

CLINICAL INVESTIGATION

Prostate

BRACHYTHERAPY VERSUS PROSTATECTOMY IN LOCALIZED PROSTATE
CANCER: RESULTS OF A FRENCH MULTICENTER PROSPECTIVE
MEDICO-ECONOMIC STUDY

CATHERINE BURON, PH.D.,* BEATRICE LE VU, M.D.,* JEAN-MARC COSSET, M.D.,†
PASCAL POMMIER, M.D., PH.D.,‡ DIDIER PEIFFERT, M.D.,§ MARTINE DELANNES, M.D.,||
THIERRY FLAM, M.D.,¶ STEPHANE GUERIF, M.D., PH.D.,# NAJI SALEM, M.D.,**
LAURENT CHAUVEINC, M.D., PH.D.,†† AND ALAIN LIVARTOWSKI, M.D.*

Department of *Medical Information and †Oncology/Radiotherapy, Institut Curie, Paris, France; ‡Department of Radiotherapy, Centre Leon Berard, Lyon, France; §Department of Radiotherapy, Centre Alexis Vautrin, Nancy, France; ||Department of Radiotherapy, Centre Claudius Regaud, Toulouse, France; ¶Department of Urology, Hôpital Cochin, Paris, France; #Department of Radiotherapy, Centre Hospitalier Universitaire, Poitiers, France; **Department of Radiotherapy, Institut Paoli-Calmettes, Marseille, France; ††Department of Radiotherapy, Clinique Hartmann, Neuilly sur Seine, France

Purpose: To prospectively compare health-related quality of life (HRQOL), patient-reported treatment-related symptoms, and costs of iodine-125 permanent implant interstitial brachytherapy (IB) with those of radical prostatectomy (RP) during the first 2 years after these treatments for localized prostate cancer.

Methods and Materials: A total of 435 men with localized low-risk prostate cancer, from 11 French hospitals, treated with IB (308) or RP (127), were offered to complete the European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire QLQ-C30 version 3 (EORTC QLQ-C30) and the prostate cancer specific EORTC QLQ-PR25 module before and at the end of treatment, 2, 6, 12, 18, and 24 months after treatment. Repeated measures analysis of variance and analysis of covariance were conducted on HRQOL changes. Comparative cost analysis covered initial treatment, hospital follow-up, outpatient and production loss costs.

Results: Just after treatment, the decrease of global HRQOL was less pronounced in the IB than in the RP group, with a 13.5 points difference ($p < 0.0001$). A difference slightly in favor of RP was observed 6 months after treatment (-7.5 points, $p = 0.0164$) and was maintained at 24 months (-8.2 points, $p = 0.0379$). Impotence and urinary incontinence were more pronounced after RP, whereas urinary frequency, urgency, and urination pain were more frequent after IB. Mean societal costs did not differ between IB (€8,019 at T24) and RP (€8,715 at T24, $p = 0.0843$) regardless of the period.

Conclusions: This study suggests a similar cost profile in France for IB and RP but with different HRQOL and side effect profiles. Those findings may be used to tailor localized prostate cancer treatments to suit individual patients' needs. © 2007 Elsevier Inc.

Localized prostate cancer, Prostatectomy, Brachytherapy, Health-related quality of life, Societal costs.

INTRODUCTION

Prostate cancer is the commonest male cancer in many industrialized countries and the second leading cause of

cancer death in men. In France, more than 40,000 new cases of prostate cancer were diagnosed in 2000 (1) and the increase in the annual number of new cases can be explained by aging of the population and by changes in the

Reprint requests to: Alain Livartowski, M.D., Department of Medical Information, Institut Curie, 25 rue d'Ulm, 75005 Paris, France. Tel: (+33) 1-4432-4683; Fax: (+33) 1-5310-4039; E-mail: alain.livartowski@curie.net

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Brabois, France), Jean-Claude Pennequin (Management Accounting Department, Centre Alexis Vautrin, Nancy, France), Jacques Irani (Department of Urology, Centre Hospitalier Universitaire, Poitiers, France), Elisabeth Hulier (Clinical Trial Management Unit, Institut Curie, Paris, France), Muriel Laumond (Clinical Trial Management Unit, Centre Claudius Regaud, Toulouse, France), Dominique Pontvert (Department of Oncology/Radiotherapy, Institut Curie, Paris, France).

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mode of detection with the recent widespread use of prostate-specific antigen (PSA) screening, which has resulted in a dramatic increase in the number of men diagnosed at both a younger age and at an earlier stage of the disease.

Currently the most common curative options for men with clinically localized (T1–T2) prostate cancer are radical prostatectomy (RP), external beam radiation therapy (EBRT), and interstitial brachytherapy (IB), which consists of inserting permanent radioactive sources into prostatic tissue. Management of localized prostate cancer by high-intensity focused ultrasound and active monitoring is also being explored, but no long-term follow-up data are available so far.

At present, there are no published trials that directly compare long-term survivals after the various treatments of clinically localized disease, leaving the question of survival benefit unanswered. However, studies have reported biochemical relapse-free survival rates that are similar up to 10 years after RP, EBRT, or IB for localized “low-risk” patients (T1–T2a, PSA \leq 10 ng/mL, and Gleason score $<$ 7) (2–5). In the absence of any evidence of overall differences in survival between IB and conventional treatments, health-related quality of life (HRQOL), treatment-related symptoms, and economic cost impact may become key factors.

The objective of this article is to compare IB with RP in terms of HRQOL, patient-reported treatment-related symptoms, and cost impact during the first 2 years after these treatments for localized prostate cancer. In this study, IB is compared with RP, as RP is considered to be the reference treatment in routine French medical practice for men with localized prostate cancer and a life expectancy of more than 10 years (6). Although EBRT can also be used as a treatment option, most of the time it is proposed for patients with a larger extension or for patients who are unsuitable for RP (*e.g.*, age, comorbidities). In addition, at present, neither active monitoring nor high-intensity focused ultrasound are considered to be a treatment option in France for these patients with a life expectancy of more than 10 years (6).

