

Review

Quality of Life Following Treatment for Early Prostate Cancer: Does Low Dose Rate (LDR) Brachytherapy Offer a Better Outcome? A Review

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Abstract

Objective: Due to a lack of evidence from randomised studies, there is little agreement on the best form of treatment among men who require curative treatment for prostate cancer. The relative impact of the various treatments on symptoms and health-related quality of life is also controversial. We review the literature on quality of life changes following low dose rate brachytherapy (BXT) and compare BXT to other treatments for early prostate cancer.

Methods: Systematic literature review 1988–2003 (Medline). Keywords: Brachytherapy; Radical prostatectomy; External beam radiotherapy; Quality of life; Symptoms.

Results: Review of the current literature suggests that radical prostatectomy, external beam radiotherapy and BXT either alone or in combination with supplementary external beam radiotherapy offer good long-term health-related quality of life. However differences exist in the toxicity of treatment in terms of erectile function, voiding difficulty, incontinence and bowel function. These differences seem to persist for at least 3–5 years post-treatment though longer-term quality of life outcomes from modern techniques are unknown.

Conclusion: BXT offers a high probability of maintaining continence, potency and normal rectal function though both storage and voiding urinary symptoms have been reported. Addition of androgen deprivation and EBRT to BXT may increase urinary, bowel and sexual toxicity of treatment. Quality of life outcome following brachytherapy compares favourably with other radical treatment options for the management of early prostate cancer.

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Keywords: Early prostate cancer; Radical prostatectomy; Brachytherapy; External beam radiotherapy; Quality of life; Symptoms

1. Introduction

Prostate cancer is the most commonly diagnosed malignancy in Western men [1]. The death rate from prostate cancer is significant, however patients who are diagnosed with early (organ-confined) disease may survive for considerable periods untreated [1–3]. No objective evidence from randomised studies is available comparing the established radical treatments to each

other in their current forms and the only contemporary randomised study, failed to show a survival benefit for radical prostatectomy over watchful waiting at a median 6.2 years of follow-up [4].

The available evidence from non-randomised cohort studies suggests that the differences in outcome between radical prostatectomy (RP), conformal external beam radiotherapy (EBRT) and low dose rate brachytherapy (BXT) at least in the short term [5–7] are likely to be small in terms of cancer control and survival. Increasingly patients are asked to decide on their therapy of choice based on their suitability for treatment and the side effect profile of their therapeutic options. In this environment the need for better information for patients

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to allow them to assess the likelihood of experiencing significant side effects has emerged and a variety of quality of life instruments (questionnaires) have been developed to address this need. We attempt to summarise here the patient-reported outcome of treatment for early prostate cancer (EPC) and compare the toxicity of low dose rate BXT to the other commonly utilised radical treatments for EPC.

2. Assessing quality of life in early prostate cancer

Since the World Health Organisation (WHO) defined health as ‘a state of complete physical, mental and social well-being, and not merely an absence of disease’ in 1946, interest has been increasing in collecting data which attempts to measure a variety of symptoms and increasingly the more holistic construct of quality of life.

Evolution of questionnaires (or instruments) for measuring quality of life has been rapid. A range of instruments now exist which attempt to reflect the effect of illness and treatment on the patient. Instruments range from simple symptom indices like the International Prostate Symptom Score (IPSS) to measure urinary symptoms which reflect only the severity of a limited range of symptoms to general instruments such as the RAND Short Form-36 (SF36) which are designed to measure the more complete construct of health-related quality of life (HRQoL). It is arguable that given the demonstrable difference in significant symptoms reported by the physician when compared to those reported by the patient using a questionnaire [8], that questionnaire studies of toxicity are the only valid method of measuring the experience of treatment by the patient.

Unfortunately HRQoL literature has in the past suffered from methodological weakness. These have often resulted from HRQoL studies being added as an afterthought to prospective research on prostate cancer outcomes. Clearly when HRQoL measures are used to compare treatments a baseline assessment adds valuable information and helps to confirm that patients were comparable prior to treatment. Repeated administration of the instrument will be necessary to give the best understanding of the patient’s experience of symptoms over time. If retrospective study designs are used then recall bias, where patients report symptoms less accurately than in studies where the questionnaires are administered in a contemporary setting, may be a significant problem [9–11].

It is also clear that late toxicity may occur following either radiotherapy or surgery after the first year and

though this is rarely severe, inadequate follow-up or cross-sectional studies with assessment at variable time intervals may mask significant toxicity. Though there are not currently any studies available comparing HRQoL in patients randomly allocated to radical treatment in EPC; increasing evidence from well-followed cohorts, studied with prospective longitudinal designs is becoming available and most of the studies which are currently recruiting, comprise some form of HRQoL assessment. It was disappointing to see that the first study [12] to achieve recruitment of patients randomised to RP or watchful waiting (a major achievement in itself) gave suboptimal quality of life data due to omission of a baseline questionnaire, use of a non-validated instrument and a lack of control data in age matched men with the chosen instrument.

