Economic Evaluation of Treatments for Patients with Localized Prostate Cancer

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TESI DOCTORAL UPF / 2015

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A mis hijas, dueñas del tiempo que dediqué a este trabajo.

Acknowledgements

Poder depositar la tesis doctoral refuerza en positivo aquélla decisión del año 2007 de emigrar de Uruguay para poder crecer profesionalmente y de vivir en Barcelona por conjugar intereses académicos y cercanía con mi hermano y su familia.

Siete años en Barcelona me dieron mucho más de lo que imaginaba. Me dieron la enorme oportunidad de haber pasado por la "URSS" del IMIM-Hospital del Mar, de cursar el Master en Salud Pública con una beca de la Fundació IMIM y hasta de haber regresado a Montevideo por primera vez luego de la emigración, a la Reunión de ISOQOL en 2008. Me dieron la oportunidad de trabajar en un entorno multinacional, de aprender muchísimo, conocer personas muy valiosas y hasta me dieron hijas gemelas.

Quiero agradecer especialmente a Montse por la primera oportunidad, y todas las que le siguieron. Al Carrer Rocafort 49 vam passar de ser dos a quatre. I aixö es per sempre. Gracias también por la confianza de que seguiría para adelante, aún con todos los cambios de rumbo que emprendí. Entre otras cosas, aprendí que para terminar algo, por más prisa que se tenga, se ha de hacer una cosa atrás de la otra, desde el principio. Y acá estamos.

A Jordi Alonso por el lugar en su casa y sus clases maravillosas. A todos los demás miembros de la Unitat de Recerca en Serveis Sanitaris por su apoyo y buena onda. Y en particular a Yolanda por ser mi amiga durante mi estadía, a Mónica por ser mi partner los últimos años y a Jorge por un estupendo trabajo remoto sin siquiera conocernos. A Olatz tanto por la colaboración académica como por los mimos y a Àngels, Áurea, Gemma y todos quienes corrieron y dedicaron adrenalina para sacar adelante la última parte del trabajo, ponerlo todo en orden y hasta entregarlo en mi nombre. Hubiera sido imposible sin el empeño que pusieron chicas y me honra que le hubieran dedicado tanto esfuerzo.

A Francesc Cots por la cotutoría y la confianza en mi trabajo. A los investigadores del *Grupo Multicéntrico Español de Cáncer de Próstata Localizado* por haber emprendido este estudio que me dio el marco para la tesis, y a todos los pacientes por su consentimiento y continuada participación.

Hay otras personas a quienes también debo su apoyo académico y personal y quienes también me ayudaron mucho a crecer profesionalmente como para llegar a este momento. A Vicente Ortún, porque en aquella primera visita que le hice en su despacho de la UPF en

2006 antes de emigrar, y sin él saberlo, me terminó de convencer que la Economía de la Salud valía la pena y porque me dio su apoyo una vez que llegué a Barcelona, fue muy importante para mí. Ojalá y sigámonos viendo por el mundo, es un lujo. A Nuria González-Rojas Guix por la primera oportunidad de trabajar en el sector farmacéutico y a Alfredo Gracia por confiarme tan buenos proyectos. Lo que aprendí y las cosas que generé allí me han hecho crecer muchísimo.

En lo personal he de agradecer a mi madre, inagotable. Bien dice ella misma que "amor de madre, abismo sin medida". A Rodrigo por su existencia, por las charlas, y sobre todo por los sobrinos, que tampoco hubieran sido posibles sin tu emigración, hermano. Rodrigo y Matías Becerra fueron el 70% de la decisión del destino y ahora Catalunya es y seguirá siendo parte de nosotros. A mis primas Graciela, Ines y Patricia por su apoyo durante la crisis y por estar siempre. Sin ustedes en marzo de 2015, no hubiera llegado a escribir esto en noviembre. A Enzo, mi esposo, quien desde que me conoce confía en mí más que yo misma y me apoya en cada emprendimiento. Por habernos creído juntos la posibilidad de vivir fuera de nuestro país y por haber regresado cuando la ecuación resultó en que volver a Uruguay parecía ser más eficiente, emocionalmente hablando. Por haber puesto el freno a volver sólo con ganas, aunque ahora todavía sea difícil. En Bartolito escribí mi tesina de grado y ahora escribo mi tesis doctoral. Y finalmente, a mis hijas Irene y Martina que aunque de momento no entienden por qué mamá estudia, no lo cuestionan nunca y una y otra vez me han cedido su tiempo.

Desde mis primeros cursos de Metodología de la Investigación en Sociología en los años noventa hasta el día de hoy me he caracterizado por transitar diferentes disciplinas, pero siempre atraída por el rigor científico y la ciencia; que poco a poco fui aceptando como relativa, incompleta, pero por eso mismo más desafiante. A un año de haber regresado a vivir a mi país aún no sé qué tanto podré seguir investigando, pero no seré yo quien deje de intentarlo.

MOLTES GRÀCIES A TOTS!

Abstract

The global aim of this thesis was to assess the efficiency, from the health systems perspective, of the most established treatments for patients diagnosed with localized prostate cancer. The "Spanish Multicentric Study of Clinically Localized Prostate Cancer" is an observational, prospective study that consecutively recruited patients in 10 centers in Spain between 2003 and 2005, treated either with radical prostatectomy, prostate brachytherapy or external 3D conformal radiotherapy, and followed intensively during the first twelve months and yearly thereafter until the 10-year post-treatment point. What becomes outstanding among the results is that, despite slight differences between treatments costs, each of the alternatives could be considered economically attractive for patients with localized prostate cancer at low and intermediate risk.

Resumen

El objetivo global de esta tesis fue evaluar la eficiencia, desde la perspectiva de los sistemas de salud, de los tratamientos más establecidos para los pacientes diagnosticados con cáncer de próstata localizado. El "Estudio Multicéntrico Español de cáncer de próstata localizado" es un estudio observacional, prospectivo con pacientes reclutados consecutivamente en 10 centros en España entre 2003 y 2005, tratados con prostatectomía radical retropúbica, braquiterapia prostática o radioterapia conformacional externa 3D, y seguidos intensivamente durante los primero doce meses y anualmente a partir de entonces, hasta 10 años post-tratamiento. Lo que destaca entre los resultados es que, a pesar de ligeras diferencias entre los costes de los tratamientos, cualquiera de las alternativas podría considerarse económicamente atractiva para los pacientes con cáncer de próstata localizado de riesgo bajo e intermedio.

Preface

"If we are ever going to get the 'optimum' results from our national expenditure on the NHS we must finally be able to express the results in the form of the benefit and the cost to the population of a particular type of activity, and the increased benefit that would be obtained if more money were made available."

Archie Cochrane's Introduction to his classic Effectiveness and Efficiency: Random Reflections on Health Services.

Nuffield Provincial Hospitals Trust, 1972

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 presented as a compendium of scientific manuscripts that are either already published in indexed peer reviewed journals or are currently under revision.

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

Along the first part, a narrative review summarizes the general background of the work. It describes the epidemiology and available treatment options for patients with localized prostate cancer, as well as a general description of cost estimation in healthcare and of conducting an economic evaluation.

The main body of the thesis is composed by three scientific manuscripts.

The first manuscript deals with the estimation of the total healthcare cost of each treatment 6 months after the intervention, which is typically considered the initial cost of treatment.

It describes the methods of micro-cost calculation and cost comparison in a subsample of patients of the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort.

> *Becerra Bachino V, Cots F, Guedea F, Pera J, Boladeras A, Aguiló F, Suárez JF, Gallo P, Murgui L, Pont A, Cunillera O, Pardo Y, Ferrer M; Grupo Multicéntrico Español de Cáncer de Próstata Organoconfinado.* **Cost comparison of three treatments for localized prostate cancer in Spain: radical prostatectomy, prostate brachytherapy and external 3D conformal radiotherapy.** *Gac Sanit. 2011Jan-Feb;25(1):35-43.*

The second manuscript presents a systematic literature review conducted to assess the evidence currently available from European economic evaluations of treatments for localized prostate cancer.

> *Becerra V, Ávila M, Jimenez J, Cortes-Sanabria L, Pardo Y, Garin O, Pont A, Alonso J, Cots F, Ferrer M.* **Economic Evaluation of Treatments for Patients with Localized Prostate Cancer in Europe: A Systematic Review**. *(Submitted)*

The third manuscript presents the cost-effectiveness and cost-utility analysis of these three main treatments, from the perspective of the Spanish Health System and based on 10 years of primary data from the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort.

> *Becerra V, Garin O, Guedea F, Suárez JF, Fernández P, Macías V, Mariño A, Hervás A, Herruzo I, Ortiz MJ, Ponce de León J, Sancho G, Ávila M, Pont A, Alonso J, Cots F, Ferrer M and the Multicentric Spanish Group of Clinically Localized Prostate Cancer.* **Economic Evaluation of localized prostate cancer treatments: Ten year follow - up cohort study.** *(Under review)*

I hope the results of this doctoral thesis will contribute to better determine the appropriate treatment for each patient diagnosed with localized prostate cancer. I also hope that other research projects continue the investigation around the efficiency of available treatments, specially noticing that high quality evidence on the efficacy and effectiveness of each treatment alternative is the base for a high quality economic evaluation. I further hope that this work can make practitioners and health care policy makers aware of the benefit of assessing economic aspects of their daily issues.

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1. BACKGROUND

1.1 Clinically Localized Prostate Cancer

a) Epidemiology

Prostate cancer is the second most common diagnosed tumor in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, with almost 70% of the cases occurring in more developed regions and 345.000 cases in the European Union. (Bray et al. 2013). In Spain, prostate cancer ranks first in incidence and in third place of cancer-related deaths (Ferlay et al. 2014) The estimated age-standardized rates of cancer incidence for EU-27 for 2012 were 110.8 per 100,000, compared to 96.8 in Spain (Ferlay et al. 2013).

Incidence of prostate cancer has been rising due to a higher life expectancy and the increasing use of prostate-specific antigen (PSA) screening allowing an early detection, which led to a migration of the diagnosis to early stages of the disease, with patients diagnosed at younger ages and mostly at clinical asymptomatic disease stages (Jemal et al.) (Shao et al. 2009). Nowadays, about 90% of patients are diagnosed at these localized stages of disease (Mottet et al. 2015). Recently, recommendations against PSA screening have been related to a reduction in early-stage prostate cancer incidence and PSA-based screening rates in men 50 years and older with significant public health implications (Jemal et al. 2015).

The European mean age-standardized 5-year relative survival for prostate cancer increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 (De Angelis et al. 2014). These survival advances can be partly related to earlier diagnosis, as well as to better diagnostic imaging, genetic profiling, and treatment techniques. The 5-year relative survival of 84.7% in Spain is slightly above the EU mean (83.4%) (De Angelis 2014).

There are only three well-established risk factors for prostate cancer (increasing age, ethnic origin, and genetic predisposition), and all are non-modifiable. There is currently no high-level evidence that preventative measures may reduce the risk of prostate cancer (A Heidenreich et al. 2011).

Localized prostate cancer may be asymptomatic, but treatments may have substantial side effects. Available evidence, even if scarce (Shao et al. 2009) suggests a high relative survival rate regardless of the treatment option.

b) Diagnosis and most established treatment options

Clinical diagnosis is usually suspected on the basis of digital rectal examination and/or prostate-specific antigen (PSA) levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or unexpected discovery from specimens from TURP or prostatectomy for benign prostatic enlargement (A Heidenreich et al. 2011).

In 1994, the Food and Drug Administration approved the use of the PSA test (in conjunction with DRE) to test asymptomatic men for prostate cancer. Since then, PSA screening has been widely adopted and was associated with increases in prostate cancer incidence (Potosky et al. 1995). Currently, there is an important debate on prostate cancer screening (Dahm, Neuberger, and Ilic 2013; Castle 2015; Cuzick and Thorat 2015) and, so far, the available evidence is inconsistent (Gerald L Andriole et al. 2009; G. L. Andriole et al. 2012; Schröder et al. 2009; Schröder et al. 2012; Roobol et al. 2013) or does not find a significant reduction in prostate cancer-specific or overall mortality in the treatment of screen-detected cases (Ilic et al. 2013). Moreover, there is substantial information that over diagnosis and overtreatment are common and are associated with frequent medium to severe treatment-related harms (Ilic et al. 2013; Hayes and Barry 2014).

Recommendations regarding PSA screening have been changing substantially over the past recent years. The US Preventive Services Task Force (USPSTF) recommended against PSA screening for all men in 2012 (Moyer 2012). Current clinical guidelines (Carter et al. 2013; Qaseem et al. 2013; Axel Heidenreich et al. 2014; Wolf et al.) have narrowed their recommendations to specific age intervals and life expectancy, based on shared decision-making, man's preferences and consideration of longer intervals than one year between PSA screenings. Table 1 reproduces a recently published synthesis of recommendations of major societies (Hayes and Barry 2014).

Table 1: Screening Recommendations of Major Societies (Limited to Guidelines Based on Systematic Reviews and Updated Since the Publication of the European Randomized Study of Screening for Prostate Cancer and Prostate, Lung, Colorectal, and Ovarian Screening Trial Randomized Controlled Trials)

Organization	Who Should Be Screened	Screening Interval	Basis
US Preventive Services Task Force, 2012 (Moyer 2012)	Screening should not be offered		Systematic review
American Urological Association, 2013 (Carter et al. 2013)	Men aged 55-69 y or ≥70 y with >10- to 15-y life expectancy: use shared decision-making approach Men at higher risk <55 y: individualize approach	Consider 2-y interval over annual screening; may individualize intervals based on initial PSA	Systematic review and meta-analysis of the literature, 1995-2013
American Society of Clinical Oncology, 2012 (Basch et al. 2012)	Men with life expectancy >10 y: use shared decision-making approach		Updating of Agency for Healthcare Research and Quality literature review; PubMed search through 2012; expert opinion
American Cancer Society, updated 2010 (Wolf et al.)	Men aged >50 y at average risk with >10-y life expectancy: use shared decision-making Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y	Base interval on initial PSA: annual if ≥2.5 ng/mL; biannual if <2.5 ng/mL Biopsy recommended for all men with PSA>4 ng/mL Biopsy for PSA levels between 2.5 and 4 ng/mL should be individualized	Systematic review of the literature and consensus process

Organization	Who Should Be Screened	Screening Interval	Basis
American College of Physicians, 2013 (Qaseem et al. 2013)	Men aged 50-69 y with life expectancy >10-15 y: use shared decision-making approach. Men at higher risk (black, first-degree relative diagnosed before 65 y) at 45 y Men at appreciably higher risk (multiple family members diagnosed before 65 y) at 40 y	Consider longer intervals than 1 y between screening PSAs	Review of available guidelines
Canadian Urologic Society, 2011 (Izawa et al. 2011)	Men ≥50 y with a 10-y life expectancy: use shared decision-making approach Men ≥40 y at high risk Consider baseline PSA in men 40-49 y	Consider intervals up to every 4 y	Systematic literature search 2004-2010
European Association of Urology, 2013 (Axel Heidenreich et al. 2013)	Baseline PSA≥40-45 y	Risk-adapted strategy based on initial PSA in men with life expectancy >10 y Screening intervals every 2-4 y for men with serum PSA>1.0 μg/L at 45-59 y and up to 8 y in men with serum PSA <1 μg/L	Systematic literature review and meta-analysis

Abbreviation: PSA, prostate-specific antigen.

Reproduced from: (Hayes and Barry 2014)

For staging and risk classification, the 2009 Tumor Node Metastasis (TNM) classification and the European Association Urology risk group classification (based on D'Amico's classification system) are used in Europe (Axel Heidenreich et al. 2014).

Table 1 shows the international Tumor Node Metastasis (TNM) system (Sobin LH, Gospodariwicz M 2009), commonly used to establish how far the disease has progressed. The letter T refers to the size of the primary tumor, N describes the extent of lymph node involvement and M refers to the presence or absence of metastases.

Table 2: Tumor Node Metastasis (TNM) classification of prostate cancer
(Sobin LH, Gospodariwicz M 2009)

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

1 Tumor 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, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

3 The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.

4 Laterality does not affect the N-classification

5 When more than one site of metastasis is present, the most advanced category should be used

The definition by D'Amico et al. (D'Amico et al. 1998) is used to classify patients into risk groups: low-risk patients are T1c or T2a, PSA <10 ng/mL and Gleason <6; intermediate-risk patients are T2b, PSA 11-20 ng/mL or Gleason 7; and high-risk patients are T2c, PSA >20 ng/mL or Gleason >7.

Prostate cancer is defined as "localized" when the tumor is confined within the prostate.

The primary goal of treating prostate cancer is to prevent death and disability while minimizing complications and discomfort from interventions. Factors such as tumor stage, age, pre-existing medical conditions, and patient values regarding the risks of potential complications and side effects, are taken into account in the determination of appropriate treatment options.

For several years, patients with localized prostate cancer have chosen between treatments, such as surgery, radiotherapy, or active surveillance, with a substantially different pattern of side effects. Furthermore, current European Association Urology Guidelines (Mottet et al. 2015) reference that many men with localized prostate cancer will not benefit from definitive treatment (Hayes et al. 2013) and that about 45% of men with PSA-detected prostate cancer are candidates for deferred management (Godtman et al. 2013).

Radical prostatectomy has traditionally been considered the gold standard for localized prostate cancer. External beam radiation therapy has also been widely used, mainly in patients for whom surgery carries greater risk. Both with excellent results in cancer control but significant side effects. Brachytherapy, with the direct implant, results in less damage to surrounding tissue and fewer side effects. The publication of two studies in the late 90s (D'Amico et al. 1998; Stokes 2000) showing comparable results for brachytherapy to those of radical prostatectomy in cancer control have spread its use.

Cooperberg et al.(Cooperberg et al. 2007) analyzed riks trends in prostate cancer from a national US registry with men diagnosed between 1990 and 2006. Results show that the proportion of low-risk tumors has changed from 27.5% in 1990-1994 to 46.4% in 2000-2001 and that the overall time trend in primary treatment selection among low-risk patients was statistically significant. Radical prostatectomy increased in the 2000s to nearly 60% of low-risk patients and use of brachytherapy peaked, increasing from 3.6% in the early 1990s to 19% in 2000-2001, then decreasing to 13% in 2004-2006. Use of external-beam

radiotherapy decreased (13% for1990-94 and 5.3% for 2004-2006) as well as criotherapy and primary androgen deprivation therapy monotherapy.