The present article is part of a larger “French prostate cancer medico-economic study” whose purpose was threefold: (1) to compare HRQOL and economic data of IB with RP; (2) to document an EBRT patient cohort with the same HRQOL and economic criteria; and (3) to compare the physician’s and patient’s points of view concerning treatment-related symptoms. A total of 546 patients (T1/T2N0M0 localized prostate cancer, PSA \leq 20 ng/mL, biopsy Gleason score $<$ 8) were included in the whole study. The present paper deals with the first part and main objective; the two other points will be subsequently reported.

METHODS AND MATERIALS

Patients and treatments

Between March 2001 and June 2002, 435 patients diagnosed with localized prostate carcinoma, from 11 French hospitals, were treated without randomization of treatment with permanent implant IB ($n = 308$) or with RP ($n = 127$). Interstitial brachytherapy was performed in five cancer centers and one teaching hospital,

while RP was performed in six teaching hospitals. For each type of treatment, patients were followed prospectively for at least 2 years.

In the IB group, all patients were implanted with radioactive iodine ^{125}I seeds. The majority ($n = 243$) were treated using a real-time ultrasound (US)-based planning technique (real-time computer-assisted dosimetry with dynamic seed localization performed in the operating room suite). The other 65 patients were treated by a US-based preplanning technique in a single center. Based on US-based dosimetry, the mean dose to 90% of the outlined prostate volume (D90) was 185.9 Gy and the mean percentage of prostate volume receiving at least 100% of the prescribed dose, 145 Gy (V100) was 99.4%. According to the reference posttreatment computed tomography (CT)-based dosimetry, the mean D90 was 172.6 Gy, the mean V100 was 96.0%, and the mean rectal volume receiving 145 Gy was 1.4 cc.

Among RP patients, the surgical approach was retropubic for 86% and laparoscopic for 14%. Iliac node sampling was performed for 75% of cases, and the absence of nodal involvement was confirmed in all patients. A blood transfusion was necessary for 28% of the RP patients, and a second surgical procedure was necessary for 6% of these patients. Nine patients in the RP group (7%) received adjuvant EBRT. Neoadjuvant hormonal therapy was given to 6% of RP patients vs. to 43% of IB patients (Table 1).

Procedures

The study received national approval from French authorities. At the pretreatment visit with the urologist or radiation oncologist, the treatment options were presented to the patients and treatment choice was most of the time tailored conjointly by the patient and the physician in charge. Patients were invited to participate in the medico-economic study and were informed about the follow-up

Table 1. Patient baseline demographics and clinical conditions

	RP $n = 127$	IB $n = 308$	$P_{\text{IB-RP}}$
Mean age (σ)	62.7 (6.0)	65.2 (6.3)	0.0003
Level of education (%)			
Low	39.3	32.0	
Middle	27.9	32.0	0.3590
High	32.8	36.0	
Working status (working %)	30.0	18.2	0.0083
Neoadjuvant hormonal therapy (%)	6.3	43.5	<0.0001
Mean prostate volume (σ)	38.8 (16.9)	37.3 (13.0)	0.3909
Clinical T stage (%)			
T1	52.8	64.8	
T2	47.2	35.2	0.0228
Mean PSA level (σ)	8.9 (4.0)	7.5 (2.7)	0.0003
Mean Gleason score (σ)	5.9 (1.1)	5.5 (1.1)	0.0003
Comorbidities (%)			
Hypertension	29.7	33.3	0.5564
Mean IPSS score	7.8	5.9	0.0071

Abbreviations: RP = radical prostatectomy; IB = interstitial brachytherapy; PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score.

modalities. Eligible patients who accepted to participate were given a booklet with self-administered questionnaires concerning HRQOL, treatment-related symptoms and outpatient resource utilization. They were asked to complete them before treatment (T0), at the end of treatment (TE), 2 (T2), 6 (T6), 12 (T12), 18 (T18), and 24 (T24) months after hospital discharge for RP and IB. Individual clinical data and hospital resource utilization data were prospectively collected by the medical team by means of an individual record chart specifically designed for the study.

HRQOL and treatment-related symptom measures

The basic assumption of this study was that the various treatment strategies assessed had a similar efficacy in terms of survival (2–5). Two outcome measures were therefore used in the analysis: HRQOL and treatment-related symptom measures, both evaluated by the patients.

The cancer-specific European Organization for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire QLQ-C30 version 3 (7) and the prostate cancer specific EORTC QLQ-PR25 module (8) were used to measure HRQOL and treatment-related symptoms, respectively, at regular intervals to longitudinally monitor changes in these scores. The EORTC QLQ-C30, developed for the measurement of HRQOL in cancer patients, is composed of five functional scales, a global HRQOL scale, three symptoms scales, and six single-item measures. The EORTC QLQ-PR25, designed to be used with the core questionnaire, includes 25 items covering topics which include common side effects of prostate treatments: urinary symptoms, bowel symptoms, treatment-related symptoms, and sexual function.

All scales of the QLQ-C30 and QLQ-PR25 are scored from 0 to 100. For functional scales and the global HRQOL scale, higher scores represent a higher level of functioning or global HRQOL. For symptoms scales and single items, higher scores indicate more severe symptoms or problems. HRQOL and treatment-related symptoms changes over time from 5 to 10 points, on a 0 to 100 point scale, were considered to be minor changes; changes from 10 to 20 points were considered to be moderate changes; and changes greater than 20 points were considered to be major changes (9).

Cost measures

Costs were computed from a societal perspective from the date of treatment over a 2-year follow-up and covered hospital costs, outpatient costs, and indirect costs linked to productivity losses.

Complete hospital cost computation was performed for both the initial treatment phase and for the follow-up phase, including the following components: medical and nonmedical personal costs, depreciation, maintenance and medical logistics of medical equipment, consumable costs, and overhead costs (such as hotel medical accommodation costs, laundry costs, general management costs).

