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ORIGINAL ARTICLE

A comprehensive analysis of cost of an active surveillance cohort compared to radical prostatectomy as primary treatment for prostate cancer

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Abstract

Introduction Active surveillance (AS) seems to be a cost-effective strategy. However, most publications are based on simulation models of theoretical cohorts, and long-term implications are not usually considered.

Objective To assess the real cost differences of two cohorts of men with low-risk prostate cancer (PCa) treated with AS or laparoscopic radical prostatectomy (LRP) in a public health system.

Materials and methods Patients diagnosed from 2005 to 2009 were included in an AS program (Group 1) or treated with LRP at diagnosis (Group 2), with a minimum follow-up of 5 years. Actual costs for each patient were calculated on an individual basis: Group 1: semiannual PSA measurements and repeat biopsies are scheduled every 1–3 years. Costs of outpatient clinic visits were calculated, as well as all tests required for monitoring or active treatment. Group 2: costs of the procedure, emergency visits, re-admissions and outpatient clinic visits were calculated, as well as costs of oncological salvage therapies or functional surgical procedures.

Results Out of 151 men diagnosed with low-risk PC, 54 (35.8%) were included in an AS (Group 1) and 97 (64.2%) were submitted to LRP (Group 2). Mean follow-up for both groups was 6.5 years (SD 1.8) and 6.7 years (SD 1.4), respectively, $p = 0.49$. Group 1 had a total cost per patient of 2970.47€. Group 2 had a total cost per patient of 5694.06€.

Conclusions AS was associated with cost-saving over LRP. This cost reduction of AS in the management of low-risk PCa is based on the accounting of real costs of individual patients and confirms previously published estimation-based reports.

Keywords Prostate cancer · Cost analysis · Active surveillance · Radical prostatectomy

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Introduction

Since prostate cancer (PCa) screening was first described, the incidence of PCa has increased dramatically in western countries [1] resulting in an increase in diagnosing low-risk PCa, leading to a reduction in PCa mortality [2].

However, mortality needs to be balanced against the disadvantages of early detection of PCa. Around 5–46% men who receive active treatment do not obtain any clinical benefit from their treatment due to the slow progression of early-stage low-risk cancer [3, 4]. Moreover, overdiagnosis of PCa would not be an issue if treatment had no morbidity. Indeed, the side effects of radical prostatectomy or external radiotherapy are considerable. Despite the fact that some patients recover in the long term, these adverse effects will significantly reduce health-related quality of life (QoL) [5] and negatively impact the long-term cost.

Active surveillance (AS) is an alternative strategy, formally described for the first time in 2005 as a variant of watchful waiting [6, 7], which aims to individualize therapy by selecting only those men who harbor significant cancers for curative therapy and thereby reducing the burden of treatment side effects without compromising survival [8, 9]. A wide variety of protocols for AS have been described to date [10]. In spite of certain differences, they involve close follow-up with frequent PSA measurement and regular surveillance prostate biopsy to detect early signs of disease progression and trigger definitive therapy.

AS seems to be a cost-effective strategy for managing low-risk PCa [11]. However, most publications studying costs of AS for managing PCa share a common limitation. They are based on simulation models that estimate direct costs of theoretical cohorts of patients accrued over time, whereas long-term implications of treatment are not usually considered [11, 12].

The aim of this study was to thoroughly assess the real cost differences of two cohorts of men with newly diagnosed low-risk PCa treated with AS or laparoscopic radical prostatectomy (LRP) as a primary treatment in a public health system, taking into account the cost of every diagnostic or therapeutic intervention that patients were submitted to during the follow-up time.

Materials and methods

Patients and diagnosis

Consecutive patients newly diagnosed with low-risk PCa, from 2005 to 2009 who were managed with AS (Group 1) or treated with LRP at diagnosis (Group 2) were analyzed.

Patients included in the analyses were potential candidates for curative treatment. Life expectancy was estimated over 10 years considering age and comorbidities measured by the Charlson score. No predictable tools were used, due to the lack of an accurate model suitable for implementation in clinical decision-making, according to the literature [13].

Low-risk cancer definition was based on the NCCN criteria [14]: clinical stage T1c–T2a, PSA $\leq$ 10 ng/ml, Gleason score $\leq$ 6, two or fewer cores with cancer, and $\leq$ 50% cancer involvement of any core. PSA density was not taken into account. Patients with less than 4 years of follow-up were excluded from the analyses.

Assignment to each treatment group was made according to advice from their treating physician and patient preferences. Detailed information about the diagnosis and alternative treatments, protocol and follow-up [14] was given to patients. This study was approved by the institutional review board.