Radical prostatectomy involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of radical prostatectomy by any approach must be eradication of disease, while preserving continence and, whenever possible, potency (Mottet et al. 2015). Nerves preservation is preferred, which reduces the likelihood of long-term impotence, but it is not possible to know before surgery whether the procedure will be able preserving them.

New technology is increasingly applied to prostate cancer surgery, with a rapid uptake of da Vinci (Intuitive Surgical, Sunnyvale, CA, USA) robotic-assisted, laparoscopic, radical prostatectomy (Bolenz et al. 2014) and other established modalities of radical prostatectomy such as open, retropubic or laparoscopic prostatectomy.

Robotic-assisted prostatectomy has perceived advantages such as facilitating laparoscopic techniques for open surgeons, better magnification, and reduced blood loss, but there is a lack of evidence for clear superiority in functional or oncologic outcomes over conventional surgical approaches to radical prostatectomy (Ficarra et al. 2009; Hu et al. 2009; Lowrance et al. 2010). A recent systematic review noticed that robotic-assisted laparoscopic prostatectomy may cost more than conventional, open, retropubic radical prostatectomy due to several factors, including higher costs for disposables, equipment, and longer operating room time when medical staff are still in the learning curve process to gain experience with the procedure (Bolenz et al. 2014).

External Beam Radiotherapy is a method for delivering external radiotherapy to a patient's tumor. Three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated external-beam radiotherapy (current gold standard for external radiotherapy (Mottet et al. 2015)) are the techniques to deliver dose escalation. Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists and computer scientists. In localized prostate cancer no trials have shown that dose escalation results in an overall survival benefit. However, the trials have been remarkably consistent in reporting improvements in freedom from biochemical

progression in patients treated with dose-escalated radiotherapy (Dearnaley et al. 2014; Beckendorf et al. 2011; Zietman et al. 2010; Kuban et al. 2011).

Prostate Brachytherapy is an internal radiation therapy that involves the implantation of permanent radioactive 'seeds' (Iodine-125) in the prostate in a single session. The seeds are about the size of a grain of rice and are inserted through the perineum by an ultrasound-guided needle, catheter or any other delivery device. There have been no randomized trials comparing brachytherapy with other curative treatment modalities, outcomes are based on non-randomized case series (Grimm et al. 2001; Potters et al. 2004; Potters et al. 2005; Zelefsky et al. 2007; Morris et al. 2013).

As shown by systematic reviews (Wilt 2008, Bannuru 2011), high-quality evidence on comparative treatment effectiveness for localized prostate cancer is scarce, and the relative advantages and disadvantages per therapeutic option are not well-characterized. Presently, there are no published randomized clinical trials comparing radical prostatectomy with external or interstitial radiotherapy (Crook et al. 2011; Donovan et al. 2009). The Prostate testing for cancer and Treatment (ProtecT) trial will be closed during 2015 and provide evidence on prostate cancer mortality at a median 10-year follow-up in men with clinically localized prostate cancer treated with active monitoring (surveillance strategy), radical prostatectomy, or three-dimensional conformal external-beam radiotherapy recruited between 2001 and 2009 (Lane et al. 2014).

On the other hand, particularly in the United States there is a recent concern on the relative decline of some techniques (Martin et al. 2014) and rapid adoption of newer and more expensive technologies (Nguyen et al. 2011; Jacobs et al. 2013). Additionally, active surveillance has become to be a reasonable option for men with clinically localized prostate cancer (Hayes et al. 2010).

This poses a significant uncertainty in the choice of treatment, which translates into uncertain allocation of health care resources.

1.2 Overview of Economic Evaluation in Healthcare

Scarcity, choice and opportunity cost are central concepts in Economics.

Resources are scarce; therefore the choice to use them in a particular way denies the opportunity of using them in other ways. Economic evaluation, an area of extensive progress during the last two decades, can be seen as a framework to assist in the optimal allocation of the, by definition, scarce health care resources in order to maximise the society's health, by analysing the costs and benefits of alternative health care interventions.

Either from a welfare or non-welfare approach, economic evaluation methods could therefore be seen as a 'decision-aiding' instrument but not the only instrument to guide allocation of health care resources. On the other hand, society may have other goals when allocating resources (Coast 2004) such as equity or ethical issues, not only the goal of efficiency.

As pointed out by Michael Drummond et al. in the 90s (Drummond 2005), economic analysis, regardless its application, has two common characteristics. First, it deals with inputs and outputs, sometimes called costs and consequences. Second, it deals with elections. Therefore, the definition provided is: "economic evaluation as the comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes, effects)"(Drummond 2005). Thus, the basic tasks of any economic evaluation (including health) are to identify, measure, evaluate and compare the costs and consequences of the alternatives being considered.

Generally referred to as "health technologies", diagnostic or surgical procedures, medicines, public health interventions or combinations of these may be subject to economic evaluation.

The next sections briefly describe very well established forms of economic evaluation (which aid for scarce resources allocation), the methodological issues pertaining to the identification, measurement and valuation of costs (opportunity cost) and the outcomes considered in cost-utility analysis (intended to capture patient's choice or preferences).

a) Types of economic evaluation and outcomes incorporated

There are four types of economic evaluation, all based on comparing the costs of different alternatives to achieve an outcome (Table 3).

All types compare the costs (resource use) associated with one or more alternative interventions (e.g. intervention X versus comparator Y) with their consequences (outcomes, effects). All types value resources in the same way (i.e. by applying unit costs to measured units of resource use).

The unit of measurement for health benefits is the key characteristic that distinguishes the different types of economic evaluation (J Brazier et al. 1999). The differences in the way they itemize and value effects reflect the diverse aims and viewpoints of different decision problems (or economic questions) (Shemilt et al. 2008).

All types are based on an *incremental or marginal approach*. There is a consensus that the relevance is on the cost per additional unit of effectiveness obtained by applying a more expensive, but more effective, technology and not only the cost of achieving a given health outcome. Thus, in this particular frame, a cost analysis (i.e. cost of illness study) can inform about the cost incurred by a particular agent, but not constitute an economic evaluation if it does not analyze the difference between one or more alternatives to produce certain results.

Accordingly, the results of an economic evaluation are reported in terms of incremental cost per unit of effectiveness (Incremental cost-effectiveness ratio – "ICER"; or incremental cost-utility ratio –"ICUR").

Table 3: Measurement of costs and consequences in economic evaluation

Type of study	Measurement of costs	Measurement of consequences
Cost-minimization analysis (CMA)	Monetary units	N/A (equal efficacy is assumed)
Cost-effectiveness analysis (CEA)	Monetary units	Natural units (e.g. life-years gained, points of blood pressure reduction, etc
Cost-utility analysis (CUA)	Monetary units	Healthy years, typically measured as Quality Adjusted Life Years (QALYs)
Cost-benefit analysis	Monetary units	Monetary units

Based on: (Drummond 2005)

- **Cost-Minimization Analysis:**

In this approach only costs are evaluated and the outcome is assumed constant or identical. If two or more technologies reach the same level of health benefits for patients, those alternatives that suppose a lower cost will be more cost-effective and should be recommended.

The difficulty with this method is to decide whether the evaluated technologies are truly identical in their health outcomes (quality of life, mortality, or any other considered). This assumption that the results are equivalent (and therefore the analysis is reduced to

comparing costs) is reasonable where there is no clear evidence about which treatment is preferable for the patient or the health system.

- **Cost-Effectiveness Analysis:**

Cost-effectiveness analysis is widely used in healthcare and it is useful in analyses where the purpose or relevance of the intervention is not being questioned. It has been considered as the most classical type of economic evaluation (J Brazier et al. 1999).

Cost-effectiveness analysis relates the additional cost to its incremental impact on any clinically relevant measure of benefit. The consequences (effects) of an intervention (and its comparators) are measured in identical units of outcome (e.g. mortality, myocardial infarctions, lung function, bleeding, or any other natural unit). Alternatives are compared in terms of 'cost per unit of effect'. (Drummond 2005)

However, it should be noted that this analysis has several limitations: first, it is difficult to use for comparing interventions that differ by more than one result and it only allows the comparison of those interventions that use the same unit of effectiveness. Therefore it cannot inform decisions about the efficient allocation of resources among diseases or health programs with different results.

Second, there is no consensus on which measure(s) of effectiveness must be used for each analysis. Researchers have to select a specific outcome for the purpose of the analysis, and this election may have a strong impact on the conclusions derived. This problem is especially important when surrogate endpoints are used (Drummond 2005).

Another aspect to consider is that it is often difficult to know the effectiveness of the intervention or technology. There may be available information on the potential capacity of the technology (efficacy, typically through randomized clinical trials) but its real ability to get the evaluated result under real conditions (effectiveness) is more difficult to determine. In an economic assessment, the interesting results are those obtained in real conditions, so that this distinction between efficacy and effectiveness is not trivial. Regardless its limitations this type of analysis is currently predominant in economic evaluation of health technologies.

- **Cost-Utility Analysis:**

When alternative interventions produce different levels of effect in terms of quantity and/or quality of life, the effects may be expressed in utilities. Utilities are measures which comprise subjective levels of well-being, and can be elicited by different techniques (i.e standard gamble, time trade-off, multi-attribute scales) (J Brazier et al. 1999).

The quality-adjusted life year, so called "QALY" is a measure of disease burden combining the value of both the length and quality of life. It is calculated by multiplying the time spent in a certain health state with the utility for this health state. Alternative interventions are compared in terms of cost per QALY gained (Drummond 2005; Shemilt et al. 2008).

Cost-utility analysis is interpreted as a special type of cost-effectiveness analysis, where the outcome used (QALY) allows the comparison of all technologies whose implementation involves a health improvement. When combined with costs and compared to at least one alternative, the results of cost-utility analysis are presented in terms of incremental cost per quality-adjusted life year gained.

Like the cost-effectiveness analysis, cost-utility analysis limits the benefits of the intervention purely to health gains, comparisons are confined within the health budget without informing about alternatives from other sectors.

The cost-utility framework is accepted as the reference case for health technology assessment agencies such as the National Institute for Health and Care Excellence in UK and the Canadian Agency for Drugs and Technologies in Health in Canada (National Institute for Health and Care Excellence 2013; Canadian Agency for Drugs and Technologies in Health (CADTH) 2006).

The expressions "economic evaluations", "cost-effectiveness analysis" and "cost-utility analysis" are commonly used interchangeably. The notion of the ICER relates also to the incremental cost per QALY gained, or other measures of effectiveness (ICER per Life Year Gained or others).

- **Cost-Benefit Analysis:**

In this type of economic evaluation, both resource inputs and effects of alternative interventions are expressed in monetary units, so that they compare directly and across

programmes within the healthcare system, or with programmes outside the health sector (e.g. healthcare intervention vs. criminal justice intervention) (Drummond 2005; Shemilt et al. 2008).

This means that non-monetary results, such as survival or quality of life improvements have to be also expressed in monetary units. Consequently, an intervention or technology is efficient if the monetary value of benefits exceed costs.

Cost-benefit analysis has a major advantage over the previous ones: it is also useful to determine whether an intervention, technology, treatment or program is worthwhile for society and not only within the health budget. Thus, it allows comparison with non-healthcare alternatives, such as educational or environmental interventions that may be more socially beneficial or might compete for the same resources. However, cost-benefit analysis is less frequent for economic evaluation in healthcare because of the difficulty of monetary valuation of indirect costs and the reluctance in the health sector to express of health outcomes in monetary terms (Drummond 2005).

b) Conducting and reporting economic evaluations of health interventions

There is abundant literature published describing methods for conducting economic evaluations in healthcare. The classic textbook from Michael Drummond and colleagues, first published in 1987 (Drummond 2005) is worthy of notice. Also relevant is chapter 15 of the Cochrane Handbook for Systematic Reviews of Interventions, produced by the Cochrane Economics Methods Group which provides a clear description and guidance about the consideration of economic evidence in the healthcare decision making process (Shemilt et al. 2008).

Even if economic evaluations are being increasingly published over the last decades (P. J. Neumann et al. 2015) and the methods have evolved over time, there are still many important challenges and methodological gaps (McCabe, Claxton, and Culyer 2008; Dolan and Edlin 2002; Sculpher et al. 2004; Drummond 2005; Mathes et al. 2013) that can partially explain the still limited role played by economic evaluation in healthcare decision making.

With participation of several experts, a task force supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recently developed the "Consolidated Health Economic Evaluation Reporting Standards" (CHEERS). Aimed to optimize the reporting of health economic evaluations, it provides a comprehensive review and update of previous health economic evaluation guidelines into one current, useful reporting guidance. Even if not intended for this, the statement and associated report are very useful references for conducting and evaluating an economic evaluation (Husereau et al.). For illustrative purposes we reproduce the CHEERS checklist of items to include when reporting economic evaluations of health interventions in Table 4.

Table 4: Items to include when reporting economic evaluations of health interventions (Consolidated Health Economic Evaluation Reporting Standards)

Section/item	Item No	Recommendation
Title and abstract		
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses) and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study.
		Present the study question and its relevance for health policy or practice decisions.
Methods		
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.

Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.

Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
Characterizing uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
Discussion		
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.
Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.

Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

Extract from CHEERS Checklist. (Husereau et al.)

c) Estimation of healthcare costs

In any type of economic evaluation, costs are costs, and these can be calculated using similar methods regardless the type of economic evaluation conducted. But, even if their estimation may seem very straightforward, there are several practical considerations or decisions to be made throughout the process.

Three main stages have been described for estimating costs in the context of an economic evaluation (Drummond 2005; Miners 2008): identification of relevant resources; estimation of the resources consumed and valuation of these resources.

Generically, the resources used to obtain a result are valued at their opportunity cost, this is the next best alternative foregone, or the alternative value that is lost because of choosing this alternative. Consequently, there are two aspects in this identification: what the resources are used and who has the ownership or right to use them; therefore who incurs this cost of opportunity.

Traditionally, costs have been typified as direct costs, indirect costs and intangible costs. *Direct costs* are costs that are directly related to the resource used associated with obtaining the outcome of interest, they may include outpatient visits, pharmaceutical cost, costs of managing adverse effects, laboratory services, etc. *Indirect costs* are those not clearly attributable to the production of that result. In the healthcare context they have been associated with lost production capacity and include time lost from work by the patient and time lost from work by the caregiver. There is no consensus yet on the most appropriate method of valuating productivity costs, with two very well-known methods for valuation (human-capital and friction-cost). *Intangible costs* are the ones associated with pain and

suffering, usually incorporated in the utilities assigned to health states that reflect quality of life.

Limitations of this above mentioned typology have been pointed out and an alternative has been proposed to directly link the *perspective* that is assumed in the evaluation to determine what kind of costs are relevant to be included (Drummond 2005). Therefore, the perspective (point of view of the study) determines which cost categories should be included in the analysis. In a societal perspective, cost analysis preferably takes into account direct and indirect costs inside and outside the healthcare sector. Within the financer and health care perspective, only direct healthcare costs need to be included.

In general, direct healthcare costs are the only costs that have been considered in the vast majority of published economic evaluations of health technologies. However, of notice, inclusion of informal care (that informal caregivers provide to patients, with sacrifice in time and physical or emotional fatigue) in economic evaluation has been encouraged and several methods have been proposed (Brouwer et al. 1999; van den Berg et al. 2006).

Following the identification of the relevant costs to be considered in the analysis, two elements remain in costing: measurement of the quantities of resource use and assignment of unit costs or *prices*. Thus total cost is the result of multiplying quantities by their price.

Although the theoretical proper price for a resource is its opportunity cost, the pragmatic approach to costing is to take existing market prices unless there is some particular reason to do otherwise. There are important methodological limitations regarding price valuation and identification of prices, owing to the economic imperfections or non-existence of healthcare markets (Drummond 2005; Arrow 1963).

Together with imputation for non-market items, in the estimation of healthcare costs there are also considerations to be made regarding discounting costs (and benefits) that occur at different times (given a positive rate of individuals' time preference that generally prefer to incur costs in the future and receive benefits in advance), choice of time period for the analysis (how long costs should be tracked), and overhead and capital cost allocation, all of them subject to debate (Brouwer and Koopmanschap 2000) (Drummond 2005).

There is a consensus that micro-costing (activity based costing or the bottom-up approach) is the preferred method but also more costly and time consuming. Also that the sources of monetary value estimates may depend on the study perspective adopted, that uncertainties

should be addressed by using statistical and sensitivity analysis and that distribution of cost data can be highly skewed. When reporting an economic evaluation, methods for estimating both the resources and prices should be provided separately.

There seems to be a consensus also on the possible difficulty to solve the conceptual differences and methodological issues for calculating healthcare costs (Mogyorosy and Smith 2005).

d) Outcomes for Cost Utility Analysis

Positive and negative outcomes of treatments are to be taken into account when therapeutic decision is being made. Patients are, and should be, informed by their physicians regarding treatment options, harms and benefits.

As presented, cost-utility analysis evaluates two alternative interventions in terms of incremental quality adjusted life years (QALY) and costs and summarizes the result in an incremental cost-effectiveness ratio representing the cost per QALY gained.

In this particular framework analysis of economic evaluation of healthcare interventions, it is generally assumed - and also debated (Mooney 1989; P. J. Neumann and Greenberg) : that the QALY measure captures enough aspects of health to be considered an appropriate outcome in the field of curative healthcare. This has the advantage that all intervention outcomes would be comparable in terms of QALY gains.

Health utilities have been pointed out as useful tools in supporting shared decision making between patients and physicians (Kramer et al. 2005). To estimate QALYs, life years gained are weighted by patient's preferences (regarding their health states) that are assumed to be reflected by their health utilities.