For the initial treatment phase, the following hospital resource utilization was quantified for each patient: number of hours of operating theater occupation, number of blood products, number of days of hospitalization, and number of immediate postoperative CT scans (IB group). The cost of blood products was determined by their purchase price by the hospital. Concerning the costs of seeds, four of five cancer centers paid a lump sum for a fixed number of seeds, whereas one center chose a unit (per seed) payment. For the first type of center, the lump sum paid by each hospital to the manufacturer was used to compute the per patient consumables cost. For the other center, the number of seeds used

for each patient was valued at the unit purchase cost. To derive unit IB costs, the following annual expenses were drawn from the 2001 cost-accounting systems of the five cancer centers performing IB:

- medical and nonmedical staff expenses, medical equipment depreciation, maintenance and medical logistics expenses of the IB theater and of the unit admitting IB patients;
- hotel medical accommodation, laundry, general management and general logistics expenses of the unit admitting IB patients;

IB unit costs of each hospitalization sector was then obtained by dividing the total annual expenses of the corresponding hospitalization sector by the following drivers: annual hour capacity of the IB theater and annual number of days in the IB hospitalization unit. In view of the difficulty of obtaining good cost-accounting data for RP in teaching hospitals, unit RP costs were derived from the prostatectomy hospital stay itemized costs of the 2001 French Diagnosis Related Group (DRG) cost schedule.

Hospital follow-up costs included hospitalization costs for subsequent complications and outpatient radiotherapy sessions when performed. The number of days of hospitalization and the reason for admission were recorded for each patient and valued, according to the French DRG cost schedule, by relating the reason for admission, the length of hospital stay, and the number of patients concerned to the daily cost of the corresponding DRG. Adjuvant hormonal therapy was not taken into account.

Outpatient costs consisted of examinations (PSA determination, CT scans, radiographic imaging), visits to general practitioners, specialists, physician home visits, nurse home visits, and visits for urogenital retraining. All these quantities of consumed resources were valued on the basis of the 2001 French National Security fee schedule. Production loss costs were calculated by multiplying the number of days off work for all patients with an occupation by the French daily national average wage.

Cost data were collected prospectively on the same patient sample as that used in the HRQOL and treatment-related symptoms analysis and over the same period. Costs were not discounted. In this multicenter study, center-specific hospital quantities were multiplied by center-specific unit prices whenever feasible. All costs, expressed in 2001 euros, are presented in terms of arithmetic mean costs, and statistical analysis was based on cost differences between IB and RP. IB and RP costs comparison was performed without neoadjuvant hormone therapy costs, because the data that were available did not allow us to precisely estimate the cost of neoadjuvant hormone therapy.

Statistical analysis

Baseline demographic data and clinical condition before treatment were compared between IB and RP groups using chi-square analysis or Fisher exact test for categorical variables and using the two-sample *t* test for quantitative variables.

All changes in HRQOL and treatment-related symptoms scores over time were measured in comparison to the pretreatment QLQ-C30 or QLQ-PR25 scores. QLQ-C30 changes over time in each treatment group, relative to baseline, were assessed using the paired *t* test and Bonferroni's method, to adjust for multiple comparisons. Analysis of covariance was used to assess treatment group differences in QLQ-C30 changes relative to baseline after adjusting for potential confounding factors including age, working status, PSA level, Gleason score, use of neoadjuvant hormonal therapy, and pretreatment International Prostate Symptom Score (IPSS).

Because the QLQ-PR25 prostate module is still being validated in

an international study and no scoring system is yet available, single-item treatment-related symptoms rather than global symptom scores (urinary, bowel, treatment-related, and sexual functioning) were examined. We selected the following single items from this questionnaire to explore treatment-related symptoms: urinary incontinence, urinary urgency, urinary pain, diurnal urinary frequency, nocturnal urinary frequency, fecal incontinence, rectal bleeding, and erectile dysfunction. QLQ-PR25 results over time are reported as the percentage of patients with an increase in symptoms relative to baseline.

As costs were determined from the study population, a stochastic cost analysis was performed using usual statistical methods on observed difference in costs between treatments. We used *t* test based methods to compare arithmetic mean costs between IB and RP groups. Cost data are expressed as the mean and 95% confidence intervals.

The 5% significance level was used in all tests and comparisons (except for the intragroup analysis), and all statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, NC, version 9.1).

RESULTS

Demographic data of treatment groups

Data on the subjects' baseline demographics and clinical condition before treatment are indicated in Table 1. A comparison of the IB and RP groups demonstrated significant differences at baseline. Men in the IB group were significantly older, had less frequent working status, lower clinical stage, lower PSA level, and lower pretreatment IPSS score than men treated by RP. The percentage of men receiving neoadjuvant hormonal therapy was higher in the IB group (43.5%) than in the RP group (6.3%). No significant differences were demonstrated between the IB and RP groups concerning level of education, prostate volume, and comorbidities.

HRQOL and treatment-related symptoms results

Mean (standard deviation) follow-up was 25.8 (2.9) months for IB and 25.0 (2.6) months for RP. Booklet questionnaire response rates for each treatment group are indicated in Table 2. Patients in the IB group were more likely to return questionnaires than those in the RP group.

Table 2. Booklet questionnaire response rates over time

	Prostatectomy (%)	Brachytherapy (%)	(%)
T0	89	94	92
TE	70	85	80
T2	72	85	82
T6	57	78	72
T12	47	63	59
T18	39	60	54
T24	41	65	58

Abbreviations: T0 = before treatment; TE = immediately after treatment; T2, T6, T12, T18, and T24 = 2, 6, 12, 18, and 24 months after hospital discharge for prostatectomy or brachytherapy.

Analysis of the HRQOL changes over time within the IB group showed that the global HRQOL score decreased slightly between T0 and TE (-5.8 points, $p < 0.0001$) and that this decline was maximum between T0 and T2 (-6.8 points, $p < 0.0001$). At 6, 12, 18, and 24 months after IB, the difference in the global HRQOL score from the baseline score was not significant in the IB group (Table 3). Concerning the RP group, although patients reported a marked decrease of global HRQOL immediately after treatment (-18 points, $p < 0.0001$), together with most of the QLQ-C30 scores they appeared to recover fairly rapidly: at 2, 6, 12, 18, and 24 months after RP, the global HRQOL score was not significantly different from the baseline score (Table 3).

