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Quality of life after prostate cancer treatments in patients comparable at baseline

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Background: Previous studies on the effects of different prostate cancer treatments on quality of life, were confounded because patients were not comparable. This study examined treatment effects in more comparable groups.

Methods: From 2008–2011, 240 patients with localised prostate cancer were selected to be eligible for both radical prostatectomy (RP) and external beam radiotherapy (EBRT). Brachytherapy (BT) was a third option for some. Health-related quality of life was measured by expanded prostate cancer index composite (EPIC) up to 12 months after treatment.

Results: In the sexual domain, RP led to worse summary scores ($P < 0.001$) and more often to a clinically relevant deterioration from baseline than BT and EBRT (79%, 33%, 34%, respectively). In the urinary domain, RP also led to worse summary scores ($P = 0.014$), and more deterioration from baseline (41%, 12%, 19%, respectively). Only on the irritative/obstructive urinary scale, more BT patients (40%) showed a relevant deterioration than RP (17%) and EBRT patients (11%). In the bowel domain, the treatment effects did not differ.

Conclusion: This study provides a more unbiased comparison of treatment effects, as men were more comparable at baseline. Our results suggest that, for quality of life, radiotherapy is at least as good an option as RP for treating localised prostate cancer.

Many studies have focused on the effect of prostate cancer treatments on quality of life. The most common treatments for localised prostate cancer are prostatectomy and radiotherapy (interstitial or external). Differences in associated health-related quality of life (HR-QOL) have been reported. Radical prostatectomy (RP) causes more urinary incontinence and erectile dysfunction, whereas radiotherapy causes more irritative symptoms and bowel problems, as reported in reviews (Penson, 2007).

To date, however, this comparison has been confounded by the fact that the patients in the different treatment groups were not comparable. In most studies, for example, the surgery patients were

younger (Madalinska *et al*, 2001; Wei *et al*, 2002; Talcott *et al*, 2003; Korfage *et al*, 2005; Ferrer *et al*, 2008; Smith *et al*, 2009; Huang *et al*, 2010), had less aggressive tumours (Madalinska *et al*, 2001; Wei *et al*, 2002; Korfage *et al*, 2005; Ferrer *et al*, 2008; Huang *et al*, 2010) and better pre-treatment functioning (Talcott *et al*, 2003; Ferrer *et al*, 2008; Huang *et al*, 2010) than the patients receiving external beam radiotherapy (EBRT). Patients characteristics differed because they were used as selection criteria for treatment choice. This is problematic, because, for example, age at diagnosis and pre-treatment functioning are significant predictors of HR-QOL in all domains (Stanford *et al*, 2000; Talcott *et al*, 2003;

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Huang *et al*, 2010). Reducing the baseline differences between the patients would yield a more unbiased comparison of the treatment effects.

As randomisation to treatment groups is not feasible, see, for example, the attempted RCT by Crook *et al* (Crook *et al*, 2011), we chose a different approach to reduce the differences. In the present study, only patients who were eligible for both prostatectomy and EBRT were asked to participate. We used this improved design, to obtain patients that were more comparable at baseline with regard to patient and tumour characteristics. In this more homogeneous population, this study aims to compare treatment effects on HR-QOL scores and their clinically relevant changes.

MATERIALS AND METHODS

Patients. Between March 2008 and February 2011, patients with primary localised prostate cancer (T1–3aN0M0), intending to be treated and eligible for both radiotherapy and RP, were asked to participate in this prospective study. Exclusion criteria were contra-indication for surgery (based on e.g., cardiovascular problems) or external radiotherapy (based on e.g., Crohn's disease), mental or cognitive problems as assessed by the physician, inadequate knowledge of the Dutch language, which might interfere with filling out the questionnaires, or a preference for active surveillance.

Radical prostatectomy and EBRT were offered to all patients. Some patients were, in addition, eligible for brachytherapy (BT). To those patients, BT was offered, as a third option. Exclusion criteria for BT were a small or large prostate volume (<20 cc or >50 cc), PSA >15, Gleason >7 and/or severe urinary symptoms (requiring medication or, if available, IPSS >12 and/or Q_{\max} <15 ml s⁻¹).

Recruitment took place in three training hospitals in the Netherlands, that is, the Radboud University Nijmegen Medical Centre, the Canisius Wilhelmina Hospital in Nijmegen, and the Rijnstate Hospital in Arnhem. The latter two are large non-academic centres. The study was approved by the research ethics committees of these hospitals.

