

Original article

A prospective analysis of long-term quality of life after permanent I-125 brachytherapy for localised prostate cancer

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Abstract

Background and purpose: To prospectively evaluate long-term urinary, bowel and sexual function after I-125 brachytherapy for localised prostate cancer using patient administered validated Quality of Life (QoL) instruments.

Materials and methods: Between March 1995 and March 2004, 673 men underwent brachytherapy and recorded urinary symptoms prospectively using the International Prostate Symptom Score (IPSS). In addition, in a subgroup of 116 patients, the Expanded Prostate Cancer Index Composite (EPIC) was used to record QoL information on urinary, bowel and sexual function before treatment and at regular time intervals for at least two years.

Results: Initially, there was a sharp rise in urinary symptoms which was most marked within the first three months. Scores then resolved slowly and returned to within one or two units of pre-treatment level at one year. Subsequently, there was no significant deterioration in urinary symptoms up to nine years following brachytherapy. Few had significant bowel symptoms. Sexual function deteriorated initially and then improved but failed to return to pre-treatment levels by two years. Patients requiring neo-adjuvant hormones experienced significantly more dysfunction.

Conclusions: After an initial period of mild to moderate urinary symptoms prostate brachytherapy is well tolerated with relatively little deterioration in long-term quality of life. Long-term reduction in sexual function may be seen particularly in those requiring hormones.

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Keywords: Brachytherapy; Morbidity; Prostate cancer; Quality of life

Many reports are now available which confirm that radio-active iodine seed implantation for localised prostate cancer produces good outcomes in selected patients with PSA relapse free survivals that are equivalent to those achieved by external beam radiotherapy or surgery [2,5,6,16,23]. There are also several publications which give details of the side effects and complications which can occur following brachytherapy [4,7,8,10–12,15,17,19,20]. These reports confirm that the risk of serious long-term side effects is low. Patients with early prostate cancer who opt for active treatment are offered a range of treatment options and often choose brachytherapy because of its perceived convenience and favourable toxicity profile. It is therefore essential that accurate and representative information on long-term treatment related toxicity and overall quality of life be available. It is well established that physician derived toxicity data underestimate the true prevalence of symptoms in a treated population [9]. To obtain accurate information patient derived and validated Quality of Life (QoL) instruments should be used. Many previous QoL studies have

been limited by either being cross-sectional, providing only a 'snapshot', or lacking information about symptoms that pre-date treatment [11,18]. This work is a longitudinal study that documents baseline QoL and subsequent changes in urinary, bowel and sexual function after brachytherapy for a minimum of two and up to nine years following treatment.

Materials and methods

Patient group

Between March 1995 and March 2004, 1253 men underwent trans-perineal TRUS guided I-125 prostate brachytherapy alone for localised adenocarcinoma of the prostate in our centre. A modified peripheral loading technique was used to deliver a dose of 145 Gy and has been described previously [6]. Patients presenting with a prostate volume >50 ml underwent three months of neo-adjuvant hormone manipulation, using either LHRH agonists or anti-androgens

alone, before undergoing brachytherapy. Hormone therapy was discontinued within one month of implantation.

In 673 of these patients, IPSS scores were available pre-treatment and at subsequent follow-up. Many patients travelled long distances for treatment and were subsequently discharged back to the referring clinician following treatment and therefore, IPSS results were not routinely available for those patients. The follow-up schedule was four to six weeks after treatment, 4 monthly for the first year, 6 monthly until the end of year 5 and then yearly. Patient data were recorded prospectively. The median follow-up for the IPSS group was 4.9 years (range 2.03–11.7 years).

