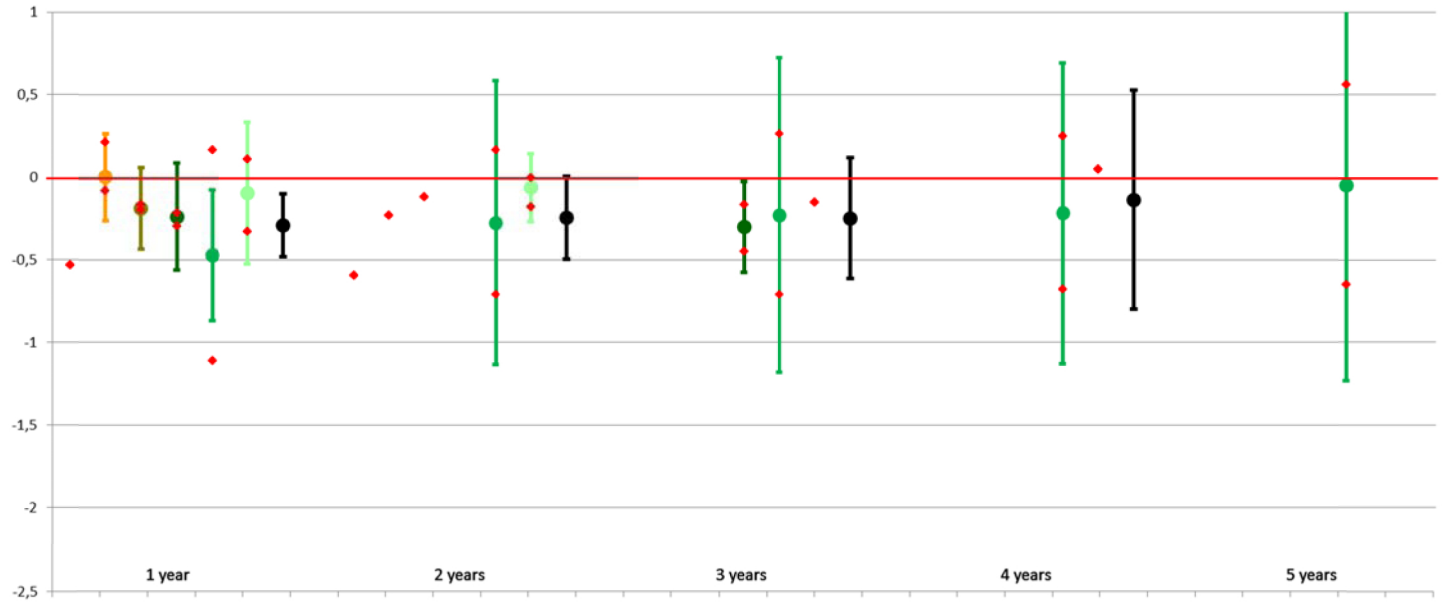
3.C SEXUAL FUNCTION



	1 year							2 years							3 years							4 years							5 years						
	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All
SN	1	3	8	2	7	3	24	1	1	7		2	2	13				2	2	2	6					2	1	3					2		
PN	255	235	858	74	780	792	2994	255	102	816		411	194	1778				289	411	674	1374					411	76	487					411		
I^2		.0	42.2	.0	83.3	.0	64.9			2.3		87.9	.0	6.0				.0	86.1	.0	87.9					82.2		81.9					.0		
p		.802	.097	.421	<.001	.679	<.001			.274		.004	.660	.003				.388	.007	.780	<.001					.018		.004					.457		
χ^2							15.7							14.0							33.2							5.5						
p							.008							.007							<.001							.020						

- PT (Proton Therapy)
- SB (Stereotactic Body Radiotherapy)
- IM (Intensity Modulated Radiotherapy)
- EB (External Beam Radiotherapy)
- 3D (3-Dimensional Conformational Radiotherapy)
- VT (Various Techniques of Radiotherapy)
- All (Global Estimator)

3.C SEXUAL BOTHER

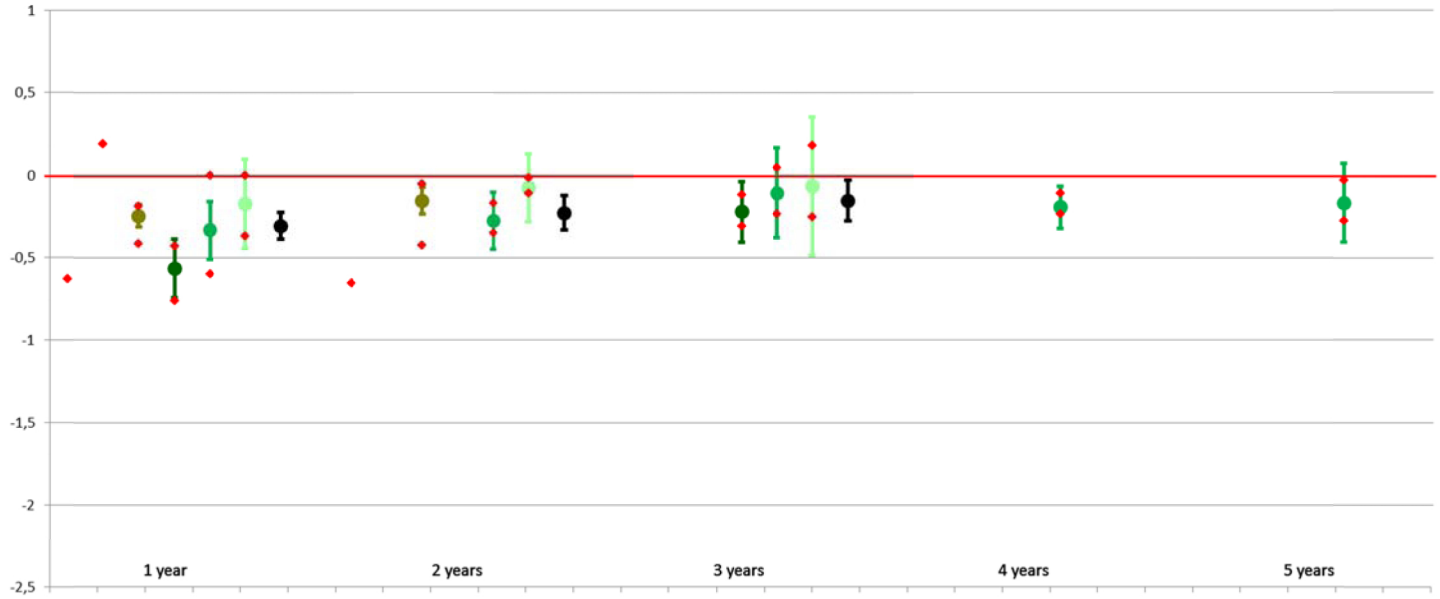


	1 year							2 years							3 years							4 years							5 years						
	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All
SN	1	2	2	2	6	2	15	1	1	1		2	2	7				2	2	1	5					2	1	3					2		
PN	255	274	133	73	676	191	1602	255	228	91		407	191	1172				289	407	73	769					407	73	480					407		
I^2		43.9	.0	.0	91.4	75.7	85.8					97.4	.0	89.3				63.6	97.8		92.1					97.6		95.7					98.6		
p		.182	.912	.836	<.001	.042	<.001					<.001	.419	<.001				.097	<.001		<.001					<.001		<.001					<.001		
χ^2							34.2							17.7							1.9							4.4						
p							<.001							.001							.397							.037						

SN Studies Number; **PN** Patients Number; I^2 and **p-value** testing heterogeneity; χ^2 and **p-value** test by studies' subgroups;
PT Proton Therapy; **ST** Stereotactic Body Radiotherapy; **IM** Intensity Modulated Radiotherapy; **EB** External Beam Radiotherapy;
3D 3-Dimensional Conformational Radiotherapy; **VT** Various Techniques of Radiotherapy; **All** Global estimator

Figure 3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies in each modality.

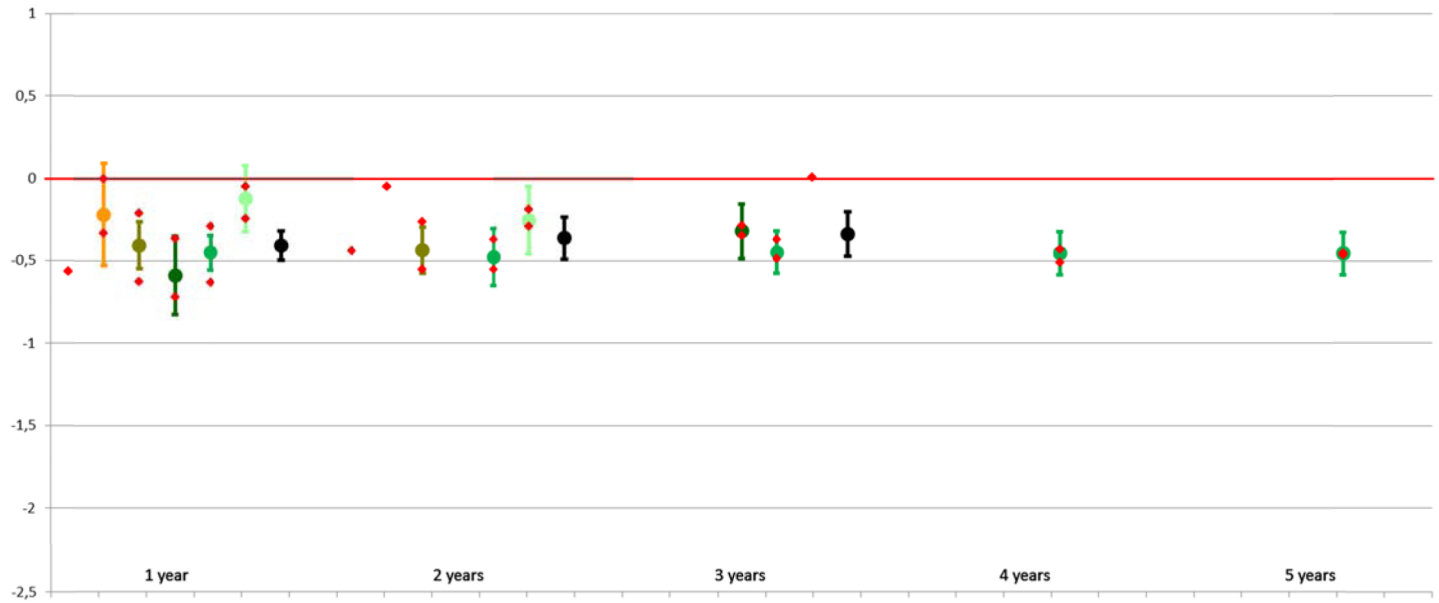
3.D BOWEL FUNCTION



	1 year							2 years							3 years							4 years							5 years						
	PT	**SB**	**IM**	**EB**	**3D**	**VT**	**All**	**PT**	SB	**IM**	EB	**3D**	**VT**	**All**	PT	SB	IM	**EB**	**3D**	**VT**	**All**	PT	SB	IM	EB	**3D**	VT	All	PT	SB	IM	EB	**3D**	VT	All
SN	1	1	8	3	7	3	23	1		7		2	2	12				2	2	2	6					2							2		
PN	255	46	1842	258	784	794	3979	255		1800		415	196	2666				289	415	676	1380					415							415		
I²			.0	.0	62.7	76.6	62.5			16.2		38.8	.0	68.0				21.2	74.7	81.2	55.6					.0							67.2		
p			.767	.655	.013	.014	<.001			.306		.201	.662	<.001				.260	.047	.021	.046					.373							.081		
χ²							29.1							25.4							.8													
p							<.001							<.001							.688													

- PT (Proton Therapy)
- SB (Stereotactic Body Radiotherapy)
- IM (Intensity Modulated Radiotherapy)
- EB (External Beam Radiotherapy)
- 3D (3-Dimensional Conformational Radiotherapy)
- VT (Various Techniques of Radiotherapy)
- All (Global Estimator)

3.D BOWEL BOTHER

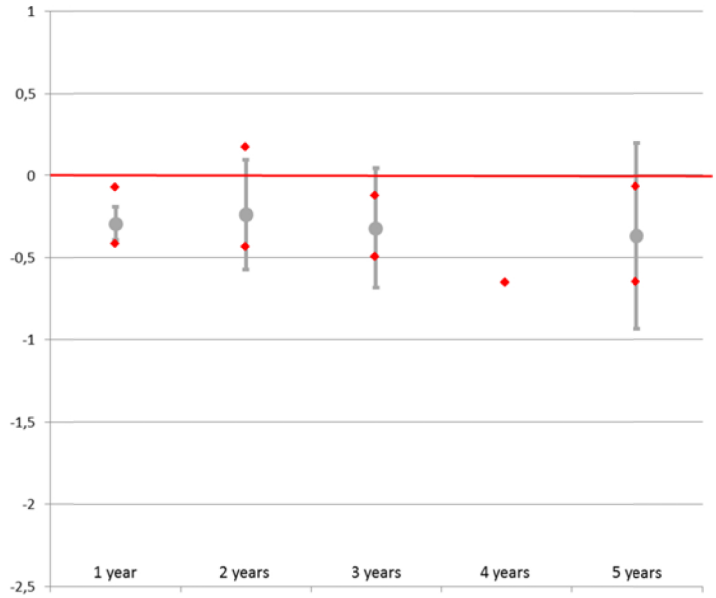


	1 year							2 years							3 years							4 years							5 years						
	PT	**SB**	**IM**	**EB**	**3D**	**VT**	**All**	**PT**	**SB**	**IM**	EB	**3D**	**VT**	**All**	PT	SB	IM	**EB**	**3D**	**VT**	**All**	PT	SB	IM	EB	**3D**	VT	All	PT	SB	IM	EB	**3D**	VT	All
SN	1	2	5	3	6	2	19	1	1	4		2	2	10				2	2	1	5					2							2		
PN	255	274	473	261	682	196	2141	255	228	431		413	196	1523				289	413	78	780					413							413		
I²		53.4	1.3	27.0	.0	.0	46.6			.0		38.9	.0	68.1				.0	.0		42.8					.0							.0		
p		.143	.347	.254	.485	.361	.014			.501		.201	.632	.001				.736	.413		.136					.576							.943		
χ²							19.1							24.0							6.2													
p							.002							<.001							.045													

SN Studies Number; **PN** Patients Number; **I²** and **p-value** testing heterogeneity; **χ²** and **p-value** test by studies' subgroups;
PT Proton Therapy; **ST** Stereotactic Body Radiotherapy; **IM** Intensity Modulated Radiotherapy; **EB** External Beam Radiotherapy;
3D 3-Dimensional Conformational Radiotherapy; **VT** Various Techniques of Radiotherapy; **All** Global estimator

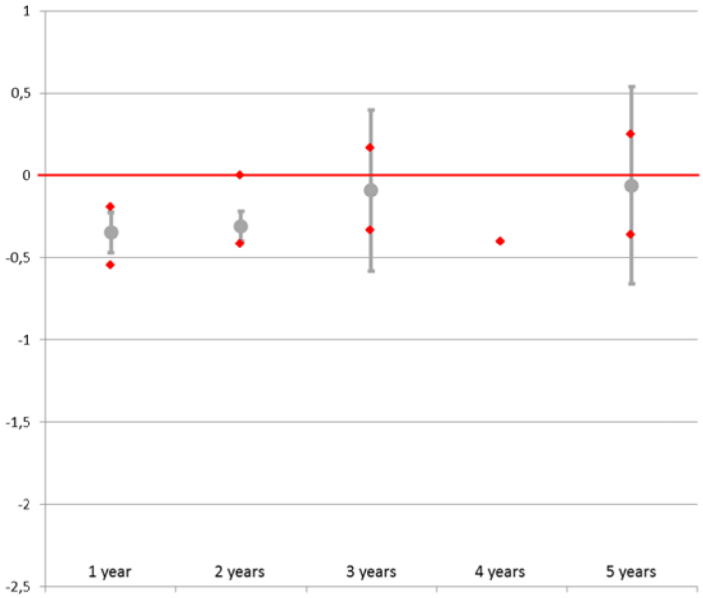
Figure 4. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy (continues in next page). Red diamonds represent maximum and minimum estimators from individual studies.