The study took place within a randomised-controlled trial of a decision aid. One group only discussed the treatment choice with their specialist, the other group had an additional consult with the researcher, during which the pros and cons of the different treatment options were discussed by means of a decision aid. No effect of the decision aid on HR-QOL was found. The study was described previously in more detail (van Tol-Geerdink *et al*, 2013).

Measures. Data were collected on several variables that were expected to affect the HR-QOL. The assessments were at baseline, that is, pre-treatment and at 12 months after treatment. For EBRT, this was defined as 12 months after the last radiotherapy session.

Patients' demographic and medical characteristics. Self-report data were collected on demographic variables (age, education). Tumour characteristics (T status, pre-treatment PSA value and Gleason score) were extracted from the medical records.

Health-related quality of life. HR-QOL was assessed by means of the EPIC (Wei *et al*, 2000). This prostate-specific instrument includes questions on function (do you have certain symptoms) and on bother (to what extent are the symptoms a problem for you) in the urinary, bowel, sexual and hormonal domain. It provides three scales per domain, a function score, a bother score and a summary score, ranging from 0–100, with higher scores reflecting better functioning. The expected effect on urinary functioning differs between the treatments, with incontinence related more to prostatectomy and irritative/obstructive symptoms related more to radiotherapy. Therefore, we also assessed the

incontinence and irritative/obstructive subscales, yielding 11 EPIC scale scores in total.

In addition to scale scores, we examined scores on distinctive items from each domain separately. These single items were added because they are believed to be more illustrative and informative than scale scores to some clinicians. For the urinary domain, we used the item 'How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?', with answers dichotomised to 'none' vs 'one or more pads per day' (Miller *et al*, 2005). This strict definition of incontinence was chosen, as recommended, because quality of life was found to be higher for none than for one or more pads per day (Liss *et al*, 2010). For the bowel domain, we used the item 'How often have you had stools (bowel movements) that were loose or liquid during the last 4 weeks?', with answers dichotomised to 'no/seldom loose stool' vs 'at least half of the time loose stool' (Madalinska *et al*, 2001). For the sexual domain, we used 'How would you describe the usual quality of your erections during the last 4 weeks?', with answers dichotomised to 'firm enough for intercourse' vs 'not firm enough for intercourse' (Stanford *et al*, 2000).

Analyses. Our primary research question was to compare treatment effects on HR-QOL. The patients' quality of life was assessed with the EPIC scales ranging from 0–100. Unadjusted scores are presented for all scales. The effect of treatment was analysed in analyses of variance. These ANOVAs were corrected for the corresponding baseline scores. For example, differences between RP and BT on the urinary function score at 12 months were corrected for the baseline urinary function scores. In addition, variables were considered as possible confounding factors if they differed at baseline between the treatment groups ($P < 0.15$), and were related to HR-QOL. None of the demographic or medical variables, however, met these criteria. Therefore, analyses were not corrected for such confounders, and all presented means are unadjusted.

The scores were also expressed as the proportion of patients with a clinically significant deterioration from baseline. This was defined as a minimally important difference (MID) of more than half a s.d. (Norman *et al*, 2003). The s.d. values in this study for urinary, bowel and sexual summary scores were 14, 7 and 22, respectively, yielding MID values of 7, 3.5 and 11, respectively. The urinary incontinence and irritative/obstructive subscales had standard deviations of 28 and 10, respectively, yielding MID values of 14 and 5, respectively. These MID values correspond well with those reported by others (Morton *et al*, 2011). The percentage of patients with a clinically relevant deterioration from baseline was analysed by χ^2 -tests.

From the urinary, bowel and sexual domain, a single representative item was selected: the need for urinary pads, the frequency of loose stool and the firmness of the erections, respectively. The scores on these items were dichotomised (see above) and analysed by treatment, using the χ^2 -test. In addition, a separate analysis was done on patients with good baseline functioning on the three selected single items. The proportion of patients that changed to poorer outcome at 12 months after treatment were analysed by χ^2 -tests.

Baseline differences between the treatment groups were examined using t -tests for continuous variables and using χ^2 -tests for dichotomous or ordinal variables. In case of missing data, EPIC scale values were calculated only if at least 80% of the items were filled out, by imputing the mean of the remaining items.