Multivariate analysis adjusted for covariates showed that, just after treatment (T0–TE), the difference in global HRQOL score change was 13.5 points ($p < 0.0001$, Fig. 1) between IB and RP, in favor of IB. Significant differences between T0 and TE in favor of IB were observed for all other QLQ-C30 scales (except for nausea/vomiting, diarrhea, and financial problem scales, Table 3). Two months after treatment (T0–T2), no significant differences were observed between IB and RP in the global HRQOL change (-4 points, $p = 0.2720$, Fig. 1) and in any of the other QLQ-C30 scales except in the role functioning scale which was in favor of IB (11 points, $p = 0.0014$, Table 3). Six months after treatment (T0–T6), a significant difference in the global HRQOL change was observed between IB and RP (-7.5 points, $p = 0.0164$, Fig. 1) slightly in favor of RP. This difference in favor of RP was maintained at 12 months (-7.9 points, $p = 0.0195$), 18 months (-8.3 points, $p = 0.0377$), and 24 months (-8.2 , $p = 0.0379$). However, from 6 months until 24 months, no significant differences in the changes of any of the other QLQ-C30 scales were observed between IB and RP (Table 3).

Figure 2 presents the percentage of patients with an increase in urinary, bowel, and sexual symptoms over time for each treatment. Urinary incontinence problems were more frequent after RP than after IB at all time-points. Immediately after treatment, 68.4% of RP patients reported that their urinary continence had deteriorated compared with baseline vs. 12.7% in the IB group. Although a decrease in the percentage of men who reported this dysfunction after surgery was observed at 2, 6, 12, and 18 months, 49% reported that urinary incontinence was worse at 24 months than at baseline in the RP group vs. 19.7% in the IB group.

On the other hand, other urinary problems, fecal incontinence, and rectal bleeding were more frequent after IB than after RP (Fig. 2). Deterioration of urinary urgency in the IB group reached a maximum at 2 months, with 63.9% of IB men reporting that this symptom was worse than before treatment vs. 31.4% in the RP group. Twenty-four months after treatment, these figures were 37.9% in the IB group and 26.5% in the RP group, respectively. Urinary pain was particularly marked 2 months after IB, with 63.7% of IB patients reporting an increase in urinary pain vs. 18.4% in the RP group, and 24 months after treatment these figures were 19% in the IB group vs. 2.1% in the RP group.

Table 3. Intragroup and intergroup QLQ-C30 score changes over time

	RP		IB		IB vs. RP			Preferred strategy for the corresponding scale
	Mean _{RP}	<i>p</i> [*]	Mean _{IB}	<i>p</i> [*]	Mean _{IB/RP}	95% CI	<i>p</i> [†]	
T0-TE								
QL	-18.	<.0001 [‡]	-5.8	<.0001 [‡]	13.5	[7.5;19.6]	<.0001 [‡]	IB
PF	-28.7	<.0001 [‡]	-2.8	<.0001 [‡]	25.9	[20.9;30.9]	<.0001 [‡]	IB
RF	-48.3	<.0001 [‡]	-7.2	<.0001 [‡]	39.9	[30.7;49.1]	<.0001 [‡]	IB
EF	-6.4	0.0139	2.8	0.0082	9.8	[3.5;16.1]	0.0008 [‡]	IB
CF	-7.6	0.0019	1.0	0.1890	9.2	[4.0;14.4]	0.0001 [‡]	IB
SF	-40.5	<.0001 [‡]	-7.3	<.0001 [‡]	32.7	[24.4;40.9]	<.0001 [‡]	IB
FA	38.1	<.0001 [‡]	7.1	<.0001 [‡]	-31.2	[-38.3;-24.0]	<.0001 [‡]	IB
PA	28.9	<.0001 [‡]	6.0	<.0001 [‡]	-21.7	[-29.4;-14.1]	<.0001 [‡]	IB
DY	8.5	0.0022	-0.1	0.9031	-8.5	[-15;2.0]	0.0065 [‡]	IB
IN	15.0	0.0004 [‡]	0.8	0.6052	-15.7	[-25;-6.4]	0.0002 [‡]	IB
AL	20.9	<.0001 [‡]	2.6	0.0073	-19.1	[-25.5;-12.7]	<.0001 [‡]	IB
CO	15.0	<.0001 [‡]	3.8	0.0009	-12.5	[-19.8;-5.3]	0.0002 [‡]	IB
T0-T2								
QL	-2.9	0.1800	-6.8	<.0001 [‡]	-4	[-10.;3.0]	0.2720	None
PF	-6.3	0.0001 [‡]	-2.2	0.0006	-3.5	[-0.3;7.2]	0.0812	None
RF	-16.8	<.0001 [‡]	-5.9	<.0001 [‡]	11.1	[3.7;18.5]	0.0014 [‡]	IB
SF	-13.3	<.0001 [‡]	-8.8	<.0001 [‡]	4.4	[-2.7;11.6]	0.3128	None
FA	9.8	0.0001 [‡]	6.7	<.0001 [‡]	-1.	[-7.7;5.8]	0.9376	None
PA	2.2	0.3793	6.9	<.0001 [‡]	5.7	[-1.3;12.7]	0.1340	None
DI	2.2	0.1812	4.8	0.0002 [‡]	3.3	[-3.2;9.8]	0.4588	None
T0-T6								
QL	1.8	0.3863	-3.6	0.0044	-7.5	[-13.9;-1.1]	0.0164 [‡]	RP
EF	6.4	0.0034	8.9	<.0001 [‡]	3.6	[-3.5;10.5]	0.4698	None
T0-T12								
QL	4.3	0.1063	-0.6	0.6052	-7.9	[-14.8;-1.]	0.0195 [‡]	RP
EF	8.5	0.0038	7.0	<.0001 [‡]	-1.3	[-8.9;6.2]	0.9087	None
T0-T18								
QL	6.9	0.0274	-0.6	0.6524	-8.3	[-16.;-0.4]	0.0377 [‡]	RP
EF	10.6	0.0028	6.9	<.0001 [‡]	-5.6	[-10.9;5.6]	0.7312	None
AL	-5.7	0.0585	0.8	0.3953	7.9	[1.7;14.2]	0.0083 [‡]	RP
T0-T24								
QL	7.7	0.0101	0.8	0.5223	-8.2	[-16.;-0.4]	0.0379 [‡]	RP
EF	12.1	0.0003 [‡]	9.3	<.0001 [‡]	-2.7	[-11.4;6.0]	0.7422	None

Abbreviations: QLQ-C30 = European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire QLQ-C30, version 3; RP = radical prostatectomy; IB = interstitial brachytherapy; QL = global health status/quality of life; PF = physical functioning; RF = role functioning; EF = emotional functioning; CF = cognitive functioning; SF = social functioning; FA = fatigue; VO = nausea/vomiting; PA = pain; DY = dyspnea; IN = insomnia; AL = appetite loss; CO = constipation; DI = diarrhea; FD = financial problems.