4.A URINARY INCONTINENCE



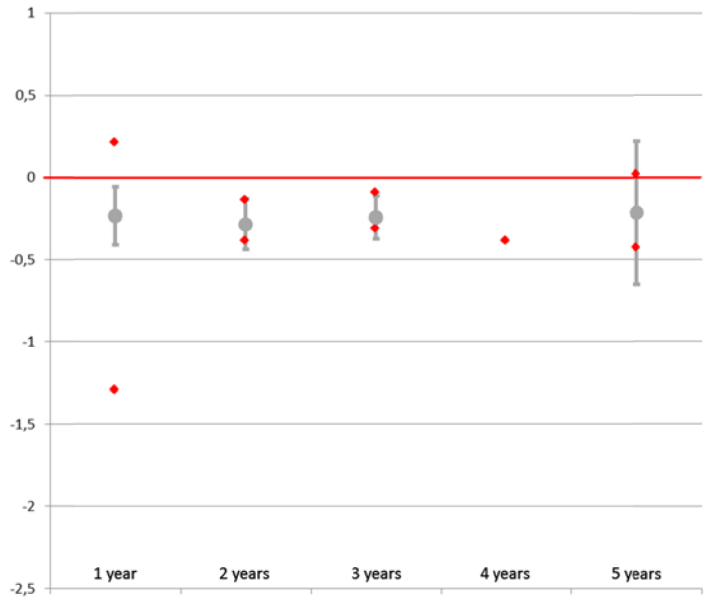
	1 year	2 years	3 years	4 years	5 years
SN	**6**	**3**	**2**	**1**	**2**
PN	808	672	392	272	392
I²	0.0%	88.0%	80.5%		91.7%
p	0.829	0.000	0.024		0.001

4.A URINARY IRRITATIVE-OBSTRUCTIVE



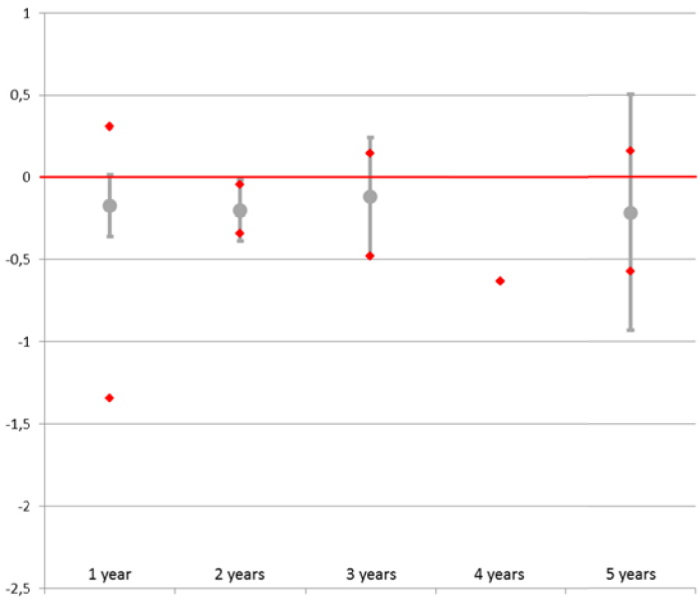
	1 year	2 years	3 years	4 years	5 years
SN	**7**	**5**	**2**	**1**	**2**
PN	979	875	392	272	392
I²	35.3%	0.0%	89.3%		92.6%
p	0.159	0.443	0.002		0.000

4.A URINARY FUNCTION



	1 year	2 years	3 years	4 years	5 years
SN	**10**	**3**	**4**	**1**	**2**
PN	800	482	497	272	392
I²	59.1%	21.1%	0.0%		86.0%
p	0.009	0.281	0.616		0.007

4.A URINARY BOTHER

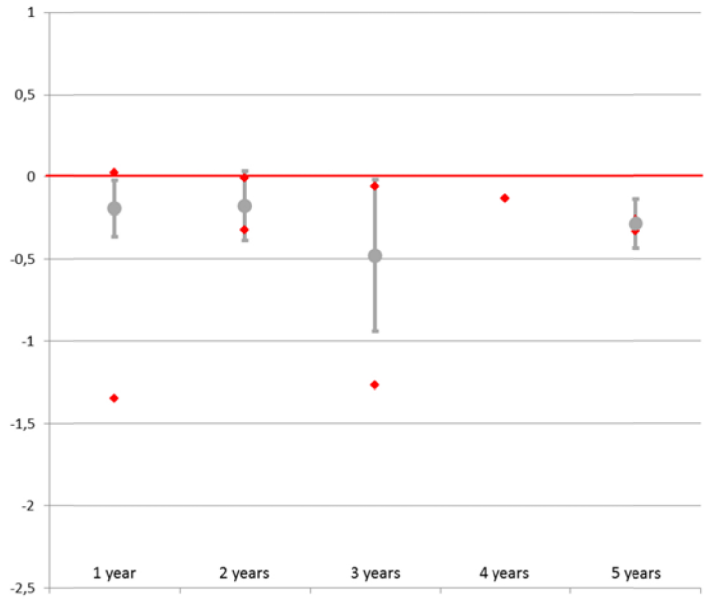


	1 year	2 years	3 years	4 years	5 years
SN	**9**	**3**	**4**	**1**	**2**
PN	748	482	497	272	392
I²	61.2%	43.3%	84.0%		94.8%
p	0.008	0.172	0.000		0.000

SN Studies Number; **PN** Patients Number; **I^2** and **p-value** testing heterogeneity

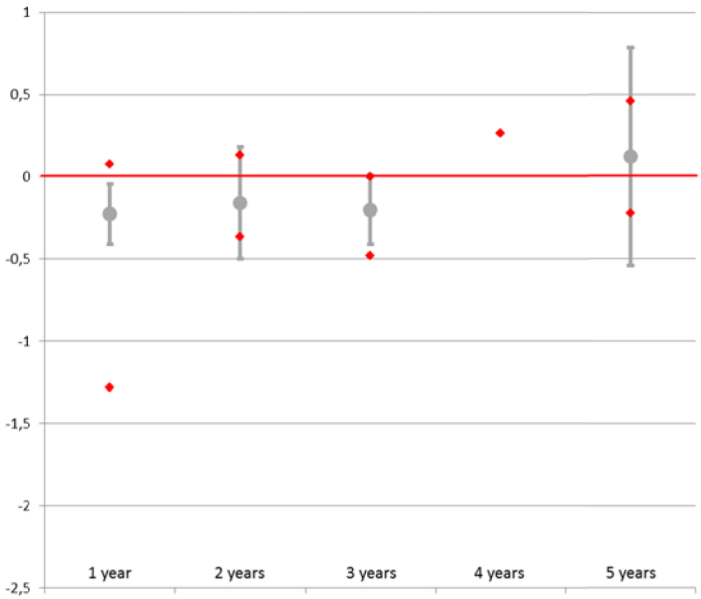
Figure 4. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy (continuation). Red diamonds represent maximum and minimum estimators from individual studies.

4.B SEXUAL FUNCTION



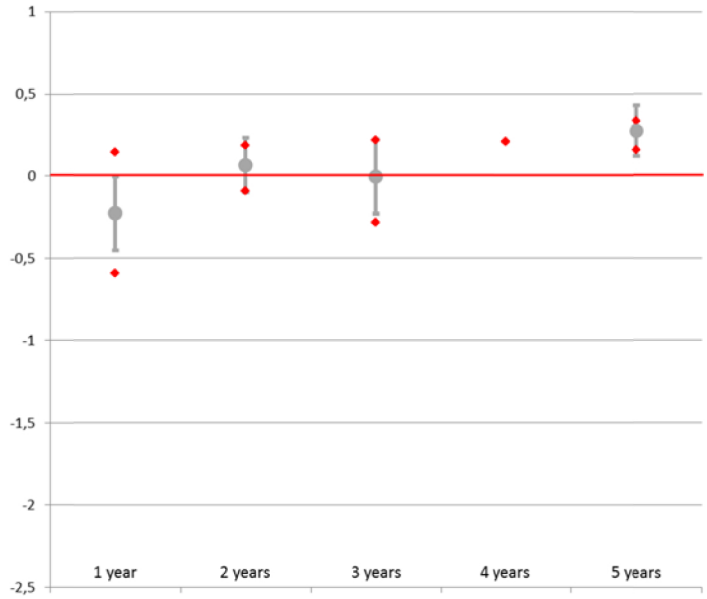
SN	**9**	**3**	**4**	**1**	**2**
PN	744	479	497	272	392
I²	52.2%	55.1%	90.0%		0.0%
p	0.033	0.108	0.000		0.691

4.B SEXUAL BOTHER



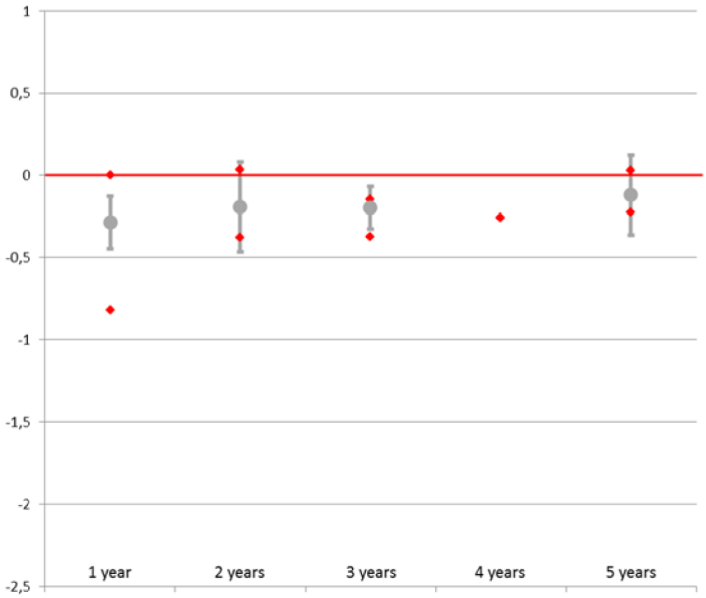
SN	**9**	**3**	**4**	**1**	**2**
PN	745	480	497	272	392
I²	58.9%	82.5%	53.1%		93.9%
p	0.012	0.003	0.094		0.000

4.B BOWEL FUNCTION



SN	**9**	**3**	**4**	**1**	**2**
PN	748	482	497	272	392
I²	73.0%	31.3%	59.4%		6.2%
p	0.000	0.233	0.061		0.302

4.B BOWEL BOTHER



SN	**10**	**3**	**4**	**1**	**2**
PN	769	482	497	272	392
I²	47.6%	73.0%	0.0%		57.1%
p	0.046	0.025	0.825		0.127

SN Studies Number; **PN** Patients Number; **I^2** and **p-value** testing heterogeneity

Table 1. Characteristics of the cohorts included in the metanalyses grouped by treatments.

TREATMENT	Study Design/ Number cohorts		N of patients Median (range)		Age Median (range)		PSA(ng/mL) Median (range)		Follow-up (month) Median (range)		Specific HRQoL instrument/ N cohorts	
	I	Not I	I	Not I	I	Not I	I	Not I	I	Not I	I	Not I
PROSTATECTOMY	40	53										
Open Radical Prostatectomy	PLS=26 RCT=1	PLS=32 RCT=1	127 (24-1806)	166 (22-3706)	65 (58-70)	63 (53-71)	8 (4.2-16.9)	7.3 (4.8-12.4)	24 (12-72)	24 (12-72)	UCLA-PCI=14 EPIC=12	UCLA-PCI=12 EPIC=10 QLQ-PR25=4 PCQoL=1 PCSI=1 PORPUS=1
Laparoscopic Prostatectomy	PLS=3	PLS=3	161 (105-210)	122 (93-229)	62 (58-66)	61 (58-68)	7.6 (5.7-8.6)	6 (5.7-7.7)	12 (12-36)	12 (12-12)	EPIC=2 UCLA-PCI=2	EPIC=2 UCLA-PCI=1
Robot Assisted Laparoscopic	PLS=7	PLS=15	90 (45-361)	129 (21-945)	61 (58-65)	61 (47-66)	7.2 (5-9)	6.4 (5-10.5)	15 (12-36)	18 (12-48)	EPIC=3 UCLA-PCI=4	UCLA-PCI=6 EPIC=5 QLQ-PR25=3 PCQoL=1
Various surgery techniques	PLS=3	PLS=2	627 (170-1670)	315 (140-290)	63 (60-64)	61 (59-63)	5.9 (3.1-8.6)	6.1 (5.6-6.7)	36 (12-36)	36 (12-60)	EPIC=3	EPIC=2
RADIOTHERAPY	44	43										
3D-Conformational Radiation Therapy	PLS=6 RCT=1	PLS=3	60 (54-153)	153 (149-153)	70 (67-71)	67 (67-68)	7.3 (7-7.5)	11.8 (11.8-11.8)	24 (16-72)	60 (12-60)	EPIC=6	QLQ-PR25=3
External Beam Radiation Therapy	PLS=8	PLS=13 RCT=1	126 (26-598)	122 (27-491)	65 (62-68)	68 (60-72)	11.9 (8.2-14.6)	14.2 (9-24)	36 (12-52)	36 (12-180)	EPIC=3 UCLA-PCI=8 PORPUS=1 PCSI=1	UCLA-PCI=4 EPIC=2 PCSI=3 FACT-P=1
Intensity Modulated Radiation Therapy	PLS=4 RCT=5	PLS=4 RCT=2	153 (16-692)	87 (20-204)	69 (64-71)	69 (65-73)	7.7 (5.3-11.9)	9 (9-9)	24 (12-36)	24 (14-60)	EPIC=9 PCSI=1	EPIC=2 QLQ-PR25=2
Proton Therapy	PLS=4 RCT=2	PLS=3	91 (33-262)	226 (65-1243)	65 (56-68)	66 (63-66)	5.2 (5.2-5.2)	4.7 (4.5-4.8)	24 (24-72)	24 (24-24)	EPIC-=5 PCSI=2	EPIC=3
Stereotactic Body Radiation Therapy	PLS=7 RCT=4	PLS=8 RCT=3	102 (30-864)	75 (28-912)	69 (66-70)	69 (66-71)	5.7 (3.4-7.0)	6.9 (5.8-8.2)	36 (12-60)	24 (12-72)	EPIC=11	EPIC=8 QLQ-PR25=3 UCLA-PCI=1
Various Radiation Therapy	PLS=3	PLS=1	118 (78-292)	60	71 (67-75)	65	13.6 (9.1-29.4)	4.5	24 (24-36)	36	EPIC=1 UCLA-PCI=2	EPIC=1
EBRT+BT		PLS=5		95 (75-1010)		67 (66-67)		8 (8-8)		12 (12-120)		EPIC=3 UCLA-PCI=2
BRACHYTHERAPY	18	26										
	PLS=16 RCT=2	PLS=26	84 (26-306)	98 (12-684)	67 (62-70)	66 (64-69)	6.8 (5-10.6)	7.2 (6-11.2)	21 (12-60)	36 (12-120)	EPIC=12 UCLA-PCI=7	QLQ-PR25=10 EPIC=6 UCLA-PCI=4 PCSI=3 FACT-P=2
CRYOTHERAPY		2										
		PLS=1 RCT=1		102 (81-122)		70 (69-71)		7 (6-8)		36 (36-36)		UCLA-PCI=2
HIFU		6										
		PLS=5 RCT=1		55 (20-326)		64 (60-68)		7.1 (6.6-12.7)		18 (12-36)		FACT-P=4 EPIC=2
ACTIVE SURVEILLANCE		11										
		PLS=9 RCT=2		195 (50-545)		66 (65-66)		4.9 (4.0-5.7)		36 (12-72)		EPIC=7 UCLA-PCI=2 PCSI=1 QLQ-PR25=1

PLS- Prospective Longitudinal Study, RCT-Randomized Clinical Trial, **UCLA-PCI**-University California, Los Angeles- Prostate Cancer Index, **EPIC** – Expanded Prostate Cancer Index, **QLQ-PR25-** European Organisation for Research and Treatment of Cancer – Quality of Life Prostate Specific Tool. **PORPUS**- Patient Orientated Prostate Cancer Utility Score, **PC**SI- Prostate Cancer Symptoms Indices, **FACT-** Functional Assessment of Cancer Therapy.

Supplementary material. Table 1. Search Strategy

MEDLINE

Search term
1. ((((((("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields]) OR ("prostate"[MeSH Terms] OR "prostate"[All Fields] OR "prostatic"[All Fields])) OR ("prostate"[MeSH Terms] OR "prostate"[All Fields])) OR (("prostate"[MeSH Terms] OR "prostate"[All Fields] OR "prostatic"[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]))) OR "prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR "prostate"[All Fields]) AND "cancer"[All Fields] OR "prostate cancer"[All Fields] OR ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostatic"[All Fields] AND "cancers"[All Fields]) OR "prostatic cancers"[All Fields]) OR ("prostatic hyperplasia"[MeSH Terms] OR ("prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "prostatic hyperplasia"[All Fields] OR ("prostatic"[All Fields] AND "adenoma"[All Fields]) OR "prostatic adenoma"[All Fields]) NOT ("prostatic hyperplasia"[MeSH Terms] OR ("prostatic"[All Fields] AND "hyperplasia"[All Fields]) OR "prostatic hyperplasia"[All Fields] OR ("benign"[All Fields] AND "prostate"[All Fields] AND "hyperplasia"[All Fields]) OR "benign prostate hyperplasia"[All Fields]) NOT "Prostatic Hyperplasia"[MeSH Terms])
2. ("Quality of Life"[MeSH Terms] OR "Quality of Life"[All Fields] OR "QOL"[All Fields] OR ("quality"[All Fields] AND "life"[All Fields]) OR "health related quality of life"[All Fields] OR ("health related"[All Fields] AND "Quality of Life"[All Fields]) OR "HRQOL"[All Fields] OR ("health related"[All Fields] AND "QoL"[All Fields]) OR (("Self-reported"[All Fields] OR "self-reported"[All Fields]) AND ("Quality of life"[All Fields] OR "patient measures"[All Fields])) OR "Patient Reported Outcomes"[All Fields] OR "PRO"[All Fields] OR "Patient Reported Outcome Measures"[All Fields] OR "PROM"[All Fields]) AND ("2005/01/01"[PDAT] : "2015/02/29"[PDAT])
3. 1 AND 2

Update between: 2015/03/01 to 2017/03/27.

Supplementary material 2. Characteristics of studies assessing the impact of PCa Treatment on HRQoL included in Meta-analysis.