RESULTS

Patients. In total, 307 patients were asked to participate in the study. Of these patients, 36 declined (12%) and 271 gave informed

consent (88%). Of these 271 patients, 31 were excluded because additional screening revealed other health problems ($n=14$) or because they chose active surveillance after all ($n=17$). This yielded a total of 240 patients included in this study. Of the 240, a total of 36 (15%) were lost during follow-up up to 12 months after treatment. Those 36 patients did not differ significantly in age, education or tumour characteristics from those with complete follow-up. Reasons for drop out are given in Figure 1. The drop out was comparable in the RP, BT and EBRT groups (16%, 11% and 14%, respectively). For the sexual domain, follow-up data were missing for an additional eight patients, due to their reluctance to answer questions on sexual functioning.

Treatments received. The treatments received were RP ($n=170$), BT ($n=28$) and EBRT ($n=42$). Prostatectomy was performed by robot-assisted laparoscopic prostatectomy (60%), laparoscopic procedure without robot (25%) or open surgery (15%). The procedures were either nerve sparing (81%) or non-nerve sparing (19%). None of the surgical patients received postoperative radiotherapy in the year after treatment. Brachytherapy was performed in the hospital in Arnhem with low-dose seed implants. External beam radiotherapy was given by IMRT at an (equivalent) dose of 78 Gy. All but seven EBRT patients were irradiated at the Radboud University Nijmegen, using an endorectal balloon with the intention to limit rectal toxicity, and five EBRT patients received additional androgen deprivation therapy.

Baseline differences. At baseline, no significant differences between patients eventually receiving RP, BT or EBRT were found for patient characteristics nor for general health assessment (Table 1). In general, the EPIC scores did not differ significantly either, except for better baseline scores on the urinary domain in the group receiving BT (Table 2). The latter was expected because urinary symptoms are an exclusion criterion for BT. Analyses were corrected by including the baseline scores as covariates.

Health-related quality of life effects of treatment received. Table 3 gives an overview of the unadjusted EPIC scores at 12 months after treatment for RP, BT and EBRT. The statistical tests

to compare treatments were corrected for the patients' baseline EPIC scores. Significant differences were only found between RP and the other two treatments (BT and EBRT), and only in the urinary and sexual domain. Radical prostatectomy gave worse

Table 1. Baseline patients characteristics by treatment: radical prostatectomy (RP), brachytherapy (BT) or external beam radiotherapy (EBRT)

	RP N = 170	BT N = 28	EBRT N = 42	P-value
Demographic				
Age in years (mean (s.d.))	64 (5)	64 (5)	65 (6)	0.44
Education: college or more (%)	33%	30%	31%	0.94
Living with partner (%)	89%	89%	83%	0.56
Tumour characteristics				
T1-2 (%)	91%	100%	84%	0.13
Gleason ≤ 7 (%)	97%	100%	91%	0.15
PSA ≤ 20 (%)	94%	100%	91%	0.27
General health score ^a (mean (s.d.))	7.9 (1.4)	7.9 (1.6)	7.8 (1.4)	0.89

Abbreviation: PSA = prostate-specific antigen.
^aSelf-rated general health on scale from 1 (poor health) to 10 (excellent health).

Table 2. Baseline EPIC^a scores by treatment received: radical prostatectomy (RP), brachytherapy (BT) or external beam radiotherapy (EBRT)

	RP N = 160 mean (s.d.)	BT N = 28 mean (s.d.)	EBRT N = 42 mean (s.d.)	P-value
Urinary scales				
Summary score	87 (12) ^b	93 (8) ^{b,c}	85 (13) ^c	0.02
Function score	93 (11)	97 (7)	91 (14)	0.09
Bother score	83 (15) ^b	91 (9) ^{b,c}	82 (15) ^c	0.02
Incontinence scale	93 (16)	96 (12)	92 (14)	0.43
Irritative-Obstructive scale	85 (13) ^b	92 (7) ^{b,c}	82 (14) ^c	0.01
Bowel scales				
Summary score	96 (7)	98 (3)	95 (8)	0.21
Function score	95 (8)	97 (4)	95 (8)	0.29
Bother score	97 (6)	99 (3)	96 (8)	0.16
Sexual scales				
Summary score	60 (21)	56 (23)	58 (24)	0.66
Function score	52 (21)	50 (25)	49 (26)	0.70
Bother score	78 (25)	70 (26)	78 (28)	0.33
Single items				
'No urinary pads required'	99%	96%	93%	0.10
'No/seldom loose stool'	91%	100%	90%	0.26
'Erections firm enough for intercourse'	56%	62%	48%	0.48

The single items were expressed as % of patients with that answer and were analysed by χ^2 -tests.
^aAll EPIC scales range from 0-100, with higher scores representing better functioning.
^bSignificant difference between BT and RP (Posthoc Bonferroni test).
^cSignificant difference between BT and EBRT (Posthoc Bonferroni test).