From March to September 2002, 150 consecutive patients were invited to complete more detailed QoL questionnaires. Local Research Ethics Committee approval was obtained prior to commencement. All were asked to complete the IPSS and EPIC questionnaires before brachytherapy (T0 baseline), four to six weeks after the implant (T1), every four months in the first year (T2, T3) and then every six months in the second year (T4, T5). At baseline patients completed the questionnaires during their visit for a formal prostate volume study, usually carried out two to three weeks before the implant procedure. Questionnaires at the first post-treatment visit were completed in the clinic. Subsequently, patients were mailed the questionnaire which they completed at home and returned to the research coordinator. Those patients who did not respond within two weeks of mailing were reminded by telephone.

Assessment of QoL

Two instruments were used to assess symptoms and QoL. The validated International Prostate Symptom Score (IPSS) is used extensively in routine practice to both assess urinary function before treatment and monitor urinary toxicity following treatment [1,4]. Although not specific to brachytherapy, it is a useful screening tool in initial patient assessment and provides an objective measure of urinary toxicity following treatment. Lower IPSS sum scores (range 0–35) represent better urinary function.

Second, the Expanded Prostate Index Composite (EPIC) was chosen because it is a well-validated comprehensive QoL instrument used in previous studies [11,13,21,22]. The detailed questionnaires record patient derived information on urinary incontinence/irritation, bowel, sexual and hormonal functions within separate subsections or domains. A summary, function and bother score is generated for each domain. Higher overall and domain scores (range 0–100) represent better functioning and QoL.

Statistical analysis

Descriptive statistics (mean, confidence intervals) were used to assess changes in QoL scores with time. In the analysis of EPIC data only those patients returning questionnaires at all time points were included. Patients were divided into hormone or no hormone treatment groups for the analysis of the EPIC sexual domain. A paired *t*-test was used to check statistical significance. A Pearson correlation coefficient, based on chi square, was used to correlate initial IPSS with that at five years.

Results

Patient compliance with EPIC questionnaire

From the initial 150 patients invited to complete the EPIC questionnaire, 116 returned information at all time points and were available for analysis (77% compliance). Table 1 demonstrates compliance at each time point.

Urinary function

Initially both IPSS and EPIC urinary scores deteriorated. The IPSS mean score doubled in the first three months from 6 to nearly 16. Subsequently, the IPSS mean score improved slowly and returned to within one or two points of pre-treatment level at one year. IPSS scores then appeared to remain stable up to nine years following treatment (Fig. 1). There was a significant positive correlation between initial IPSS score and the score recorded after five years of follow up with persistently high scores correlating with high baseline scores (Fig. 2).

As regards EPIC data, Fig. 3 demonstrates the urinary summary score for the 116 patients studied. Before treatment the mean summary score was 87.4 and after six

Table 1
Number of patient responses to EPIC QoL questionnaire for each time point over two years

Time	Number of responses	% of invited N = 150
Baseline (T0)	127	84.7
Six weeks (T1)	116	77.3
Six months (T2)	122	81.3
10 months (T3)	121	80.7
18 months (T4)	119	79.3
24 months (T5)	117	78.0

The data presented in the paper represent the 116 patients who returned responses at all time points (77%).

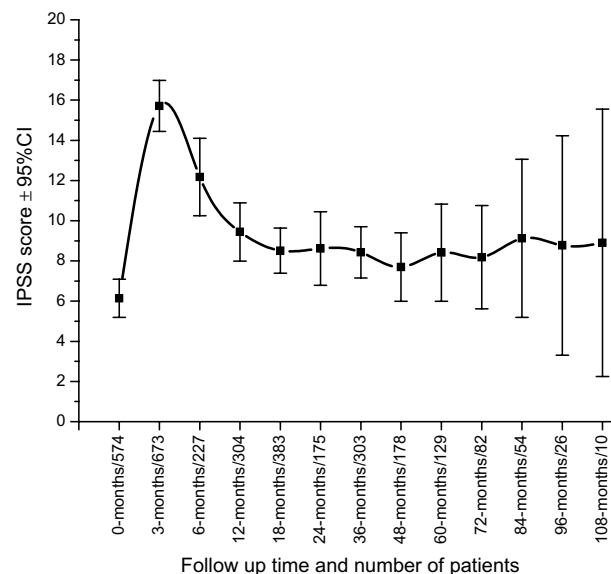


Fig. 1. Mean IPSS score and 95% confidence intervals for the large cohort of 673 patients over a period of 108 months. The confidence intervals become wider with time as the number of patients available for analysis decreases.