*Reference numbers correspond to the bibliography in the main article reference list

Author and publication year (reference number)*	Study design	Treatment	(n)	Age Mean/median (SD or range)	PSA Mean/median (SD or range)	Follow-up (months)	HRQoL instrument	HT %	Objective(s)
Barocas D, et al, 2017(18) Tyson M, et al, 2016(19)	PLS	RP EBRT AS	1523 598 429	61.5(61.1-61.8) 68.1(67.6-68.7) 66.1(65.4-66.9)	NR	36 (0,6,12,24,36)	EPIC-26		To report the acute and long-term toxicity of a phase II, multi-institutional study of SBRT for low to intermediate risk PCa
Hamstra D, et al, 2017(20) Mariados N, et al, 2015(21)	RCT	IMRT with Without hydrogel	222	67.7 66.4	5.7 5.6	36 (0,6,12,18,24,36)	EPIC-50	0	To assess outcomes following absorbable spacer (SpaceOAR system) implantation at three years.
Donovan JL, et al, 2016(9)	RCT	ORP 3D CRT AS	553 545 545	62(50-69)	4.6(3-19.9)	72 (0,6,12,24,36,48,60,72)	SF-12 QLQ-C30 EPIC-50	NR	To investigate the effects AS, RP and RT with hormones on patient-reported outcomes.
Quon H, et al, 2016(22)	RCT	SBRT	84 30	67(61-71) 68(65-73)	5.3(4.2-7.3) 4,7(3.5-7.5)	42 (0,6,12,18,24,30,36,42)	EPIC-50	NR	This study compares long-term HRQoL from two prospective trials of prostate SBRT to investigate the effect of increasing dose
Bryant C, et al, 2016(23) Mendenhall,N, et al, 2013(24) Bryant C, et al, 2016(25)	PLS	PT	211	68 (40-88)	NR	+72 (0,6,12,48,60,+72)	EPIC-50	12	To report 5-year clinical outcomes of 3 prospective trials of image-guided proton therapy for PCa.
Morton G, et al, 2017(26)	RCT	HD-BT 19Gy 13.5Gy	87 33	65(7) 65(7)	6.7(2.9) 6.9(3.1)	30 (0,5w,3,6,12,18,24,30)	EPIC	NR	To determinte toxicity and effect on HRQoL of single fraction 19Gy or 13.5Gy x2.
Dearnaley,D, et al, 2016(27) Wilkins, A, et al, 2015(28)	RCT	IMRT 74Gy IMRT 60Gy IMRT 57Gy	676 686 692	69 (65-73) 69 (64-73) 68 (64-73)	11.3 (5.3) 11.9 (5.8) 11.3 (5.4)	24 (0,10w,6,12,18,24,36,48,60,72)	UCLA-PCI EPIC	NR	To assess PROs up to 24 months after conventionally fractionated or hypofractionated radiotherapy in the Conventional or Hypofractionated High Dose IMRT in PCa (CHHiP) trial

Hannan R, et al, 2016(29). Kim N, et al, 2014(30)	RCT	SBRT	91	66(53-80)	5.4(0.2-16.2)	18 (0,12,15,18)	EPIC-50	47	To report the toxicity outcomes of a phase I/II clinical trial of SBRT for low and select intermediate risk PCa patients.
Jeldres C, et al, 2015(31) Pham KN, et al, 2016.(32)	PLS	AS RP	77 228	65 (45-75) 58(40-74)	4.0 (0.3-9.2) 4.2(0.2-10)	36 (0,3,6,9,12,18,24,36)	EPIC-50	NR	To compared longitudinal HRQoL in a prospective, racially diverse, and contemporary cohort of patients who underwent RP or AS for low-risk PCa
Strom T, et al, 2015(33)	PLS	BT-HDR BT-LDR IMRT	85 249 79	67(44-85) 66(38-86) 71(50-84)	5(1-15.4) 5.1(0.5-19.1) 5.3(1.5-17.6)	18 (0,1,3,6,9,12,18)	EPIC-26	0	To compare urinary, bowel, and sexual HRQoL changes due to HDR-BT or LDR-BT brachytherapy or IMRT.
Vargas C, et al, 2015(34)	RCT	PT 38Gy 79.2Gy	49 33	65(52-75) 65(49-80)	NR	24 (0,3,6,12,18,24)	EPIC-26	NR	To identify differences in terms of quality of life, the American Urological Association Symptom Index or adverse events among patients with PCa treated with either standard fractionation or hypo fractionation PT.
Woo JA, et al, 2015(35)	PLS	SBRT	155 149 134	NR	6.0 (1.8-32.5)	36 (0, 1, 3,12, 24, 36)	EPIC-26	NR	To report the urinary and bowel QOL outcomes following SBRT in patients with clinically localized PCa.
Brajtbord JS, et al, 2014(36) Daskivich TJ, et al, 2010(37) Bellizi KM, et al, 2008(38) van de Poll-Franse LV, et al, 2008 (39) Wright JL, et al, 2008(40) Latini DM, et al, 2006(41)	PLS	RP	1806	61.1(6.9)	NR	24 (0,12,24)	SF-36 UCLA-PCI	NR	To examine the impact of age on sexual and urinary function and bother during the first 2 years after radical prostatectomy.

Hu J, et al,2006(42) Arredondo SA, et al,2006(43) Anast JW, et al, 2005(44)									
Mantz C, et al, 2014.(45)	RCT	SBRT	102	NR	3.42 (7.3-10)	60 (0,3,6,12,18,24,36,48,60)	EPIC-26	0	To describe toxicity, HRQoL, and biochemical disease outcomes from an IRB-approved, phase II trial of conventional linear accelerator-based SABR monotherapy in the treatment of low-risk PCa using the Calypso® System for intrafractional real-time target tracking.
Bhattasali O, et al, 2014(46)	PLS	SBRT	228	69(44-90)	6.1(1.3-32.5)	24 (0,1,3,6,9,12,18,24)	EPIC-26	NR	To report on patient-reported outcomes following SBRT for localized PCa.
Davison J, et al, 2014(47)	PLS	ORP RALP	73 78	63(7) 61(6)	7.8(5.8) 6.2(2.8)	12 (0,3,6.12)	EPIC-50	0	To measure the impact of the RARP and ORP surgical procedures on patient sexual and urinary function, and determine the impact of these outcomes on decision regret.
Hashine K, et al, 2014(48)	PLS	LRP	105	66(51-78)	7.56	12	SF-8 EPIC	9.5	To assess HRQoL in the first year after LRP compared with that after ORP.
Scorsetti M, et al, 2014(49)	PLS Phase II trial	SBRT	46	70(48-80)	6.95(3)	12 (0, 3,6,12)	EPIC-50	NR	To appraise the patient reported HRQoL according to EPIC questionnaire for SBRT.
Yamamoto S, et al, 2014(50)	PLS	IMRT	91	70(56-79)	7.7(4-28.1)	24 (0,3,6,12,24)	SF-8 EPIC	NR	To assess longitudinal changes in general and disease specific HRQoL indices after IMRT monotherapy for patients with localized PCa.
Berge V, et al, 2013(51)	PLS	LRP RALP	210 210	61.7(42-76) 61.7(40-76)	8.6(2.3-28) 9.0(2.3-40)	36 (0,3,12,24,36)	UCLA-PCI	NR	To compare HRQoL outcomes after conversion from LRP to RALP as the routine procedure for surgical treatment in localized PCa
Ferrer M, et al, 2013(52)	PLS	ORRP BT 3D-CRT SBRT	193 194 317 216	64.2(5.5) 70.1(5.3) 67.5(6.4) 69.2(44-89)	7.6(2.9) 8.1(3.4) 7.0(2.2) 5.4(0.7-21)	60 (0,3,6,12,18,24,36,48,60)	SF-36 EPIC-50	NR	To assess long-term HRQoL impact of treatments in localized PCa patients treated with RP, EBRT or BT.

Chang P, et al, 2017(53) Lee J, et al, 2016(54) Pardo Y, et al, 2010(55) Guedea F, et al, 2009(56) Ferrer M, et al, 2008(57) Katz A, et al, 2012(58)									
Gray PJ, et al, 2013(59).	PLS	PT IMRT 3D-CRT	95 153 123	64(49-78) 69(47-83) 70(54-82)	5,2(2.3-15) 5,8(0.5-25.8) 7,5(0.9-77.4)	24 (0,2,3,12.24)	PCSI EPIC-50	NR	To report HRQoL data for 3 contemporary cohorts that received treatment with 3DCRT, IMRT and PBT monotherapy
King CR, et al, 2013(60)	PLS	SBRT	864	69(8)	NR	24 (0,1,2,3,6,9,12,24,36,48, 60,72)	EPIC-50	14	To evaluate early and later HRQoL outcomes among PCa patients following SBRT.
Van Tol-Geerdink JJ, et al, 2013(61)	PLS	ORP+LR P+RALP BT IMRT	 170 28 42	 64(5) 64(5) 65(6)	NR	12 (0,12)	EPIC-50	NR	To compare treatment effects on HRQoL scores and their clinically relevant changes.
Coen JJ, et al, 2012(62)	PLS	PT	87	66 (49-78)	5.2 (2.3-15)	60 (0,3,12,24,36,48,60)	PCSI	NR	To report long-term HRQoL outcome in a group of prospectively followed patients receiving high-dose conformal PT for PCadav
Hoppe BS, et al, 2012(63)	PLS	PT	262	56(41-60)	NR	24 (0,3,6,12,24)	EPIC-50	0	To evaluate patient-reported HRQoL following PT for PCa in men ≤60 years old
McBride SM, et al, 2012(64)	PLS	SBRT	45	70(54-83)	4.9(1.36-9.4)	54 (0,3,6,9,12,18,24,30,36,42 ,48,54)	EPIC-50	0	To report the own multi-institutional experience with extreme hypo fractionated SBRT for early stage disease

Steinsvik E, et al, 2012(65) Storas A, et al, 2015(66)	PLS	RP EBRT	627 126	62.8(5.4) 67.2(3.6)	8-6(3.6) 9.5(4.1)	36 (0,3,12,24,36)	SF-12 EPIC-50	NR	To explore the sexual function and bother problems after curative treatments for PCa patients.
Vainshtein J, et al, 2012(67)	RCT (II)	IMRT	16	64(7)	7.74(0.62)	24 (0,1,3,12,24)	EPIC-50	NR	To compare HRQoL between, urethra sparing IMRT and standard IRMT and non-urethral sparing IMRT
Willis DL, et al, 2012(68)	PLS	LRP RALP	161 121	58(7) 58(6)	5.7(2.9) 5.0 (2.2)	12 (0,3,6,12)	EPIC-50	NR	To compare peri operative, oncological, and functional outcomes of LRP and RALP with emphasis on HRQoL data as few studies exist
Dragićević S, et al, 2012(69)	PLS	RP WW	56 48	66.3(7.1) 73.2(7.8)	8.0 7.2	12 (0,1,2,3,6,12)	EPIC-50	NR	To compare HRQoL of patients with PCa, who had RP, with patients who were carefully monitored (WW).
Wang R, et al, 2012(70)	PLS	RALP + ORRP	1670	60.4 (6.4) 59.7 (8.0)	2.4 (38.7) 3.9 (55.8)	12 (0,12)	EPIC	2.7 4.8	To evaluate the difference in vesicourethral anastomotic stenosis, ORRP vs RALP, and to analyse associated factors and effect on HRQoL
Pinkawa M, et al, 2011(71) Pinkawa M, et al, 2009(72) Pinkawa M, et al, 2009(73)	PLS	3D-CRT Whole Only prostate BT	 60 60 52	 71(56-81) 71(56-82) 68(51-77)	 NR 7(1.5-14)	16 (0,2,16)	EPIC-50	 44 44 27	To compare of HRQoL after whole pelvic and prostate only EBRT for PCa.
Rice K, et al, 2010(74)	PLS	ORRP 3D-CRT 3D-CRT +HT BT WW	369 153 54 27 43	58(8) 67(9) 70(8) 63(8) 69(10)	8.0(16.7)	24 (0,3,6,9,12,18,24,36)	SF-36 EPIC-50	10.8	To identify radical and demographic factors that influence treatment choice and its resulting impact on HRQOL in PCa patients
Dragićević S, et al, 2010(75)	PLS	ORRP BT	96 88	66(51-79) 69(52-84)	9.0(1.3-60.3) 6.3(2.0-22.3)	12 (0,1,3,6,12)	SF-8 EPIC-50	3 19	To evaluate HRQOL and make the treatment decisions less difficult.
Hashine K, et al, 2009(76)	PLS	ORRP BT	96 88	66(51-79) 69(52-84)	9.0(1.3-60.3) 6.3(2.0-22.3)	12 (0,1,3,6,12)	SF-8 EPIC-50	3 15	To evaluate the HRQOL after RRP and BT using EPIC

Krahn MD, et al, 2009(77)	PLS	RP EBRT	68 66	68(6) 66(6)	8.81(6.9) 14.33(14.6)	12 (0,2,12)	QLQ-C30 UCLA-PCI PORPUS-P	7 60	To examine and compare changes in HRQoL after two common treatments for PC, RP and RT.
Smith DP, et al, 2009(78)	PLS	AS RP EBRT ADT EBRT+ ADT LDR BT HDR BT	200 981 123 61 166 58 47	66(63-69) 60(60-61) 64(63-65) 64(63-65) 64(63-65) 64(63-65) 62(61-64)	5.7(0.3-41.5) 7.2(0.3-60.2) 8.2(0.2-45) 28.2(1.5-250.9) 14.6(2.7-190) 7.2(2.1-23.3) 10.5(2.5-75.9)	36 (0,36)	SF-12 UCLA-PCI	NR	To quantify the risk and severity of negative effects of treatment for localized PCa on long term HRQoL
Hashine K, et al, 2008(79)	PLS	ORRP BT	122 82	68(42-78) 70(50-85)	9.6(1.4-299.9) 6.7(3.1-56.7)	12 (0,3,6,12)	SF-36 UCLA-PCI	6.5 21	To compare the HRQoL after a radical retro pubic prostatectomy or a permanent prostate BT at a single institute.
Sanda MG, et al, 2008(80) Chang P, et al, 2017(53) Evans J, et al,2015(81)	PLS	RP BT EBRT	603 306 292	59 (38-79) 65 (44-84) 69 (45-84)	6.7 (5.7) 5.8 (3.6) 9.1 (10.1)	24 (0,2,6,12,24)	EPIC-26	0 7 31	To identify determinates of HRQoL after primary treatment of PCa and to measure the effects of such determinates on satisfaction with the outcome of treatment in patients and their partners.
Inoue S,et al,2009(82)	PLS	OPRP	194	70	6.5	60 (0,3,6,12,24,36,48,60)	SF-36 UCLA-PCI	NR	To investigate the longitudinal alteration of HRQoL up to 5 years after RP perineal among Japanese patients with localized PCa.
Shikanov A, et al, 2008(83)	PLS	RALP	361	NR	NR	12 (0,12)	UCLA-PCI	0	To evaluate urinary and sexual HRQoL 1 year following RALP, and identified pre-operative variables predictive of a severe decrease from baseline.
Ash D, et al, 2007(84)	PLS	BT	116	NR	NR	24 (0,4-6wk,6,10,18,24)	EPIC-50	58	To evaluate long-term urinary bowel and sexual function after BT for localized PCa using administered HRQoL instruments.
Litwin MS, et al, 2007(85)	PLS	RP EBRT BT	307 78 90	60(7) 71(7) 68(7)	7.3(6.9) 13.6(21.6) 10.6(14.6)	24 (0,1,2,12,18,24)	UCLA-PCI	NR	To compare HRQoL outcomes after the most commonly used treatments.

Namiki S, et al, 2007(86) Namiki S, et al, 2005(87) Namiki S, et al, 2007(88) Namiki S, eta al 2010(89)	PLS	ORRP RALP 3DCRT or IMRT	121 45 118	67(6) 65(6) 75(3)	8.9(5.8) 8.3(4.5) 29.4(41.2)	36 (0,1,3,6,12,18,24,36)	SF-36 UCLA-PCI	NR	To compare the HRQoL after RP and RT.
Kubler HR, et al, 2007(90)	PLS	OPRP NNS NS	153 112	NR NR	NR NR	30 (0,6,12,18,24,30)	EPIC-50		To investigate the impact of nerve sparing technique on erectile function, urinary continence and HRQoL after RPP using a validated self-assessment questionnaire.
Namiki S, et al, 2006(91)	PLS	ORRP BT	67 70	64(7) 67(6)	8.8(6.8) 7.0(3.4)	12 (0,3, 6,12)	SF-36 UCLA-PCI	0	To investigate HRQoL in Japanese men with localized PCa who underwent prostate BT or RP
Symon Z, et al, 2006(92)	PLS	RP EBRT	24 26	57.5(7.7) 61.9(2.7)	NR	12 (0,12)	SF-12 EPIC-50	NR	To measure patient expectations regarding how they anticipate their HRQoL to be shortly after and 1 year after treatment.
Tseng TY, et al, 2006(93)	PLS	RALP	90	58(7)	5.9 (3.5)	18 (0,1,3,6,9,12,18)	EPIC-50	0	To prospectively assess the HRQoL outcomes of patients undergoing robot-assisted laparoscopic RP using a validated patient self-assessment
Korfage IJ, et al, 2005(94)	PLS	RP EBRT	127 187	62.3 (5.2)	68.2 (5.8)	52 (0,6,12,52)	SF-36 EQ-5D UCLA-PCI	NR	To assess the frequency of side effects of primary therapy and to determine HRQoL in men with localized PCa up to 5 years after primary treatment with radical prostatectomy or external beam radiotherapy
Matsubara A, et al, 2005(95)	PLS	OPRP	41	69 (57-75)	7 (2-38)	12 (0,1,3,6,12)	UCLA-PCI	NR	To obtain a longitudinal assessment of urinary continence and urinary, bowel, and sexual domain-related HRQoL in Japanese patients undergoing perineal RP

Haffner MC, et al, 2005(96)	PLS	ORRP	342	NR	NR	24 (0,3,6,12,24)	UCLA-PCI	NR	To examine the impact of neurovascular bundle preservation on longitudinal HRQoL outcomes after anatomical RP retropubic using a validated questionnaire
Namiki S, et al, 2005(97) Namiki S,et al, 2008(98) Namiki S,et al ,2009(99)	PLS	ORRP RALP	121 45	67 (6) 65 (6)	8.9 (5.8) 8.3 (4.5)	12 (0,1,3,6,12)	SF-36 UCLA-PCI	NR	To compare the general and disease-specific HRQoL after laparoscopic RP with that after retropubic RP
Namiki S, et al, 2007(100) Namiki S, et al, 2005(101) Namiki S, et al 2005(102)	PLS	RP RP+NHT	203 26	67(5.4) 68 (5)	9.6(7.6) 16.9 (13.2)	24 (0,3,6,12,24)	SF-36 UCLA-PCI	21.6	To investigate the changes in HRQoL in patients who underwent RP with or without NHT
Maliski SSL, et al, 2005(103)	PLS	BT WW ORRP EBRT	26 33 88 NR	NR	NR	12 (0,6,12)	SF-36 UCLA-PCI	NR	To investigate if post-treatment fatigue varies by treatment, demographic or pre-treatment HRQoL

RP- Radical Prostatectomy ;**LPR**- Laparoscopic Prostatectomy; **RALP**- Robot Assisted Laparoscopic Prostatectomy; **ORRP**- Open Retropubic Radical Prostatectomy, **OPRP**- Open Perineal Radical Prostatectomy, **BT**- Brachytherapy, **LDR-BT-** Low-dose-rate Brachytherapy, **HDR-BT**- High-dose-rate Brachytherapy; **EBRT**- External Beam Radiation Therapy (**3D-CRT**-3D- Conformational Radiation Therapy, **IMRT**- Intensity Modulated Radiation Therapy); **SBRT**- Stereotactic Body Radiation Therapy, **PT**-Proton Therapy, **ADT**- Androgen Deprivation Therapy; NHT- Neoadjuvant Hormonal Therapy,**AS**- Active Surveillance, **WW**- Watchful waiting, **CT**- Cryotherapy, **PLS**- Prospective Longitudinal Study, **RCT**- Randomized Clinical Trial, **UCLA-PCI**- University California, Los Angeles- PCa Index, **SF-36**- Short Form- 36, **PROMIS** Global Health Short Form**, EPIC**- Expanded PCa Index, **FACT**- Functional Assessment of Cancer Therapy, **EORTC- QLQ**- European Organisation for Research and Treatment of Cancer Quality of Life (**PR25** – Prostate Specific Tool, **C30**- General Cancer Tool), **PORPUS**- Patient Orientated PCa Utility Score, **PCSI**- PCa Symptoms Indices, **NR** = Not Reported, **HRQoL**- Health-Related Quality of Life ,**PROs-** Patient-Reported Outcomes**.**