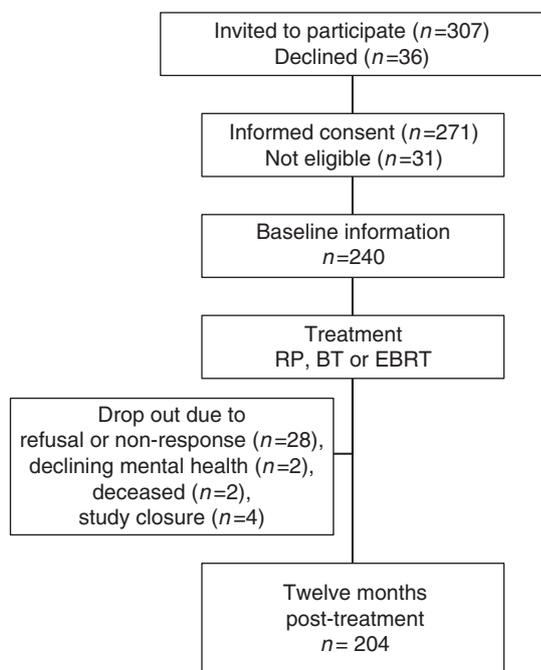


Figure 1. Patient flow.

Table 3. Unadjusted EPIC^a scores at 12 months after treatment by treatment received: radical prostatectomy (RP), brachytherapy (BT) or external beam radiotherapy (EBRT)

	RP N = 143 mean (s.d.)	BT N = 25 mean (s.d.)	EBRT N = 36 mean (s.d.)	P-value
Urinary scales				
Summary score	82 (15)	90 (10)	88 (13)	0.014
Function score	81 (18) ^{b,c}	96 (10) ^b	91 (13) ^c	<0.001
Bother score	83 (14)	87 (12)	85 (14)	0.58
Incontinence scale	69 (28) ^{b,c}	95 (16) ^b	86 (19) ^c	<0.001
Irritative-Obstructive scale	91 (9)	88 (10)	89 (11)	0.22
Bowel scales				
Summary score	95 (7)	95 (6)	94 (10)	0.44
Function score	94 (8)	94 (6)	92 (12)	0.43
Bother score	96 (7)	96 (7)	94 (11)	0.28
Sexual scales				
Summary score	29 (17) ^{b,c}	46 (23) ^b	52 (26) ^c	<0.001
Function score	22 (17) ^{b,c}	39 (23) ^b	43 (27) ^c	<0.001
Bother score	43 (26) ^{b,c}	62 (28) ^b	73 (32) ^c	<0.001
Single items				
'No urinary pads required'	61%	96%	89%	<0.001
'No/seldom loose stool'	92%	96%	92%	0.74
'Erections firm enough for intercourse'	8%	36%	39%	<0.001

The P-values are based on analysis of variance corrected for baseline scores. The single items were expressed as % of patients with that answer and were analysed by χ^2 -tests.
^aAll EPIC scales range from 0-100, with higher scores representing better functioning.
^bSignificant difference between RP and BT corrected for baseline scores (Posthoc Bonferroni test).
^cSignificant difference between RP and EBRT corrected for baseline scores (Posthoc Bonferroni test).

outcomes than BT and EBRT in both domains. With regard to the scales in the bowel domain, no differences were found between the treatments.

Analysing single items from the different domains yielded similar results. For example, the proportion of patients not requiring urinary pads was comparable at baseline (Table 2) for RP, BT and EBRT, but differed at 12 months ($P < 0.001$) (Table 3). Similarly, the proportion of patients reporting erections firm enough for intercourse was comparable at baseline (Table 2), but differed at follow-up ($P < 0.001$) (Table 3). The frequency of loose stool was comparable between the treatments at baseline (Table 2) and remained so at follow-up (Table 3).

Table 4 shows the proportions of patients experiencing a clinically relevant deterioration in EPIC scores, from baseline to 12 months after treatment. These proportions were again significantly affected by treatment received for the urinary and sexual domains and not for the bowel domain. After RP, more patients deteriorated on EPIC scores.