* Ninety pairwise comparisons were made for the intragroup changes in health-related quality of life. A *p* value of 0.0006 (0.005/90) was considered to represent a statistically significant difference.

† Multivariate covariance analysis adjusted for baseline covariates. *Note:* This table only reports QLQ-C30 results for scales with statistically significant intragroup or intergroup differences (gray boxes).

‡ For statistically significant difference.

Diurnal and nocturnal urinary frequency problems were also more frequent after IB, with a peak occurring 2 months after treatment (66% and 62.8% in the IB group vs. 34.9% and 34.5% in the RP group). Twenty-four months after treatment, 36.8% of IB men reported increased diurnal frequency and 30.8% reported increased nocturnal frequency vs. 16.3% and 14.3% in the RP group, respectively.

Fecal incontinence and rectal bleeding, relatively uncommon after surgery, were more frequent after IB. At 24 months, 8.9% of IB patients reported an increase of fecal incontinence compared with baseline vs. 2% in the RP group, and 15.1% of IB men reported more rectal bleeding than before treatment vs. none in the RP group.

Men treated with RP more frequently reported a decreased ability to achieve or maintain an erection, relative to baseline, than IB men at all time-points (Fig. 2). Deterioration of erectile function in the RP group reached a maximum at 6 months, with 88% of sexually active RP men reporting poorer erectile function than at baseline vs. 50.8% in the IB group (the percentage of IB patients receiving neoadjuvant hormonal therapy must be kept in mind in this context). This deterioration persisted for 18 months after treatment in the RP group (83.3% vs. 45.8% in the IB group). Of note, treatment for impotence was more frequent in the RP group than in the IB group (32% in the RP group vs. 12.5% in the IB group, 12 months after treatment). The

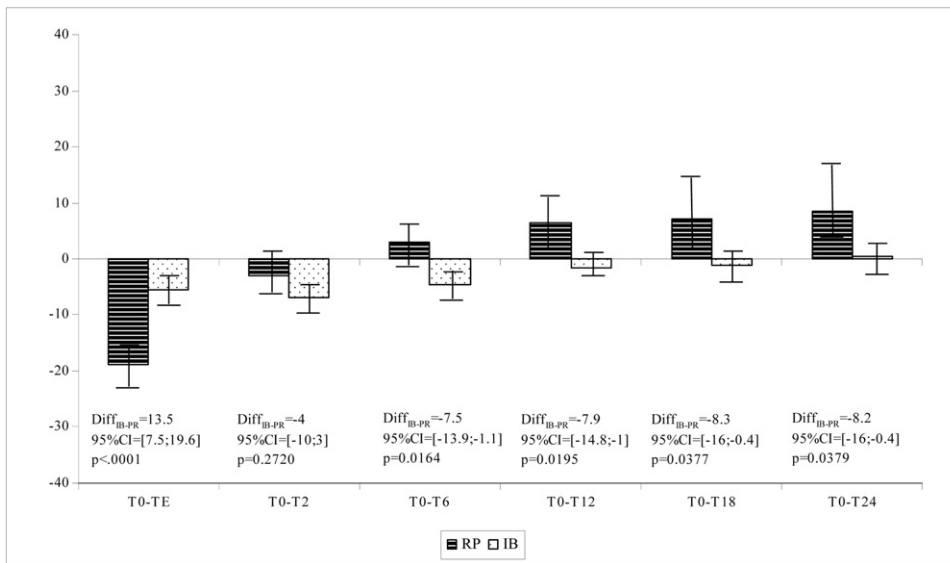


Fig. 1. Differences in mean global European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire version 3 (QLQ-C30) score change between treatments. RP = radical prostatectomy; IB = interstitial brachytherapy; T0 = before treatment; TE = immediately after treatment; T2, T6, T12, T18, and T24 = 2, 6, 12, 18, and 24 months after hospital discharge for prostatectomy or brachytherapy. I represent 95% confidence intervals (95% CI) of mean global QLQ-C30 change, relative to the baseline score, for each treatment group. Data below histograms reflect mean difference in the global QLQ-C30 change over time between interstitial brachytherapy and radical prostatectomy (Diff_{IB-RP}) with its corresponding 95% confidence intervals and *p* value (*p*).

impact of neoadjuvant hormonal therapy on sexual function will be specifically addressed in a subsequent publication.

Costs results

Mean initial treatment costs were higher for the IB group (€7,159) than for the RP group (€6,472) with a significant mean difference of €687 ($p < 0.0001$), as shown in Table 4. The structure of these costs was quite different between these two groups: costs of iodine-125 implants represented 73% of the IB initial treatment costs, whereas the major cost for the RP group was hospital stay, representing 68% of total costs. Whereas the mean length of hospital stay was 11.6 days for RP, men treated by IB were hospitalized for an average of 2.2 days. In the present study, no significant costs difference was found between the retropubic and laparoscopic surgical approach. However, type of treatment planning technique and type of seeds payment had implications on IB costs, with a mean initial IB treatment cost significantly lower in the five centers using a real-time planning technique and paying a lump sum for seeds (€6,702) than in the center using preplanning and having unit payment (€8,836, $p < 0.0001$).

On the other hand, mean hospital follow-up costs were significantly lower in the IB group than in the RP group for all time-points. Moreover, this discrepancy in favor of IB increased over time as, because of the fewer hospitalizations for complications than after RP, IB generated €340 savings per patient over the first 2 months ($p = 0.0340$), €687 savings over the first year ($p = 0.0007$), and €724 savings over the first 2 years ($p = 0.0022$).

When taking into account both initial treatment costs and

hospital follow-up costs, mean hospital costs were not significantly different between IB and RP, at any time-point, as the extra cost of IB due to implants was counterbalanced by the lower hospitalization costs for complications. The mean differences between IB and RP were €347 over T0–T2, €1 over T0–T12, and –€36 over T0–T24.