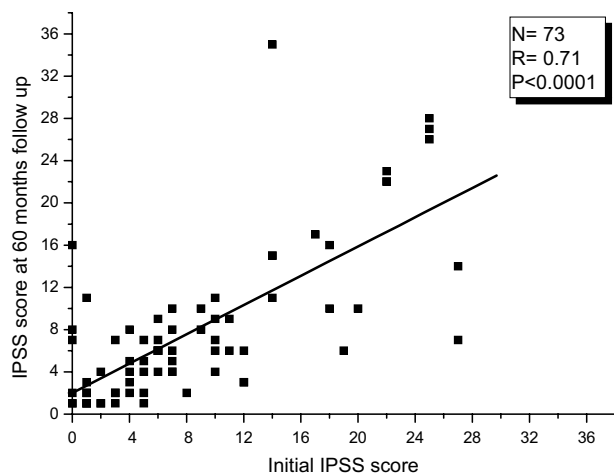


Fig. 2. Correlation between initial IPSS score and the score recorded after five years of follow up.

weeks this fell to 69.3 as patients experienced treatment related urinary symptoms. The change in EPIC urinary scores with time mirrored the change in IPSS scores. By one year the mean EPIC urinary symptom score had returned to the pre-treatment level of 87.4. Fig. 4 demonstrates the detail of the EPIC urinary scores. Symptoms are divided into urinary function, urinary bother, urinary incontinence and urinary irritation/obstructive scores. Individual domains demonstrate a similar pattern of change to the summary score. At six weeks there was considerable urinary bother with irritation and obstruction but also some incontinence which is probably related to urgency. The incontinence settled to pre-treatment levels by six months and no change was seen up to two years after treatment.

Bowel function

Few patients had bowel symptoms prior to treatment. At six weeks the bowel summary score deteriorated from 92.2 to 84.7, predominantly due to patients experiencing loose bowel motions. By one year bowel summary scores had returned to baseline levels (Fig. 5).

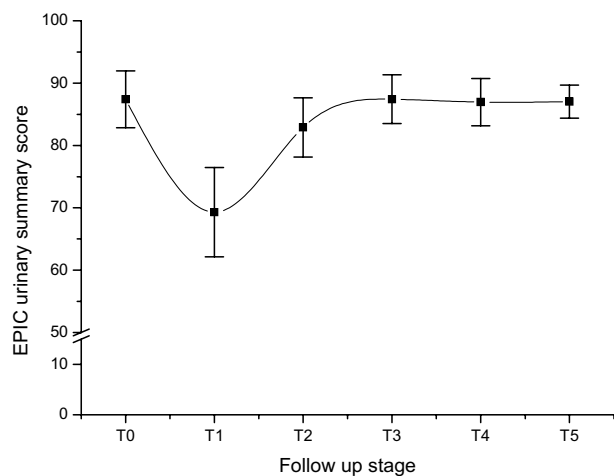


Fig. 3. The change in mean EPIC urinary summary score in the two years following I-125 brachytherapy.