In Table 5, the results of patients with good baseline scores on specific items are presented. For patients who did not require urinary pads at baseline, the risk of requiring pads at 1 year after treatment was higher after RP (38%) than after BT (0%) or EBRT (6%, $P < .001$). Similarly, for patients with erections firm enough for intercourse at baseline, the risk of having insufficient erectile functions at 1 year after treatment was higher after RP (89%) than after BT (57%) or EBRT (33%, $P < 0.001$). The risk of having loose or liquid stool was not affected by treatment received.

Table 4. Percentage of patients with a clinically relevant deterioration in EPIC scores at 12 months after treatment compared with their baseline scores, defined as a decrease of \geq half a s.d.

	RP N = 142	BT N = 25	EBRT N = 36	P-value
Urinary				
Deterioration in summary score	41%	12%	19%	0.003
Deterioration in function score	42%	12%	19%	0.002
Deterioration in bother score	30%	40%	25%	0.45
Deterioration on incontinence scale	55%	12%	29%	<0.001
Deterioration on irritative/obstructive scale	17%	40%	11%	0.012
Bowel				
Deterioration in summary score	21%	26%	29%	0.63
Deterioration in function score	17%	16%	25%	0.52
Deterioration in bother score	14%	22%	26%	0.19
Sexual				
Deterioration in sexual summary score	79%	33%	34%	<0.001
Deterioration in function score	76%	36%	43%	<0.001
Deterioration in bother score	74%	33%	33%	<0.001

Abbreviations: BT = brachytherapy; EBRT = external beam radiotherapy; RP = radical prostatectomy.

Table 5. Percentage of patients with good baseline functioning that changed to poorer functioning at 12 months after treatment for a given item in each domain

	RP N (%)	BT N (%)	EBRT N (%)	P-value
Urinary				
From 'no urinary pads' at baseline (N = 196) to 'one or more per day' at 12 months	N = 139 N = 53 (38%)	N = 24 N = 0 (0%)	N = 33 N = 2 (6%)	<0.001
Bowel				
From 'no/seldom loose stool' at baseline (N = 115) to 'at least half of the time loose stool'	N = 81 N = 3 (4%)	N = 14 N = 0 (0%)	N = 20 N = 1 (5%)	0.72
Sexual				
From 'erections firm enough for intercourse' (N = 107) to 'not firm enough'	N = 75 N = 67 (89%)	N = 14 N = 8 (57%)	N = 18 N = 6 (33%)	<0.001

Abbreviations: BT = brachytherapy; EBRT = external beam radiotherapy; RP = radical prostatectomy.

Outcome by treatment modality. Some variations existed within the three types of treatments. Nerve sparing was performed in the majority (81%) of the prostatectomy patients. Patients with and without nerve sparing had comparable outcomes; at 12 months after treatment they did not differ significantly on the urinary (83 ± 15 vs 88 ± 13 , respectively) or sexual summary scores (30 ± 17 vs 27 ± 18 , respectively). No effect was found for the surgery techniques either; open, laparoscopic or robot-assisted laparoscopic surgery yielded urinary summary scores of 85, 79 and 83 respectively. The effect of hormonal therapy in combination with radiotherapy was not analysed due to the small number of patients receiving this combined therapy ($n = 5$).

DISCUSSION

In this study, men were selected to be eligible for both surgery and radiotherapy. This enabled us to compare quality of life effects of different treatments in men more comparable at baseline than in previous studies. The effects on the urinary and sexual domain were in line with earlier reports. A striking result in our study is that the bowel domain was not affected by the treatment received. The bowel problems usually reported after EBRT, were not found in this study.

A possible explanation for the good radiotherapy outcome may be that in our study the EBRT patients were selected to be comparable to the RP patients. As a result, the EBRT patients in our study were relatively young (mean age of 65) compared with those usually studied (mean ages ranging from 64 to 76 (Ferrer *et al*, 2008; Korfage *et al*, 2005; Miller *et al*, 2005; Smith *et al*, 2009; Wei *et al*, 2002)). It has been shown that younger men are less prone to treatment-related toxicity than older men (Stanford *et al*, 2000; Huang *et al*, 2010). In our study, the patients receiving EBRT showed good bowel scores compared with previous studies. For example, the bowel function score at follow-up was 92, whereas others reported scores from 80 to 85 (Korfage *et al*, 2005; Smith *et al*, 2009; Huang *et al*, 2010). Similarly, the bowel bother score was 94, whereas others reported scores from 75 to 80 (Korfage *et al*, 2005; Smith *et al*, 2009; Huang *et al*, 2010).