Though recommendations for reporting HRQoL and symptoms following BXT are available [13] there is no consensus as to the most accurate method of reporting toxicity in studies comparing BXT to RP or EBRT. It is important that validated questionnaires, which attempt to reflect changes in those symptoms most relevant to patients, are adopted in all future studies to gain the maximum information from these costly studies in which recruitment still remains a significant obstacle.

It is also important to recognise the differences between cohorts of patients compared in most of the currently available literature and avoid direct comparisons between groups of patients in non-randomised studies. Such reports may have significant confounding due to selection criteria for men currently deemed suitable for treatment using the different modalities. Even more important to resist is the temptation to directly compare patient and physician reported endpoints which are often significantly different [8].

3. How is quality of life assessed in prostate cancer?

As with measures more familiar to urologists, such as serum PSA, the preparation of a new HRQoL instrument requires extensive testing to determine their reliability, reproducibility and clinical value. The psychometric validation process is unfamiliar; however it is essential that the questionnaires chosen for and reported in HRQoL studies are validated, ideally within the group being investigated. The website of the MAPI research institute gives useful background information on questionnaire choice for studying a variety of diseases (<http://www.qolid.org/>). Included in Table 1 is a summary of questionnaires commonly used in EPC with their advantages and disadvantages.

Table 1
Common questionnaires in prostate cancer HRQol research

Name	Type	Items	Assesses	Advantages	Disadvantages
RAND SF36	HRQol	36	HRQol	Benchmark, well-validated questionnaire for assessment of general health-related Qol. Available in 44 languages	Insensitive in EPC, doesn't attempt to measure disease-specific items
FACT-G	CSQol	34	CSQol	Well-validated instrument applied to cancers in general	No disease-specific items. Usually paired with disease-specific subscale (FACT-P)
EORTC QLQ C30	CSQol	30	CSQol	Well-validated instrument widely used in oncology trials. Validated in most European languages	Like FACT usually paired with a disease-specific module (PR-25)
TAG Life/Family	CSQol	8	CSQol and impact on family	One of few questionnaires to capture the impact of treatment on family	Little used, insensitive. Instruments administered to spouse might be better
FACT-P	PCSQol	13	Weight loss, role, ED, LUTS	Brief, designed to work with FACT-G and scored as a total with FACT-G	Assessment of LUTS but not urinary incontinence. May be insensitive to change in EPC
EORTC PR-25	PCSQol	25	ED, bowel, urinary function, and toxicity from androgen deprivation	More comprehensive, suitable for assessment of localised and metastatic disease. Suitable for assessment of patients post-surgery, BXT or EBRT	Newer questionnaire still awaiting publication of validation studies
UCLA-PCI	PCSQol	20	Urinary, sexual and bowel function and bother	Comprehensive assessment of common side effects following RP and EBRT	Often paired with SF36 to assess HRQol. Lack of brevity may decrease return rates. Urinary function assesses solely incontinence and does not include irritative LUTS
EPIC	PCSQol	50	ED, bowel, and urinary function, and toxicity from androgen deprivation	Designed to compare results of treating early disease with BXT, EBRT or RP. Expanded version of UCLA-PCI	Validated in the USA only, lack of brevity limits clinical use. Does not assess HRQol so usually paired with SF12 or SF36. Heavy weighting towards LUTS vs. incontinence
IIEF	SI	15	ED	Well-validated, familiar, available in abbreviated form (sexual health index for men, comprises five erectile subscales of IIEF)	Concentrates on function and doesn't assess effect of ED on HRQol
IPSS	SI	8	LUTS	Well-validated index of LUTS, familiar to urologists	Not exhaustive (doesn't assess incontinence or dysuria)

Health Related Quality of Life (HRQol), Cancer Specific Quality of Life (CSQol), Prostate Cancer Specific Quality of Life (PCSQol), Symptom Index (SI), Short Form 36 (SF36), Functional Assessment of Cancer Therapies—General (FACT-G), FACT—Prostate (FACT-P), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30), EORTC Prostate-25 (EORTC PR-25), Technology Assessment Group Life/Family (TAG Life/Family), University of California Los Angeles—Prostate Cancer Index (UCLA-PCI), Expanded Prostate Cancer Index Composite (EPIC), International Index of Erectile Function (IIEF), International Prostate Symptom Score (IPSS). Items refers to number of questions asked.