Biopsy procedure

TRUS-guided biopsy was performed as an outpatient procedure by a urologist and a nurse in the Urology clinic. Prophylaxis with a short-course fluoroquinolone (1-day regimen) and sodium biphosphate enema were given 2 h prior to the biopsy.

Biopsy was performed under local anesthesia in a standard fashion. For those cases in which sedation was needed due to poor tolerability, the procedure was performed in the operating room.

At the time of the recruitment of the study sample population the protocol followed for the initial biopsy was an 8-core template which was later extended to 12 cores. For patients with an initial biopsy of eight cores, an extended confirmation biopsy was mandatory previous to their inclusion in the program. Some patients were diagnosed after saturation biopsy (18–20 cores) with an initial negative biopsy.

During the follow-up in the AS group, saturation biopsies including 18–20 cores were taken. Samples included lateral and medial peripheral zones (PZ), transition zone, apex and the base of the prostate. Extra cores of suspicious areas outside this systematic area were also taken.

Samples were interpreted by two experienced faculty uropathologists.

Active surveillance protocol

Patients with above-mentioned low-risk criteria were followed up with digital rectal examination (DRE) and PSA measurement every 6 months. First biopsy after diagnosis was scheduled during the first year of follow-up. Subsequent AS biopsies were repeated every 2 or 3 years depending on

the age of the patient, previous biopsy results, PSA kinetics or DRE findings. Imaging was not routinely performed.

Time in AS was defined from diagnosis to the time of curative treatment, death or time to last follow-up event. Curative treatment (radiation or surgery) was recommended whenever adverse pathological features on surveillance biopsies were found (Gleason score ≥ 7, ≥ 2 positive cores for cancer, or $\geq 50\%$ of involvement in any core) or at patient's request for a change in management at any time during follow-up [15].

Laparoscopic radical prostatectomy

Radical prostatectomy was performed laparoscopically using a preperitoneal anterograde approach. Nerve-sparing was only performed in those patients without previous history of erectile dysfunction (ED). ED was self-reported by the patient as a consistent or recurrent inability to attain and/or maintain an erection sufficient for sexual intercourse.

Patients were discharged with a urethral catheter which was removed between 12 and 15 days post-operation, in the outpatient clinic. Patients were reviewed in our outpatient department at 4 weeks post-op with a first PSA determination. Although standard follow-up consisted of biannual PSA tests during the first 2 years and annually afterward, it was always adjusted by the individual risk of the patient. Moreover, imaging tests were ordered on a case-by-case basis.

Biochemical recurrence was defined as two consecutive PSA values ≥ 0.2 ng/mL [16]. To those patients for whom local recurrence was suspected, salvage radiotherapy was offered.

Cost analyses

A detailed analysis was possible after gathering data from our PCa institutional data base, which is registered and collected in a prospective way. Costs related to treatment, long-term postoperative complications, urinary incontinence and ED as well as adjuvant or salvage therapies were taken into account.

The actual costs for each patient were calculated on an individual basis, as follows, through the exploitation analytical accounting system. For externalized interventions (RDT) a public referral rate was also included in the calculations.

Group 1 (active surveillance):

- Outpatient clinic visits, including time and staff involved in each visit.
- Prostate biopsies: taking into account those which were performed in the outpatient office and those in the operating room.
- PSA tests.
- Imaging tests during follow-up if needed.
- Emergency room visits due to urological causes, mainly after biopsies.
- Hospitalization in the Urology Department.
- Different treatments during follow-up:

  (i) Bladder outlet obstruction (BOO) surgery: transurethral resection of the prostate (TURP).
  (ii) Salvage prostatectomy or radiotherapy: depending on patient's preferences, comorbidities and history of previous abdominal surgery.
  (iii) Re-admissions and visits to emergency room due to any cause within 90 days after these treatments.
  (iv) Follow-up after these treatments: outpatient clinic, imaging and blood tests, etc.

Group 2 (radical prostatectomy):

- Intervention costs include the costs of the individual procedure, which considered surgery (time and material used per patient) and time in the recovery unit (number of hours) and days of hospitalization.
- Re-admissions or need to visit the emergency room within the first 90 days after surgery.
- Outpatients' clinic visits.
- PSA tests.
- Imaging or other urological tests or examinations required for monitoring these patients during follow-up.
- Emergency room visits due to urological causes during follow-up.
- Hospitalization in urological department.
- Need of other treatments:

  - Salvage treatments: radiotherapy or Androgen Deprivation Therapy (ADT).
  - Functional surgical procedures: artificial urinary sphincter, male sling, penile prosthesis.
  - Complication and re-admissions after these procedures.