Supplementary material 3. Characteristics of studies assessing the impact of PCa Treatment on HRQoL NOT included in Meta-analysis

*Reference numbers correspond to the reference list at the end of this table

Author and Publication Year (reference number)*	Study design	Treatment	(n)	Age Mean/median (SD or range)	PSA Mean/median (SD or range)	Follow-up (months)	HRQoL instrument	Objectives
LACK INFORMATION (SD)								
Banerji J, et al, 2017 (1)	PLS	3DCRT or IMRT or PT AS	60 103	65(7) 64(8)	4.5(1.8) 4.2(1.9)	36 (0,6,12,18,24,36)	SF-36 EPIC-50	To determine whether patients with low risk PCa who undergo EBRT report poorer HRQoL outcomes compared to those managed on AS over a 3-year period
D´Agostino G, et al, 2016 (2)	RCT Phase II	SBRT	90	71 (48-82)	6.9(2.7-17)	24 (0, end RT,3,6,12,18,24)	EPIC-50	To evaluate the efficacy and toxicity of SBRT in patients with low or intermediate risk PCa.
Miyake, H,et al, 2016(3)	PLS	RALP	298	66.3 (49-79)	8.9 (1.7-72.7)	24 (0,1,3,6,12,24)	SF-8 EPIC-50	To characterize changes in the HRQoL of Japanese patients following RALP.
Parker, et al 2016(4)	PLS	AS	180	67.2 (8.9)	3.3 (1.6)	24 (0, 6, 12, 18, 24, 30)	EPIC	To evaluate prospectively the associations between illness uncertainty, anxiety, fear of progression and general and HRQoL in men with favourable-risk PCa undergoing AS.
Resnick MJ, et al, 2013(5) O'Neil,B et al, 2016(6) Hoffman RM, et al, 2006(7)	PLS	RP EBRT	1164 491	64(59-68) 69(64-71)	NR	15y (0,6,12,24,60,15y)	UCLA-PCI	To compare long-term urinary, bowel, and sexual function after radical prostatectomy or external-beam radiation therapy.
Katz AJ, et al, 2014(8) Katz AJ, et al, 2011(9) Katz AJ, et al, 2010(10)	PLS	SBRT	515	69 (44-89)	6.6 (1.0-42.9)	72 (3,3week,3,6,12,18,24,36, 48,60,72,84,96)	EPIC-50	To presents a 7-year update on treatment toxicity and HRQoL from patients treated with SBRT.

Aluwini S, et al, 2013(11)	PLS	SBRT	50	68(48-80)	8.2(1.3-1.6)	24 (0,6,9,12,24)	QLQ-PR25	To report results on toxicity, PSA response and HRQoL in patients treated with SBRT for favourable risk PCa.
Ju AW, et al, 2013(12)	PLS	SBRT	41	69(60-92)	6.9(3.5-18.3)	15 (0,1,3,6,9,12,15)	EPIC-26 SF12	To examine the does distributions and early clinical outcomes using SBRT for treatment of intermediate-risk PCa.
Kaye D, et al, 2013(13).	PLS	RP Excellent NS Standard NS	75 24	53(6) 56(6)	4.8 (2.1) 5.1 (2.0)	12 (0,3,6,9,12)	EPIC-50	To assess the effect of NS quality on self-reported patient urinary outcomes after RP.
Pugh TJ, et al, 2013.(14)	PLS	PT PSPT SSPT	226 65	63(47-82) 66(50-83)	4.5(0.1-18.6) 4.8(0.3-19.2)	24 (0,6,12,18,24)	EPIC-50	To report and compare HRQoL /toxicity in men treated with some PT techniques.
Pinkawa M, et al, 2012(15)	PLS	Various techniques of radiotherapy	46 21	72 (59-83) 71 (61-81)	NR	19 (0,2,19)	EPIC-50	To evaluate HRQoL after IMRT with vs. without 18F-choline PET-CT detected with simultaneous integrated boost(SIB).
Barkati M, et al, 2012.(16)	PLS	BT	79	66(47-77)	6.8(2-10)	60 (1,3,6,12,24,36,48,60)	EPIC-26	To explore the value of high dose BT as monotherapy in low-inter risk PCa.
Beckendorf V, et al, 2011(17)	PLS	3D-CRT 70 Gy 80 Gy	153 153	67 67	11.79 11.79	60 (12,24,36,48,60)	QLQ-C30 QLQ-PR25	To perform a randomized trial comparing 70 and 80 Gy radiotherapy for PCa.
Steenland K, et al, 2011.(18)	Population-based study PLS	EBRT ADT BT+EBRT BT WW RP	66 10 79 34 14 57	64(7)	7.3 (2.2)	12 (0,6,12)	SF-12 EPIC	To perform a population based study of the HRQoL after PCa treatment in a rural and disadvantaged population, because these have been sparse.
Parker WR, et al, 2011(19)	PLS	ORRP+ RALP	490	63 (8)	6.7 (4.8)	60 (0,1,4,12,24,36,48,60)	EPIC-50	To document the EPIC results for men followed for 5 years after RP
Evers, J, et al, 2010(20)	PLS	BT No NHT-BT NHT-BT	81 40	65 (6) 66 (6)	7,2 (3.0) 7.2 (3.3)	12 (0,6 weeks,3,12)	QLQ-C30 QLQ-PR25	To prospectively investigate the influence of 3-month neoadjuvant ADT before BT for low-risk PCa on urinary function and HRQoL.
Hashine K, et al, 2011(21)	PLS	RP BT	107 91	67(51-79) 69(52-84)	9.8(1.3-88.7) 6.4(2-22.3)	36 (0,3,6,12,24,36)	SF-8 EPIC-50	To examine HRQoL for 3 years after RP or BT and to determine differences between treatments.

Malcolm JB, et al, 2010(22)	PLS	ORP RALP BT CT	135 447 122 81	59(7) 59(6) 66(7) 71(7)	5.7 (4.7-7.3) 5.2 (3.9-6.8) 6.0 (4.5-8.2) 6.2 (5.0-8.6)	36 (0,3,6,12,18,24,30,36)	UCLA-PCI	To describe HRQoL impact and recovery profiles of 4 commonly used operative treatments for localized PCa
Dalkin BL,et al, 2006(23)	PLS	RP	176	63(35-79)	8.5(0.5-6)	24 (0,12,24)	SF-36 UCLA-PCI	To define accurately HRQoL outcomes in men undergoing RP by a single surgeon.
Soderdahl D, et al, 2005 (24)	PLS	RP LRP BT	86 93 71	59 61 68	6.0 5.7 6.0	12 (0,1,3,6,12)	SF-36 UCLA-PCI	To compare HRQoL after treatment RP,LRP and BT.
Link R, et al 2005(25)	PLS	LRP	122	58(6)	6.0 (3.1)	12 (0,3,6,9,12)	EPIC-50	To assess recovery in urinary and sexual function after LPR with respect to baseline preoperative function.
LACK INFORMATION (MEAN, SD, N)								
Boyer M, et al, 2017(26)	PLS	SBRT	60	66(49-86)	5.8(0.5-13.5)	36 (0,6,12,24,36)	SF-36 EPIC-26	To report the acute and long-term toxicity of a phase II, multi-institutional study of SBRT for low to intermediate risk PCa..
Du K, et al, 2017(27)	PLS	RP	499	60(56-65)	5.0(4.0-7.0)	24 (0,3,6,9,12,18,24)	EPIC-50	To examine post-prostatectomy orgasmic function (OF) and assessed for potential predictors
Koike H, et al, 2017(28)	PLS	LRP RALP	229 105	68(52-78) 66(49-76)	7.7(3.01-48.7) 7.5(4-23.9)	12 (0,3,6,9,129	SF-8 EPIC-50	To compare HRQoL outcomes between LRP and RALP.
Osman S, et al, 2017(29)	PLS	LDR-BT	12	NR	NR	36 (0,1,3,6,9,12,24,36)	EPIC-50	To test the hypothesis that levels of biological DNA damage biomarkers relative to baseline would correlate with HRQoL measures determined using the EPIC questionnaire
Chen R, et al, 2017(30)	PLS	AS EBRT BT RP	314 249 109 469	67(7.3) 67(7.1) 66(7.3) 62(6.8)	NR	24 (0, 6,12,24)	SF-12 PCSI	To analyse HRQoL changes from baseline (pre-treatment) through2 years after treatment for men who received RP, EBRT, or BT vs those who pursued AS
Qi XS, et al, 2016 (31)	PLS	SBRT	86	NR	NR	12 (0,3,6,9,12)	EPIC-26	To study the association between dosimetric parameters with patient-reported HRQoL in urinary irritative/incontinency and bowel functions for prostate SBRT.
Patabendi et al 2016 (32)	PLS	EBRT+BT	1010	66 (60.0-71.7)	NR	12 (0,12,24)	EPIC-26	To use CaP clinical registry data to evaluate variation in patient adverse effects after EBRT in Victoria.

Dess R, et al, 2016(33)	PLS	SBRT	713	69 (64-73)	NR	60 (0,3,6,12,24,36,60)	EPIC-26	To assess the incidence and predictors of a global decline in HRQoL after SBRT
Jackson M, et al, 2016(34)	PLS	ORP RALP	63 116	60.4(6.4) 58.6(5.8)	NR	10y	EPIC-50	To report PROs from a randomized trial comparing hypofractionated and conventional prostate radiotherapy.
Johnson SB, et al, 2016(35)	PLS	SBRT Moderate hypofractionation	534 378	NR	NR	24 (0,12,24)	UCLA-PCI EPIC-26	To evaluate changes in bowel, urinary and sexual patient-reported HRQoL following treatment with moderately hypofractionated radiotherapy (<5 Gray/fraction) or SBRT;5–10 Gray/fraction) for PCa
Yap T, et al, 2016(36)	RCT	HIFU	118	63 (52-70)	6.8 (5.6-9.3)	12 (0,1,3,6,9,12)	EPIC-50	This analysis pools the sexual domain related patient reported outcomes from three prospective registered studies that represent a range of inclusion criteria.
Shoji S, et al, 2015(37)	PLS	HIFU Urethra-sparing Whole-gland	45 65	65 (51-79) 66 (58-80)	6.6 (3.92-19.7) 7.6(3.27-20)	36 (0,3,6,12,24,36)	FACT-P	To evaluate longitudinal changes in urinary function and quality of life, and oncological outcomes of patients treated with urethra-sparing HIFU for localized PCa.
Gomez CL, et al, 2015(38)	RCT Phase II	SBRT	75	71(46-92)	NR	12 (0,3,6,9,12,15,18,24)	EPIC-26	To evaluate correlations between short-term HRQoL outcomes and dosimetric parameters to guide future prostate SBRT planning.
Son CH, et al, 2015(39)	PLS	IMRT	179	69 (63-74)	9 (5.7-14.9)	24 (0,2,5,6,12,18,24)	EPIC-26	To study the impact of IMRT and ADT on sexual function over time and to report the effectiveness of sexual medications or aids.
Murphy,G,et al, 2015(40)	PLS	RALP	737	61.0(55.9-65.7)	5(4.0-6.8)	24 (0,24)	EPIC-26	To characterize changes in indices of urinary function in prostatectomy patients with presurgical voiding symptoms.
Jereczek-Fossa B, et al, 2014(41) Jereczek-Fossa BA, et al, 2013(42)	PLS	Hypo IGRT	337	71(6.5)	6.1(0.6-43)	24 (0,6,12,24)	QLQ-C30 QLQ-PR25	To report the image-guided hypofractionated radiotherapy (hypo-IGRT) outcome for patients with localised PCa according to the new outcome models Trifecta and SCP.

Reeve BB, et al, 2014(43)	PLS	RP EBRT BT	127 191 379	66(46-74) 60(51-82) 66(47-81)	NR	36 (0,3,12.24,36)	SF-36 PCSI	To examine the impact of baseline comorbidity on HRQL outcomes in an analysis of two pooled, prospective cohort studies.
Hoppe MJ,et al, 2014(44)	PLS	IMRT PT	204 1243	69(46-84) 66(40- >89)	NR	24 (0,6,12,24)	EPIC-50	To compare HRQoL outcomes after PT and IMRT for PCa.
Stensvold A, et al, 2013(45)	PLS	RALP RT RT+HT	150 104 208	61.6 (5.9) 67.1 (5.6) 65.8 (5.5)	9.9 (9.4) 14.7 (11.7) 24.0 (14.1)	24 (0,3,6,12,24)	SF-12 UCLA-PCI	To examine changes of sexual, urinary, and bowel bother after RALP, after high dose radiotherapy alone, or with adjuvant androgen deprivation therapy
Kim JH, et al, 2013(46)	PLS	RP RALP	140	59(7)	5.6(2.7)	12 (0,3.6,12)	EPIC-50	To analyse variables that were associated with patient-perceived satisfaction after RARP using the EPIC survey.
Van der Poel HG, et al, 2013(47)	PLS	RALP	925	61.7(37-79)	10.5(1.2-254)	24 (0,3,6,12,24)	QLQ-C30 QLQ-PR25	To study the interview- and questionnaire-based recovery patterns of continence, erectile function, and physical and overall HRQoL after RALP
Ahmed H, et al, 2012(48)	PLS	HIFU	41	63(58-66)	6.6(5.4-7.7)	12 (0,1,3,6,9,12)	FACT EPIC-50	To report on whether selective focal ablation of unifocal and multifocal cancer lesions can reduce this treatment burden.
Thiel DD, et al, 2012(49)	PLS	RALP	82	61.6 (45-75)	NR	12 (0,12)	EPIC-50	To examine 1-year functional and oncologic outcomes for RALP from a single surgeon entering practice directly from fellowship training.
Thornton AA, et al, 2011(50)	PLS	RALP	71	61 (7.7)	NR	12 (0,3,12)	PCQoL	To describing changes in cognitive, behavioural, and emotional components of PCa-related QoL over the first year following RALP.
Gore J, et al, 2010(51).	PLS	RP EBRT BT	307 78 90	60(7) 71(7) 68(7)	7.3(6.9) 13.6(21.8) 10.6(14.6)	48 (0,1,2,4,8,12,18,24,30,36,42,48)	SF-36 UCLA-PCI	To determine factors associated with bother, the distress patients experience as a result of functional detriments after treatment for localized PCa.
Punnen S, et al, 2015(52) Huang GJ,et al, 2010(53)	PLS	RP NS NNS BT EBRT ADT WW/AS EBRT+BT	 1139 860 684 386 161 64 75	 60.0(6.8) 62.9(6.6) 68.3(7.2) 71.3(6.2) 73.6(8.1) 72.5(7.9) NR	NR	10y (0,24,48,60,120)	SF-36 UCLA-PCI	To evaluate long-term HRQoL following various treatments for localized PCa.

Robinson J, et al, 2009(54)	RCT	EBRT CT	122 122	68.6(53.2-78.6) 69.4(52.8-81.4)	9.0 (2.5 -23.3) 8.1 (0.7-19.9)	36 (0,1.5,3,6,12,18,24,36)	QLQ-C30 UCLA-PCI	To evaluate HRQoL outcomes for 2 primary treatments of PCa: EBRT and cryoablation.
Chen RC, et al, 2009.(55)	PLS	RP EBRT BT	127 190 92	60(46-74) 69(51-82) 64(47-77)	NR	36 (0,3,12,14,36)	PCSI	To identify differences in the outcomes between patients with different baseline levels of function.
Giberti C, et al, 2009(56)	PLS	RP BT	200 100 100	65.5 (57-74) 65.6 (56-74)	7.8 (56-74) 7.5 (2.9-9.3)	60 (0,6,12,60)	QLQ-C30 QLQ-PR25	To compare oncological and functional outcomes reported after RP (retropubic) vs BT in the treatment of low-risk PCa.
Gilberti C, et al, 2009(57)	PLS	RALP	90	64 (52-71)	NR	12 (0,12)	QLQ-PR25	To measure oncological and functional results in patients treated with RALP.
Wiltz AL, et al, 2009(58)	PLS	RALP (divided by BMI) <25 25-≤30 >30	945 216 464 265	 60 (7) 60 (7) 60 (6)	 6.3 (5.1) 6.4 (3.9) 6.4 (4.3)	24 (0,1,3,6,12,24)	SF36 UCLA-PCI	To determine the impact of BMI on perioperative function and oncological outcomes in patients undergoing robotic laparoscopic RP when stratified for BMI.
Schmeller N, et al, 2007(59)	PLS	RP	150	63-66	8.8 8.0-8.9	24 (0,1,3,6,12,24)	UCLA-PCI	To compare three different surgical approaches used by 3 experienced surgeons.
Buron C, et al, 2007(60)	PLS	RP BT	127 308	63 (6.0) 65 (6.3)	8.9 (4.0) 7.5 (2.7)	24 (0, 2, 6, 12,18,24)	QLQ-C30 QLQ-PR25	To prospectively compare HRQoL, patient-reported treatment-related symptoms, and costs of iodine-125 permanent implant interstitial BT with those of RP during first 2 years after these treatments for localized PCa.
Zorn KC, et al, 2007(61)	PLS	RALP Age<50 50-59 ≥60	300 21 129 150	 47 (42-49) 55 (50-59) 65(60-76)	 5.2 (0.6-17) 6.1 (0.9-25.4) 6.9 (1.4-32)	12 (0,1,3,6,12)	SF 36 UCLA-PCI	To evaluate post-operative return of urinary and sexual function in men undergoing RALP.
Kuwata Y, et al, 2007(62)	PLS	RP -NNS RP- NS	44 22	70.7 (3.8) 66.3 (6.7)	13.0 12.7) 12.4(9.5)	24 (0,3,6,9,12,18,24)	UCLA-PCI SF-36	To investigate HRQoL, including sexual function and sexual bother, in patients who underwent RP-NNS in comparison with those who underwent a RP-NS.
Montgomery JS, et al, 2006(63)	PSL	RRP	376	59	5.6	36 (1,4,12,36)	EPIC-50 SF-12	To use a validate HRQoL measure to examine the effects of obesity on disease specific HRQoL before and following RRP.