Patients' preferences can be directly elicited using direct methods such as standard gamble (J. von Neumann and Morgenstern 2007) and time trade-off (Torrance, Thomas, and Sackett 1972) or indirectly using multi-attribute utility scales (preference-based indexes). Indirect elicitation through econometric instruments is considered more appropriate than direct methods in the field of health planning policies, because they get preferences in general population samples and represent the value that society places on the different states of health. Questionnaires designed to obtain preferences by the indirect method are

easier to complete that the more complex direct elicitation exercises, and may have higher reliability than direct preferences elicitation.

A limitation of these instruments when applied to a particular disease is that generic questionnaires may not detect clinically important differences if they do not address relevant dimensions of that particular disease.

The most used preference-based indexes in the last decade have been the EuroQol 5-Dimensions (EQ-5D) (Brooks 1996; Herdman et al. 2011), the Short Form-6 Dimension (SF-6D) (John Brazier, Roberts, and Deverill 2002) and the Health Utility Index. (HUI) (Horsman et al. 2003), in detriment of previous instruments as Quality of Wellbeing scale (QWB) and 15-Dimensions (15D) (J Brazier et al. 1999). (Table 5)

Table 5. Generic preference-based instruments

Instrument	Dimensions	Health states	Technique	Source of preference weights
EQ-5D	5 (Mobility, self-care, usual activities, pain/discomfort and anxiety/depression)	245	TTO	Random sample of approx 3000 adults (UK)
HUI	8 (Vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain)	972000	SG ; VAS	Random sample adult population (Canada)
SF-6D	6 (Physical functioning, role limitation, social functioning, pain, mental health and vitality)	18000	SG	Random sample adult population (UK)

Modified from (Whitehead and Ali 2010)

1.3 Economic evaluation of treatments for localized prostate cancer

Although the most established treatments for localized prostate cancer show similar overall survival, they have shown a very different patterns of adverse effects and quality of life impact (Sanda et al. 2008; Pardo et al. 2010; Ferrer et al. 2013).

There is a lack of evidence on the comparative cost-effectiveness of these treatment alternatives (Ramsay et al. 2012), together with important variations in the cost estimates. The vast majority of the literature on costs or economic evaluations of localized prostate cancer treatments is from studies conducted outside Europe, mainly in the United States or Canada (Cooperberg et al. 2013; Amin, Sher, and Konski 2014).

From those studies that estimated cost treatments, there have been several reporting on the initial cost of treatment (Ciezki et al. 2000; Makhlouf et al. 2002; Poon et al. 2004; Silverstein et al. 2004; Anderson et al. 2005; Buron et al. 2007; Becerra et al. 2011; Hohwü et al. 2011). More recently, there have been studies considering longer follow-up periods (Andersson et al. 2011; Laviana et al. 2015) and providing results for expectant management (Andersson et al. 2011; Laviana et al. 2015).

Regarding economic evaluation, there are few studies that conduct cost-effectiveness analysis of localized prostate cancer and very few that compare treatments rather than different alternatives of the same treatment (e.g. intensity modulated radiotherapy vs 3D conformal radiotherapy; open radical prostatectomy versus laparoscopic radical prostatectomy or robot assisted laparoscopic prostatectomy). These latter are based solely on theoretical cohorts (Hummel et al. 2003; Cooperberg et al. 2013; Hayes et al. 2013).

In a report published in 2003 Hummel et al. (Hummel et al. 2003) reported the development of a cost-utility analysis as part of a systematic review on new treatment modalities for localized prostate cancer and found brachytherapy and 3D conformal radiotherapy as potentially cost-effective versus traditional treatment (radical prostatectomy, 2D conformal radiotherapy and watchful waiting). Results rely on the assumption of equally effective disease-free survival.

The cost utility analysis performed by Cooperberg et al. (Cooperberg et al. 2013) based on a Markov model with probabilities taken from an extensive systematic review, showed that

from the a United States payer perspective and lifetime horizon, radiotherapy methods were consistently more expensive than surgical methods, with modest differences across treatments in quality-adjusted life years, and no statistically significant differences among surgical methods, which tended to be more effective than radiotherapy methods. Also published in 2013 the study by Hayes et al. (Hayes et al. 2013) found that in men aged 65 and 75, observation was more effective and less costly than initial treatment and brachytherapy was the most effective and least expensive treatment option.

2. THESIS RATIONALE

Prostate cancer is the second most common diagnosed tumour in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, with almost 70% of the cases occurring in more developed regions and 345.000 diagnosed in the European Union (Bray et al. 2013), who must choose between substantially different treatments, including surgery, radiotherapy, or active surveillance. Increased detection associated with use of prostate-specific antigen (PSA) testing has changed the epidemiology of this tumor. Currently, most cases are diagnosed at local stages, and patients' average age has decreased to 65 years (Shao et al. 2009).

Prostate cancer has been estimated as the fourth economic cancer cost for the European Union in 2009 (€8.43 billion, 7% of the total) after colorectal (€13.1) breast (€15) and lung cancer (€18.8) (Luengo-Fernandez et al. 2013). Furthermore, United States projections for the 2010-2020 period indicate a 27% increase in cancer medical costs, where the largest is the continuing care phase of prostate cancer (42%) (Mariotto et al. 2011).

Published studies on the costs of treatments show significant variations in the cost estimate that may be due to failure to consider the tumor stage, age of patients at the time of diagnosis, the types of costs included, or the time frame of the analysis. Some of the studies infer costs from total expenses incurred instead of estimating costs from the healthcare resource units consumed (Gianino et al. 2007).

Only two systematic reviews have been published on economic evaluations. One, focusing on radiotherapy (Amin, Sher, and Konski 2014), identified 14 studies. The other one, evaluating radical prostatectomy, did not identify any complete economic evaluation meeting inclusion criteria, but instead included 11 cost comparison studies (Ramsay et al. 2012). To our knowledge, there is no global systematic review that takes into account the economic evaluations of all treatments published during the last 15 years, including those comparing different therapies, such as radical prostatectomy versus radiotherapy or active surveillance.

However, as shown by systematic reviews (Wilt et al. 2008; Bannuru et al. 2011), high-quality evidence on treatment effectiveness for localized prostate cancer is scarce, and the relative advantages and disadvantages per therapeutic option are not well-characterized. Presently, there are no published randomized clinical trials comparing radical

prostatectomy with external or interstitial radiotherapy (Crook et al. 2011; Donovan et al. 2009).

The few cost-effectiveness or cost-utility analysis comparing radical prostatectomy with radiation alternatives were based on theoretical cohorts (Hummel et al. 2003; Hayes et al. 2013; Cooperberg et al. 2013) and showed some contradictory results. This poses a significant uncertainty in the choice of treatment, which translates into uncertain allocation of resources.

This doctoral thesis was developed within the prospective study of the "Multicentric Spanish Group of Localized Prostate Cancer". It addressed the economic evaluation of treatments of this study including: cost estimation, eost-effectiveness analysis and cost-utility analysis. The project followed-up 704 patients diagnosed and consecutively recruited in 10 Spanish centers.

The cost analysis assumed the healthcare system perspective, considering direct healthcare costs, through micro costing approach. For the economic evaluation outcomes considered were overall survival and quality-adjusted life years for the patients involved using the SF-6D values (derived from SF-36 values obtained for these patients).

This thesis project aimed to meet the need for reliable economic evaluation of treatments for localized prostate cancer; not only for immediate clinical intervention but also providing evidence for long term decision making at different levels.

3. OBJECTIVES OF THE DOCTORAL THESIS

The global aim of this thesis was to assess the efficiency, from health systems perspective, of the most established treatments for patients diagnosed with localized prostate cancer.

Specific objectives:

To compare the initial costs, from diagnosis up to 6 months post-treatment, of radical prostatectomy, external beam radiotherapy, and prostate brachytherapy, using data from a subsample of the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort. As well, to assess the effect of risk group, age, and comorbidity on treatment costs.

To assess the efficiency of treatments in patients with localized prostate cancer, by synthesizing the available evidence from European economic evaluations through a systematic review.

To perform a cost effectiveness analysis, from the Spanish Health System perspective, comparing radical prostatectomy, external radiotherapy and brachytherapy, based on 10 years of primary data from the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort.

4. SCIENTIFIC ARTICLES

Manuscript 1. Cost comparison of three treatments for localized prostate cancer in Spain: radical prostatectomy, prostate brachytherapy and external 3D conformal radiotherapy.

Becerra Bachino V, Cots F, Guedea F, Pera J, Boladeras A, Aguiló F, Suárez JF, Gallo P, Murgui L, Pont A, Cunillera O, Pardo Y, Ferrer M; Grupo Multicéntrico Español de Cáncer de Próstata Organoconfinado. **Cost comparison of three treatments for localized prostate cancer in Spain: radical prostatectomy, prostate brachytherapy and external 3D conformal radiotherapy.** *Gac Sanit. 2011Jan-Feb;25(1):35-43.*

Manuscript 2. Economic Evaluation of Treatments for Patients with Localized Prostate Cancer in Europe: A Systematic Review.

Becerra V, Ávila M, Jimenez J, Cortes-Sanabria L, Pardo Y, Garin O, Pont A, Alonso J, Cots F, Ferrer M. **Economic Evaluation of Treatments for Patients with Localized Prostate Cancer in Europe: A Systematic Review**. *(Submitted)*

Manuscript 3. Economic Evaluation of localized prostate cancer treatments: Ten year follow - up cohort study.

Becerra V, Garin O, Guedea F, Suárez JF, Fernández P, Macías V, Mariño A, Hervás A, Herruzo I, Ortiz MJ, Ponce de León J, Sancho G, Ávila M, Pont A, Alonso J, Cots F, Ferrer M and the Multicentric Spanish Group of Clinically Localized Prostate Cancer. **Economic Evaluation of localized prostate cancer treatments: Ten year follow - up cohort study.** *(Under review)*

4.1 Manuscript 1. Cost comparison of three treatments for localized prostate cancer in Spain: radical prostatectomy, prostate brachytherapy and external 3D conformal radiotherapy.

Becerra Bachino V, Cots F, Guedea F, Pera J, Boladeras A, Aguiló F, Suárez JF, Gallo P, Murgui L, Pont A, Cunillera O, Pardo Y, Ferrer M; Grupo Multicéntrico Español de Cáncer de Próstata Organoconfinado. **Cost comparison of three treatments for localized prostate cancer in Spain: radical prostatectomy, prostate brachytherapy and external 3D conformal radiotherapy.** *Gac Sanit. 2011Jan-Feb;25(1):35-43.*

Becerra Bachino V, Cots F, Guedea F, Pera J, Boladeras A, Aguiló F, Suárez JF, Gallo P, Murgui L, Pont A, Cunillera O, Pardo Y, Ferrer M; Grupo Multicéntrico Español de Cáncer de Próstata Organoconfinado. [Cost comparison of three treatments for localized prostate cancer in Spain: radical prostatectomy, prostate brachytherapy and external 3D conformal radiotherapy]. Gac Sanit. 2011 Jan-Feb;25(1):35-43. doi: 10.1016/j.gaceta.2010.10.008

4.2 Manuscript 2. Economic Evaluation of Treatments for Patients with Localized Prostate Cancer in Europe: A Systematic Review.

Becerra V, Ávila M, Jimenez J, Cortes-Sanabria L, Pardo Y, Garin O, Pont A, Alonso J, Cots F, Ferrer M. **Economic Evaluation of Treatments for Patients with Localized Prostate Cancer in Europe: A Systematic Review**. *(Submitted)*

Economic Evaluation of Treatments for Patients with Localized Prostate Cancer in Europe: A Systematic Review

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Financial support for this study was provided by Instituto de Salud Carlos III FEDER: Fondo Europeo de Desarrollo Regional (FIS PI08/90090 and PI13/00412) and DIUE of Generalitat de Catalunya (2014 SGR 748). The funding agreements ensure the authors' independence in designing the study, interpreting the data, and writing and publishing the report. All authors declared no conflicts of interest.

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Running title: Economic Evaluations in Localized Prostate Cancer.

Word count:

Abstract: 250 words

Main text: 3,056

Figures and tables: 5 (2 figures, 3 tables).

ABSTRACT

Background: Our objective was to assess the efficiency of treatments in patients with localized prostate cancer, by synthesizing available evidence from European economic evaluations through systematic review.

Methods: Search for articles published 2000-2015 performed in MEDLINE, EMBASE and NHS EED (Prospero protocol CRD42015022063). Two authors selected studies independently for inclusion and extracted the data. A third reviewer resolved discrepancies. We included European economic evaluations or cost comparison studies, of any modality of surgery or radiotherapy treatments, regardless of the comparator/s. Drummond's Checklist was used for quality assessment.

Results: After reviewing 8,099 titles, 13 European eligible studies were included: eight cost–utility, two cost–effectiveness, one cost–minimization, and two cost-comparison analyses. Of them, five compared interventions with expectant management, four contrasted robotic with non robotic-assisted surgery, three assessed new modalities of radiotherapy, and three compared radical prostatectomy with brachytherapy. All but two studies obtained a score $\geq$8 in the quality checklist. Considering scenario and comparator, three interventions were qualified as dominant strategies (active surveillance, robotic-assisted surgery and IMRT), and six were found to be cost-effective (radical prostatectomy, robotic-assisted surgery, IMRT, proton therapy, brachytherapy, and 3DCRT).

Conclusions: Currently, relevant treatment alternatives for localized prostate cancer are scarcely evaluated in Europe. Very limited available evidence supports the cost-effectiveness of radical prostatectomy over watchful waiting, brachytherapy over radical prostatectomy, and that of new treatment modalities over traditional procedures. Despite acceptable methodological quality of economic evaluations, relevant disparities between studies were detected. These contradictory results indicate that available effectiveness evidence is far from robust.

Keywords: Cost, Cost-Effectiveness Analysis, Cost-Utility Analysis, Cost-Benefit Analysis, Economic Evaluation, Prostate Cancer, Prostatic Neoplasms, QALY, Quality-Adjusted Life Years.

INTRODUCTION

Prostate cancer is the second most common cancer in men [1]. Estimates of public health expenditure on cancer indicate that prostate was the third contributor (6% of the total), after colorectal and breast tumours [2]. Furthermore, United States (US) projections for the 2010-2020 period indicate a 27% increase in cancer medical costs, where the largest is the continuing care phase of prostate cancer (42%) [3].

While Active Surveillance is one recommended option [4;5] for men with clinically localized prostate cancer [6], the number of new variants of surgical and radiotherapy treatments continues to increase. Despite their similar proven efficacy in terms of overall survival [7], they differ substantially in their side effects pattern [8-11]. With so many different alternatives, health economics may contribute with relevant information for decision-making on treatment for localized prostate cancer [12], and there has been an increasing number of economic evaluations worldwide: comparing surgery versus radiotherapy [13;14], different variations of prostatectomy [15-17] or radiotherapy [18-21].

The National Institute for Clinical Excellence (NICE) published a global systematic review of economic evaluations for localized prostate cancer treatments in 2003 [22], before the new surgical and radiotherapy modalities appeared. Since, only two other systematic reviews have been published on economic evaluations. One, focusing on radiotherapy [23], identified 14 studies. The other one, evaluating

radical prostatectomy, did not identify any complete economic evaluation meeting inclusion criteria, but instead included 11 cost comparison studies [24]. To our knowledge, there is no global systematic review that takes into account the economic evaluations of all treatments published during the last 15 years, including those comparing different therapies, such as radical prostatectomy versus radiotherapy or active surveillance.

It is also necessary to highlight that most of the economic evaluations were conducted in the US [25, 26], and they are hard to extrapolate to the European countries where health systems are mainly publicly funded. The aim of this study was to assess the efficiency of treatments in patients with localized prostate cancer, by synthesizing the available evidence from European economic evaluations through systematic review.

MATERIAL AND METHODS

The protocol is registered in PROSPERO international database of prospectively registered systematic reviews as number CRD42015022063 (http://www.crd.york.ac.uk/Prospero). We conducted systematic searches in MEDLINE, EMBASE and NHS EED (NHS Economic Evaluation Database, CRD York) databases with a specific strategy (see Online Appendix 1) from January 1st 2000 to May 15th 2015.

We looked for economic evaluations (cost minimization, cost-effectiveness, cost-utility, and cost-benefit analyses) or cost comparison studies that assessed any modality of surgery or radiotherapy treatments, regardless of the comparator/s, for patients with localized prostate cancer (T1-T2). Articles were considered when referring to any European Country, and published in any European language.

Studies were excluded if they only performed cost estimations without comparing treatments (such as cost studies, cost of illness studies, or budget impact analyses); they were not primary studies; they assessed patients with advanced prostate cancer; or they evaluated diagnosis or screening procedures, but no treatments.

Two members of the study team (JJ and VB) independently reviewed articles found in the literature search by examining them in three consecutive phases: titles,

abstracts, and full text. A third reviewer (MA) resolved discrepancies. A pilot test was performed to homogenize criteria among reviewers. Finally, the reference lists of the selected articles and those of previous systematic reviews were reviewed to identify other possible studies that could be included.

Assessment of studies' quality and data extraction was performed by the consensus of two reviewers (VB and MA). Drummond's Checklist was used for quality assessment [27]. Data was extracted using a standardized, pre-piloted data collection form. The pre-defined primary outcome to be extracted was the incremental cost per Quality-Adjusted Life-Year (QALY) gained. Other Incremental Cost-Effectiveness Ratios (ICERs) and comparative costs per treatment were considered secondary outcomes. For illustrative purposes a figure has been designed to show all estimations of accumulated cost converted into euros (considering the current 2015 exchange rates), and plotted them through the time horizon for each intervention. .

RESULTS

Figure 1 shows the diagram of the literature flow in the review. Once 1,196 duplicates were excluded, 8,099 titles and 1,355 abstracts were reviewed, 156 articles were fully read, and finally only 13 eligible studies were included. From the reviewed full text articles: 47 were excluded because they were not economic evaluations or cost comparison studies; 39 were not performed in Europe; 35 because only abstracts were published; 12 were not primary studies; three were studies referring to other pathologies or treatments; two included patients with advanced disease (stages T3 and T4); two were written in Japanese; two were non localizable; and one assessed screening.