By means of the analytical accounting system, the costs related to disposables and drugs, the surgical costs of the standard procedure including real working time of the personnel involved in the procedure and, when applicable, the real cost of a penile prosthesis or an artificial urinary sphincter were calculated. Moreover, the real costs of hospitalization were calculated taking into account the number of days that each patient was admitted and included all medical and staff costs, drugs, material used and indirect costs due to power supply consumption, cleaning services, etc.

All costs (€) were adjusted to 2014 values.

Statistical analysis

The quantitative variables in asymmetric distributions were expressed as median (interquartile range, IQR), whereas the measurement data in symmetric distributions were presented as means ± standard deviation (SD). Categorical variables were summarized as numbers (percentages). The Kaplan–Meier product-limit method was used to analyze patient survival in AS program. The log-rank test was used to compare survival distributions. Patients lost during follow-up were included in the analyses as censored in their last check-up. All tests were bilateral and $p < 0.05$ was considered to be statistically significant. Data analysis was carried out with SPSS v17.

Results

A total of 151 men were diagnosed with low-risk PCa from 2005 to 2009 in our institution. At that time, 54 of them (35.8%) were included in an AS program (Group 1) and 97 (64.2%) were submitted to laparoscopic radical prostatectomy (Group 2). Baseline characteristics are shown in Table 1.

Patients in Group 1 (AS) were followed during a median time of 6.4 years (IQR 5.00–8.15). During follow-up, an average number of two biopsies were taken. No patient underwent more than four biopsies during his follow-up. In 15 cases (13.76%) biopsies had to be performed in the operating room. No major complications were registered after biopsies. Two patients underwent TURP because of BOO.

Out of 54 patients, 21 (38.8%) required active treatment within a median time of 2.5 years (IC95% 2.05–5.26). Patients underwent active treatment due to progression of number of cores (three patients, 14.3%), progression of Gleason score (five patients, 23.8%), progression of number of cores and Gleason score (eight patients, 38%), rising PSA > 10 (two patients, 9.5%) or patient wish (three patients, 14.3%). Median PSA at the moment of active treatment was 6 ng/mL (CI95% 4.95–7.89). Salvage LRP was performed in 12 patients and 9 underwent RT.

The AS protocol had a total cost per patient of 2970.47€. Detailed costs analysis is shown in Table 2.

Follow-up was 6.66 years (IQR 5.8–7.8) in Group 2 (LRP). Median time of hospitalization was 2 days (IQR 2–4). Median time of surgery was 255 min per case (IQR 233–285). None of the patients required salvage treatments during the follow-up. Seven patients underwent urinary incontinence surgery and two patients needed a penile prosthesis implantation. Radical prostatectomy group meant a total cost of 5.694,06 € per patient. Detailed cost analysis is shown in Table 3.

Discussion

AS may allow men with early PCa to be spared the side effects of overtreatment as well as complications that may arise from surgery, without compromising their survival [17, 18]. High acceptance and safety make AS a reasonable management alternative to radical prostatectomy. In spite of what was previously thought, anxiety in men who have chosen AS is not higher than in men who elect initial curative treatment [17–19]. In our experience, only 17% of patients left the AS program because of personal preferences [15]. These results are comparable to other reports [20, 21].

This option is not only attractive for patients, but also for health economists, as it is already proven to save valuable resources [22–30]. However, most of the literature published to date is based on economic or theoretical models [12]. This study does not expect to accurately estimate the costs of each kind of treatment, but rather to prove that AS results in cost reduction on a daily basis. The findings of our study demonstrate that AS with selective intervention for those men with evidence of PCa progression can result in significant cost savings (48%) over immediate curative treatment. This cost reduction is consistent with previously published estimation-based reports [22–24, 26, 27, 29, 30].

Reinhold et al. [24] published their results based on the German multicenter observational study HAROW comparing direct and indirect costs in patients with localized PCa who underwent different treatments including RP and AS. They found a substantial difference of costs between both treatments in favor of AS, but within a short follow-up (2.5 years). A Danish group compared the real costs of 317 patients enrolled in an AS program to the hypothetical costs of curative RP for all patients, showing 35% saving costs [31]. Recently, Lao et al. [22], using theoretical models, concluded that AS in low-risk localized PCa is less likely to be cost effective compared to radical prostatectomy for younger men (< 55 years old).

In contrast to the vast majority of publications, this study is based on the accounting of real costs of individual patients with low-risk PCa who underwent AS vs LRP. Furthermore, our study includes not only the costs related to treatment, but also the costs associated with long-term postoperative complications such as urinary incontinence and erectile dysfunction, as well as adjuvant or salvage therapies. Another strength of the current study is the prospective fashion in which we enter data into our institutional database. Long-term follow-up of 6.5 years and the excellent patient compliance that results in a lack of patients leaving the AS program due to personal decision are also strong aspects of this report.