Mean outpatient costs were higher in the IB group (€290) than in the RP group (€224) over the first 6 months after treatment (Table 5). This was mainly due to examinations (CT dosimetric scans) which represented 67% of the outpatient costs in the IB group. No significant difference was observed between the groups after 6 months.

The mean cost difference resulting from loss of productivity among working patients was significantly in favor of IB compared with RP (Table 6), for all time-points (30% of working patients in the RP group and 18% in the IB group), as the mean number of days off work among working patients was 10 in the IB group vs. 49 in the RP group over the T0–T6 period (respectively 10 days vs 65 days over the T0–T24 period).

Finally, mean societal costs did not differ significantly between IB and RP (Table 7). Over the first 2 months, mean societal costs were €7,465 for the RP group vs. €7,525 for the IB group, corresponding to a nonsignificant difference of €60 ($p = 0.8852$). Over the first 24 months, these figures were €8,715 for the RP group vs. €8,019 for the IB group ($p = 0.0843$).

DISCUSSION

The purpose of this article was to compare IB with RP, performed for localized prostate cancer patients, in terms

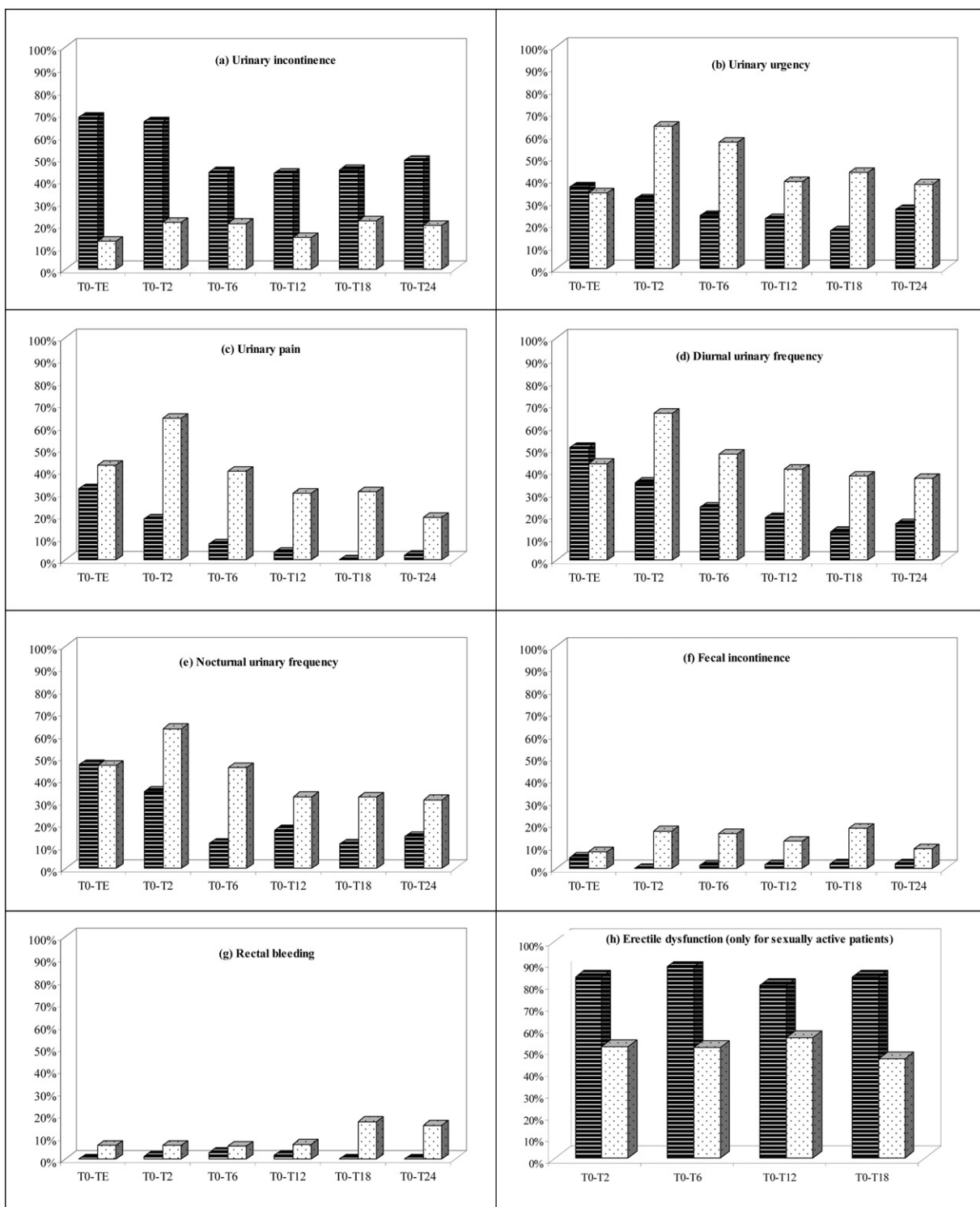


Fig. 2. Percentage of patients with European Organization for Research and Treatment of Cancer prostate cancer specific QLQ-PR25 module morbidity increase over time, relative to baseline. (a) Urinary incontinence. (b) Urinary urgency. (c) Urinary pain. (d) Diurnal urinary frequency. (e) Nocturnal urinary frequency. (f) Fecal incontinence. (g) Rectal bleeding. (h) Erectile dysfunction (only for sexually active patients). Panel h does not report results between T0-TE and T0-T24 because of insufficient data. Gray lined bars = radical prostatectomy; stippled white bars = interstitial brachytherapy.

of HRQOL, treatment-related symptoms, and costs. The entire study was based on an assumed equivalent level of efficacy.