-- Figure 1, about here –

Table 1 shows the characteristics of the 13 economic evaluations identified which met the inclusion criteria [22;28-39] . Most were conducted in the United Kingdom (UK), Sweden, and France. All were complete economic evaluations, except two cost-comparisons [30;34]: eight were cost–utility analyses, two cost–effectiveness analyses [31;39] and one cost–minimization analyses [38]. Studies were classified according to the treatments they evaluated: a) in five studies [22;28-31] interventions were compared with expectant management (watchful waiting or active surveillance); b) four studies compared robotic-assisted laparoscopic prostatectomy with other surgical techniques [32-35]; c) three studies contrasted

conventional external radiotherapy with new modalities [22;36;37] (Intensity-Modulated Radiation Therapy - IMRT, proton therapy and brachytherapy); and d) three studies compared radical prostatectomy with radiotherapy [22;38;39]. Only the 2003 Hummel et al. study [22] provided data for more than one of these classification groups (a, c and d).

--Table 1, about here –

Most of the evaluations (nine out of 13) were conducted from a payer's perspective, three from a societal perspective [28;35;39], and only the Italian study was limited to the hospital perspective [34]. Regarding the time horizon, lifetime was considered in five studies [22;28;32;36;37], one decade in three other studies [29;30;33], and shorter periods for the rest (from hospital stay to five years). Source of cost was medical records from study cohorts, such as the Scandinavian Prostatic Cancer Group Study Number 4 (SPCG-4) [40], or national database registers of activities such as the British National Health System (NHS) or, more rarely, only literature review (two studies) [36;37]. Similar sources were used for effects on health.

--Table 2, about here –

The main findings from the economic evaluations identified were summarized in table 2. Of the interventions evaluated, three were found to be not only cost–

effective but also dominant strategies (more effective and less costly): active surveillance over radical prostatectomy from a societal perspective in Germany [28], robotic-assisted over non-robotic surgical techniques [32], and IMRT over 3-Dimensional Conformal Radiation Therapy (3DCRT) when assuming a survival improvement of 6.6 years [36]. The following six interventions were found to be cost-effective: radical prostatectomy over watchful waiting in patients aged 70 or younger [29], robotic-assisted over non-robotic laparoscopic radical prostatectomy if more than 150 procedures performed per year [33], IMRT over 3DCRT when survival improvement is $\geq$3.8 years [36], and proton therapy [37], brachytherapy [22] and 3DCRT [22] over conventional radiotherapy. Conversely, the highest cost per QALY gained (least efficient options) were shown for radical prostatectomy versus watchful waiting in patients older than 75 [29], robotic-assisted versus non-robotic radical prostatectomy performing 50 procedures per year [33] (over £100,000), and for IMRT versus 3DCRT at equal doses and same survival to PSA progression [36] (over €100,000).

--Figure 2, about here –

Estimations of accumulated direct costs in euros were plotted through the time horizon in Figure 2 for each intervention. In total, the figure shows 38 estimates reported by 11 studies. The lowest costs (around €2,000) were obtained for expectant management (specifically, watchful waiting) at time horizons of five and 35 years, as reported by Bauvin et al. [31] and Hummel et al. [22], respectively.

The highest costs (around €24,000) were obtained for robotic-assisted surgery during hospitalization [34] and for radical prostatectomy at 12 years [30]. The quality of the studies according to Drummond's 10-item checklist is illustrated in Table 3. From the 11 economic evaluations, nine studies scored $\geq$8 points.

--Table 3, about here –

DISCUSSION

Our systematic literature review identified 13 European studies published from January 2000 to March 2015 conducting either an economic evaluation or a cost comparison study (11 and 2, respectively) of any modality of surgical or radiotherapy treatments for localized prostate cancer patients. These studies varied widely in compared alternatives, costing methodologies, and time horizon. Estimations of incremental cost per QALY gained were provided by eight studies. Depending on the scenario and the comparator considered, three interventions were qualified as dominant (active surveillance [28], robotic-assisted surgery [32], and IMRT [36]), and six as cost-effective (radical prostatectomy [29], robotic-assisted surgery [33], IMRT [36], proton therapy [37], brachytherapy [22] and 3DCRT [22]). All studies obtained a high score of the methodological quality, except for two of the oldest ones [31;37].

Two cost-utility analyses comparing radical prostatectomy with expectant management show contradictory results on effectiveness: Koerber et al. [28] found that active surveillance was the dominating alternative (more QALYs at less cost), while Lyth et al. [29] showed that radical prostatectomy was more cost-effective than watchful waiting. However, the gain in QALYs estimated by Koerber et al. [28] was extremely small (-0.013 during 15 years), and they assumed that life under active surveillance had the same utility as life after treatment without side effects. This latter assumption, clearly in favour of active surveillance effectiveness, is

questionable. On the other hand, differences in the comparator used in both studies (active surveillance [28] and watchful waiting [29]) could also partly explain this disparity. No immediate treatment was performed in watchful waiting patients [29], while active surveillance involved [28] monitoring with PSA, digital rectal examination, and biopsy. Consistent with results reported by Lyth et al. [29], the cost-effectiveness study by Bauvin et al [31] showed that radical prostatectomy is more effective than watchful waiting. Unfortunately, although the economic evaluation of Hummel et al. [22] also evaluated radical prostatectomy, they did not report its comparison with watchful waiting.

The previous systematic review of economic evaluations comparing robotic-assisted vs non-robotic laparoscopic surgery [24] proved to be insufficient for decision making, leading the authors to build a de novo economic evaluation [33], which has been included in our review. Two of the three cost-utility studies that we identified consistently support the cost-effectiveness of robotic-assisted surgery [32;33]. Lord et al. [32] showed that robotic-assisted technique is the dominating alternative among surgery, while Close et al. [33] estimated a cost of £18,329 per QALY gained. Hohwu et al. [35] found no QALY gain for robotic-assisted surgery, but the authors underlined the uncertainty of their QALY estimates due to a high degree of missing data. When using ‘successful treatment’ as the denominator for the ICER, they estimated a cost of €64,000 per unit [35]. Again, disparity among these economic evaluations is due to contradictory results on effectiveness. In fact, current guidelines of the European Association of Urology [5] consider all

approaches (i.e., open, laparoscopic, and robotic) as acceptable for patients who are surgical candidates, because no single modality has shown a clear superiority in terms of functional or oncological results. On the other hand, it is important to highlight that the recommendation of the NICE Clinical Guideline [41] to provide robots in centres with an expected performance of at least 150 robotic-assisted operations per year, is only based on the economic evaluation published by Close et al. [33]. It would be advisable to confirm this recommendation with future specific studies to help decision makers.

The systematic review of cost-effectiveness analysis by Amin et al. [23], comparing different radiation treatments, identified 14 studies (most from the United States, and only two from Europe [22;36]). Although evidence suggested that brachytherapy and IMRT were more cost-effective than external beam radiotherapy, the authors highlighted the uncertainties and variation among studies [23]. We only identified three European economic evaluations comparing radiation therapies, each focusing on a different new modality (IMRT [36], proton therapy [37], and brachytherapy [22]). The three showed to be more cost-effective than conventional radiotherapy. However, these results came from only one study, and further research is needed to confirm them. Additionally, the cost-utility analysis of Hummel et al. [22], when considering watchful waiting as the comparator, showed brachytherapy as the most cost effective, with £834 - 12,828 per QALY gained, followed by the 3DCRT, with £1,030 - 26,776 per QALY gained. The European Association of Urology guidelines (5) recommend IMRT for definitive treatment with

external radiotherapy, and brachytherapy for patients fulfilling specific criteria (low risk, prostate volume below 50 mL, no urinary obstruction, and no previous transurethral resection).

Of the three studies comparing prostatectomy with radiation treatment, only Hummel et al [22] published a cost-utility analysis showing that brachytherapy was more cost-effective than surgery, with an incremental cost of €2,021 - 2,760 per QALY gained. Buron et al. [39] did not calculate ICERs but showed similar societal costs between radical prostatectomy and brachytherapy, though different treatment side effects: radical prostatectomy caused higher rates of urinary incontinence and erectile dysfunction, while brachytherapy presented irritative urinary and bowel symptoms more frequently. These results are consistent with the well-known side effect profiles of these treatments [8-11]. The cost-minimization published by Becerra et al. [38] assumed equal effectiveness in terms of survival, but they did not take into account other relevant outcomes such as relapses and treatment side effects. Thus, evidence supporting the cost-effectiveness of brachytherapy over open radical prostatectomy originates from one single study [22], and there are no economic evaluations comparing brachytherapy with robotic-assisted surgery.

All estimates of accumulated direct cost per treatment were below an equivalent total cost of €17,000, with the exception of three [28;30;34] (which could be considered outliers), as shown in Figure 2. The cost-comparison study performed

in Sweden reported the highest estimation of costs for radical prostatectomy and watchful waiting (€24,247 and €18,124) [30]. Also, the cost-comparison study published by Barbaro et al. [34] showed an extreme perioperative cost in an Italian hospital for robotic surgery (€23,610). Instead of 'real' outliers, the high cost estimated in these two empirical cost-comparison studies (based on the observation of health care activities in real cohorts) could indicate underestimation of real costs when they are based on models from theoretical cohorts. Furthermore, the surprisingly low accumulated costs estimated at 35 years reported in most studies with a lifetime horizon [22;32;36], similar or even lower than those reported for studies with a shorter time horizon [31;33], also suggest an underestimation of real costs in these studies. On the other hand, it is important to highlight the similarities in costs of the new treatment modalities compared with the traditional techniques, such as robotic versus non-robotic surgery [33] and IMRT versus external beam radiotherapy [36], when provided under rational conditions.

Besides watchful waiting (the cheapest), all other treatments seem to be quite similar in healthcare costs. Thus, evidence on efficacy and effectiveness in the economic evaluation of alternative therapeutic approaches for these patients is highly relevant. However, as reflected by the aforementioned disparities among studies, not only in the quantity of QALYs gained, but also in the identification of the most effective treatment (such as surgery versus expectant management or robotic versus non-robotic techniques), available evidence is far from robust. This highlights the importance of conducting randomized clinical trials before adopting

new technology, as in the case of the evolution of 3DCRT from two-dimensional technology (32). However, recruitment for randomized trials presented considerable difficulties in these patients [42;43], and the only available trial, the SPCG-4 [40] - which was used in several of these economic evaluations, was conducted at the beginning of PSA era. On the other hand, the wide range of relevant outcomes to take into account when treating patients with localized prostate cancer (from urinary or sexual side effects to death) increases the complexity for estimating QALYs.

There are various limitations that may affect our review findings. First, we can not be sure that no relevant study was missed. However, we have searched, as recommended [44], in PubMed and EMBASE, the most comprehensive databases in health sciences, as well as in a specific database for economic evaluations. In addition, we designed a very sensitive search strategy (yielding the 8,099 titles revised) and we performed an additional manual reference search of references. Second, internal validity of the synthesis provided by a systematic review depends on the quality of primary studies. In our systematic review quality could be considered good for most studies, scoring eight or higher, and the two scoring below this cut-off were published ten or more years ago [31;37]. However, this is an arbitrary cut-off, and there is no agreed-upon method to provide a summary score on this tool. Third, studies with a cost-comparison design were included despite not being economic evaluations. However, the information they provided clearly contributed to the amount and robustness of evidence on costs. Fourth,

figure 2 shows reported direct healthcare costs without transforming them into a single year to avoid arbitrary manipulation. We only converted currency into euros, using 2015 exchange rates, to facilitate comparisons. Finally, the review process may imply a selection bias given its subjective nature. The participation of two independent reviewers, and a third evaluator for discrepancies intended to avoid this.

To our knowledge, this is the first systematic literature review of the European economic evaluations of surgical and radiotherapy treatments for localized prostate cancer published during the last 15 years. In conclusion, the 13 studies identified (five comparing interventions with expectant management, four contrasting robotic with non-robotic assisted surgery, three assessing new modalities of radiotherapy, and three comparing radical prostatectomy with brachytherapy) show that currently relevant treatment alternatives for localized prostate cancer are scarcely assessed in economic evaluations in the European countries. Very limited available evidence supports the cost-effectiveness of radical prostatectomy versus watchful waiting, and that of brachytherapy versus radical prostatectomy. Regarding the evaluation of new treatment modalities, also limited evidence supports the cost-effectiveness of robotic-assisted laparoscopic radical prostatectomy versus non-robotic procedures, and that of brachytherapy, IMRT and proton therapy versus traditional external radiotherapy. Differences between cost-comparison and cost-effectiveness studies suggest underestimation of costs in studies based on models from theoretical cohorts. Despite the acceptable methodological quality of the

economic evaluations included, relevant disparities between studies were detected. These contradictory results are mainly based on effectiveness, which indicates that available evidence is far from robust.

Conflict of interest statement

None of the funding organizations had any role in the design or conduction of the study, in the data collection, management or interpretation, nor in the manuscript writing, reviewing or approval. All authors declared no conflicts of interest.

ACKNOWLEDGEMENTS

Financial support for this study was provided by Instituto de Salud Carlos III FEDER: Fondo Europeo de Desarrollo Regional (FIS PI08/90090 and PI13/00412) and DIUE of Generalitat de Catalunya (2014 SGR 748). The funding agreements ensure the authors' independence in designing the study, interpreting the data, and writing and publishing the report.

We would like to thank Aurea Martin for her writing assistance, proofreading, manuscript editing and the submission preparation process.

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Supplementary material associated with this article can be found in the online version:

Appendix 1. MEDLINE and EMBASE specific search strategies

Appendix 2. Patient Intervention Comparator Outcome (PICO) strategy

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FIGURE CAPTIONS

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow of Literature Diagram

Figure 2. Estimations of accumulated direct costs (euros) for each intervention plotted through the time horizon (years). Numbers correspond to the articles in the reference list.

Table 1: Characteristics of Economic Evaluations Identified in the Systematic Review

Authors (Year) Country [Reference]	Population	Interventions (No. patients)	Economic Perspective (Time Horizon)	Source for Costs data (year)	Source of effects	Type of Evaluation (Design / Model)
A. EXPECTANT MANAGEMENT (ACTIVE SURVAILLANCE OR WATCHFUL WAITING) VS OTHER TREATMENTS						
Koerber, et al. (2014) Germany [28]	Theoretical cohort Mean 65 Years LE>15 years PSA ≤10 ng/ml Gleason: ≤6 Stage:≤T2a No severe comorbidities	Active Surveillance RP (No. patients Not applicable)	Societal (Lifetime, age limit 100 years)	Published literature German DRG, physician's fee, pharmaceutical prices catalogues (2011) Discount rate 3%	Disease mortality from SCPG-4 data Baseline utilities: German survey with EQ-5D Health state specific utilities: published literature	Cost - utility analysis (Markov model)
Lyth, et al. (2012) Sweden [29]	Randomized trial SPCG-4 Age< 75 years, LE>10 years PSA <50 ng/ml No other cancer	WW RP (n total =695)	Payer (10 years)	Retrospectively collected in SPCG-4 trial patient records. (2007) Discount rate 3.5%	Individual-patients data from SPCG-4 with a 77-item questionnaire	Cost - utility analysis (Semi-Markov model)
Andersson, et al. (2011), Sweden [30]	Randomized trial SPCG-4 Age <75 years LE>10 years, PSA <50 ng/ml	WW (n=105) RP (n=107)	Payer (12 years)	Medical records and price list at the University Hospital in Örebro (2007)	NA	Cost Comparison (Not modeling)
Bauvin, et al. (2003) France [31]	Retrospective control-cohort study (patients diagnosed in 1995)	WW (n=46) RP (n= 56)	Payer (5 years)	Delphi method (1995) Discount rate 3%	Survival at 5 years from individual-patients data	Cost-effectiveness analysis (Not modeling)
Hummel, et al (2003) UK [22]	Theoretical cohort Age: 65-year old	WW RP BT 2DRT 3DCRT	Payer (Lifetime, age limit 100 years)	Literature review and NHS trusts (2002) Discount rate 6%	Literature review for Utilities Authors assume equal disease-free survival effectiveness	Cost-utility (Markov model)

B. ROBOT-ASSISTED LAPAROSCOPIC PROSTATECTOMY (RALP) VS OTHER SURGICAL TECHNIQUES						
Lord, et al. (2013) UK [32]	Theoretical cohort	RRP (n=1,000) PRP (n=1,000) LRP (n=1,000) RALP (n=1,000)	Payer (Lifetime, age limit 100 years)	NHS data & Literature review. (2010 - 11) Discount Rate 3.5%	Disease registries and recent UK systematic reviews and meta-analyses.	Cost-utility analysis (Individual-level Discrete event simulation)
Close, et al. (2013) UK [33]	Theoretical cohort Mean 61.5 years	RALP (n=5,000) LRP (n=5,000)	Payer (10 years)	UK NHS da Vincy Surgical System prices provided by the manufacturer. (2009) Discount rate: 3.5%	Systematic literature review and meta-analysis of clinical effectiveness and expert advisory group	Cost - utility analysis (Discrete event simulation model)
Barbaro, et al. (2012) Italy [34]	Observational prospective cohort study Treatment 2007-8 Mean 63.8 years	RRP (n = 99) RALP (n = 24)	Hospital (hospital stay)	Patient's medical health record and operating room report. Hospital accounting office reimbursement fees. (2008)	Primary data from the study itself	Cost Comparison
Hohwu, et al. (2011) Denmark [35]	Retrospective cohort Age: 50-69 years Treatment 2004-7	RALP(n=77) RRP (n=154)	Societal (1 year)	Medical records, price list hospital and national registries. Absence from work using the human capital method. (2008)	Primary data from the study itself SF-6D from SF-36 questionnaire	Cost - utility analysis
C. CONVENTIONAL EXTERNAL RADIOTHERAPY VS NEW MODALITIES						
Hummel, et al. (2012) UK [36]	Theoretical cohort Age 70 years	IMRT 3DCRT (10.000 patients for each model)	Payer (Lifetime, age limit 100 years)	St Bartholomew's hospital Literature review, expert opinion. None primary data collected on resource use. (2008) Discount rate 3.5%	Systematic literature review	Cost - utility analysis Discrete event simulation model
Lundkvist, et al. (2005) Sweden [37]	Theoretical cohort Age: 65-year	Proton Therapy External Radiotherapy	Payer (Lifetime, age limit 100 years)	Published literature and assumptions (2002) Discount rate 3%	Published literature	Cost - utility analysis Markov model
Hummel, et al (2003) UK [22]	Theoretical cohort Age: 65-year old	RP BT 2DRT 3DCRT	Payer (Lifetime, age limit 100 years)	Literature review and NHS trusts. (2002) Discount rate 6%	Literature review for Utilities Authors assume equal disease-free survival effectiveness	Cost-utility (Markov model)

D. PROSTATECTOMY VS RADIATION TREATMENT						
Becerra, et al. (2011) Spain [38]	Observational prospective cohort Mean age: RP =63.7 years BT=67.6 years 3DCRT=69 years	RP (n=181) BT (n=64) 3DCRT (n=153)	Payer (6 months)	Micro costing from reference hospitals, patient charts, tariffs and previously published data. (2004-2005). Not discount rate	Equally effective	Cost minimization Not modelling
Buron, et al. (2007) France [39]	Observational retrospective cohort 11hospitals PSA ≤20 ng/ml Gleason <8.	RP (n=127 BT (n=308)	Societal (2 years)	French National Security fee schedule for DRG and outpatient. Production loss: French daily national average wage. (2001)	EORTC core QLQ-C30 and EORTC QLQ-PR25.	Cost-effectiveness analysis Not modelling
Hummel, et al (2003) UK [22]	Theoretical cohort Age: 65-year old	RP BT 2DRT 3DCRT	Payer (Lifetime, age limit 100 years)	Literature review and NHS trusts. (2002) Discount rate 6%	Literature review for Utilities Authors assume equal disease-free survival effectiveness	Cost-utility (Markov model)

Abbreviations: BT, brachytherapy; DRG, Diagnosis Related Group; SPCG-4 trial, Scandinavian Prostate Cancer Group Study Number 4 trial; IMRT, intensity-modulated radiation therapy; LE, Life expectance; LRP, laparoscopic prostatectomy; RALP, robot-assisted laparoscopic prostatectomy; RP, radical prostatectomy; PRP, transperineal radical prostatectomy; RRP, radical retropubic prostatectomy; PSA, prostate specific antigen; QALYs, quality-adjusted life years; WW, watchful waiting; 2DRT, two dimensional radiotherapy; 3DCRT, three dimensional conformal radiotherapy.