Van Gellekom M,et al,2005(64)	PLS	BT	127	NR	NR	24 (0,1,6,12,24)	SF-36 QLQ-C30 QLQ-PR25	To investigate changes in HRQoL after permanent BT and to correlate these changes with post implant dosimetry based on magnetic resonance images.
Feigenberg SJ, et al, 2005(65)	PLS	BT	98	NR	NR	12 (0,3,6,9,12)	FACT-P	To prospectively assess health-related quality of life during the first year after treatment with prostate brachytherapy alone for T1c-2a PCa
LACK INFORMATION (n)								
Wagner A, et al,2016(66)	PLS	ORP	482	NR	6.3(5.1)	12 (0,3,6,12)	EPIC-CP	To evaluate the feasibility of using EPIC-CP to measure HRQoL in patients before and after radical prostatectomy in the clinical setting outside.
Aluwini S, et al, 2015(67)	PLS	BT	166	68 (47-79)	8 (1-16)	60 (0,3,6,12,18,24,36,48,60)	QLQ-PR25	To report results on toxicity and QoL after HDR-BT monotherapy for PCa patients.
Shoji S, et al, 2010(68)	PLS	HIFU	326	68(7)	12.7(9.4)	24 (0,6,12,24)	FACT-G FACT-P	To report our HRQoL and functional outcomes following HIFU for localized PCa.
Marchand V, et al 2010(69)	PLS	HD-IMRT	55	73(54-80)	NR	18 (0,2,6,18)	QLQ-C30 QLQ-PR25	To determine prospectively intermediate-term toxicity and HRQoL of PCa patients after IMRT.
Freedland SJ, et al, 2005(70)	PLS	RP	340	56	5.4	24 (0,6,12,24)	UCL-PCI	To study the impact of obesity on the HRQoL outcomes after RP.
LACK ESTIMATORS BY TREATMENT								
Chambers S, et al, 2016(71)	PLS	RP BT EBRT WW	1064	63.7 (7.8)	11(27.5)	72 (0,2,6,12,24,36,48,60, 72)	EPIC	To describe trajectories of HRQoL, life satisfaction, and psychological adjustment for men with PCa over the medium to long term andidentify predictors of poorer outcomes using growth mixture models.
Punnen S, et al, 2013(72)	PLS	RP AS	557 122	60(6.7) 60.5(6.5)	NR	36 (0,12,36)	EPIC-26	To evaluate the impact of these symptoms at baseline on urinary and sexual QoL at follow-up.
Tanaka N,et al, 2010(73)	PLS	BT +EBRT EBRT	110	67	7.6	12 (0,1,3,6,12)	SF36 UCLA-PCI	To assess the variations in HRQoL in patients who underwent t low-dose rate prostate BT using iodine 125 seed sources in the first year
Jayadevappa R, et al, 2006(74)	PLS	RP RT	69 46	69.5(4.5) 67.4(1.5)	NR	12 (0,3,6,12)	SF-36 UCLA-PCI	To analyse HRQoL and satisfaction with care across potential curative treatments for older patients newly diagnosed with PCa

Jayadevappa R, et al, 2007(75) Jayadevappa R, et al, 2009(76)								
LACK ESTIMATORS								
Dixit A, et al, 2017(77)	PLS	SBRT	45	71(46–86)	6.9(1.7–23.2)	18 (0,6,12,18)	QLQ-C30 QLQ-PR25	To evaluate biochemical response, acute toxicity and HRQoL outcomes among PCa patients following SBRT in the first Australian CyberKnife facility.
Tambas M, et al. 2016(78)	PLS	SBRT IMRT	28 20	68(6.5) 65(7.4)	NR	13.5 (0,1.5,4.5,7.5,10.5,13.5)	QLQ-PR25	To investigate the HRQoL after different treatment modalities for low-risk PCa, including BT, RALP, and surveillance with validated questionnaires.
Acar C, et al, 2014 (79)	PLS	RALP BT AS	65 29 50	59(6) 64(6) 64(7)	6,4(2.1) 6.8(1.9) 5.8(2.4)	48 (0,24,36,48)	QLQ-C30 QLQ-PR25	To investigate the HRQoL after different treatment modalities for low-risk PCa, including BT, RALP, and surveillance with validated questionnaires.
Mc Caughan E, et al, 2013(80)	PLS	3D-CRT+ADT	149	68(53-79)	NR	12 (0,1,6,12)	QLQ-C30 QLQ-PR25	To report a study measuring the HRQoL and side effects in men receiving RT and ADT for PCa up to 1y after treatment
Jakobsson, L, et al, 2013(81)	PLS	RP	222	62.7(6.1)	7.7(0.4-34)	60 (3,1,2,3,5)	QLQ-C30 QLQ-PR25	To determine areas of functioning and factors impacting quality of life, during and five years after RP.
Ratcliff CG, et al, 2013 (82)	RCT	RP	95	60.9(6.6)	NR	12 (0,12)	SF-36 PCQoL	To examine the associations of treatment regret with general and PCa specific HRQoL .
Jongkamp VG, et al, 2012(83)	PLS	BT	132	66(50-81)	11.2(1.7-100)	12 (0,1,6,12)	SF-36 QLQ-C30 QLQ-PR25	To describe depression rate after BT up to 8 years follow-up. In addition, the correlation between depression, coping, and general HRQoL is examined.
Roeloffzen EM, et al, 2010(84) Roeloffezen E, et al, 2010(85)	PLS	BT	127	66 (50-78)	10.1 (1.7-38)	72 (0,1,6,12,72)	SF-36 QLQ-C30 QLQ-PR25	To assess long term HRQoL 6 years after BT.

Vordermark D, et al, 2009.(86)	PLS	BT	74	67(6)	NR	12 (0,1,12)	QLQ-C30 QLQ-PR25	To investigate and gain detailed knowledge of HRQoL after permanent BT.
Davison BJ, et al, 2007 (87)	PLS	RP	130	63(6.0)	NR	12 (0,12)	QLQ-C30 QLQ-PR25	To examine the effect of changes in HRQoL and levels of sexual function on decisional regret after surgical treatment of localized PCa.
INSTRUMENT								
Hoffman K, et al, 2016(88)	RCT	IMRT HIMRT	82 91	67(49-84) 68(46-83)	NR	60 (0,24,36,48,60)	Independent Instrument	To report PROs from a randomized trial comparing hypofractionated and conventional prostate radiotherapy.
Derogar M, et al, 2016(89)	PLS	RP	3706	63(37-79)	NR	24 (1.5,3 12,24)	Independent instrument	To study the level of preparedness before radical prostatectomy and the level of bother experienced from urinary incontinence and decreased sexual health after surgery.
Veccia A, et al, 2015.(90) Caffo O, et al, 2006.(91)	PLS	BT	251	66 (49-77)	NR	36 (0, 1,12,24,36)	Independent instrument	To assess the relationship between dosimetric parameters and the HRQoL outcomes of patients with low-intermediate-risk localised PCa treated with LDR-BT
Kasperzyk J, et al, 2011(92).	PLS	WW Other Tx	125 1105	72.3 68.1	6.0 6.7	15y	Uncomplete EPIC	To examine patient-reported outcomes among PCa pts managed by AS in a nationwide cohort.
Johansson E, et al, 2009.(93)	PLS	RP WW	166 160	64 (48-74) 65 (51-74)	NR	8y (0,3,5,8y)	Independent instrument	To evaluate how follow-up time, number of physical symptoms, and presence of ADT affected HRQoL among men randomised to RP or WW.
Fransson P, et al, 2009.(94)	PLS	EBRT WW	27 27	77 (54-87)	NR	10 y (4,10y)	PCSS QLQ-C30	To evaluate long-term randomized comparisons of patient-reported outcome of symptoms and HRQOL in men with localized PCa 10yrs after EBRT or WW
PORPUS								
Ku J, et al, 2009(95)	PLS	RP	213	60.8(7.1)	5.6(4.2-8.4)	30 (0,3,9,18,30)	PORPUS-P	To include the assessment of changes in specific domains of HRQoL over time after RP.

FACT-P								
Komiya, A,et al, 2013(96)	PLS	HDR-BT	51	68.9(6.3)	11.0(10.6)	24 (0,2w,1,3,6,9,12,24)	FACT-P	To evaluate the early quality of life outcomes in PCa patients managed by high-dose-rate brachytherapy as monotherapy
Monga U, et al, 2005(97)	PLS	RT	40	68(55-78)	3.1-83.2	12 or more (0,1,2,12 or more)	FACT-P	To evaluate QoL in localized PCa undergoing RT.
ACTIVE SURVEILLANCE								
Cohen A,et al, 2016(98)	PLS	AS	223	66.8(7.2)	NR	24 (0,6,12,24)	PROMIS EPIC-26	To determine the extent to which low testosterone levels impact health-related quality of life in patients undergoing AS for PCa.
Pearce SM, , et al, 2015.(99)	PLS	AS	195	66.5(6.8)	5.2(3.9)	24 (0,6,12,18,24)	EPIC-26	To examine the relationship between sexual dysfunction, repeat biopsies and other demographic and clinical factors in men on AS.
Daubenmier,et al, 2006(100)	RCT	AS	44 49	64.8 (7.1) 66.5 (7.6)	6.3 (1.7) 6.3 (1.7)	12 (0,12)	SF-36 UCLA-PCI	To assess the impact of lifestyle on HRQoL, perceived stress, and self-reported sexual function in men with PCa electing AS.
EBRT+BT								
Shahid N, et al, 2017(101;101) Morton GC, et al, 2011(102) Morton GC, et al, 2011(103) Morton GC, et al, 2010(104)	PLS	HDR-BT+ EBRT	125	67.8(7.3)	7.7(3.9)	36 (0,6,12,24,36,48,60)	EPIC-50	To report HRQoL and toxicity in PCa patients treated with single-fraction HDR-BT and EBRT.
HIFU								
Ahmed H, et al, 2011(105)	PLS	HIFU	20	60(5)	7.3(2.8)	12 (0, 1, 6, 9, 12)	FACT	To test the principal that focal therapy using HIFU might confer fewer side effects than other treatment options

RP- Radical Prostatectomy ;**LPR**- Laparoscopic Prostatectomy; **RALP**- Robot Assisted Laparoscopic Prostatectomy; **ORRP**- Open Retropubic Radical Prostatectomy, **OPRP**- Open Perineal Radical Prostatectomy, **BT**- Brachytherapy, **LDR-BT-** Low-dose-rate Brachytherapy, **HDR-BT**- High-dose-rate Brachytherapy; **EBRT**- External Beam Radiation Therapy (**3D-CRT**-3D- Conformational Radiation Therapy, **IMRT**- Intensity Modulated Radiation Therapy, **SIB**-Simultaneous integrated boost, **HIMRT**-Hypofractionated Intensity Modulated Radiation Therapy, , **HD-IMRT**-High-dose-Intensity Modulated Radiation Therapy); **SBRT**- Stereotactic Body Radiation Therapy, **PT**-Proton Therapy, **CT-** Carbon-ion Radiotherapy, **ADT**- Androgen Deprivation Therapy; NHT- Neoadjuvant Hormonal Therapy, **HIFU**- High Intensity Focused Ultrasound **AS**- Active Surveillance, **WW**- Watchful waiting, **CT**- Cryotherapy, **PLS**- Prospective Longitudinal Study, **RCT**- Randomized Clinical Trial, **UCLA-PCI**- University California, Los Angeles- PCa Index, **SF-36**- Short Form- 36, **PROMIS** Global Health Short Form**, EPIC**- Expanded PCa Index, **FACT**- Functional Assessment of Cancer Therapy, **EORTC- QLQ**- European Organisation for Research and Treatment of Cancer Quality of Life (**PR25** – Prostate Specific Tool, **C30**- General Cancer Tool), **PORPUS**- Patient Orientated PCa Utility Score, **PCSI**- PCa Symptoms Indices, **NR** = Not Reported, **HRQoL**- Health-Related Quality of Life ,**PROs-** Patient-Reported Outcomes**.**

REFERENCES OF SUPPLEMENTARY MATERIAL 3

(1) Banerji JS, Hurwitz LM, Cullen J, Wolff EM, Levie KE, Rosner IL, et al. A prospective study of health-related quality-of-life outcomes for patients with low-risk prostate cancer managed by active surveillance or radiation therapy. Urol Oncol 2017 Jan 19.

(2) D'Agostino G, Franzese C, De RF, Franceschini D, Comito T, Villa E, et al. High-quality Linac-based Stereotactic Body Radiation Therapy with Flattening Filter Free Beams and Volumetric Modulated Arc Therapy for Low-Intermediate Risk Prostate Cancer. A Mono-institutional Experience with 90 Patients. Clin Oncol (R Coll Radiol) 2016 Jul 4.

(3) Miyake H, Miyazaki A, Furukawa J, Hinata N, Fujisawa M. Prospective assessment of time-dependent changes in quality of life of Japanese patients with prostate cancer following robot-assisted radical prostatectomy. J Robot Surg 2016 Sep;10(3):201-7.

(4) Parker PA, Davis JW, Latini DM, Baum G, Wang X, Ward JF, et al. Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. BJU Int 2016 Mar;117(3):469-77.

(5) Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013 Jan 31;368(5):436-45.

(6) O'Neil B, Koyama T, Alvarez J, Conwill RM, Albertsen PC, Cooperberg MR, et al. The Comparative Harms of Open and Robotic Prostatectomy in Population Based Samples. J Urol 2016 Feb;195(2):321-9.

(7) Hoffman RM, Barry MJ, Stanford JL, Hamilton AS, Hunt WC, Collins MM. Health outcomes in older men with localized prostate cancer: results from the Prostate Cancer Outcomes Study. Am J Med 2006 May;119(5):418-25.

(8) Katz AJ, Kang J. Quality of Life and Toxicity after SBRT for Organ-Confined Prostate Cancer, a 7-Year Study. Front Oncol 2014;4:301.

(9) Katz AJ, Santoro M, Ashley R, Diblasio F. Stereotactic Body Radiation Therapy for Low- and Low-Intermediate-Risk Prostate Cancer: Is there a Dose Effect? Front Oncol 2011;1:49.

(10) Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy for organ-confined prostate cancer. BMC Urol 2010;10:1.

(11) Aluwini S, van RP, Hoogeman M, Kirkels W, Kolkman-Deurloo IK, Bangma C. Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: early results. Radiat Oncol 2013;8:84.

(12) Ju AW, Wang H, Oermann EK, Sherer BA, Uhm S, Chen VJ, et al. Hypofractionated stereotactic body radiation therapy as monotherapy for intermediate-risk prostate cancer. Radiat Oncol 2013;8:30.

(13) Kaye DR, Hyndman ME, Segal RL, Mettee LZ, Trock BJ, Feng Z, et al. Urinary outcomes are significantly affected by nerve sparing quality during radical prostatectomy. Urology 2013 Dec;82(6):1348-53.

(14) Pugh TJ, Munsell MF, Choi S, Nguyen QN, Mathai B, Zhu XR, et al. Quality of life and toxicity from passively scattered and spot-scanning proton beam therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2013 Dec 1;87(5):946-53.

(15) Pinkawa M, Piroth MD, Holy R, Klotz J, Djukic V, Corral NE, et al. Dose-escalation using intensity-modulated radiotherapy for prostate cancer - evaluation of quality of life with and without (18)F-choline PET-CT detected simultaneous integrated boost. Radiat Oncol 2012 Jan 30;7:14.

(16) Barkati M, Williams SG, Foroudi F, Tai KH, Chander S, van DS, et al. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a Phase II trial. Int J Radiat Oncol Biol Phys 2012 Apr 1;82(5):1889-96.

(17) Beckendorf V, Guerif S, Le PE, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011 Jul 15;80(4):1056-63.

(18) Steenland K, Goodman M, Liff J, Diiorio C, Butler S, Roberts P. Quality of life among men with prostate cancer in rural Georgia. Urology 2011 Apr;77(4):927-33.

(19) Parker WR, Wang R, He C, Wood DP, Jr. Five year expanded prostate cancer index composite-based quality of life outcomes after prostatectomy for localized prostate cancer. BJU Int 2011 Feb;107(4):585-90.

(20) Evers J, Kupper N, Kessing D, Davits R, Engelen A, Poortmans P, et al. No long-term effects of hormonal therapy preceding brachytherapy on urinary function and health-related quality of life among prostate cancer patients. Urology 2010 Nov;76(5):1150-6.

(21) Hashine K, Yuasa A, Shinomori K, Ninomiya I, Kataoka M, Yamashita N. Health-related quality of life after radical retropubic prostatectomy and permanent prostate brachytherapy: a 3-year follow-up study. Int J Urol 2011 Dec;18(12):813-9.

(22) Malcolm JB, Fabrizio MD, Barone BB, Given RW, Lance RS, Lynch DF, et al. Quality of life after open or robotic prostatectomy, cryoablation or brachytherapy for localized prostate cancer. J Urol 2010 May;183(5):1822-8.

(23) Dalkin BL, Christopher BA, Shawler D. Health related quality of life outcomes after radical prostatectomy: attention to study design and the patient-based importance of single-surgeon studies. Urol Oncol 2006 Jan;24(1):28-32.

(24) Soderdahl DW, Davis JW, Schellhammer PF, Given RW, Lynch DF, Shaves M, et al. Prospective longitudinal comparative study of health-related quality of life in patients undergoing invasive treatments for localized prostate cancer. J Endourol 2005 Apr;19(3):318-26.

(25) Link RE, Su LM, Sullivan W, Bhayani SB, Pavlovich CP. Health related quality of life before and after laparoscopic radical prostatectomy. J Urol 2005 Jan;173(1):175-9.

(26) Boyer MJ, Papagikos MA, Kiteley R, Vujaskovic Z, Wu J, Lee WR. Toxicity and quality of life report of a phase II study of stereotactic body radiotherapy (SBRT) for low and intermediate risk prostate cancer. Radiat Oncol 2017 Jan 13;12(1):14.