4. What changes in quality of life are observed after brachytherapy?

Most men in the USA are not symptomatic before treatment for EPC and hence HRQol questionnaires have difficulty in separating age-matched controls from prostate cancer patients [14]. Recent consensus from the American Brachytherapy Society [13] has identified urinary, bowel and sexual morbidity as areas

most commonly affected after treatment with prostate brachytherapy and recommended prospective reporting of toxicity in these areas using validated questionnaires. The effects of treatment will depend greatly on patient selection (age, pre-treatment potency, pre-treatment urinary symptoms, prostate volume etc.) and whether BXT comprises seed monotherapy, or includes neo-adjuvant androgen deprivation or short course EBRT.

4.1. Acute morbidity

Acute morbidity might be defined as toxicity experienced by the patient within the first year post-implant. Acute morbidity is likely to result from a combination of radiation effects and local trauma due to needle placement and usually resolves with conservative treatment. Though a statistically significant decrease in HRQol at 1 month post treatment has been demonstrated following BXT as monotherapy using the Functional Assessment of Cancer Therapy—General (FACT—G) instrument in a study with longitudinal design [15,16], the changes at ≥ 3 months were not statistically significant suggesting that the effects of BXT on HRQol are short-lived. When the Functional Assessment of Cancer Therapy—Prostate (FACT-P) module was added, statistically significant differences were detected at up to 3 months. This correlated with clinically significant changes in IPSS (>3 points [17]) which persisted for 3 months post-implant. However Lee et al. [15,16] and other investigators [18] have shown using the IPSS that urinary function within the first year does not return to baseline though the changes are not clinically significant at >3 months. Incontinence is rare following BXT with 1% incidence of new pad use 1 year post-treatment in patients from a longitudinal study treated with seeds alone [19].

Common toxicity as assessed using HRQol questionnaires or symptom indices is summarised in Table 2.

4.2. Late morbidity

Cross-sectional studies of patients following BXT have revealed a variable incidence of late toxicity which was more prevalent in older studies [20] when case selection and treatment planning to minimise radiation dose to critical structures (urethra, rectum) prior to BXT was evolving. However as no longitudinal studies are available it is difficult to assess the impact of treatment on a population which is known to report a significant prevalence of incontinence (33%), rectal symptoms (33%) and erectile dysfunction (60%) in the absence of a prostate cancer diagnosis [21]. Much of the late morbidity in the past has been due to prolonged urinary symptoms that have resulted in a need for TURP leading to increased risk of incontinence [20]. In early series it may not have been recognised that a generous TURP following BXT results in physician-reported incontinence rates of up to 40% [22–26], however since this complication has been recognised and a protocol of conservative management of LUTS within the first year followed by minimal resection where necessary adopted, most physician-reported

Table 2

Patient reported complications following prostate brachytherapy and impact on quality of life

Morbidity	Incidence	Mean duration	Impact On HRQol	Ref.
Increased LUTS	80–95%	6–24 months	Symptoms assessed with IPSS tend to peak at 4–8 weeks and result in decreased HRQol for up to 3 months [15,16]. Kleinberg et al. describe typical changes of increased nocturia (80%), dysuria (48%) and frequency (71%) with a modified (unvalidated) RTOG scale	[15,16,18,36]
Urinary retention	12%	2 weeks	Assessed with postal questionnaire. Similar figures from recent reviews [37,38] suggest that for urinary retention requiring catheterisation physician reporting is acceptable. HRQol impact not separately assessed in questionnaires but probably normalised by 3-months in line with urinary bother [15,16]	[39]
Urinary incontinence	1–2%	Reported at 12 months FU	Several cross-sectional studies and one prospective longitudinal study [19] using the UCLA-PCI report highly variable prevalence (see Table 3)	[19]
Impotence	39% previously potent men at 6 years	Permanent	COMMENT: only one study which included patients treated with EBRT has prospectively reported using a validated symptom index (IIEF). If the higher scores achieved following treatment with sildenafil (Viagra™) where necessary are used then the 6-year impotence rate was 8%	[40]
Rectal bleeding/diarrhoea	–		No longitudinal studies available using validated SI or HRQol measure and ABS guidelines have not suggested a patient completed questionnaire. Several cross-sectional studies report bowel function and bother to be more prevalent than in age matched controls but await prospective confirmation (see comparative studies, Table 3)	–