Table 2. Main Findings of Economic Evaluations Identified in the Systematic Review

Authors (Year) Country [Reference]	Mean Cost Mean Incremental (Δ) Cost	Effectiveness measure or Incremental (Δ) QALYs	ICER	Sensitivity Analyses	Conclusions
A. EXPECTANT MANAGEMENT (ACTIVE SURVAILLANCE OR WATCHFUL WAITING) VS OTHER TREATMENTS					
Koerber, et al. (2014) [28]	**Mean Cost:** RP €16,468; AS €9,585 **Mean Δ Cost RP vs AS:** €6,883	**Life expectancy:** RP 12.15; AS 12.07 **QALYs:** RP 7.56; AS 7.60	**€/ Life year gained for RP**: 96,420 **€/ QALY gained:** AS resulted a dominant strategy over RP.	-Probability of metastases in AS -AS utility weights -Time horizon: 5, 15 and 30 years. -Discount rate 0,5,7 and 10%	"AS is likely to be a cost-saving treatment strategy for some patients with early stage localized prostate cancer. However, cost-effectiveness is dependent on patients' valuation of health states […]"
Lyth, et al. (2012) [29]	**Mean Δ Cost RP vs WW:** **S1-** SEK 40,116 **S2-** SEK 49,784 **S3-** SEK 59,160 **S4-** SEK 63,834 **S5-** SEK 70,074 **S6-** SEK 72,439	**Δ QALY:** **S1-** 0.57 **S2-** 0.86 **S3-** 0.25 **S4-** 0.42 **S5-** 0.08 **S6-** 0.15	**SEK/ QALY gained for RP:** **S1-** 70,766 **S2-** 58,045 **S3-** 232,409 **S4-** 150,274 **S5-** 858,703 **S6-** 472,327	**Scenarios:** **S1**-65y Gleason 0-4 **S2**-65y Gleason 5-6 **S3**-70y Gleason 0-4 **S4**-70y Gleason 5-6 **S5**-75y Gleason 0-4 **S6**-75y Gleason 5-6	"Assuming a threshold value of 200,000 SEK /QALY gained, for patients aged ≤70 years the treatment is always cost-effective, except at age 70, Gleason 0–4 and PSA ≤10[…]"
Andersson, et al. (2011) [30]	**Mean Cost:** RP €24,247; WW €18,124	Not Applicable	Not Applicable	Not Applicable	"In this economic evaluation of RP versus WW of localized prostate cancer in a randomized study, RP was associated with 34% higher costs. […]"
Bauvin, et al. (2003) [31]	**Mean Cost:** RP €8,533; WW €2,143	**5 year survival:** RP 89%; WW 78% **5 year relative survival**: RP 97%; WW 95%	ICER not reported	Not reported	Results supported the cost-effectiveness of radical prostatectomy over watchful waiting.
Hummel, et al (2003) [22]	**Mean Cost:** WW £1,714 BT £6,880 3DCRT £2,103	**QALYs:** WW 8.88 BT 9.28 3DCRT 8.89	**£/ QALY gained (WW as reference):** - 12,828 for BT - 26,766 for 3DCRT	- Incidence of adverse events -Utilities -Age -Costs	"[…]It is difficult therefore to draw conclusions on the relative benefits or otherwise of the newer technologies owing to the lack of substantive evidence of any quality and the lack of comparisons between the newer technologies and with standard treatments. […]"

B. ROBOT-ASSISTED LAPAROSCOPIC PROSTATECTOMY (RALP) VS OTHER SURGICAL TECHNIQUES					
Lord, et al. (2013) [32]	**Mean Costs:** RRP £6,485; LRP £6,534 PRP £6,510; RALP £6,458	**QALYs:** RRP 7.937; LRP 7.936 PRP 7.936; RALRP 7.943	**£/ QALY gained:** RALP resulted a dominant strategy over all other	-Willingness-to-pay threshold	"[…]The practical usefulness of our models to guideline developers and users should also be investigated, as should the feasibility and usefulness of whole guideline modelling alongside development of a new Clinical Guidelines."
Close, et al. (2013) [33]	**Mean Costs:** RALP £9,040; LRP £7,628 **Nº Procedures/year (P/year)** **200** RALP £9040; LRP £7628 **150** RALP £9799; LRP £7628 **100** RALP £11,312; LRP £7628 **50** RALP £15,859; LRP£7,628 Three-arm robot(Da Vinci®) with **200 P/year:** RALP £8,168; LRP £7,628	**QALYs:** RALP 6.52; RLP 6.44	**£/ QALY gained for RALP:** - 18,329 for **200** P/year - 28,172 for **150** P/year - 47,822 for **100** P/year - 106,839 for **50** P/year Three-arm robot(DaVinci®)) £7,009 /QALY for **200** P/year	-Positive margin rate after RALP -Procedures/year -Patient's lifetime -Price of robotic system	"Higher costs of robotic prostatectomy may be offset by modest health gain resulting from lower risk of early harms and positive margin, provided >150 cases are performed each year. Considerable uncertainty persists in the absence of directly comparative randomised data."
Barbaro, et al. (2012) [34]	**Mean Surgical Costs:** RALP €20,103.4; RRP €2,764 **Mean Hospital Costs:** RALP €3,357.6; RRP €2,790.7 **Mean Total Costs:** RALP €23,609.7; RRP €5,635.1	Not Applicable	Not Applicable	-Case volumes -Operating times	" In the current circumstances, increasing the use of RAP at the San Giovanni Battista Hospital does not appear expedient. This conclusion is corroborated by the sensitivity analysis which showed that RAP carries higher costs than RRP."
Hohwu, et al. (2011) [35]	**Mean direct costs:** RALP €8,369 RRP €3,863 **Mean Indirect costs**: RALP €13,411 RRP €12,465	**Successful treatment:** RALP 34%; RRP 27% **QALYs:** RALP 0,0103; RRP 0,0116	**€/ extra successful treatment for RALP** -64,343 for direct costs -13,514 for indirect costs **€/ QALY gained for RALP:** RALP resulted a dominant strategy over RRP.	-Life time for robot -Procedures/year	"RALP was more effective and more costly. A way to improve the cost effectiveness may be to perform RALP at fewer high volume urology centres and utilise the full potential of each robot"

C. CONVENTIONAL EXTERNAL RADIOTHERAPY VS NEW MODALITIES					
Hummel, et al. (2012) [36]	**Mean total discounted costs: IMRT / 3DCRT** **S1**- £6,173 / 5,184 **S2**- £4,946 / £4,214 **S3**- £4,946 / £4,486 **S4**- £5,687 / £7,489	**Total discounted QALY: IMRT / 3DCRT** **S1**- 6,802 / 6,792 **S2**- 7,070 / 7,046 **S3**- 7,070 / 6,983 **S4**- 7,015 / 6,402	**£/ QALY gained for IMRT:** **S1**-104,066 **S2**- 31,162 **S3**- 5,295 **S4**- dominant strategy.	**Scenarios:** S1- equal dose& PSA relapse S2- 15% difference in late gastro intestinal toxicity S3- 3.8 y survival difference S4- 6.6 y survival difference	"If IMRT can be used to prolong survival, it is very cost-effective. Otherwise cost-effectiveness is uncertain"
Lundkvist, et al. (2005) [37]	**Δ total cost for standard case Proton Therapy vs External Radiotherapy:** €7,953 per patient,	**Δ QALY for Proton Therapy:** 0.297 / patient	**€ / QALY gained for Proton Therapy:** - 26,776	Not reported	"Proton therapy was cost-effective if appropriate risk groups were chosen. The results must be interpreted with caution, since there is a lack of data, and consequently large uncertainties in the assumptions used"
Hummel, et al (2003) [22]	**Mean total costs:** WW £1,714 BT £6,880 3DCRT £2,103	**QALYs:** RT 8.56 BT 9.28 3DCRT 8.89	**£/ QALY gained (2DRT as reference):** - 8,575 for BT - 683 for 3DCRT	- Incidence of adverse events -Utilities -Age -Costs	See above
D. PROSTATECTOMY VS RADIATION TREATMENT					
Becerra, et al. (2011) [38]	**Mean total cost:** RP €6863,7 BT €5453,6 3DCRT € 3336,1	Not Applicable	Not Applicable	-Cost of 3DCRT	"Radical prostatectomy therapeutic proved to be the most expensive treatment option. […] Most of the costs were explained by the therapeutic option, and neither comorbidity nor risk groups showed an effect of total costs independent of treatment."
Buron, et al. (2007) [39]	**Mean societal cost:** BT €8,019; RP €8,715 **Mean Initial treatment costs:** BT €7,159; RP €6,472 **Mean hospital follow-up costs:** BT €268; RP €992 **Mean Outpatient costs**: BT €482; RP €419, **Mean loss productivity costs:** BT€620; RP €3,678	Urinary incontinence BT 20%; RP 49% Fecal incontinence BT 9%; RP 2% Rectal Bleeding BT 15%; RP 0% Erectile Dysfunction BT45.8%; RP 83.3%	ICER not reported	Not reported	"This study suggests a similar cost profile in France for BT and RP but with different health-related quality of life and side effect profiles. Those findings may be used to tailor localized prostate cancer treatments to suit individual patients' needs."

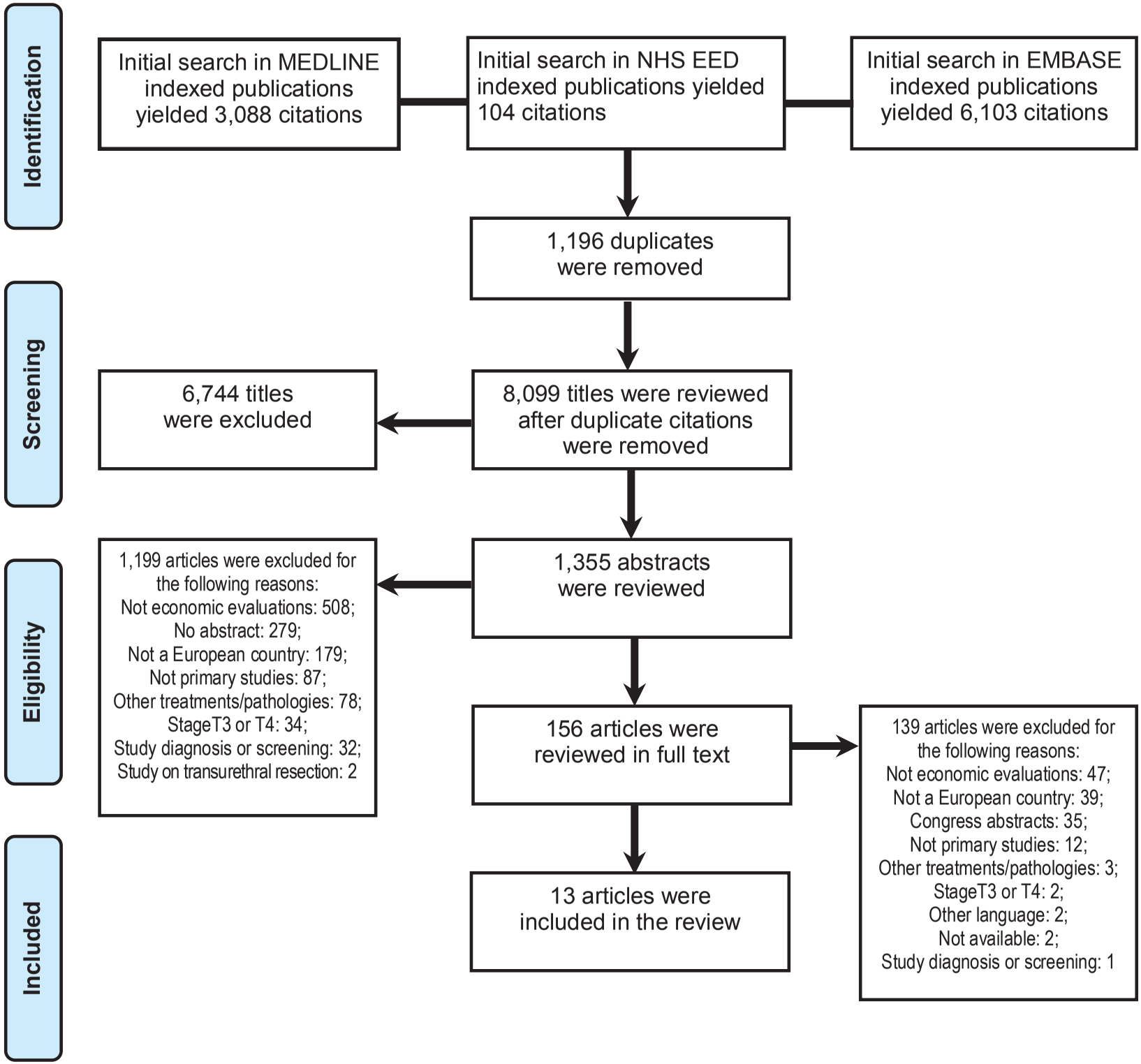
Hummel, et al (2003) [22]	**Mean total costs:** WW £1,714 BT £6,880 3DCRT £2,103	**QALYs** RP 8.93 BT 9.28 3DCRT 8.89	**£/ QALY gained (RP as reference):** - 2021 for BT - (NA costs less than RP) for 3DCRT	- Incidence of adverse events -Utilities -Age -Costs	See above

Abbreviations: AS, active surveillance; BT, brachytherapy; ICER, Incremental cost-effectiveness ratio; IMRT, intensity-modulated radiation therapy; LRP, laparoscopic prostatectomy; RALP, robot-assisted laparoscopic prostatectomy; RP, radical prostatectomy; PRP, transperineal radical prostatectomy; RRP, radical retropubic prostatectomy; QALYs, quality-adjusted life years; WW, watchful waiting; 2DRT, two dimensional radiotherapy; 3DCRT, three dimensional conformal radiotherapy.

Table 3. Methodological quality assessment of economic evaluations using Drummond's 10-item Checklist.

(yes / no / can't tell)	Koerber 2014 [28]	Lyth 2012 [29]	Bauvin 2003 [31]	Hummel 2003 [22]	Lord 2013 [32]	Close 2013 [33]	Hohwu 2011 [35]	Hummel 2012 [36]	Lundkvist 2005 [37]	Becerra 2011 [38]	Buron 2007 [39]
1. Was a well-defined question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the effectiveness of the programme or services established?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes
4. Were all the important and relevant costs and consequences for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes
5. Were costs and consequences measured accurately in appropriate physical units'	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes
6. Were costs and consequences valued credibly?	Yes	Yes	Can't Tell	Yes	Yes	Yes	No	Yes	Can't Tell	Yes	Yes
7. Were costs and consequences adjusted for differential timing?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
10. Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes	Can't Tell	Yes	Yes	Yes	Yes	Yes	Can't Tell	Yes	Yes
Score (Total)	**10**	**10**	**5**	**10**	**10**	**10**	**8**	**10**	**4**	**9**	**9**

Number between square brackets corresponds to reference list position.