(27) Du K, Zhang C, Presson AP, Tward JD, Brant WO, Dechet CB. Orgasmic function after radical prostatectomy. J Urol 2017 Mar 18.

(28) Koike H, Kohjimoto Y, Iba A, Kikkawa K, Yamashita S, Iguchi T, et al. Health-related quality of life after robot-assisted radical prostatectomy compared with laparoscopic radical prostatectomy. J Robot Surg 2017 Jan 27.

(29) Osman SO, Horn S, Brady D, McMahon SJ, Yoosuf AB, Mitchell D, et al. Prostate cancer treated with brachytherapy; an exploratory study of dose-dependent biomarkers and quality of life. Radiat Oncol 2017 Mar 14;12(1):53.

(30) Chen RC, Basak R, Meyer AM, Kuo TM, Carpenter WR, Agans RP, et al. Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer. JAMA 2017 Mar 21;317(11):1141-50.

(31) Qi XS, Wang JP, Gomez CL, Shao W, Xu X, King C, et al. Plan quality and dosimetric association of patient-reported rectal and urinary toxicities for prostate stereotactic body radiotherapy. Radiother Oncol 2016 Oct;121(1):113-7.

(32) Patabendi Bandarage VR, Billah B, Millar JL, Evans S. Prospective evaluation of patient-reported quality of life outcomes after external beam radiation treatment for prostate cancer in Victoria: A cohort study by the Victorian Prostate Cancer Registry. J Med Imaging Radiat Oncol 2016 Jun;60(3):420-7.

(33) Dess RT, Jackson WC, Suy S, Soni PD, Lee JY, Abugharib AE, et al. Predictors of multidomain decline in health-related quality of life after stereotactic body radiation therapy (SBRT) for prostate cancer. Cancer 2016 Dec 21.

(34) Jackson MA, Bellas N, Siegrist T, Haddock P, Staff I, Laudone V, et al. Experienced Open vs Early Robotic-assisted Laparoscopic Radical Prostatectomy: A 10-year Prospective and Retrospective Comparison. Urology 2016 May;91:111-8.

(35) Johnson SB, Soulos PR, Shafman TD, Mantz CA, Dosoretz AP, Ross R, et al. Patient-reported quality of life after stereotactic body radiation therapy versus moderate hypofractionation for clinically localized

prostate cancer. Radiother Oncol 2016 Nov;121(2):294-8.

(36) Yap T, Ahmed HU, Hindley RG, Guillaumier S, McCartan N, Dickinson L, et al. The Effects of Focal Therapy for Prostate Cancer on Sexual Function: A Combined Analysis of Three Prospective Trials. Eur Urol 2016 May;69(5):844-51.

(37) Shoji S, Nakano M, Fujikawa H, Endo K, Hashimoto A, Tomonaga T, et al. Urethra-sparing high-intensity focused ultrasound for localized prostate cancer: Functional and oncological outcomes. Int J Urol 2015 Nov;22(11):1043-9.

(38) Gomez CL, Xu X, Qi XS, Wang PC, Kupelian P, Steinberg M, et al. Dosimetric parameters predict short-term quality-of-life outcomes for patients receiving stereotactic body radiation therapy for prostate cancer. Pract Radiat Oncol 2015 Jul;5(4):257-62.

(39) Son CH, Chennupati SK, Kunnavakkam R, Liauw SL. The impact of hormonal therapy on sexual quality of life in men receiving intensity modulated radiation therapy for prostate cancer. Pract Radiat Oncol 2015 May;5(3):e223-e228.

(40) Murphy G, Haddock P, Doak H, Jackson M, Dorin R, Meraney A, et al. Urinary Bother as a Predictor of Postsurgical Changes in Urinary Function After Robotic Radical Prostatectomy. Urology 2015 Oct;86(4):817-23.

(41) Jereczek-Fossa BA, Zerini D, Fodor C, Santoro L, Maucieri A, Gerardi MA, et al. Reporting combined outcomes with Trifecta and survival, continence, and potency (SCP) classification in 337 patients with prostate cancer treated with image-guided hypofractionated radiotherapy. BJU Int 2014 Dec;114(6b):E3-E10.

(42) Jereczek-Fossa BA, Santoro L, Zerini D, Fodor C, Vischioni B, Dispinzieri M, et al. Image guided hypofractionated radiotherapy and quality of life for localized prostate cancer: prospective longitudinal study in 337 patients. J Urol 2013 Jun;189(6):2099-103.

(43) Reeve BB, Chen RC, Moore DT, Deal AM, Usinger DS, Lyons JC, et al. Impact of comorbidity on health-related quality of life after prostate cancer treatment: combined analysis of two prospective cohort studies. BJU Int 2014 Dec;114(6b):E74-E81.

(44) Hoppe BS, Michalski JM, Mendenhall NP, Morris CG, Henderson RH, Nichols RC, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. Cancer 2014 Apr 1;120(7):1076-82.

(45) Stensvold A, Dahl AA, Brennhovd B, Smastuen MC, Fossa SD, Lilleby W, et al. Bother problems in prostate cancer patients after curative treatment. Urol Oncol 2013 Oct;31(7):1067-78.

(46) Kim JH, Ha YS, Jeong SJ, Kim S, Kim WJ, Jang TL, et al. Factors related to patient-perceived satisfaction after robot-assisted radical prostatectomy based on the expanded prostate cancer index composite survey. Prostate Cancer Prostatic Dis 2013 Dec;16(4):341-5.

(47) van der Poel HG, Tillier C, de Blok WM, Acar C, van Muilekom EH, van den Bergh RC. Interview-based versus questionnaire-based quality of life outcomes before and after prostatectomy. J Endourol 2013 Nov;27(11):1411-6.

(48) Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 2012 Jun;13(6):622-32.

(49) Thiel DD, Hutchinson R, Diehl N, Tavlarides A, Williams A, Parker AS. Impact of fellowship training on one-year outcomes of robotic-assisted prostatectomy. JSLS 2012 Apr;16(2):195-201.

(50) Thornton AA, Perez MA, Oh S, Crocitto L. A prospective report of changes in prostate cancer related quality of life after robotic prostatectomy. J Psychosoc Oncol 2011;29(2):157-67.

(51) Gore JL, Gollapudi K, Bergman J, Kwan L, Krupski TL, Litwin MS. Correlates of bother following treatment for clinically localized prostate cancer. J Urol 2010 Oct;184(4):1309-15.

(52) Punnen S, Cowan JE, Chan JM, Carroll PR, Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. Eur Urol 2015 Oct;68(4):600-8.

(53) Huang GJ, Sadetsky N, Penson DF. Health related quality of life for men treated for localized prostate

cancer with long-term followup. J Urol 2010 Jun;183(6):2206-12.

(54) Robinson JW, Donnelly BJ, Siever JE, Saliken JC, Ernst SD, Rewcastle JC, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer 2009 Oct 15;115(20):4695-704.

(55) Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. J Clin Oncol 2009 Aug 20;27(24):3916-22.

(56) Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. World J Urol 2009 Oct;27(5):607-12.

(57) Gilberti C, Schenone M, Cortese P, Gallo F, Gastaldi E, Ninotta G. [Robot-asssisted laparoscopic radical prostatectomy (ralp). Oncological and functional findings after 90 cases]. Urologia 2009 Apr;76(2):87-9.

(58) Wiltz AL, Shikanov S, Eggener SE, Katz MH, Thong AE, Steinberg GD, et al. Robotic radical prostatectomy in overweight and obese patients: oncological and validated-functional outcomes. Urology 2009 Feb;73(2):316-22.

(59) Schmeller N, Keller H, Janetschek G. Head-to-head comparison of retropubic, perineal and laparoscopic radical prostatectomy. Int J Urol 2007 May;14(5):402-5.

(60) Buron C, Le VB, Cosset JM, Pommier P, Peiffert D, Delannes M, et al. Brachytherapy versus prostatectomy in localized prostate cancer: results of a French multicenter prospective medico-economic study. Int J Radiat Oncol Biol Phys 2007 Mar 1;67(3):812-22.

(61) Zorn KC, Mendiola FP, Rapp DE, Mikhail AA, Lin S, Orvieto MA, et al. Age-stratified outcomes after robotic-assisted laparoscopic radical prostatectomy. J Robot Surg 2007;1(2):125-32.

(62) Kuwata Y, Muneuchi G, Igawa HH, Tsukuda F, Inui M, Kakehi Y. Dissociation of sexual function and sexual bother following autologous sural nerve grafting during radical prostatectomy. Int J Urol 2007 Jun;14(6):510-4.

(63) Montgomery JS, Gayed BA, Hollenbeck BK, Daignault S, Sanda MG, Montie JE, et al. Obesity adversely affects health related quality of life before and after radical retropubic prostatectomy. J Urol 2006 Jul;176(1):257-61.

(64) van Gellekom MP, Moerland MA, van VM, Wijrdeman HK, Battermann JJ. Quality of life of patients after permanent prostate brachytherapy in relation to dosimetry. Int J Radiat Oncol Biol Phys 2005 Nov 1;63(3):772-80.

(65) Feigenberg SJ, Lee WR, Desilvio ML, Winter K, Pisansky TM, Bruner DW, et al. Health-related quality of life in men receiving prostate brachytherapy on RTOG 98-05. Int J Radiat Oncol Biol Phys 2005 Jul 15;62(4):956-64.

(66) Wagner AA, Cheng PJ, Carneiro A, Dovirak O, Khosla A, Taylor KN, et al. Clinical Use of Expanded Prostate Cancer Index Composite for Clinical Practice to Assess Patient Reported Prostate Cancer Quality of Life Following Robot-Assisted Radical Prostatectomy. J Urol 2017 Jan;197(1):109-14.

(67) Aluwini S, Busser WM, Alemayehu WG, Boormans JL, Kirkels WJ, Jansen PP, et al. Toxicity and quality of life after high-dose-rate brachytherapy as monotherapy for low- and intermediate-risk prostate cancer. Radiother Oncol 2015 Nov;117(2):252-7.

(68) Shoji S, Nakano M, Nagata Y, Usui Y, Terachi T, Uchida T. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: a prospective study. Int J Urol 2010 Aug;17(8):715-9.

(69) Marchand V, Bourdin S, Charbonnel C, Rio E, Munos C, Campion L, et al. No impairment of quality of life 18 months after high-dose intensity-modulated radiotherapy for localized prostate cancer: a prospective study. Int J Radiat Oncol Biol Phys 2010 Jul 15;77(4):1053-9.

(70) Freedland SJ, Haffner MC, Landis PK, Saigal CS, Carter HB. Obesity does not adversely affect health-related quality-of-life outcomes after anatomic retropubic radical prostatectomy. Urology 2005 Jun;65(6):1131-6.

(71) Chambers SK, Ng SK, Baade P, Aitken JF, Hyde MK, Wittert G, et al. Trajectories of quality of life, life satisfaction, and psychological adjustment after prostate cancer. Psychooncology 2016 Dec 10.

(72) Punnen S, Cowan JE, Dunn LB, Shumay DM, Carroll PR, Cooperberg MR. A longitudinal study of anxiety, depression and distress as predictors of sexual and urinary quality of life in men with prostate cancer. BJU Int 2013 Jul;112(2):E67-E75.

(73) Tanaka N, Fujimoto K, Asakawa I, Hirayama A, Yoneda T, Yoshida K, et al. Variations in health-related quality of life in Japanese men who underwent iodine-125 permanent brachytherapy for localized prostate cancer. Brachytherapy 2010 Oct;9(4):300-6.

(74) Jayadevappa R, Chhatre S, Whittington R, Bloom BS, Wein AJ, Malkowicz SB. Health-related quality of life and satisfaction with care among older men treated for prostate cancer with either radical prostatectomy or external beam radiation therapy. BJU Int 2006 May;97(5):955-62.

(75) Jayadevappa R, Johnson JC, Chhatre S, Wein AJ, Malkowicz SB. Ethnic variation in return to baseline values of patient-reported outcomes in older prostate cancer patients. Cancer 2007 Jun 1;109(11):2229-38.

(76) Jayadevappa R, Chhatre S, Wein AJ, Malkowicz SB. Predictors of patient reported outcomes and cost of care in younger men with newly diagnosed prostate cancer. Prostate 2009 Jul 1;69(10):1067-76.

(77) Dixit A, Tang C, Bydder S, Kedda MA, Vosikova E, Bharat C, et al. First Australian experience of treating localised prostate cancer patients with CyberKnife stereotactic radiotherapy: early PSA response, acute toxicity and quality of life. J Med Radiat Sci 2017 Mar 8.

(78) Tambas M, Agaoglu F, Iribas A, Guveli M, Dizdar Y, Okutan M, et al. Conventionally Fractionationed Volumetric Arc Therapy versus Hypofractionated Stereotactic Body Radiotherapy: Quality of Life, Side Effects, and Prostate-Specific Antigen Kinetics in Localized Prostate Cancer. Value Health Reg Issues 2016 Sep;10:91-9.

(79) Acar C, Schoffelmeer CC, Tillier C, de BW, van ME, van der Poel HG. Quality of life in patients with low-risk prostate cancer. A comparative retrospective study: brachytherapy versus robot-assisted laparoscopic prostatectomy versus active surveillance. J Endourol 2014 Jan;28(1):117-24.

(80) Mc CE, Mc SO, Prue G, Parahoo K, Bunting B, Sullivan JO, et al. Quality of life in men receiving radiotherapy and neo-adjuvant androgen deprivation for prostate cancer: results from a prospective longitudinal study. J Adv Nurs 2013 Jan;69(1):53-65.

(81) Jakobsson L, Fransson P. Patient Reported Outcome Measure (PROM) of Quality of Life After Prostatectomy - Results from a 5-Year Study. Open Nurs J 2013 Dec 27;7:165-73.

(82) Ratcliff CG, Cohen L, Pettaway CA, Parker PA. Treatment regret and quality of life following radical prostatectomy. Support Care Cancer 2013 Dec;21(12):3337-43.

(83) Jongkamp VG, Roeloffzen EM, Monninkhof EM, de Leeuw JR, Nijeholt AA, van VM. Brachytherapy for prostate cancer does not influence long-term depression rate. Brachytherapy 2012 Nov;11(6):495-501.

(84) Roeloffzen EM, Hinnen KA, Battermann JJ, Monninkhof EM, van Roermund JG, van Gellekom MP, et al. The impact of acute urinary retention after iodine-125 prostate brachytherapy on health-related quality of life. Int J Radiat Oncol Biol Phys 2010 Aug 1;77(5):1322-8.

(85) Roeloffzen EM, Lips IM, van Gellekom MP, van RJ, Frank SJ, Battermann JJ, et al. Health-related quality of life up to six years after (125)I brachytherapy for early-stage prostate cancer. Int J Radiat Oncol Biol Phys 2010 Mar 15;76(4):1054-60.

(86) Vordermark D, Noe M, Markert K, Wulf J, Muller G, Bratengeier K, et al. Prospective evaluation of quality of life after permanent prostate brachytherapy with I-125: importance of baseline symptoms and of prostate-V150. Radiother Oncol 2009 May;91(2):217-24.

(87) Davison BJ, So AI, Goldenberg SL. Quality of life, sexual function and decisional regret at 1 year after surgical treatment for localized prostate cancer. BJU Int 2007 Oct;100(4):780-5.

(88) Hoffman KE, Skinner H, Pugh TJ, Voong KR, Levy LB, Choi S, et al. Patient-reported Urinary, Bowel, and Sexual Function After Hypofractionated Intensity-modulated Radiation Therapy for Prostate Cancer: Results From a Randomized Trial. Am J Clin Oncol 2016 Sep 15.

(89) Derogar M, Dahlstrand H, Carlsson S, Bjartell A, Hugosson J, Axen E, et al. Preparedness for side effects and bother in symptomatic men after radical prostatectomy in a prospective, non-randomized trial, LAPPRO. Acta Oncol 2016 Dec;55(12):1467-76.

(90) Veccia A, Caffo O, Fellin G, Mussari S, Ziglio F, Maines F, et al. Impact of post-implant dosimetric parameters on the quality of life of patients treated with low-dose rate brachytherapy for localised prostate cancer: results of a single-institution study. Radiat Oncol 2015;10:130.

(91) Caffo O, Fellin G, Bolner A, Coccarelli F, Divan C, Frisinghelli M, et al. Prospective evaluation of quality of life after interstitial brachytherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2006 Sep 1;66(1):31-7.

(92) Kasperzyk JL, Shappley WV, III, Kenfield SA, Mucci LA, Kurth T, Ma J, et al. Watchful waiting and quality of life among prostate cancer survivors in the Physicians' Health Study. J Urol 2011 Nov;186(5):1862-7.

(93) Johansson E, Bill-Axelson A, Holmberg L, Onelov E, Johansson JE, Steineck G. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. Eur Urol 2009 Feb;55(2):422-30.

(94) Fransson P, Damber JE, Widmark A. Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer. Scand J Urol Nephrol 2009;43(2):119-26.

(95) Ku J, Krahn M, Trachtenberg J, Nesbitt M, Kalnin R, Lockwood G, et al. Changes in health utilities and health-related quality of life over 12 months following radical prostatectomy. Can Urol Assoc J 2009 Dec;3(6):445-52.

(96) Komiya A, Fujiuchi Y, Ito T, Morii A, Yasuda K, Watanabe A, et al. Early quality of life outcomes in patients with prostate cancer managed by high-dose-rate brachytherapy as monotherapy. Int J Urol 2013 Feb;20(2):185-92.

(97) Monga U, Kerrigan AJ, Thornby J, Monga TN, Zimmermann KP. Longitudinal study of quality of life in patients with localized prostate cancer undergoing radiotherapy. J Rehabil Res Dev 2005 May;42(3):391-9.

(98) Cohen A, Lapin B, Wang CH, Helfand B, Victorson D, Novakovic K. Variation in Testosterone Levels and Health-related Quality of Life in Men Diagnosed With Prostate Cancer on Active Surveillance. Urology 2016 May 11.

(99) Pearce SM, Wang CH, Victorson DE, Helfand BT, Novakovic KR, Brendler CB, et al. A Longitudinal Study of Predictors of Sexual Dysfunction in Men on Active Surveillance for Prostate Cancer. Sex Med 2015 Sep;3(3):156-64.