Table 3

Studies comparing HRQoL following radical treatment for prostate cancer

Study	Design	Groups	Instrument	Summary and comments
Litwin et al. [14] JAMA 1995	Cross-sectional (no baseline)	RP EBRT WW controls	UCLA PCI SF36	Cross-sectional study without baseline questionnaire. Worse sexual and urinary function reported by radical prostatectomy patients did not translate into worse bother scores. Patients who received EBRT had worse bowel function but were no more bothered. No significant changes in general HRQoL were demonstrated.
Brandeis et al. [33] J Urol 2000	Cross-sectional (no baseline)	RP BXT BXTC controls	UCLA PCI SF36	Cross-sectional study without baseline questionnaire and with variable length of follow-up (mean 7.5 months). No difference in HRQoL between groups. BXT and BXTC groups analysed separately. Urinary function was best in controls, then in BXT patients and worst following RP or BXTC. Bowel function was equivalent in all groups except the BXTC group which had worse bowel function. Sexual function was best preserved in the BXT group followed by equivalent scores in the RP and BXTC groups.
Davis et al. [41] J Urol 2001	Cross-sectional (no baseline)	RP EBRT BXT controls	UCLA PCI SF36, TAG Life/Family	Cross-sectional study without baseline questionnaire and with variable length of follow-up (mean 22–37 months), which was significantly different between treatment groups. Controls had best urinary, bowel and sexual function. BXT patients had more LUTS assessed using the IPSS but better sexual and urinary function as assessed by the UCLA-PCI than RP patients, and EBRT was associated with worse bowel function and better urinary and sexual function than RP
Lee et al. [15] IJROBP 2001	Prospective longitudinal non-randomised	RP EBRT BXT	FACT-P IPSS	Well-designed but small study comparing the major treatments with a longitudinal design. Both RP and BXT produced decrease in FACT-P scores at 1 and 3 months post-implant with largest falls in the RP group. Significant improvement occurred by 3 months and by 1 year scores had returned to baseline in all groups. EBRT had less marked changes in HRQoL using the FACT-P however the follow-up period of 1 year would tend to favour outcome with EBRT as late morbidity was not assessed.
Fulmer et al. [19] Cancer 2001	Prospective longitudinal non-randomised	RP BXT BXTC	Selected elements of UCLA-PCI IPSS	Prospective study with baseline assessment of potency and urinary function prior to treatment. Shortened UCLA-PCI administered at several periods of follow-up (max 18/12). All BXT/BXTC patients had AD. RP patients had best baseline sexual function, sexual bother and urinary function followed by BXT then BXTC. RP patients had the worst post-operative urinary function (leakage) but were no more bothered than other patients, perhaps because of irritative symptoms in the BXT and BXTC patients. RP patients initially had worse sexual function and sexual bother scores but these became comparable to BXTC patients at 18 months. RP patients were the group with the lowest % chance of returning to baseline erectile function or urinary control at all points of follow-up.
Wei et al. [42] JCO 2002	Cross-sectional (no baseline)	RP EBRT BXT	SF36 FACT-P EPIC	Large study ($n = 1014$) hampered by administration of questionnaire at variable time post-therapy and lack of baseline questionnaire. HRQoL not different between primary treatment groups however greater urinary bother sexual, bother and bowel bother reported by BXT patients than EBRT or RP patients. All groups were inferior to age-matched controls in all domains.
Penson et al. [34] JCO 2003	Cross-sectional 2-years post-treatment (retrospective baseline)	WW AD RP PI	SF36 PCI	Assessed HRQoL and PCSQoL 2 years post-treatment. The 'baseline' questionnaire was not administered at a fixed point in follow-up. HRQoL was not significantly different 2 years post-treatment independent of primary treatment. RP or AD were associated with lower % chance of erections sufficient for intercourse than WW or PI although RP and PI had the best sexual function pre-treatment. Baseline potency WW 58%, AD 57%, PI 65%, RP 61% compared with 2 year potency WW 43%, AD 30.5%, PI 44.5%, RP 19.7%. RP had a 21.5% chance of resulting in frequent urinary leakage or no control compared with 1.9%, 3.3% and 4.7% for AD, PI and WW respectively. Bowel function was not separately reported.

Radical Prostatectomy (RP), External Beam Radiotherapy (EBRT), Watchful Waiting (WW), Brachytherapy monotherapy (BXT), Brachytherapy combined with external beam radiotherapy (BXTC), Androgen Deprivation (AD); Pelvic Irradiation of any sort (PI).

series [18,27] report incontinence rates of <1% for contemporary patients.

Improved late morbidity is observed in recent series, which demonstrate no significant difference in IPSS or the Expanded Prostate cancer Index Composite (EPIC) urinary subscales between BXT patients at a mean of 5.5 years post BXT and age matched controls with EPC [28]. This is likely to be due to a combination of improved case selection of more appropriate patients with smaller prostate glands and fewer urinary symptoms and realisation of the importance of minimising urethral radiation dose and avoiding post-implant TURP.