Identification
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Eligibility
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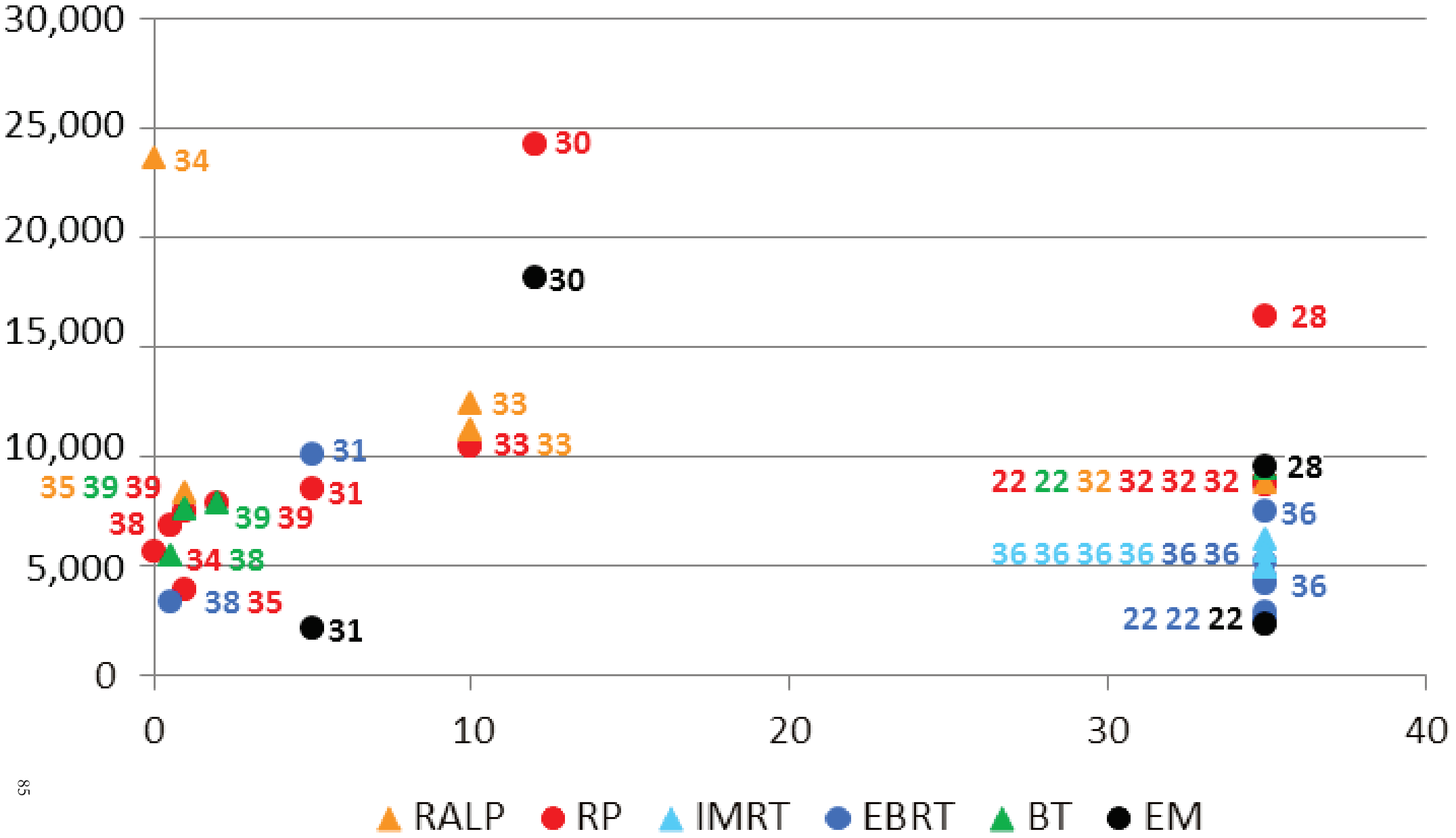
Initial search in MEDLINE indexed publications yielded 3,088 citations
Initial search in NHS EED indexed publications yielded 104 citations
Initial search in EMBASE indexed publications yielded 6,103 citations
1,196 duplicates were removed
8,099 titles were reviewed after duplicate citations were removed
6,744 titles were excluded
1,355 abstracts were reviewed
1,199 articles were excluded for the following reasons:
Not economic evaluations: 508;
No abstract: 279;
Not a European country: 179;
Not primary studies: 87;
Other treatments/pathologies: 78;
StageT3 or T4: 34;
Study diagnosis or screening: 32;
Study on transurethral resection: 2
156 articles were reviewed in full text
139 articles were excluded for the following reasons:
Not economic evaluations: 47;
Not a European country: 39;
Congress abstracts: 35;
Not primary studies: 12;
Other treatments/pathologies: 3;
StageT3 or T4: 2;
Other language: 2;
Not available: 2;
Study diagnosis or screening: 1
13 articles were included in the review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IMRT
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EM

Appendix 1. Online supplementary material.

MEDLINE and EMBASE specific search strategies

A. MEDLINE

Search term
1. (((((((("Hospital Costs"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR "Employer Health Costs"[Mesh] OR "Health Care Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Economics"[Mesh]) OR ("economics"[Subheading] OR "economics"[All Fields] OR "economics"[MeSH Terms])) OR ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR ("cost"[All Fields] AND "analysis"[All Fields]) OR "cost analysis"[All Fields])) OR ("economics"[Subheading] OR "economics"[All Fields] OR "fees"[All Fields] OR "fees and charges"[MeSH Terms] OR ("fees"[All Fields] AND "charges"[All Fields]) OR "fees and charges"[All Fields])) OR ("fees and charges"[MeSH Terms] OR ("fees"[All Fields] AND "charges"[All Fields]) OR "fees and charges"[All Fields] OR "charge"[All Fields])) OR ("hospital charges"[MeSH Terms] OR ("hospital"[All Fields] AND "charges"[All Fields]) OR "hospital charges"[All Fields])) OR ("budgets"[MeSH Terms] OR "budgets"[All Fields] OR "budget"[All Fields])) OR ("commerce"[MeSH Terms] OR "commerce"[All Fields] OR "price"[All Fields])) OR ("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]))
2. (((((("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] AND ("2000/01/01"[PDAT] : "2015/05/19"[PDAT])
3. 2 AND 3

B. EMBASE

Search term
1. ('socioeconomics'/exp or 'cost benefit analysis'/exp or 'cost effectiveness analysis'/exp or 'cost of illness'/exp or 'cost control'/exp or 'economic aspect'/exp or 'financial management'/exp or 'health care cost'/exp or 'health care financing'/exp or 'health economics'/exp or 'hospital cost'/exp or (fiscal:ab,ti or financial:ab,ti or finance:ab,ti or funding:ab,ti) or 'cost minimization analysis'/exp or (cost$ and estimate$) or (cost$ and variable$) or (unit and cost$))
2. (('prostate cancer' or 'prostatic neoplasms' or (prostate:ab,ti and cancer:ab,ti) or (prostatic:ab,ti and cancer:ab,ti) or (prostat:ab,ti and cancer:ab,ti) or (prostate:ab,ti and carcinoma:ab,ti) or (prostatic:ab,ti and carcinoma:ab,ti) or (prostat:ab,ti and carcinoma:ab,ti))
3. ('prostate hypertrophy' or (prostate:ab,ti and hyperplasia:ab,ti) or (prostatic:ab,ti and hyperplasia:ab,ti) or (prostat:ab,ti and hyperplasia:ab,ti)))
4. 2 NOT 3
5. 1 AND 4
6. #5 AND [embase]/lim
7. #5 AND [embase]/lim AND [2000-2015]/py
8. #5 AND [embase]/lim AND [2000-2015]/py AND [humans]/lim

Appendix 2. Online supplementary material.

Patient Intervention Comparator Outcome (PICO) strategy

Criteria	
Population	Men with localized prostate cancer If unclear: include participants stated to have prostate cancer, or prostate related diseases
Intervention	Treatments for localized prostate cancer: Radical prostatectomy OR External Radiotherapy OR Brachytherapy Specific interventions for prostate cancer may not be reported in the abstract
Comparators	Any treatment for stated Interventions No treatment
Outcomes	Do not exclude on outcomes at abstract screening stage. At full-text screening: outcomes include: Incremental cost per quality-adjusted life-year (primary outcome) Incremental cost-effectiveness ratios (ICERs) Other measures of cost-effectiveness Costs comparisons
Timepoints/ follow-up	Any
Study type	Cost-effectiveness, cost-benefit or cost-utility studies Comparative studies If unclear: include studies reporting costs or resource use in this population
Publication date	January 2000– March 2015
Publication language	Any European language
Setting	Any European country

4.3 Manuscript 3. Economic Evaluation of localized prostate cancer treatments: Ten year follow - up cohort study.

Becerra V, Garin O, Guedea F, Suárez JF, Fernández P, Macías V, Mariño A, Hervás A, Herruzo I, Ortiz MJ, Ponce de León J, Sancho G, Ávila M, Pont A, Alonso J, Cots F, Ferrer M and the Multicentric Spanish Group of Clinically Localized Prostate Cancer. **Economic Evaluation of localized prostate cancer treatments: Ten year follow - up cohort study.** *(Under review)*

Title: Economic Evaluation of localized prostate cancer treatments: Ten year follow-up cohort study.

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Abstract (275 words)

Purpose: There is no economic evaluation of radical prostatectomy and radiation treatments based on empirical non-modeled data. We aim to perform a cost-effectiveness analysis from the National Health System's perspective, comparing radical prostatectomy with brachytherapy, and external radiotherapy based on 10 years of primary data from the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort.

Methods: Patients diagnosed of localized prostate cancer were consecutively recruited in 2003-2005 from ten Spanish hospitals. The outcome measures to evaluate the incremental cost-effectiveness ratio between treatments (ICER) were quality-adjusted life-years (QALYs) (calculated by the SF-6D utility index and survival data), and 10-year medical activities used to derive costs. Unadjusted and propensity score adjusted outcomes were estimated.

Results: The SF-6D index decreased over time, with statistically significant differences among treatments from year 5. Survival estimates were higher for radical prostatectomy than brachytherapy (p=0.013) and external radiotherapy (p=0.002). Means of 10-year QALYs were higher for radical prostatectomy (7.7) than brachytherapy (7.3) and external radiotherapy (6.9), differences being statistically significant. Means of 10-year costs were the highest for radical prostatectomy (€9,655) followed by brachytherapy (€8,795) and external radiotherapy (€6,660). The ICER that resulted from the use of unadjusted differences in means was €2,205 for brachytherapy and €3,791 for external radiotherapy. All differences between treatments disappeared after adjusting, except for the lower cost of external radiotherapy.

Conclusion: Our findings support that no relevant differences exist on effectiveness for the three curative treatments evaluated. Similarly, although external radiotherapy is cheaper than surgery and brachytherapy, the magnitude of the incremental cost does not justify restricting the others. These results provide relevant patient-based

outcomes to characterize common primary treatments and facilitate decision-making processes between patients and physicians.

INTRODUCTION

Worldwide, 1.1 million new cases of prostate cancer were estimated in 2012, almost 70% occurring in the more developed regions where, in many countries, it is the most common cancer in men.[1] After the introduction of Prostate-Specific Antigen (PSA) testing, prostate cancer mortality has declined [2] and the epidemiology of this tumor changed. Currently, most cases are diagnosed at local stages, and patients' average age has decreased to 65 years.[3]

The optimal management of localized prostate cancer patients is controversial. There are numerous treatment alternatives available (including surgery, radiotherapy, and active surveillance, among others) with notable long-term survival regardless of intervention,[4] but substantially different patterns of side effects.[5-7] On the other hand, the relative abandon of some techniques[8] and rapid adoption of newer modalities has raised concern,[9, 10] bringing more uncertainty to the decision-making process, and increasing the number of economic evaluations for localized prostate cancer treatments. Most of these compare different variations of the same therapeutic option,[11-21] while very few provide comparison of surgery with radiation therapies.[22-24]

The few economic evaluations comparing radical prostatectomy with radiation alternatives were based on modeling theoretical cohorts for lifetime,[22-24] and found some contradictory results. From the USA payer's perspective, Cooperberg et al.[23] showed that external radiation and brachytherapy were less cost-effective than surgery, while Hayes et al.[22] found that brachytherapy was more effective and less expensive than radical prostatectomy for men aged 65 years with localized prostate cancer. Hummel et al.[24] also reported that brachytherapy was more cost-effective than surgery from the UK payer perspective.

To our knowledge, there is no economic evaluation of radical prostatectomy and radiation treatments based on empirical real world, non-modeled, data. Assessing these alternatives in a single prospective cohort with a long-term follow-up can provide relevant information to know the true efficiency of these options. Therefore, the objective of this study was to perform a cost-effectiveness analysis from the

National Health System's perspective, comparing radical prostatectomy with external radiotherapy and brachytherapy, based on 10 years of primary data from the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort.

PATIENTS and METHODS

This was an observational comparative study of costs and effectiveness from a localized prostate cancer cohort of patients treated with radical prostatectomy, external beam radiotherapy or brachytherapy, followed from time of diagnosis to 10 years post-treatment.

Spanish Multicentric Study of Clinically Localized Prostate Cancer

Participants included in the ''Spanish Multicentric Study of Clinically Localized Prostate Cancer" were consecutively recruited in 2003-2005 from ten Spanish hospitals. The study was approved by the ethics review boards of the participating hospitals, and written informed consent was obtained from the patients. Details of the study have been described elsewhere.[7, 25, 26]

Briefly, newly diagnosed patients with localized prostate cancer (stages T1 o T2), treated in one of the participating centers, and with no previous transurethral prostate resection were eligible. From the 841 patients recruited, 44 did not meet inclusion criteria, 18 were transferred to other hospitals before treatment, and 14 refused to participate. For the purpose of this analysis, 61 high-risk patients were excluded giving a total of 704 participants (See supplementary CONSORT flow diagram) . Baseline evaluation was performed before treatment registering: T stage, PSA, Gleason histological grading scores, and patient reported outcomes (the Short Form-36 version 2 (SF-36) among other questionnaires). The latter were administered centrally by telephone interviews before treatment and during follow-up at one, three, six, and 12 months after treatment the first year, and annually thereafter.

Treatment

Decisions on treatment options were made jointly by patients and physicians: 193 chose radical prostatectomy, 194 external radiotherapy, and 317 brachytherapy. The surgery group underwent radical retropubic prostatectomy with nerve-sparing technique at the surgeon's discretion. External beam radiation was 3D conformal. Treatment was delivered with 1.8-2.0 Gy daily fractions to a mean total dose of 73.7 Gy (SD=5.0) to the prostate planning target volume. In the brachytherapy group participants received ^{125}I, and the prescription dose was 144 Gy to the reference isodose (100%) according to the TG-T43.[27] The median dose of D90 and V100% was 158 Gy and 93%, respectively.

Effectiveness

Effectiveness was evaluated with Quality-Adjusted Life Years (QALYs) during 10 years post-treatment. A QALY is a measure of disease burden combining the value of both the length and quality of life. The QALYs were calculated by adding up the annual products of survival and utility weights over the 10 years of the study. Utility weights came from the SF-6D (derived from the SF-36 completed yearly by the study patients). The SF-6D[28] is a utility index based on a descriptive system composed of 11 SF-36 items. The standard gamble preference utilities applied was developed[29] from a representative sample of the UK general population. Health state values on the SF-6D are anchored to 1 (perfect health) and 0 (death). For QALYs estimation, missing data on SF-6D index was imputed using the estimations from Generalized Estimating Equation models to account for correlation among repeated measures.

Resource Use, Unitary Costs and Cost Estimates

The cost analysis assumed the healthcare system's perspective, and direct healthcare costs were estimated by micro-costing calculation and bottom-up approach. To calculate cost, we used patient-level data from a subsample of the cohort with patients recruited at a functional unit for prostate cancer composed of two hospitals (n=305); and multiple imputation for the rest of the cohort.

Inpatient and outpatient utilization data was collected for each patient retrospectively from the hospital database for the period between 90 days before and 10 years after treatment initiation, except for resource use derived from the diagnostic process before treatment, which was excluded.

Activities attributable to prostate cancer treatment were selected by comprehensive analysis of the relationship with the disease and time sequence. Specific study data was used for the relapse rescue treatment with hormonetherapy (from the clinical follow-up form), and use of diapers for urinary incontinence (patients' telephone interviews). Data on dispensed hormonal therapy by pharmacies at individual level was extracted from the Reginal Pharmacology Register.

Unit costs were obtained from accounting departments of participating hospitals, a Spanish database of costs[30] and reimbursement tariffs. Ex-factory pharmacological prices were considered. (See supplementary table).

Estimates of costs were obtained multiplying the number of times that each resource was used by the corresponding unit cost. Adding-up these costs, the direct cost of the treatment until death or 10 years after treatment was estimated for each patient. All costs were in Euros and the price year was 2015. Costs and QALYs were discounted at 3% annual rate, as recommended.[31, 32]

Statistical analysis

For each treatment group, we report means (continuous variables) and percentages (categorical variables) for the baseline demographic and clinical characteristics. Figures showing the evolution by treatment of SF-6D index and survival curves were constructed. To test for differences among treatment groups, the Chi-square test was used for categorical variables and univariate repeated measures analysis of variance (ANOVA) for continuous ones, using a p value of 0.05 as the significance threshold. We used the Tukey studentized range test for post-hoc comparisons between group means. Differences in survival were tested by Cox regression models constructed from date of treatment to date of death or the latest available information for vital status.

For each of the outcomes (QALYs and direct costs), we calculated the difference between treatment groups (using radical prostatectomy as the reference), and the 95% confidence interval (95% CI). Outcomes were reported first as unadjusted and secondly as adjusted, using propensity scores by including them in least square regression models. Propensity scores were estimated to maximize the balance in the distribution of possible confounders among treatment groups. As described previously,[26, 33] a multinomial logistic regression model was constructed to estimate the conditional probability of receiving a treatment, given measured covariates (prostate cancer characteristics, general health status, and socio-demographic variables). (See supplementary table) The C-statistic of this model was 0.92 (95%CI=0.90-0.94) for radical prostatectomy, 0.85 (95%CI=0.82-0.88) for brachytherapy, and 0.81 (95%CI=0.78-0.85) for external radiotherapy, indicating good discriminant ability. To compare efficiency between treatments we estimated the incremental cost-effectiveness ratios (ICERs): (mean cost of treatment X – mean cost of surgery) / (mean QALYs of treatment X – Mean QALYs of surgery). We assessed the statistical uncertainty of the ICERs estimating 95%CIs by use of the nonparametric bootstrap. All the analyses were run in SAS 9.3.[34]

RESULTS

Table 1 shows baseline unadjusted means and percentages of the patients' clinical characteristics, which presented statistically significant differences among treatment groups in several variables (age, tumor stage, PSA, Gleason score, risk group, and neoadjuvant hormonal treatment). Figure 1 shows unadjusted and adjusted means of SF-6D index over the 10-year follow-up period. SF-6D completion rate at ten years was 91.7%, with a median time between treatment and the tenth annual telephone interview of 10.2 years (Interquartile range = 10.1 – 10.3). SF-6D index decreased markedly over time, from means around 0.86 pre-treatment to <0.73 at the end of follow-up. Unadjusted means presented some statistically significant differences among treatment groups from the 5^{th} to the 10^{th} year, but they disappeared after adjusting by propensity scores.