(100) Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al. Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. Urology 2006 Jan;67(1):125-30.

(101) Shahid N, Loblaw A, Chung HT, Cheung P, Szumacher E, Danjoux C, et al. Long-term Toxicity and Health-related Quality of Life after Single-fraction High Dose Rate Brachytherapy Boost and Hypofractionated External Beam Radiotherapy for Intermediate-risk Prostate Cancer. Clin Oncol (R Coll Radiol) 2017 Feb 9.

(102) Morton GC, Loblaw DA, Chung H, Tsang G, Sankreacha R, Deabreu A, et al. Health-related quality of life after single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2011 Aug 1;80(5):1299-305.

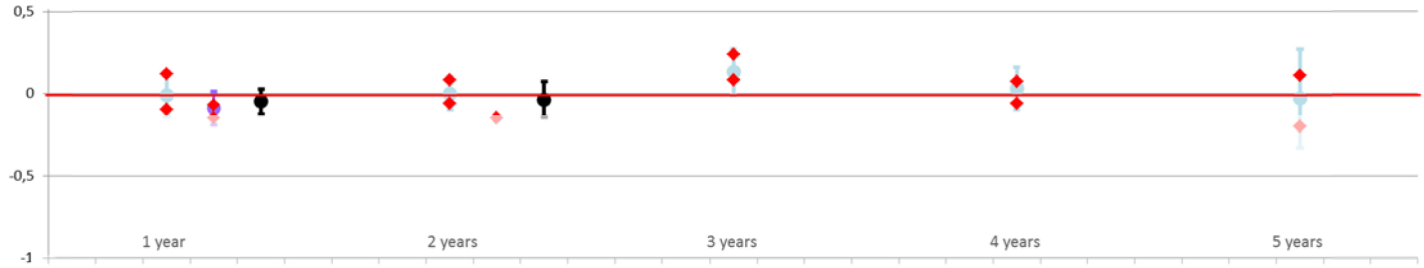
(103) Morton G, Loblaw A, Cheung P, Szumacher E, Chahal M, Danjoux C, et al. Is single fraction 15 Gy the preferred high dose-rate brachytherapy boost dose for prostate cancer? Radiother Oncol 2011 Sep;100(3):463-7.

(104) Morton GC, Loblaw DA, Sankreacha R, Deabreu A, Zhang L, Mamedov A, et al. Single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for men with intermediate-risk prostate cancer: analysis of short- and medium-term toxicity and quality of life. Int J Radiat Oncol Biol Phys 2010 Jul 1;77(3):811-7.

(105) Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol 2011 Apr;185(4):1246-54.

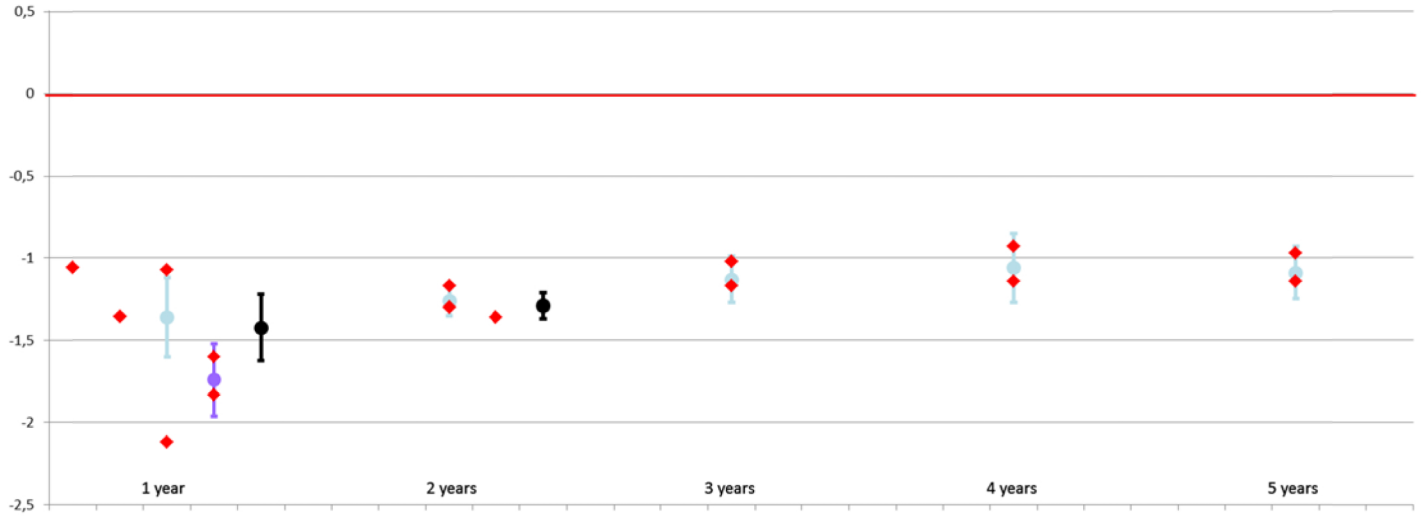
Supplementary material 4.1. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radical prostatectomy. Red diamonds represent maximum and minimum estimators from individual studies in each modality.

BOWEL SUMMARY



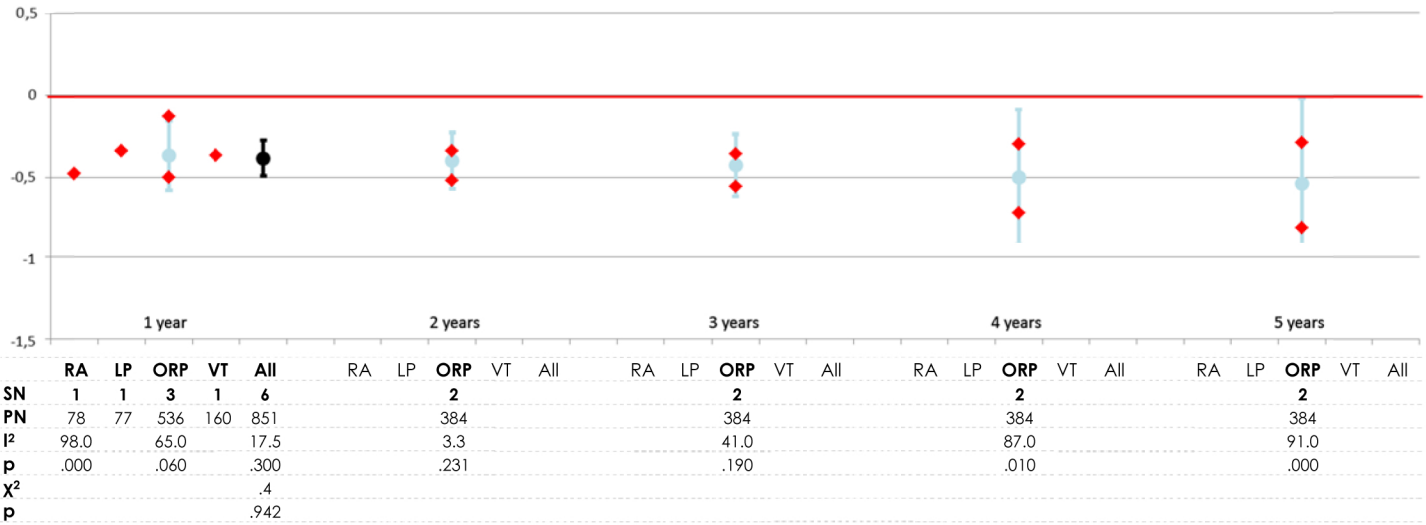
	1 year					2 years					3 years					4 years					5 years				
	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN			4	2	6			3	1	4			2					2					2		
PN			1008	695	1703			984	535	1519			381					381					381		
I^2			37.0	.0	14.5			13.0		5.2			9.0					.0					76.0		
p			.190	.510	.321			.320		.111			.290					.390					.040		
X^2					.7					3.7															
p					.417					.053															

SEXUAL SUMMARY



	1 year					2 years					3 years					4 years					5 years				
	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN	1	1	5	2	9			3	1	4			2					2					2		
PN	78	77	1131	676	1962			955	516	1471			368					368					368		
I^2			8.0	53.0	84.4			.0		.0			.0					45.0					16.0		
p			.001	.150	.001			.600		.501			.350					.180					.280		
X^2					29.0					1.3															
p					.001					.249															

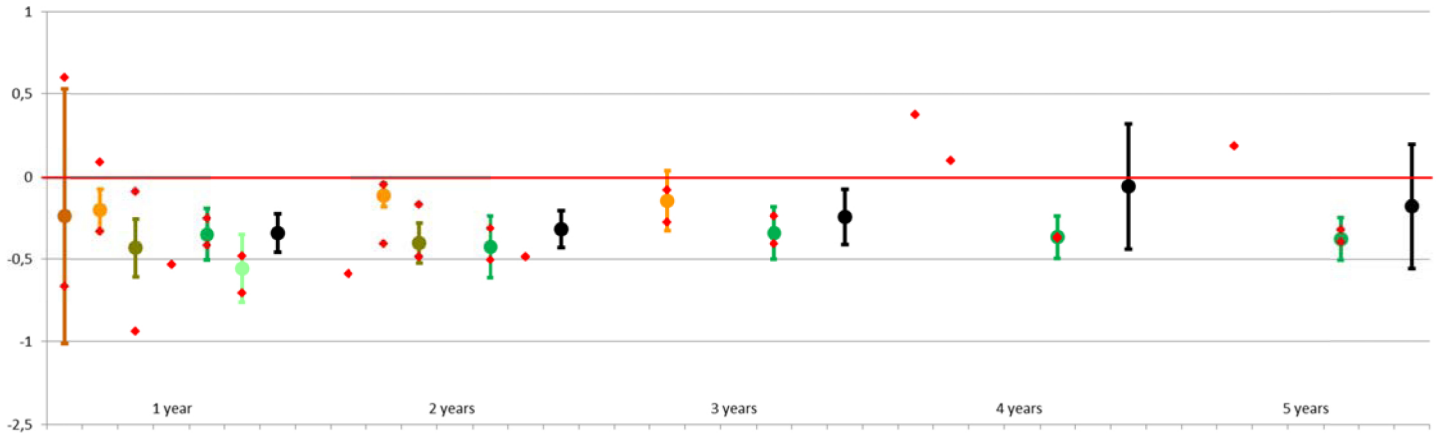
URINARY SUMMARY



	1 year					2 years					3 years					4 years					5 years				
	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All	RA	LP	ORP	VT	All
SN	1	1	3	1	6			2					2					2					2		
PN	78	77	536	160	851			384					384					384					384		
I^2	98.0		65.0		17.5			3.3					41.0					87.0					91.0		
p	.000		.060		.300			.231					.190					.010					.000		
X^2					.4																				
p					.942																				

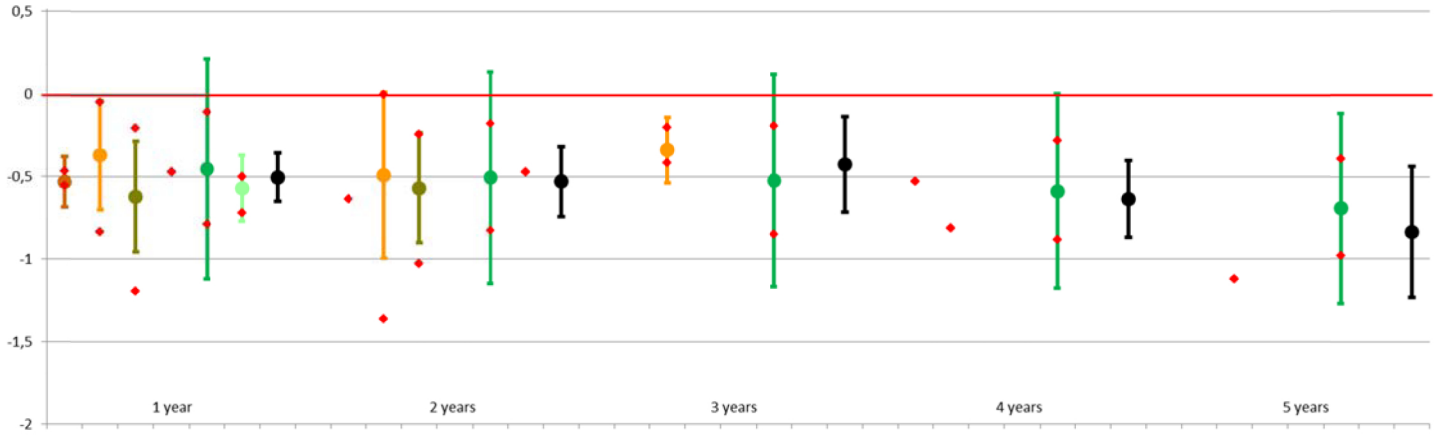
Supplementary material 4.2. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with radiotherapy. Red diamonds represent maximum and minimum estimators from individual studies in each modality.

BOWEL SUMMARY



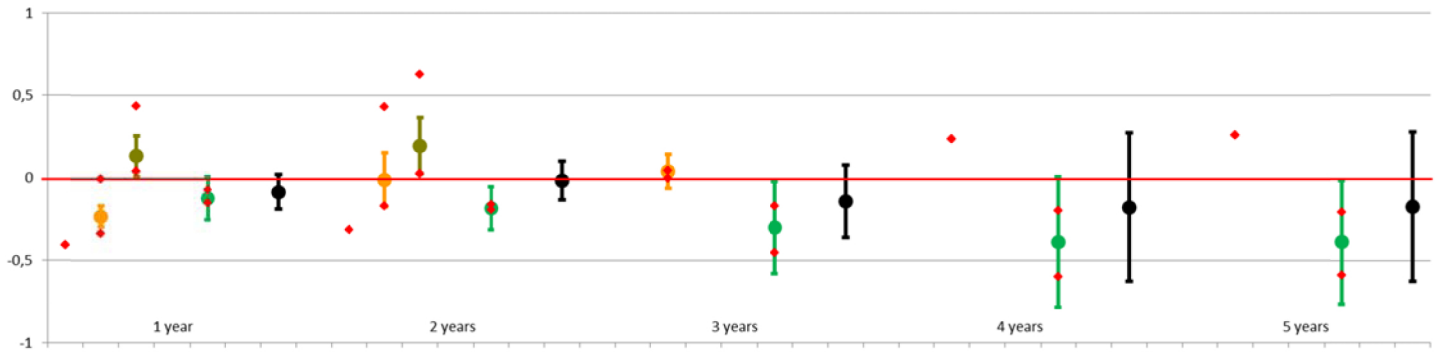
	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All
SN	3	6	8	1	2	2	22	1	6	5		2	1	15	2				2		4	1	1			2		4	1			2		3
PN	442	1234	695	26	413	381	3191	255	1009	507		413	292	2476	518				413		931	1158	271			413		1842	194			413		607
I²	96.3	39.7	56.8		25.3	36.6	78.2		.0	.0		46.4		73.1	46.3				28.8		7.0					.0		96.4				.0		91.7
p	.000	.141	.023		.247	.209	.000		.724	.719		.172		.000	.172				.236		.019					.940		.000				.597		.000
X²							15.5							45.2							6.7							82.8						23.8
p							.008							.000							.009							.000						.000

SEXUAL SUMMARY



	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All
SN	2	4	5	1	2	2	16	1	5	4		2	1	13	2				2		4	1	1			2		4	1			2		3
PN	348	1062	151	26	409	368	2364	255	907	109		409	279	1959	518				409		927	962	271			409		1642	194			409		603
I²	.0	92.4	6.8		95.6	32.1	82.4		95.4	5.7		95.2		89.7	55.8				95.2		9.3					94.3		88.8				94.0		91.9
p	.610	.000	.037		.000	.225	.000		.000	.108		.000		.000	.133				.000		.000					.000		.000				.000		.000
X²							11.3							3.2							8.0							9.1						7.8
p							.046							.518							.005							.011						.005

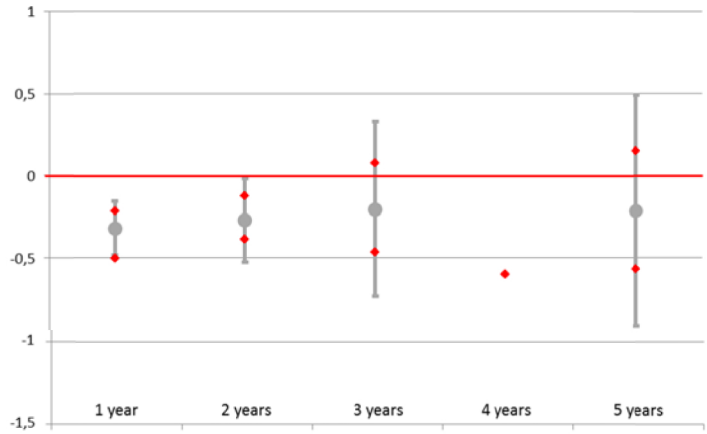
URINARY SUMMARY



	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All	PT	SB	IM	EB	3D	VT	All
SN	1	5	7		2		15	1	4	4		2		11	2				2		4	1				2		3	1			2		3
PN	255	1102	535		413		2305	255	829	347		413		1844	470				413		883		271			413		684	194			413		607
I²		.4	.0		.0		65.6		67.2	13.8		.0		69.2	.0				75.2		82.0					87.5		95.5				86.3		94.8
p		.404	.844		.575		.000		.027	.323		.797		.000	.814				.045		.001					.005		.000				.007		.000
X²							33.6							19.8							12.6							36.8						31.0
p							.000							.000							.000							.000						.000

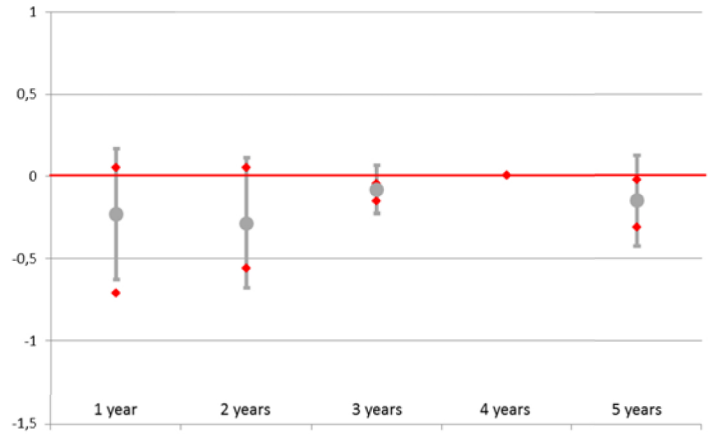
Supplementary material 4.3. Summary of pooled estimators (95% CI) obtained with meta-analyses from cohorts on patients who underwent treatment with Brachytherapy. Red diamonds represent maximum and minimum estimators from individual studies in each modality.