4.3. *Hormones and EBRT in combined brachytherapy treatments*

The place of neoadjuvant and adjuvant androgen deprivation combined with BXT is unclear. Two non-randomised studies have suggested that there might be a survival benefit associated with the use of androgen deprivation prior to a BXT implant in intermediate risk disease [29,30], however both studies had significant methodological flaws and patients who received high quality implants did not benefit from androgen deprivation [29,30]. Cross-sectional HRQol studies have suggested that the androgen deprivation cohort of patients had worse sexual function and sexual bother than patients treated with BXT alone [31]. These findings confirm the suggestion in a study of physician reported sexual function by Potters et al. [32] that androgen deprivation prior to BXT may have long term effects on potency.

Patients receiving EBRT combination therapy have been compared with cohorts of patients receiving seeds alone in studies using cross-sectional [33] and longitudinal [19] designs. Though most patients with more aggressive disease received androgen deprivation, these studies suggested that combination therapy produced significantly worse physical and emotional domain scores on the SF36, worse urinary function and bother and worse sexual and bowel bother on the University of California Los Angeles—Prostate Cancer Index (UCLA-PCI) when compared with BXT alone.

5. What are the differences between patients treated with brachytherapy and other modalities?

The currently published evidence has not yet convincingly answered the question of which therapy produces the least toxicity for patients not least because

patients choosing treatment with different modalities tend to experience different toxicities the significance of which may be weighted differently by different men. Table 3 summarises the current HRQol literature comparing curative treatment in EPC.

It is clear that all of the current treatment modalities have some adverse effects on either sexual, urinary or bowel function and that patients find these symptoms bothersome. It is also clear that the majority of men report normal or near normal general HRQol both in the first year following modern radical treatments and at further follow-up [34].

Though a lack of detail in reporting baseline function and a lack of studies with longitudinal or randomised designs have produced a somewhat confusing picture the trends in studies to date suggest that BXT patients, particularly when androgen deprivation has not been used have better sexual function than patients who received either EBRT or RP.

Incontinence is greatest following RP in most of the reported literature. The UCLA-PCI only reports urinary incontinence in the urinary function subscale but also includes a more holistic urinary bother subscale which may explain an apparent paradox where men report more incontinence following RP but similar levels of urinary bother. This is not because incontinence is not bothersome but due to the prevalence of storage or voiding symptoms following BXT or EBRT, which are bothersome to patients, but not scored in the urinary function subscale of the UCLA-PCI. Indeed Litwin et al. [35] using the UCLA-PCI found that urinary bother was worse following EBRT than RP despite better urinary function in the EBRT patients and that urinary bother was marginally associated with use of anticholinergics and incontinence procedures but not with pad use. This suggests that storage symptoms requiring anticholinergics may, at least following EBRT, be responsible for increased urinary bother.

Bowel function (diarrhoea) is reported to be worse in most of the studies comparing BXT to radical prostatectomy but several of these have not separated BXT patients from patients treated with a combination of BXT and external beam radiotherapy which adds morbidity in most of the domains of the UCLA-PCI.

6. Conclusions and the future

Patient's expectation of toxicity from a particular form of therapy will have a powerful effect on their acceptance both of the treatment at the time of selection and the side effect should it occur. It is unsurprising that patients are reasonably accepting of the complications

that they have been warned to expect. Acceptance or the development of coping strategies for decreased function might be reasons for a general decrease in symptom bother scores (when these are reported separately) which seems to occur with studies where longer follow-up is reported.

However this acceptance does not mean that the acute toxicity of treatments is equal nor equally acceptable to all men and the popularity of BXT is evidence that a significant number of men will choose the low risks of impotence and incontinence which seem to be associated with this procedure at the expense of an increase in their LUTS in the first year following treatment. This trade off as to the bother of incontinence or impotence vs. the bother of LUTS is a highly personal matter and is likely to be different for different men. It is questionable whether the views of men who have chosen a specific therapy because they believe that they would be most able to live with the toxicity of that type of treatment could safely be generalised to

other groups of patients. In particular some patients might feel that increased LUTS or risk of incontinence would be unacceptable despite a more favourable toxicity profile in other areas of function.

Despite these problems further prospective longitudinal studies with baseline assessment of function are needed to complement the planned large randomised control trials. We await with interest the results of SPIRIT (Surgical Prostatectomy vs. Interstitial Radiotherapy Intervention Trial) which we hope will answer some of the questions that remain unanswered by the wealth of literature currently available.

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