For vital status, the median duration of follow-up was 10.2 years. Of a total of 147 deaths, 26 patients had been treated with radical prostatectomy, 50 with external beam radiotherapy, and 71 with brachytherapy, as displayed in the survival curves of Figure 2. Unadjusted survival estimates were statistically significantly higher for radical prostatectomy than brachytherapy (p=0.013), and external radiotherapy (p=0.002). Again, differences between treatments disappeared after adjusting by propensity scores.

Utilization of healthcare resources is shown in table 2. The mean (SD) frequency of use of each resource is described by treatment and period (initial 6 moths, the rest of the follow-up, and for the 10 years). In general, during the initial period (diagnosis and treatment period) radical prostatectomy was the group that presented more utilization of resources, followed by brachytherapy, and external radiotherapy, with statistically significant differences (p<0.05). During follow-up, healthcare-related activities of patients from the 3 treatment groups showed a similar pattern except for use of: diapers which was the highest for radical prostatectomy (1,561; SD= 2,237.2); laboratory tests which were higher among brachytherapy patients (-13.8; SD=6.7), and hormonotherapy which was more frequent for external radiotherapy

group (12.9; SD=20.4). These differences remained statistically significant for the total 10-year period.

Figure 3 shows the timing of costs (unadjusted and adjusted) for the 3 treatment groups. The source of the health-care cost difference occurs in the first year after treatment, with prostatectomy (€6,452.20) and brachytherapy (€6,553.30) incurring first year costs more than 50% higher than external radiotherapy (€3,408.70). At year two, costs stabilize for all the groups between €271 and €376 per year, and the statistical significance of the costs differences disappear until the end of the 10-year follow-up. Similar results were found with unadjusted and adjusted costs by propensity scores.

Table 3 shows unadjusted and adjusted outcomes over the 10-year period. Unadjusted means of 10-year QALYs were higher for radical prostatectomy (7.7) than brachytherapy (7.3) and external radiotherapy (6.9). Differences with radical prostatectomy (used as reference) were statistically significant, 0.39 (95%CI 0.11-0.68) for brachytherapy, and 0.79 (95%CI 0.45-1.14) for external radiotherapy, and both disappeared after propensity score adjustment. Unadjusted means of 10-year costs were also the highest for radical prostatectomy (€9,655) followed by brachytherapy (€8,795) and external radiotherapy (€6,660). Only external radiotherapy showed statistically significantly lower costs (€3,169 95%CI 1,134 , 5,203) than radical prostatectomy, both for unadjusted and adjusted estimates. The ICER that results from the use of unadjusted differences in means was €2,205 for brachytherapy and €3,791 for external radiotherapy, per QALY gained.

DISCUSSION

We estimated the costs and quality-adjusted survival for a large cohort of men with localized prostate cancer. Over a 10-year period, patients treated with radical prostatectomy incurred greater costs than external 3D conformal radiotherapy, while no significant differences in quality-adjusted survival compared with those receiving brachytherapy or external radiotherapy were observed. However, according to traditional cost-utility thresholds, costs differences among treatments are not relevant enough, so any alternative could be considered economically attractive for patients with localized prostate cancer.

Radical prostatectomy was the most expensive treatment option (€9,671), followed by brachytherapy (€8,995) and external radiotherapy (€6,503). In general our estimates of accumulated direct healthcare costs are much lower than those reported in United States. [22, 23, 35, 36] Different health systems and cost structures may explain this. However, the vast majority of European estimations are consistent with our results in costs.[12, 13, 16, 24, 37, 38] For example, Close et al.[13] estimated the cost of the laparoscopic radical prostatectomy as €7,628 at 10-year horizon, and Lord et al.[12] as €6,534 for lifetime. Regarding radiotherapy, modelling estimations for a lifetime horizon in UK found mean costs of €6,880 and €2,103 for brachytherapy and 3D conformal radiotherapy[24], respectively, in 2003. Also with lifetime horizon, results reported more recently[16] for 3D conformal radiotherapy ranged from €4,214 to €7,489 depending on the scenario considered regarding gastrointestinal toxicity, PSA failure and survival.

QALYs have two components. The quantitative component, overall survival, did not show statistically significant differences across treatments after propensity score adjustment. In line with our findings, Zelefsky et al.[4, 39] showed no differences in prostate cancer specific mortality between surgery and radiotherapy among patients at low risk. Regarding the quality component of the QALY, it is necessary to comment the utilities trend of gradual decline over time, which could be related to co-morbidities associated to aging. In fact, means of the SF-6D index at the beginning and end of follow-up in our cohort (0.86 and 0.71) are quite similar to those

published for the general Spanish population:[40] 0.81 among individuals aged 45-64 years, and 0.72 among those aged 75 years or over.

Comparing with previous economic evaluations in localized prostate cancer, our results on effectiveness (adjusted means ranged 7.0-7.5 at 10 years) are consistent with those published by Cooperberg et al.[23] showing no relevant differences in QALYs for lifetime across treatments, which ranged 10.3-11.3 or 9.6-10.4 for patients at low and intermediate risk, respectively. Although economic evaluations published by Hayes et al.,[22] and Hummel et al.[24] showed that brachytherapy was more effective than surgery, their estimates were also very similar among treatments. For example, 9.3 vs 8.9 in well differentiated tumors [24] and 8.1 vs 8.0 [22] in men aged 65 years. The clinical relevance of these small differences of few months between alternatives is questionable, and common sense prevents from interpreting them as differences on effectiveness.

Since adjusted differences on QALYs were not statistically significant in our economic evaluation, only the unadjusted incremental cost-effectiveness ratio could be calculated to compare surgery with brachytherapy and external radiotherapy (€2,205 and €3,791 per QALY gained, respectively). It may be useless to calculate the incremental cost for gaining no benefit. However, due the wide range of relevant outcomes to take into account when treating patients with localized prostate cancer (from urinary or sexual side effects to death), further research may be needed to know whether the SF-6D index is gathering all the complexity of this specific disease.

Some limitations of this study should be taken into account. **First**, the main concern regarding observational studies is treatment-selection bias because participants were not randomly assigned. Differences among treatment groups at baseline are consistent with prescription of surgery to younger patients, and brachytherapy to those at lower risk. Propensity score methods are widely used in observational studies[41-44] to account for treatment-selection bias and, thus, identify the true treatment effects. As previously described in our cohort,[26] the propensity score adjustment achieved the balance in the distribution of baseline clinical characteristics

among treatment groups. It is worth highlighting the fact that randomized clinical trials to compare different treatments present considerable difficulties in these patients.[45, 46] **Second**, the study's 10-year time horizon, directly derived from the completed cohort follow-up, could be considered short compared with life time estimations (usually up to 15 years post-treatment). However, taking into account evidence[4] of overall survival equivalence among treatments, there would be no expected differential mortality beyond this 10-year period. **Third**, lost to follow-up is a major weakness for cohort studies, especially long-term. Nevertheless, response rate was higher than 90% in almost all follow-up evaluations and, specifically at 10-year follow-up, it was 88.5%, 90.7%, and 84.8% among prostatectomy, brachytherapy, and external radiotherapy groups, respectively. Also, telephonic interviews' completion rate was high, and only the 16.8% of the SF-6D index evaluations needed imputation. **Fourth**, since treatment was applied during 2003-2005, the procedures used (open radical prostatectomy, pre-planned brachytherapy, and 3D conformal radiation) may result in worse outcomes than modern techniques such as robotic surgery,[47] real-time brachytherapy,[48] or intensity modulated external radiotherapy.[49] Finally, although the EQ-5D could be considered the gold standard in economic evaluation for its widespread application, some head-to-head comparisons with the SF-6D[50] noticed the advantage of its lower ceiling effect to discriminate among groups with good health.

Novel long-term results are provided on cost-effectiveness for the three most established attempted curative treatments in localized prostate cancer patients at 10 years. One of the original contributions of this study is that, as far as we are aware, this is the first study comparing radical prostatectomy and radiotherapy alternatives using QALYs based on utilities directly obtained from patients. Our findings support that no relevant differences exist on effectiveness for the three treatments evaluated. Similarly, although external radiotherapy is cheaper than surgery and brachytherapy, the magnitude of the incremental cost does not justify restricting the other treatments. These results provide very relevant patient-based outcomes to characterize these common primary treatments and facilitate shared clinical decision-making processes between patients and physicians.

ACKNOWLEDGMENTS

Financial support for this study was provided by Instituto de Salud Carlos III FEDER: Fondo Europeo de Desarrollo Regional (FIS PI08/90090 and PI13/00412), Agency for Healthcare Quality and Evaluation of Catalonia (AQuAS), 436/05/2008 and DIUE of Generalitat de Catalunya (2014 SGR 748). The funding agreements ensure the authors' independence in designing the study, interpreting the data, and writing and publishing the report.

We would like to thank Gemma Vilagut for her advice and statistical consulting for the imputations. We would also like to thank Aurea Martin for her proofreading, manuscript editing and submission preparation process.

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Table 1. Patient characteristics and quality of life scores before treatment (N=704).

		Radical Prostatectomy	Brachytherapy	External-Beam Radiotherapy	p-value*
Participants		192	317	195	
Clinical Characteristics					
Age, mean (SD)		64.2 (5.5)	67.5 (6.4)	70.1 (5.3)	< 0.001
	< 65 years	100 (52.4%)	94 (30.0%)	32 (16.5%)	< 0.001
	65 – 70 years	64 (33.5%)	93 (29.7%)	49 (25.3%)	
	≥ 70 years	27 (14.1%)	126 (40.3%)	113 (58.2%)	
	missing	1 (0.5%)	4 (1.3%)	1 (0.5%)	
PSA (ng/mL), mean (SD)		7.6 (2.9)	7.0 (2.2)	8.1 (3.4)	< 0.001
	missing	1 (0.5%)	0	0	
Gleason score, mean(SD)		6.3 (0.7)	5.5 (0.9)	5.9 (1.1)	< 0.001
	missing	2 (1.0%)	0	0	
Clinical T Stage, n (%)					
	T1	130 (67.7%)	258 (81.4%)	114 (58.5%)	< 0.001
	T2	62 (32.3%)	59 (18.6%)	80 (41.0%)	
	Tx	0	0	1 (0.5%)	
Risk group, n (%)					
	Low	91 (47.6%)	283 (89.3%)	108 (55.4%)	< 0.001
	Intermediate	100 (52.4%)	34 (10.7%)	87 (44.6%)	
Neoadjuvant hormonal treatment, n (%)		17 (8.9%)	105 (33.1%)	61 (31.3%)	< 0.001

* Chi square test or one-way analysis of variance among the three treatment groups.

Table 2: Summary of health care resources units used during initial, follow-up and total period: mean (SD)

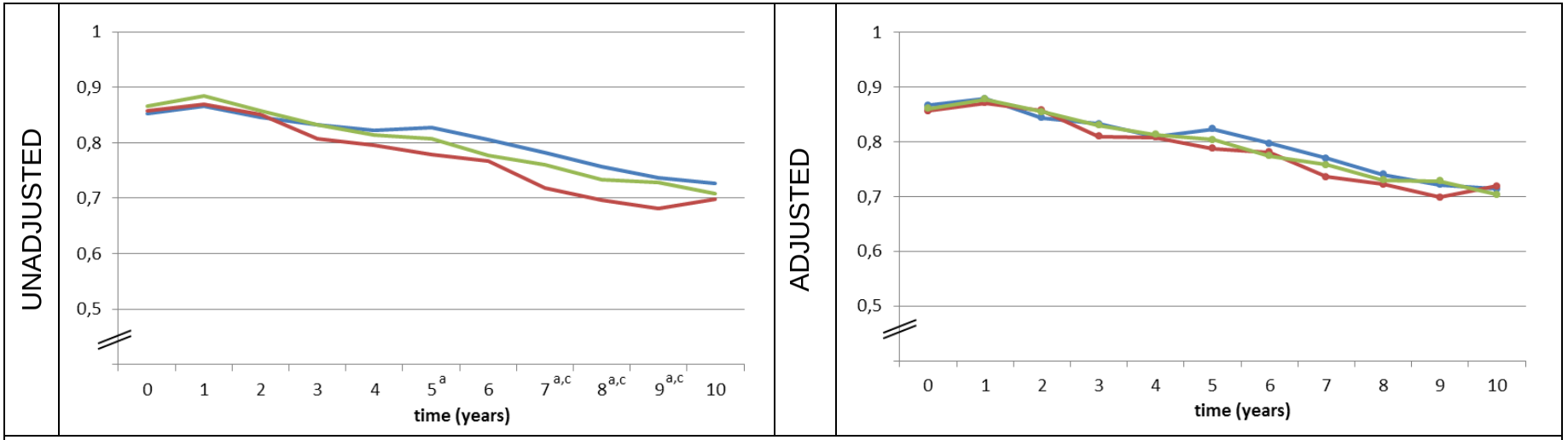
	Initial period of 6 months				Follow-up period				Total 10 years			
	RP	**BQ**	**EBRT**	**p-value**	**RP**	**BQ**	**EBRT**	**p-value**	**RP**	**BQ**	**EBRT**	**p-value**
n	157	58	90		157	58	90		157	58	90	
Hospitalization												
Number	1.1 (0.5)	1.0 (0.2)	0.0 (0.0)	< 0.001	0.1 (0.4)	0.1 (0.3)	0.1 (0.5)	0.987	1.2 (0.7)	1.1 (0.4)	0.1 (0.5)	< 0.001
days	7.8 (4.9)	3.2 (0.8)	0.0 (0.0)	< 0.001	0.3 (2.6)	0.4 (1.9)	0.6 (5.4)	0.847	8.1 (6.6)	3.6 (2.2)	0.6 (5.4)	< 0.001
RDT Sessions	37.2 (2.8)	---	---		---	---	---		37.2 (2.8)	---	---	
Outpatient visits	4.8 (1.9)	5.3 (1.5)	2.9 (1.3)	< 0.001	16.6 (20.9)	19.5 (9.3)	12.1 (8.2)	0.017	21.4 (21.1)	24.8 (9.8)	14.9 (8.6)	0.001
Emergency visits	0.3 (0.7)	0.3 (1.3)	0.0 (0.0)	0.007	0.1 (0.5)	0.3 (0.8)	0.2 (0.7)	0.249	0.4 (1.1)	0.5 (1.8)	0.2 (0.7)	0.120
Tests												
laboratory	11.2 (5.5)	4.1 (4.3)	3.6 (7.9)	< 0.001	12.3 (6.2)	13.8 (6.7)	9.1 (8.6)	< 0.001	23.5 (8.3)	17.9 (8.8)	12.7 (12.2)	< 0.001
Laboratory; urgent	3.1 (3.2)	1.3 (1.6)	0.2 (1.0)	< 0.001	0.2 (0.9)	0.5 (1.7)	0.3 (1.6)	0.256	3.2 (3.3)	1.8 (2.2)	0.5 (1.8)	0.087
Biopsy	1.1 (0.2)	0.0 (0.0)	0.0 (0.0)	< 0.001	0.1 (0.3)	0.2 (0.6)	0.0 (0.1)	0.069	1.1 (0.4)	0.2 (0.6)	0.0 (0.1)	0.042
X-Rays	1.4 (0.7)	0.6 (0.5)	0.1 (0.5)	< 0.001	0.9 (2.5)	0.3 (1.3)	0.8 (2.6)	0.320	2.3 (2.6)	0.9 (1.5)	0.9 (2.8)	0.174
Echography's	0.2 (0.5)	0.3 (0.6)	0.1 (0.3)	0.031	0.2 (0.8)	0.3 (0.9)	0.2 (0.5)	0.500	0.4 (1.0)	0.6 (1.3)	0.2 (0.6)	< 0.001
CT-Scan	0.1 (0.3)	0.0 (0.0)	0.0 (0.1)	0.018	0.2 (0.8)	0.1 (0.4)	0.2 (0.5)	0.301	0.3 (0.9)	0.1 (0.4)	0.2 (0.5)	< 0.001
Gammagraphy	0.1 (0.2)	0.0 (0.2)	0.1 (0.4)	0.019	0.2 (0.8)	0.6 (1.5)	0.3 (0.9)	0.129	0.3 (0.9)	0.6 (1.5)	0.5 (1.0)	< 0.001
Electrocardiogram	0.6 (0.5)	0.1 (0.4)	0.0 (0.0)	< 0.001	0.1 (0.3)	0.1 (0.5)	0.0 (0.1)	0.068	0.7 (0.6)	0.2 (0.6)	0.0 (0.1)	0.487
Other tests	0.1 (0.2)	0.0 (0.0)	0.0 (0.0)	0.046	0.9 (1.6)	0.4 (1.4)	0.1 (0.4)	< 0.001	0.9 (1.6)	0.4 (1.4)	0.1 (0.4)	< 0.001
Other Surgery	0.2 (0.5)	0.0 (0.0)	0.0 (0.0)	0.001	0.1 (0.5)	0.1 (0.6)	0.0 (0.1)	0.185	0.3 (0.9)	0.1 (0.6)	0.0 (0.1)	0.031
Diapers	120.0 (242.4)	37.8 (174.4)	8.1 (76.9)	< 0.001	1441.0 (2237.8)	226.1 (889.6)	161.2 (653.7)	< 0.001	1561.0 (2337.2)	263.9 (964.7)	169.3 (692.8)	< 0.001
Hormonotherapy	---	---	---		3.0 (10.9)	2.4 (9.6)	12.9 (20.4)	< 0.001	3.0 (10.9)	2.4 (9.6)	12.9 (20.4)	< 0.001
Other resources	---	---	---		0.3 (1.9)	0.1 (0.8)	0.0 (0.3)	0.487	0.3 (1.9)	0.1 (0.8)	0.0 (0.3)	< 0.001

*detail of unit cost for every resource use analyzed is provided in the Supplementary Table

Table 3. Ten-Year Totals: QALYs, Costs, and Incremental Cost-Effectiveness Ratios (ICERs): Unadjusted and adjusted mean (Standard Deviation) and [95%CI] for each outcome.