HRQOL and treatment-related symptoms

A major finding of this study is that HRQOL differed between the IB and RP groups over time. Whereas HRQOL

Table 4. Mean hospital costs (Euro2001)

	Prostatectomy		Brachytherapy		IB-RP comparison	
	Mean	95% CI	Mean	95% CI	Diff _{IB-RP}	95% CI
Initial treatment costs						
Consumables	410	288; 533	5,192	5,025; 5,360	+4,782*	4,510; 5,054
Operating theater	1,674	1,602; 1,745	752	642; 863	-922*	-1099; -744
Hospitalizations	4,387	4,150; 4,625	1,060	1,011; 1,110	-3,327*	-3,497; -3,157
Postoperative CT	—	—	155	—	—	—
Total	6,472	6,206; 6,737	7,159	6,939; 7,380	+687*	305; 1,071
Hospital follow-up costs						
during the first 2 months (2 mo)	387	76; 699	47	0; 93	-340*	-552; -129
during the first 6 months (6 mo)	610	247; 972	64	14; 114	-546*	-790; -302
during the first year (12 mo)	775	386; 1,164	88	32; 145	-687*	-950; -424
during the first 18 months (18 mo)	874	477; 1,271	246	73; 421	-628*	-998; -258
during the first 24 months (24 mo)	992	565; 1,418	268	93; 443	-724*	-1,108; -340
Mean hospital costs (2 mo)	6,859	6,403; 7,315	7,206	6,973; 7,438	+347	-117; 811
Mean hospital costs (6 mo)	7,081	6,577; 7,586	7,223	6,990; 7,457	+142	-343; 627
Mean hospital costs (12 mo)	7,247	6,717; 7,777	7,248	7,014; 7,481	+1	-495; 497
Mean hospital costs (18 mo)	7,346	6,818; 7,873	7,406	7,123; 7,688	+60	-493; 613
Mean hospital costs (24 mo)	7,463	6,916; 8,010	7,427	7,144; 7,710	-36	597; 525

Abbreviations: RP = radical prostatectomy; IB = interstitial brachytherapy; Diff = mean difference between IB and RP; CI = confidence interval.

* Statistically significant difference.

changes were in favor of IB immediately after treatment, this situation was reversed at 6 to 24 months with minor changes in favor of RP.

With a very few notable exceptions (10–12), most studies have assessed HRQOL from several months to several years after treatment, making any comparison with our short-term results (0 to 6 months) questionable. Moreover, to our knowledge, no previous study has compared HRQOL immediately after treatments, although Lubeck *et al.* (13) showed that patients undergoing RP had very low HRQOL scores just after treatment. The absence of differences between RP and IB observed at 2 months in our study is similar to the data reported by Lee *et al.*, who did not find any significant differences at 1 month in HRQOL scores, measured by FACT-P (functional assessment of cancer therapy - prostate), between these two groups (10).

The significant difference in general HRQOL change at 6 to 24 months after treatment observed between IB and RP in

our study slightly differs from most previous studies which have concluded that, more than 6 months after therapy, HRQOL was not significantly different after IB compared with RP (10, 14–19). The following remarks can be made about this finding: first, direct comparisons of our HRQOL data with those of previous studies are difficult, as most long-term general HRQOL studies comparing IB and RP were based on a retrospective, cross-sectional design, did not include baseline HRQOL data, and used HRQOL measures other than the QLQ-C30 instrument. Second, the difference in global QLQ-C30 score change favoring RP (from 6 until 24 months after treatment) in our study comprised between 7 to 8 points (Fig. 1), and this difference, although statistically significant, is usually considered a minor clinical change (9). A possible explanation of this result in favor of RP is the persistence of irritating voiding symptoms in the IB group. Indeed, by 6 to 24 months, the percentage of IB patients reporting a deterioration from baseline was 57% and 38% for urinary urgency, 40% and

Table 5. Mean outpatient costs (Euro2001)

	Prostatectomy		Brachytherapy		IB-RP comparison	
	Mean	95% CI	Mean	95% CI	Diff _{IB-RP}	95% CI
During the first 2 months (2 mo)	118	93;144	243	219;267	+125*	83;167
During the first 6 months (6 mo)	224	178;269	290	264;316	+66*	15;118
During the first year (12 mo)	289	233;346	346	315;377	+57	5;118
During the first 18 months (18 mo)	356	289;423	420	378;461	+64	-15;144
During the first 24 months (24 mo)	419	343;494	482	435;528	+63	-29;152

Abbreviations: RP = radical prostatectomy; IB = interstitial brachytherapy; Diff = mean cost difference between IB and RP; CI = confidence interval.

* Statistically significant difference.

Table 6. Mean costs due to loss of productivity among working patients (Euro2001)

	Prostatectomy		Brachytherapy		IB-RP comparison	
	Mean	95% CI	Mean	95% CI	Diff _{IB-RP}	95% CI
During the first 2 months (2 mo)	2,012	1,368; 2,656	487	105; 869	-1,525*	-2,213; -837
During the first 6 months (6 mo)	2,667	1,710; 3,625	568	112; 1,023	-2,099*	-3,024; -1,175
During the first year (12 mo)	3,514	1,810; 5,217	588	123; 1,053	-2,926*	-4,319; -1,532
During the first 18 months (18 mo)	3,514	1,810; 5,217	588	123; 1,053	-2,926*	-4,319; -1,532
During the first 24 months (24 mo)	3,678	1,774; 5,581	620	153; 1,086	-3,058*	-4,586; -1,530

Abbreviations: RP = radical prostatectomy; IB = interstitial brachytherapy; Diff = mean cost difference between IB and RP; CI = confidence interval.

* Statistically significant difference.

19% for urinary pain, and 45% and 31% for diurnal and nocturnal frequency (Fig. 2). Another possible explanation could be the difference in the pretreatment IPSS score, higher in the RP group than in the IB group at baseline (Table 1). A likely explanation is that patients with dysuria were contraindicated for IB because of the high risk of developing urinary retention after implantation. With a significantly higher pretreatment IPSS score, it is logical that patients treated by RP feel better at 24 months than before treatment whereas, with a normal or subnormal initial IPSS score, the IB patients at best reached the same normal level at 24 months.

Not only irritative urinary symptoms differed between IB and RP, but also urinary incontinence, bowel and sexual symptoms. Our results concerning urinary continence, which more frequently deteriorated after RP than after IB, appear to be similar to previously reported data (14, 16).