The RP patients in our study were comparable to those usually studied, with a mean age of 64 compared with 60–67 reported by others (Wei *et al*, 2002; Korfage *et al*, 2005; Miller *et al*, 2005; Ferrer *et al*, 2008; Smith *et al*, 2009). This is reflected by their bowel scores being similar to those mentioned in previous reports, with a bowel function score of 94 vs reports ranging from 88 to 90, and a bother score of 96 vs reports of 90–93 (Korfage *et al*, 2005; Smith *et al*, 2009; Huang *et al*, 2010).

Another explanation for the good outcomes of the EBRT patients may be the radiation technique that was used; IMRT and applying the endorectal balloon to limit radiation-induced toxicity. This rectal balloon was shown to reduce the dose to the anorectal wall, which may reduce anorectal toxicity (Smeenk *et al*, 2010). However, to date, no HR-QOL data are available in the literature to validate this assumption.

In all, our data suggest that EBRT causes little damage in men who are comparable to surgery patients and who are irradiated with state-of-the-art techniques, using e.g., IMRT and rectal balloon.

Strengths and limitations. A strength of this study is that the selection succeeded in creating patient groups that were comparable at baseline, both for demographic and tumour characteristics. The groups receiving RP and EBRT were also comparable in their baseline HR-QOL. In addition, the intake of all patients was equal, that is, all patients were enrolled at the Urology departments.

Another strength is that the HR-QOL assessment was based on patient reported outcomes. This is an advantage because patients often don't report all morbidity to their physician. Moreover, when

physician and patient assessments are compared, physicians underestimate patients HR-QOL symptoms (Wilson *et al*, 2000; Sonn *et al*, 2009).

A limitation of the study is that the patients receiving RP and EBRT were comparable on all accounts, but the group receiving BT had somewhat better urinary scores. The latter is inherent to the selection criteria as commonly applied for BT and yields a patient group representative for the BT group in common clinical practice.

Another limitation is that comorbidity was not assessed. However, patients were only enrolled when eligible for both surgery and radiotherapy, which ruled out comorbidity interfering with treatment choice. In addition, the follow-up of 12 months may be too short to capture the long-term treatment effects. Previous reports on long-term recovery are mixed. Some studies have reported recovery after more than 1 year post-treatment, especially for sexual functioning (Gore *et al*, 2010; Huang *et al*, 2010), but most studies found little to no change in urinary and bowel scores (Talcott *et al*, 2003; Ferrer *et al*, 2008; Gore *et al*, 2010) after >1 year. In contrast, some studies found a decline in sexual functions after more than 1 year post-treatment in EBRT patients, resulting in smaller differences between RP and EBRT patients in the long term (Potosky *et al*, 2004; Korfage *et al*, 2005). This may be related to progressive injury from radiotherapy, but also to the more advanced age in the EBRT groups in those studies.

Treatment groups were unequal in size, and the BT or the EBRT groups were small due to the fact that those treatments were less frequently chosen, reflecting common treatment patterns in the Netherlands. The small sample sizes limit the power of our analyses. Nevertheless, significant results were found. In addition, the treatments were somewhat heterogeneous; prostatectomies were performed by three different procedures with or without nerve sparing, and five patients with EBRT had their treatment combined with hormone deprivation. This, again, is common variation found in clinical practice. The effect of the different prostatectomy techniques was small in our study. This was not surprising, because most studies found no difference in long-term HR-QOL in relation to open, laparoscopic and/or robot-assisted procedures, when analysed by validated instruments (Penson, 2007).

CONCLUSION

As guidelines nowadays agree that there is no treatment that is superior for survival (Thompson *et al*, 2007), quality of life effects should be taken into consideration when choosing a treatment. Our results suggest that for patients who actually have a choice, radiotherapy, delivered as EBRT or BT, is at least as good an option as RP in terms of side effects.

Our study provides some indication that the negative effects of EBRT, when applied according to the latest techniques, e.g., with IMRT and rectal balloon, appear to be less pronounced than previously assumed. More research, with longer follow-up, needs to be done to confirm this finding. We recommend that future studies comparing the effects of different treatments should only include patients selected to be eligible for both treatments.

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