	Radical Prostatectomy [A]	Brachytherapy [B]	External-Radiation [C]	Difference [A] - [B]	Difference [A] - [C]
10- Year QALYs					
Unadjusted	7.7 (1.4) [7.5 ; 7.9]	7.3 (1.8) [7.2 ; 7.4]	6.9 (1.9) [6.6 ; 7.2]	0.39 (0.14) [0.11 ; 0.68]	0.79 (0.17) [0.45 ; 1.14]
Adjusted using propensity score	7.5 [7.2 ; 7.8]	7.3 [7.1 ; 7.5]	7.0 [6.8 ; 7.3]	0.20 [-0.34 ; 0.74]	0.46 [-0.10 ; 1.02]
10- Year Costs					
Unadjusted	9,655 (4,669) [8,919 ; 10,391]	8,795 (3,945) [5,625 ; 7,695]	6,660 (4,942) [5,624 ; 7,695]	860 (689) [-499 ; 2,219]	2,995 (631) [1,753 ; 4,237]
Adjusted using propensity score	9,671 [8,765 ; 10,577]	8,995 [7,566 ; 10,425]	6,503 [5,310 ; 7,696]	676 [-1,542 ; 2,894]	3,169 [1,134 ; 5,203]
ICERs, €/QALY					
Unadjusted				2,205 [-4,542 ; 9,081]	3,791 [1,245 ; 6,660]
Adjusted using propensity score				----	----

Figure 1. Mean scores of SF-6D per treatment group at baseline and annual follow-ups: radical prostatectomy (blue line), brachytherapy (green line), and three-dimensional external beam radiotherapy (red line). Unadjusted and adjusted (using propensity scores).



Post hoc comparisons with p <0.05 for: a) radical prostatectomy vs. three-dimensional conformal radiotherapy; b) radical prostatectomy vs. brachytherapy; and c) brachytherapy vs. 3D conformal radiotherapy.

Figure 2. Survival curves by treatment group: radical prostatectomy (blue line), brachytherapy (green line), and three-dimensional external beam radiotherapy (red line). Unadjusted and adjusted (using propensity scores).

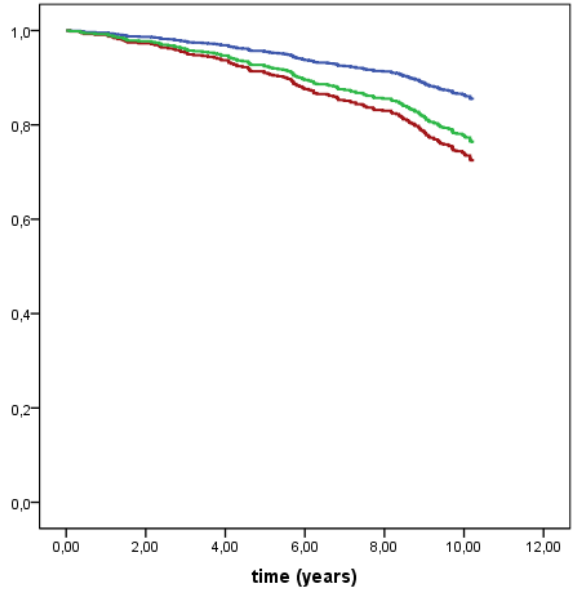
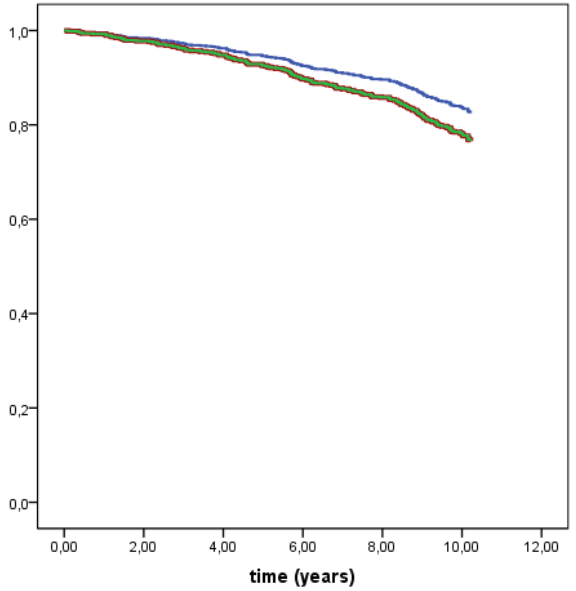
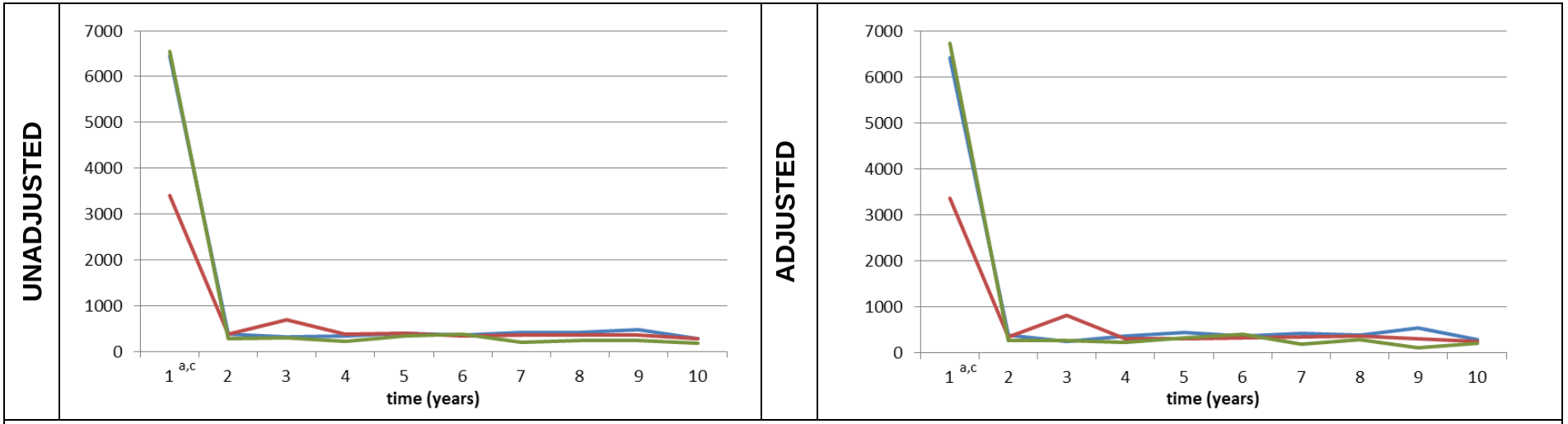
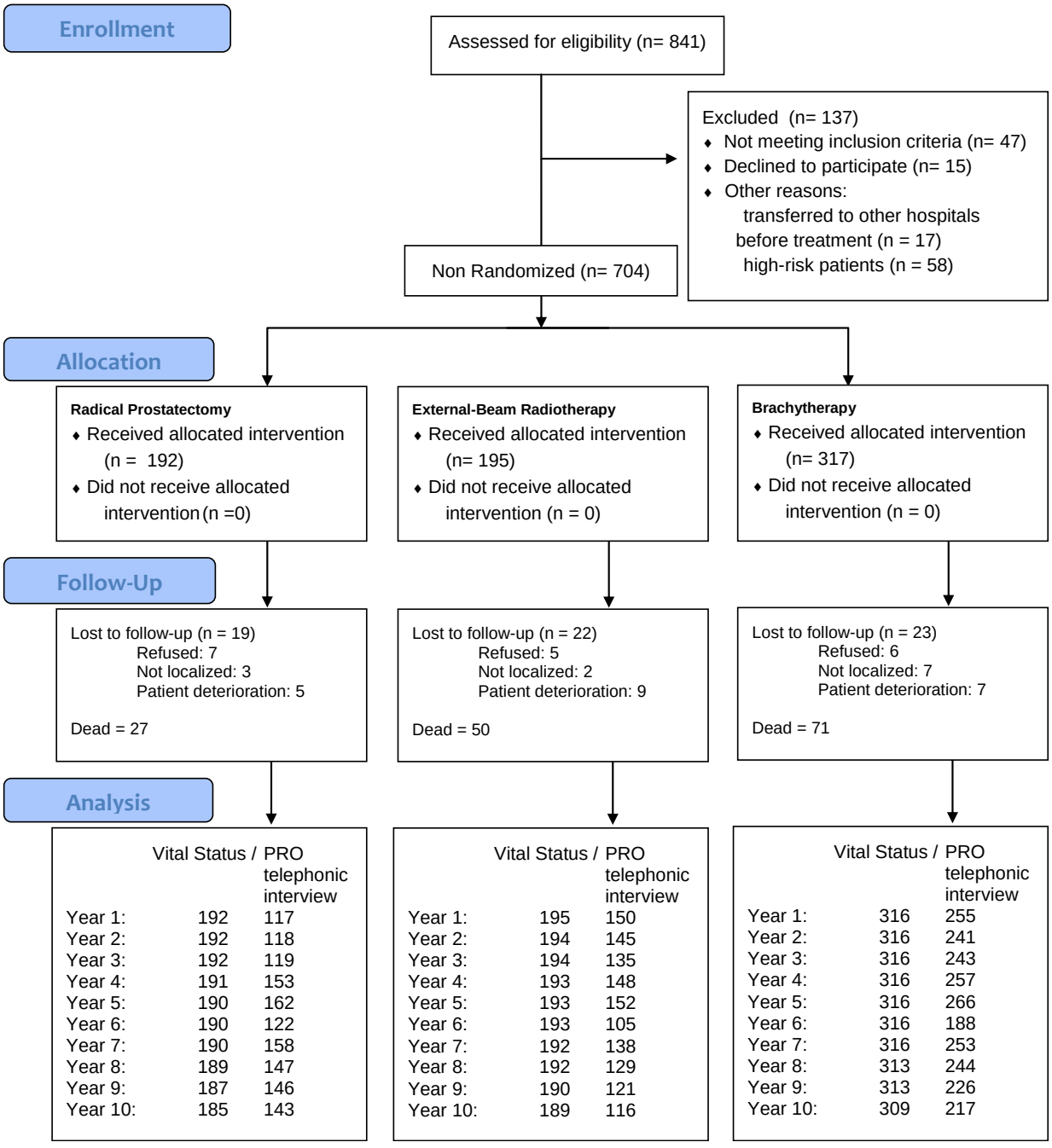
Unadjusted	Adjusted using propensity scores
	
Hazard Ratio p values, with radical prostatectomy as reference, are as follows: Brachytherapy 0.013 and External Radiotherapy 0.002.	Hazard Ratio p values, with radical prostatectomy as reference, are as follows: Brachytherapy 0.291 and External Radiotherapy 0.299

Figure 3. Direct health-care costs by year and by treatment Group: radical prostatectomy (blue line), brachytherapy (green line), and three-dimensional external beam radiotherapy (red line). Unadjusted and adjusted (using propensity scores).



Post hoc comparisons with p <0.05 for: a) radical prostatectomy vs. three-dimensional conformal radiotherapy; b) radical prostatectomy vs. brachytherapy; and c) brachytherapy vs. 3D conformal radiotherapy.

Supplementary material: CONSORT 2010 Flow Diagram



Supplementary Table 1: Healthcare Items and applied unit Costs in euros.

Item		Unit Cost
Initial treatments*		
	Radical prostatectomy, initial treatment	4,580.10
	Brachytherapy	4,344.00
	Radiotherapy (per session)	74.70
Outpatient visits		
	First visit	137.50
	Follow-up visit	67.70
Emergency visit (unitary cost / day)		156.40
Hospital Admissions (unitary cost / day)		
	Conventional hospitalization	337.40
	Outpatient clinic	343.40
	Radiotherapy Hospitalization	549.80
	Urology Hospitalization	337.40
	Anaesthesia and reanimation	337.40
	Palliative care unit	393.74
	Intensive care unit	337.40
Surgical interventions		
	Post-operative urethral stenosis	1,681.00
	Unspecified urethral stenosis	2,008.89
	Follow-up test after another surgical intervention	352.20
	Urinary complications associated with the surgical procedure (tubular necrosis or other)	699.70
	Urine retention	1749,32
	Hematuria (benign)	1,749.32
	Bleeding complicates a procedure	6,868.00
	Erectile dysfunction (organic causes)	1,717.00
	Urinary effort incontinence / artificial urinary sphincter implantation	4,270.00
	Unspecified urinary incontinence, enuresis	1,749.32
	Prostatic malign neoplasms	3,045.15
Exams and laboratory tests		
	Thoracic RX	8.87
	Abdominal Rx	8.87
	Skeletal survey RX	11.46
	CT Scan	173.34
	CT Scan (with volumetric reconstruction)	231.12
	PET (positron emission tomography)	1,018.70

	Renal and urinary echography	22.42
	Prostatic echography	43.12
	Abdominal-pelvic echography	43.12
	Echocardiogram	65.54
	Electrocardiogram	8.01
	Bone gammagraphy	184.80
	Wound healing	110.88
	Retrograde cystography	112.11
	Laboratory tests	3.39
	Emergency laboratory tests	43.12
	Treatment of bone metastasis	1,561.03
	Urodynamics	54.92
	Biopsy	98.96
	Nursing visits	21.24
	Penile prostheses	5,146.56
	Cytology	27.65
	Colonoscopy	27.65
	VCUG (voiding cystourethrogram)	133.41
	kinesiotherapy 30 minutes	16.55
	Parameter control and monitoring	21.24
	Inpatient interconsultations	170.31
	Sampling	3.94
Hormone therapy**		
	Bicalutamida	42.37 (-10%)
	Ciproterona	3.12 (-10%)
	Flutamida	29.85 (-10%)
	Goserelina	106.31 (-10%)
	Luprorelina	380.93 (-10%)
	Triptorelina	380.93 (-10%)
Other costs		
	Rehabilitation session	16.55
	Telephone consultation	10.02
	Diapers**	0.96 (-10%)

*Cost of Radical Prostatectomy was based on surgical cost of DRG 334; Brachytherapy implants are provided at a flat price regardless of dose and number of seeds per patient, and its price was obtained from national tender.
** For hormonotherapy and diapers the 10% payed by the patient was discounted. Consumer price index was used to inflate prices to year 2015 when necessary.

Supplementary Table 2: Multinomial logistic model for propensity score

		BT		RDT	
		exp(β)	p-valor	exp(β)	p-valor
Intercept		42.201	0.105	0.040	0.200
Group of risk	**Low**	-	-	-	-
	Intermediate	0.177	<0.001	1.012	0.975
T	**T1**	0.945	0.857	0.426	0.005
	T2	-	-	-	-
Previous hormones	**No**	0.126	<0.001	0.213	<0.001
	Yes	-	-	-	-
PSA		1.012	0.832	1.001	0.989
Gleason		0.432	<0.001	0.424	<0.001
Lymphatic permeation	**No**	2.814	0.010	2.246	0.046
	Yes	-	-	-	-
Prostate volume		0.948	<0.001	0.991	0.149
Percentage Right Affectation		0.999	0.874	0.998	0.686
Percentage Left Affectation		1.007	0.146	1.008	0.109
Antihypertensives	**No**	1.346	0.413	4.254	<0.001
	Yes	-	-	-	-
Familiar antecedents	**No**	0.066	<0.001	0.031	<0.001
	Yes	-	-	-	-
Urinary antecedents	**No**	0.358	0.036	0.140	<0.001
	Yes	-	-	-	-
Chronic diseases		0.990	0.908	1.015	0.870
Smoking	**No**	0.907	0.809	0.816	0.638
	Former smoker	0.756	0.461	0.800	0.577
	Smoker	-	-	-	-
Education	**Not**	0.296	0.019	0.432	0.131
	Primary	0.286	0.018	0.359	0.070
	High school	0.607	0.371	0.718	0.586
	University	-	-	-	-
Working status	**Working**	2.013	0.286	1.359	0.698
	Retired	1.576	0.479	1.159	0.845
	Others	-	-	-	-
Age		1.143	<0.001	1.233	<0.001

5. CONCLUSIONS

- In our comparison of the initial cost, first 6 months after diagnosis, based on primary data from the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort, radical prostatectomy proved to be the most expensive, followed by brachytherapy and external radiotherapy. Overall, the estimated costs in our study were lower than those published elsewhere.

- Most of the costs calculated for clinically localized prostate cancer in Spain for the first 6 months after diagnosis were explained by the therapeutic option and neither comorbidity nor risk groups showed an effect on total costs independent of treatment.

- The thirteen economic evaluations identified in our systematic review of treatments for localized prostate cancer (five comparing interventions with expectant management, four contrasting robotic with non-robotic assisted surgery, three assessing new modalities of radiotherapy, and three comparing radical prostatectomy with brachytherapy) showed that currently relevant treatment alternatives for localized prostate cancer are scarcely assessed in Europe.

- Very limited available evidence supports the cost-effectiveness of radical prostatectomy versus watchful waiting, and that of brachytherapy versus radical prostatectomy in Europe.

- Regarding the evaluation of new treatment modalities in Europe, limited evidence supports the cost-effectiveness of robotic-assisted laparoscopic radical prostatectomy versus non-robotic procedures, and that of brachytherapy, IMRT and proton therapy versus traditional external radiotherapy.

- Despite the acceptable methodological quality of the economic evaluations identified in Europe for treatments for localized prostate cancer, the contradictory results detected on effectiveness suggested that available evidence is far from robust.

- The findings of our cost-utility analysis at 10-year horizon based on primary data from the "Spanish Multicentric Study of Clinically Localized Prostate Cancer" cohort, support that no relevant differences exists on effectiveness for the three attempted curative treatments evaluated. Although external radiotherapy is cheaper than surgery and brachytherapy, the magnitude of the incremental cost does not justify the restriction of the others.

- These results provide relevant patient-based outcomes to characterize these common primary treatments and facilitate shared clinical decision-making processes between patients and physicians.

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