URINARY SUMMARY



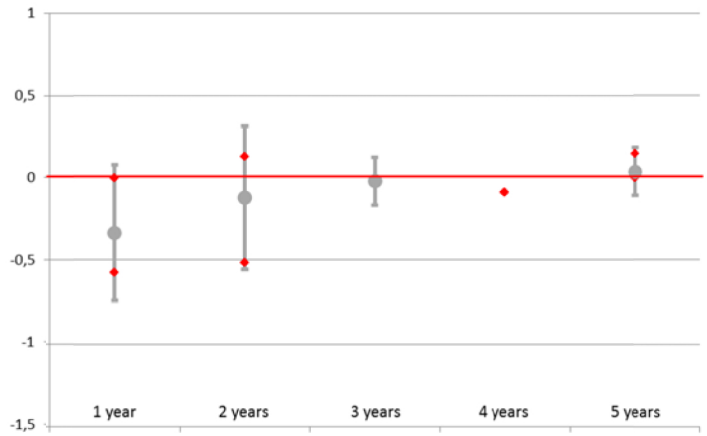
	1 year	2 years	3 years	4 years	5 years
SN	**4**	**2**	**2**	**1**	**2**
PN	469	392	392	272	392
I²	0.0%	63.8%	90.9%		94.6%
p	0.956	0.097	0.001		0.000

SEXUAL SUMMARY



	1 year	2 years	3 years	4 years	5 years
SN	**5**	**3**	**2**	**1**	**2**
PN	737	660	392	272	392
I²	87.8%	91.5%	0.0%		66.3%
p	0.000	0.000	0.511		0.085

BOWEL SUMMARY



	1 year	2 years	3 years	4 years	5 years
SN	**5**	**3**	**2**	**1**	**2**
PN	754	677	392	272	392
I²	88.9%	93.2%	0.0%		0.0%
p	0.000	0.000	0.975		0.363

Annex 2. EPIC Questionnaire

Número identificador: _____

Fecha: ___ / ___ / _____

Día Mes Año

EPIC

Este cuestionario ha sido diseñado para medir la Calidad de Vida en los pacientes con cáncer de próstata.

Para ayudarnos a conocer mejor sus problemas, es muy importante que responda con sinceridad a todas las preguntas.

Recuerde, tanto los datos médicos como la información que contiene este cuestionario será totalmente confidencial

HÁBITOS URINARIOS

Las siguientes preguntas se refieren a sus hábitos urinarios.
Le rogamos que tenga en cuenta **SÓLO LAS CUATRO ÚLTIMAS SEMANAS**.
Marque con una cruz ☒ la casilla correspondiente a cada pregunta.

1- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido perdidas de orina (SE LE ESCAPA EL PIPI)?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

2- Durante las **4 últimas semanas**, ¿con qué frecuencia ha orinado sangre?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

3- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido dolor o escozor al orinar?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

4- ¿Cuál de las frases siguientes describe mejor cómo ha controlado la orina durante las 4 **últimas semanas**?

- Ningún control, se me escapa siempre ☐ 1
- Pérdidas frecuentes ☐ 2
- Pérdidas sólo de vez en cuando ☐ 3
- Control total, no se me escapa nunca ☐ 4

5- Durante las 4 **últimas semanas**, habitualmente, ¿cuántas compresas o pañales para adultos ha utilizado al día para controlar las pérdidas de orina?

- Ninguna ☐ 0
- 1 compresa al día ☐ 1
- 2 compresas al día ☐ 2
- 3 o más compresas al día ☐ 3

6- Durante las **4 últimas semanas**, ¿hasta qué punto ha sido un problema para usted cada uno de los siguientes aspectos?
Marque con una cruz una casilla para cada línea.

	Ningún problema	Un proble-ma muy pequeño	Un problema pequeño	Un problema moderado	Un problema grande
a - Las pérdidas de orina (ESCAPÁRSELE EL PIPI)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
b - El dolor o escozor al orinar	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
c - Sangre en la orina	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
d - Chorro de orina débil o vaciado incompleto de la vejiga	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
e - Despertarse para orinar	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
f - Necesidad de orinar con frecuencia durante el día	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

7- En general, ¿hasta qué punto sus hábitos urinarios han sido un problema para usted durante las **4 últimas semanas**?

- Ningún problema ☐ 1
- Un problema muy pequeño ☐ 2
- Un problema pequeño ☐ 3
- Un problema moderado ☐ 4
- Un problema grande ☐ 5

HÁBITOS INTESTINALES

Las siguientes preguntas se refieren a sus hábitos intestinales y al dolor abdominal. Le rogamos que tenga en cuenta **SÓLO LAS CUATRO ÚLTIMAS SEMANAS**.
Marque con una cruz ☒ la casilla correspondiente a cada pregunta.

8- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido ganas de ir de vientre sin poder hacerlo?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

9- ¿Con qué frecuencia se le han escapado las deposiciones (CACAS)?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

10- Durante las **4 últimas semanas**, ¿con qué frecuencia ha hecho sus deposiciones (CACAS) blandas, sueltas o líquidas?

- Nunca ☐ 1
- Pocas veces ☐ 2
- Aproximadamente la mitad de las veces ☐ 3
- Casi siempre ☐ 4
- Siempre ☐ 5

11- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido sangre en las deposiciones (CACAS)?

- Nunca ☐ 1
- Pocas veces ☐ 2
- Aproximadamente la mitad de las veces ☐ 3
- Casi siempre ☐ 4
- Siempre ☐ 5

12- **Durante las 4 últimas** semanas, ¿con qué frecuencia ha tenido dolor al ir de vientre?

- Nunca ☐ 1
- Pocas veces ☐ 2
- Aproximadamente la mitad de las veces ☐ 3
- Casi siempre ☐ 4
- Siempre ☐ 5

13- **Durante las 4 últimas semanas**, habitualmente ¿cuántas veces ha ido de vientre al día?

- Dos o menos ☐ 1
- Tres o cuatro ☐ 2
- Cinco o más ☐ 3

14- **Durante las 4 últimas semanas**, ¿con qué frecuencia ha tenido retortijones en el abdomen (BARRIGA), el recto, la pelvis o bajo vientre?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

15- **Durante las 4 últimas semanas**, ¿hasta qué punto ha sido un problema para usted cada uno de los siguientes aspectos?
Marque con una cruz una casilla para cada línea.

	Ningún problema	Un proble-ma muy pequeño	Un problema pequeño	Un problema moderado	Un problema grande
a - Ganas urgentes de ir de vientre	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
b - Ir de vientre con mayor frecuencia	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
c - Deposiciones (CACAS) líquidas	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
d - Pérdida de control (no poder retener las deposiciones-CACAS)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
e - Deposiciones (CACAS) con sangre	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
f - Dolor en abdomen (BARRIGA), recto, pelvis o bajo vientre	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

16- En general, ¿hasta qué punto sus hábitos intestinales han sido un problema para usted durante las **4 últimas semanas**?

- Ningún problema ☐ 1
- Un problema muy pequeño ☐ 2
- Un problema pequeño ☐ 3
- Un problema moderado ☐ 4
- Un problema grande ☐ 5

FUNCIÓN HORMONAL

Las siguientes preguntas se refieren a su estado hormonal. Le rogamos que tenga en cuenta **SÓLO LAS CUATRO ÚLTIMAS SEMANAS**.
Marque con una cruz ☒ la casilla correspondiente a cada pregunta.

17- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido sofocos?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

18- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido los pechos o pezones sensibles o doloridos?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

19- Durante las **4 últimas semanas**, ¿con qué frecuencia se ha sentido deprimido?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

20- Durante las **4 últimas semana**s, ¿con qué frecuencia se ha sentido que le faltaba energía?

- Más de una vez al día ☐ 1
- Aproximadamente una vez al día ☐ 2
- Más de una vez a la semana ☐ 3
- Aproximadamente una vez a la semana ☐ 4
- Nunca o casi nunca ☐ 5

21- Durante las **4 últimas semanas**, ¿qué cambios de peso ha tenido?

- Aumento cinco kilos o más ☐ 1
- Aumento menos de cinco ☐ 2
- Ningún cambio de peso ☐ 3
- Perdida de menos de cinco kilos ☐ 4
- Perdida de cinco kilos o más ☐ 5

22- Durante las **4 últimas semanas**, ¿hasta qué punto ha sido un problema para usted cada uno de los siguientes aspectos?
Marque con una cruz una casilla para cada línea.

	Ningún problema	Un proble-ma muy pequeño	Un problema pequeño	Un problema moderado	Un problema grande
a - Sofocos	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
b - Sensibilidad o dolor/ aumento de los pechos	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
c - Pérdida de vello corporal	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
d - Sentirse deprimido	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
e - Falta de energía	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
f - Cambio de peso	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

ACTIVIDAD SEXUAL

Las siguientes preguntas se refieren a su actividad sexual y a su satisfacción sexual **actual**. Muchas de estas preguntas son muy íntimas, pero nos ayudarán a comprender aspectos importantes a los que usted se enfrenta a diario.

Recuerde que LA INFORMACIÓN DE ESTA ENTREVISTA ES COMPLETAMENTE CONFIDENCIAL. Le rogamos que tenga en cuenta **SÓLO LAS CUATRO ÚLTIMAS SEMANAS** y que conteste con sinceridad.
Marque con una cruz ☒ la casilla correspondiente a cada pregunta.

23- Durante las **4 últimas semanas**, ¿cómo calificaría usted cada uno de los siguientes aspectos? *Marque con una cruz una casilla para cada línea.*

	Muy malo o ninguno	Malo	Regular	Bueno	Muy bueno
a - Su deseo sexual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Muy mala o ninguna	Mala	Regular	Buena	Muy buena
b - Su capacidad para tener una erección	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c - Su capacidad para alcanzar el orgasmo (clímax)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

24- Durante las **4 últimas semanas** ¿cómo describiría usted la CALIDAD habitual de sus erecciones?

Ninguna calidad ☐ 1

Sin rigidez o dureza suficiente para tener cualquier tipo de actividad sexual ☐ 2

Con suficiente rigidez o dureza para masturbarse y para algunos juegos preliminares solamente ☐ 3

Con rigidez o dureza suficiente para el acto sexual (coito) ☐ 4

25- Durante las **4 últimas semanas** ¿cómo describiría usted la FRECUENCIA de sus erecciones?

NUNCA he tenido una erección cuando he querido tenerla ☐ 1

He tenido una erección MENOS DE LA MITAD de las veces que he querido tenerla ☐ 2

He tenido una erección APROXIMADAMENTE LA MITAD de las veces que he querido tenerla ☐ 3

He tenido una erección MÁS DE LA MITAD de las veces que he querido tenerla ☐ 4

He tenido una erección SIEMPRE que he querido tenerla ☐ 5

26- Durante las **4 últimas semanas**, ¿con qué frecuencia se ha despertado por la mañana o a media noche con una erección?

Nunca ☐ 1
Menos de una vez a la semana ☐ 2
Aproximadamente una vez a la semana ☐ 3
Varias veces por semana ☐ 4
Cada día ☐ 5

27- Durante las **4 últimas semanas**, ¿con qué frecuencia ha tenido algún tipo de actividad sexual?

Nunca ☐ 1
Menos de una vez a la semana ☐ 2
Aproximadamente una vez a la semana ☐ 3
Varias veces por semana ☐ 4
Cada día ☐ 5

28- Durante las **4 últimas semanas**, ¿con qué frecuencia ha realizado el acto sexual (coito)?

Nunca ☐ 1
Menos de una vez a la semana ☐ 2
Aproximadamente una vez a la semana ☐ 3
Varias veces por semana ☐ 4
Cada día ☐ 5

29- En general, ¿cómo calificaría su actividad sexual durante las **4 últimas semanas**?

Muy mala ☐ 1
Mala ☐ 2
Regular ☐ 3
Buena ☐ 4
Muy buena ☐ 5

30- Durante las **4 últimas semanas**, ¿hasta qué punto ha sido un problema para usted cada uno de los siguientes aspectos?
Marque con una cruz una casilla para cada línea.

	Ningún problema	Un proble-ma muy pequeño	Un problema pequeño	Un problema moderado	Un problema grande
a - Su deseo sexual	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
b - Su capacidad para tener una erección	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
c - Su capacidad para alcanzar el orgasmo (clímax)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

31. En general, ¿hasta qué punto su actividad sexual o falta de ella ha sido un problema para usted durante las **4 últimas semanas**?

Ningún problema ☐ 1
Un problema muy pequeño ☐ 2
Un problema pequeño ☐ 3
Un problema moderado ☐ 4
Un problema grande ☐ 5

MUCHAS GRACIAS POR SU COLABORACIÓN

Annex 3. Spanish Version PORPUS Questionnaire

ESCALA DE UTILIDADES ORIENTADA AL PACIENTE CON PATOLOGÍA PROSTÁTICA

1. **Dolor y molestias físicas** (dolor, sofocos, hinchazón dolorosa de los pechos, náuseas, somnolencia).

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Sin dolor ni molestias físicas.
Dolor o molestias físicas leves que no limitan mis actividades (por ejemplo: trabajo, sociales, sexuales).
Dolor o molestias físicas moderadas que limitan un poco mis actividades.
Dolor o molestias físicas de moderadas a graves que limitan algunas de mis actividades.
Dolor o molestias físicas graves que limitan muchas de mis actividades.

2. **Energía.**

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Muy lleno de energía, con mucha vitalidad.
Con suficiente energía, sin limitación en mis actividades (por ejemplo: trabajo, sociales, sexuales).
Disminución moderada de energía o vitalidad que limita un poco mis actividades.
Generalmente bajo de energía o vitalidad, limitando algunas de mis actividades.
Sin energía ni vitalidad en absoluto. Me siento agotado, limitando muchas de mis actividades.

3. **Apoyo de la Familia y los Amigos.**

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Casi siempre me siento apoyado por mi pareja, familia y amigos.
Muchas veces me siento apoyado por mi pareja, familia y amigos.
Algunas veces me siento apoyado por mi pareja, familia y amigos.
Casi nunca me siento apoyado por mi pareja, familia y amigos.

4. **Comunicación con mi medico (el que realiza los controles del tumor de próstata, que puede ser un especialista o el médico de cabecera).**

Por favor, escoja la frase que mejor describa cómo se ha sentido en sus dos últimas visitas médicas (Elija una):

Siempre puedo explicarle a mi médico lo que me preocupa y recibo toda la información o los consejos necesarios.
Casi siempre puedo explicarle a mi médico lo que me preocupa y recibo toda la información o los consejos necesarios.
Algunas veces puedo explicarle a mi médico lo que me preocupa y recibo toda la información o los consejos necesarios.
Casi nunca puedo explicarle a mi médico lo que me preocupa ni recibo toda la información o los consejos necesarios.

5. Bienestar emocional.

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Generalmente feliz, sin preocupaciones, tristeza ni frustración.
Con alguna preocupación, tristeza o frustración.
Moderado nivel de preocupaciones, tristeza o frustración.
Mucha preocupación, tristeza o frustración.
Muchísima preocupación, tristeza o frustración.

6. Frecuencia urinaria (necesidad de orinar frecuentemente durante el día o la noche) y urgencia urinaria (dificultad de "aguantarse" o de retrasar el momento de orinar desde el momento de sentir ganas)

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Sin necesidad de orinar frecuentemente ni urgencia urinaria.
Necesidad de orinar con cierta frecuencia o un poco de urgencia urinaria, que no interfiere con el sueño ni otras actividades (por ejemplo: trabajo, social); no necesito planificar con antelación
Necesidad de orinar con frecuencia o urgencia urinaria que interfiere con el sueño o con otras actividades; puedo necesitar planificar con antelación.
Necesidad de orinar con mucha frecuencia o mucha urgencia urinaria; necesito estar cerca de un lavabo casi siempre.
Necesidad de orinar con muchísima frecuencia o muchísima urgencia urinaria; necesito estar cerca de un lavabo siempre

7. Pérdida/ Escapes de orina.

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Nunca, en ningún caso tengo pérdidas o escapes de orina.
Casi nunca tengo pérdidas o escapes de orina, no interfieren con mis actividades (por ejemplo: trabajo, social, sexual, sueño).
Algunas veces tengo pérdidas o escapes ocasionales de orina, que interfieren con pocas actividades.
Muchas veces tengo pérdidas o escapes de orina que interfieren con algunas actividades.
Casi siempre tengo pérdidas o escapes de orina que interfieren con muchas actividades.
Necesito una pinza, sonda o colector urinario debido a las pérdidas o escapes de orina.

8. Función sexual (problemas para lograr o mantener una erección)

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Erecciones completas, suficientes para lograr la penetración.
Erecciones suficientes para lograr la penetración, pero con cierta disminución de la rigidez.
Erecciones suficientes sólo para la masturbación o juegos preliminares sexuales.
Erecciones, pero no suficientes para ninguna actividad sexual.
Sin Ningún tipo de erección.

9. Interés o apetito sexual.

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

El mismo interés (ganas) o apetito sexual habitual.
Pequeña disminución del interés (ganas) o apetito sexual.
Moderada disminución del interés (ganas) o apetito sexual.
Importante disminución del interés (ganas) o apetito sexual.
Sin ningún interés ni apetito sexual.

10. Problemas intestinales: diarrea, molestias en el recto o ano (dolor, ardor o irritación) o estreñimiento.

Por favor, escoja la frase que mejor describa cómo se ha encontrado estas últimas dos semanas (Elija una):

Sin diarrea, ni molestias en recto o ano ni estreñimiento.
Algunas veces tengo diarrea, molestias en recto o ano, o estreñimiento.

Muchas veces tengo diarrea molestias en recto o ano, o estreñimiento.
Casi siempre tengo diarrea, molestias en recto o ano o estreñimiento.