Our study is not without limitations. Treatment expenses are based on hospital costs of a single institution in the

Table 1 Baseline characteristics

	Group 1(AS) $n=54$ Mean (SD)	Group 2 (LRP) $n=97$ Mean (SD)	p value
Age (year)	66.21 (6.21)	62.87 (4.99)	$p=0.001$
Prostate volume (cc)[a]	40.2 (29.7–55.4)	40 (28–50)	$p=0.45$
PSA[a]	6 (4.9–8)	5.4 (4.5-6.9)	$p=0.62$
No. of cores	10.7 (4.8)	10.12 (4.25)	$p=0.76$
No. of positive cores	1.2 (0.4)	1.4 (0.5)	$p=0.005$
	n (%)	*n* (%)	
Clinical stage			
T1c	52 (96.3%)	95 (97.9%)	$p=0.62$
T2a	2 (3.7%)	2 (2.1%)	
Gleason			
≤6	51 (94.4%)	97 (100%)	$p=0.044$
7	3 (5.6%)	0	
Active treatment			
LRP	12 (22.2%)	–	
RT	9 (16.7%)	–	

AS active surveillance, *LPR* laparoscopic radical prostatectomy, *RT* radiotherapy

[a]Data expressed in median (IQR)

Table 2 Cost analysis Group 1 (active surveillance)

	Costs analysis Group 1: active surveillance			
	n	*n* per patient	Cost per test/ procedure	Total costs
Surveillance biopsies	109	2		20.666,00€
Outpatient clinic	94		149,00 €	14.006.00€
Surgery room	15		444,0€	6.66,00€
Outpatient clinic appointments	783	14.5	61,00€	47.763,00€
PSA tests	481	8.9	4,43€	2.130,83€
Imaging/urological tests	70	1.3		6.461,09€
US	15		27,12€	406,80€
CT	28		155,03€	4.340,84€
MRI	3		259,96€	779,88€
Bone scan	20		22,95€	459,00€
Cystoscopy	1		162,00€	162,00€
IVU	2		134,00€	268,00€
Diuretic renogram	1		45,07€	45,07€
Surgery due to BPH	2		4,422,84€	8.845,68€
TURP	2		4,422,84€	8.845,68€
Active treatment			7.063,80€	74.538,60€
RT	9		3.409,00€	30.681,00€
LRP	12		3.654,80€	43.857,60€
Total cost Group 1				160.405,20€
Cost per patient				2.970,47€

US ultrasound, *CT* computed tomography, *MRI* magnetic resonance imaging, *IVU* intravenous urography, *TURP* transurethral resection of the prostate, *RT* radiotherapy, *LPR* laparoscopic radical prostatectomy

Table 3 Cost analysis Group 2 (radical prostatectomy)

	Costs analysis Group 1: active surveillance			
	n	*n* per patient	Cost per test/ procedure	Total costs
LRP	97			340.893,80€
Re-admissions	2		1.126,40€	2.252,80€
Emergencies	12		180,00€	2.160,00€
Outpatient clinic appointments	1144	11.8		69.784,00€
PSA test	791	8.2	4,43€	3.504,13€
Imaging/urological tests		1.3		12.662,33€
US	29		27,12€	786,48€
CT	19		155,03€	2.945,57€
MRI	2		259,96€	519,92€
Bone scan	1		22,95€	22,95€
Cystoscopy	36		162,00€	5.832,00€
Urodynamics	24		61,00€	1.464,00€
VCUG	7		61,34€	429,38€
IVU	2		133,75€	267,50€
Diuretic renogram	3		45,07€	135,21€
Penile Doppler	3		86,44€	259,32€
Salvage radiotherapy	0			
Incontinence surgery	7			103.615.67€
Erectile dysfunction surgery	2			17.457.32€
Total cost Group 2				552.324,05€
Cost per patient				5.694,06€

US ultrasound, *CT* computed tomography, *MRI* magnetic resonance imaging, *VCUG* voiding cystourethrography, *IVU* intravenous urography, *TURP* transurethral resection of the prostate, *RT* radiotherapy, *LPR* laparoscopic radical prostatectomy

setting of a national healthcare system. Consequently, they may not be applicable to all health systems. Another issue is the lack of consensus about optimal frequency of re-biopsies and PSA tests, the use of new biomarkers and mpMRI in AS programs that can significantly influence the costs of the program. Almost 14% of the follow-up biopsies were performed in the operating room. The number of patients undergoing biopsies under sedation can vary depending on the center and, therefore, may influence costs. Finally, quality adjusted life years (QALYs) could not be calculated.

Conclusion

In our series, AS was associated with a 48% cost-saving over radical prostatectomy. This cost reduction of AS in the management of low-risk PCa is based on the accounting of real costs of individual patients and confirms previously published estimation-based reports.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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