Patients in the IB group reported more bowel symptoms, including fecal incontinence and rectal bleeding, than patients in the RP group. Previous studies have consistently demonstrated that bowel dysfunction was significantly more prevalent after radiation therapy than after RP (20–22). Brandeis *et al.* (14) found that IB patients had more severe bowel dysfunction than the RP group, in agreement with Arterbery *et al.* (23) who reported an increased frequency of defecation (75%), rectal ulcers (6%), and rectal bleeding (6%).

Like previous studies, we found that impairment of sexual function relative to baseline was more pronounced after RP than after IB. Although early studies evaluating the effects of IB on erections and sexuality suggested that IB

may have limited effects on erections 6 months after treatment (23), our results confirm more recent data showing that the long-term negative effects of IB on erections and sexuality might be more severe than initially reported (24). However, it should be kept in mind that a higher percentage of patients received hormonal therapy in the IB group (43.5%) than in the RP group (6.3%).

Costs

Another major finding of this study was that mean societal costs did not differ significantly between IB and RP groups, either in the short term or in the longer term. Although these costs appear to be similar, their structure differed between RP and IB. Mean initial treatment cost was higher in the IB than in the RP group, the main drivers being radioactive seed costs (73%) in the IB group and hospitalization costs (68%) in the RP group. On the other hand, hospital follow-up costs had a lower weight in the hospital costs for the IB group (0.7% during the first 2 months, 3.6% during the first 24 months) than for the RP group (5.6% during the first 2 months, 13.3% during the first 24 months). Moreover, because of the smaller number of days off work in the IB group, mean costs due to loss of productivity among working patients were lower in this group than in the RP group. Although the societal cost appears to be almost the same at 2 months for the IB and RP groups, a nonsignificant trend toward a higher societal cost was observed in the RP group at 24 months, mainly owing to hospitalizations for complications and loss of productivity.

Table 7. Mean societal costs (Euro2001)

	Prostatectomy		Brachytherapy		IB-RP comparison	
	Mean	95% CI	Mean	95% CI	Diff _{IB-RP}	95% CI
During the first 2 months (2 mo)	7,465	6,966; 7,964	7,525	7,264; 7,785	+60	-455; 575
During the first 6 months (6 mo)	7,930	7,304; 8,555	7,616	7,349; 7,882	-314	-888; 261
During the first year (12 mo)	8,353	7,612; 9,093	7,702	7,432; 7,971	-651	-1,282; 20
During the first 18 months (18 mo)	8,506	7,771; 9,242	7,929	7,616; 8,243	-577	-1,253; 99
During the first 24 months (24 mo)	8,715	7,933; 9,496	8,019	7,704; 8,334	-696	-1,394; 2

Abbreviations: RP = radical prostatectomy; IB = interstitial brachytherapy; Diff = mean cost difference between IB and RP; CI = confidence interval.

* Statistically significant difference.

Two studies have reported similar results concerning initial treatment costs. Wagner *et al.* (25) reported that the average initial treatment costs for IB (\$21,025) were significantly higher than those for RP (\$15,097, $p < 0.0001$), and Ciezki *et al.* (26), using a hospital-wide cost accounting system, found that treatment costs for IB exceeded those for RP by 85% to 105%. Both of these studies concluded that the higher initial treatment costs for IB were due to seed costs which were not offset by the reduced hospital stay cost. Other studies compared IB and RP costs, taking into account follow-up costs. Some of these (27–29) suggested that there were no major cost differences between IB and RP, as observed in our study when follow-up costs were included. The study by Kohan *et al.* (27) demonstrated that, at 12-month follow-up, total costs incurred for IB (\$13,886) and RP (\$13,905) were comparable. However, other studies have reported different results. Using a national sample of Medicare patients from 1993 to 1996, Brandeis *et al.* (30) calculated mean costs for workup, treatment, and 6-month follow-up of localized prostate cancer patients and showed that RP costs (\$19,019) were higher than IB costs (\$15,301, $p < 0.05$). Although most of the above-mentioned results are in agreement with our own results, any comparison must be performed with caution, as almost all of these studies were single-institution analyses based on small sample sizes that did not take into account time off work and, more importantly, were based on charges (Medicare fee schedule) rather than “real” costs.

Limitations

Our study presents a number of limitations that need to be addressed. First, despite our attempt to control for variables that might affect HRQOL outcomes, the study is limited by its observational, nonrandomized design, with possible confounding variables introducing biases into the analysis. A second limitation of this study is that the patient response rate for HRQOL questionnaires in the RP group was lower than in the IB group, a situation which could have also introduced potential biases. The response rate in the IB group was actually very high and most likely reflects the

radiation oncologists’ and patients’ motivations for this innovative technique. A third limitation comes from the QLQ-PR25 scoring. As this instrument is still not completely finalized, the results were presented for certain single items, but no global score could be derived for each global symptom scale, thereby limiting the scope of treatment-related symptoms analysis. Another limitation concerns the availability and homogeneity of hospital unit costs used for evaluation of resource consumption during the initial IB or RP treatment. Because IB was an emergent innovative technique at the beginning of the study, the corresponding DRG was not specific to that technique, and its cost therefore did not accurately reflect the resources used by this technique. To provide a better estimate, IB unit costs were therefore calculated from the 2001 cost-accounting systems. Although we intended to use the same methodology to reconstitute RP hospital unit costs, this approach was impaired by the difficulty of obtaining good cost-accounting data in teaching hospitals. Despite these limitations, our study represents the first multi-institutional, prospective, and comparative study of HRQOL, treatment-related symptoms, and costs in men treated by one of the two most commonly employed strategies for localized low-risk prostate cancer treatment, with a large sample size and a 24-month follow-up period.

CONCLUSION

The present study strongly suggests a similar societal cost profile for IB and RP in France but with different HRQOL and treatment-related symptoms profiles. Whereas RP is characterized by a very marked impairment in HRQOL immediately after treatment with subsequent improvement, IB shows a moderate but persistent impairment in HRQOL over 2 years. Urinary incontinence was found to be more frequent after RP, whereas urinary irritative and obstructive symptoms were more frequently registered after IB. Last but not least, impairment in sexual function was found to be constantly higher after RP than after IB over the first 2 years. These HRQOL and symptoms analysis might help to tailor treatments to suit individual patients’ needs.

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