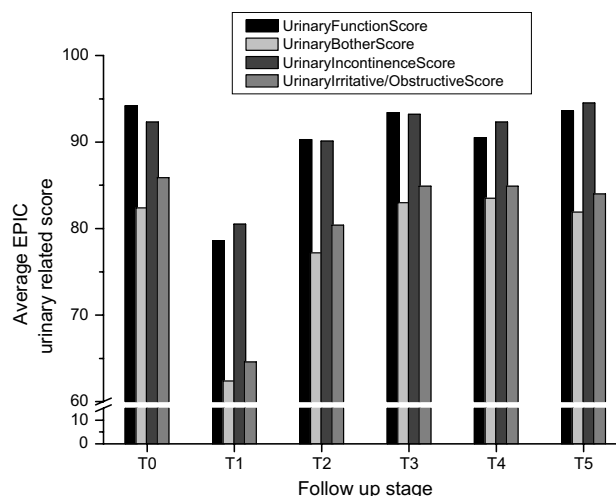


Fig. 4. Detailed EPIC scores for urinary domains in the two years following I-125 brachytherapy.

Sexual function and hormonal symptoms

Of the cohort of 116 completing all questionnaires, 58% (67 patients) were treated with neo-adjuvant hormone manipulation. As a result this group experienced significantly reduced sexual QoL at baseline (Fig. 6). Following brachytherapy sexual QoL deteriorated for all in the first six weeks. Sexual function subsequently improved but at two years there was a persisting significant difference in function between those that underwent neo-adjuvant hormone manipulation and those that did not require hormones (Fig. 7).

Fig. 8 demonstrates the EPIC hormonal summary scores for those patients on hormones (58%) compared with those not on hormones (42%). Hormone manipulation, predominantly used to reduce the size of the gland, was usually commenced three months before and stopped immediately after brachytherapy. Despite the relatively short-term use of hormones, patients experienced prolonged hormonal symptoms. This is shown in Fig. 9 where the mean score was 82.7 before brachytherapy, deteriorating slightly to 80.9 after brachytherapy and then slowly and steadily increased until it was 92.8 after two years.

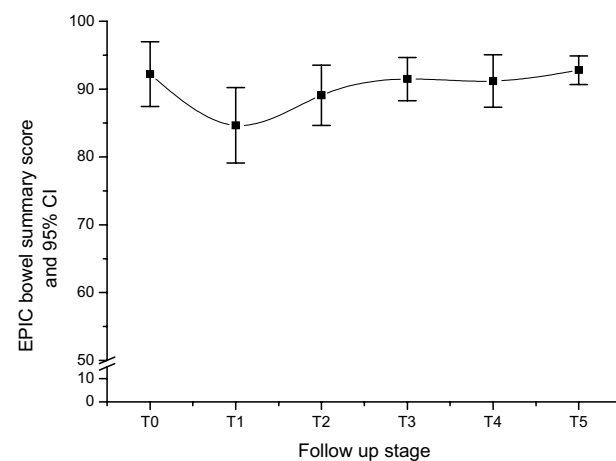


Fig. 5. The mean change in EPIC bowel summary score in the two years following I-125 brachytherapy.

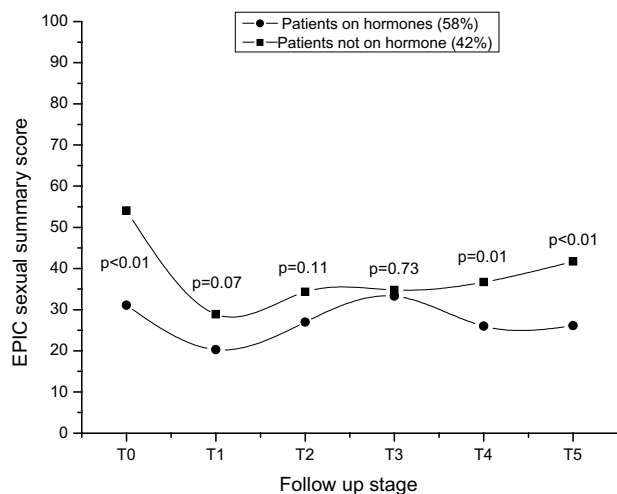


Fig. 6. EPIC sexual summary scores for patients depending on whether they underwent neo-adjuvant hormone treatment or not.

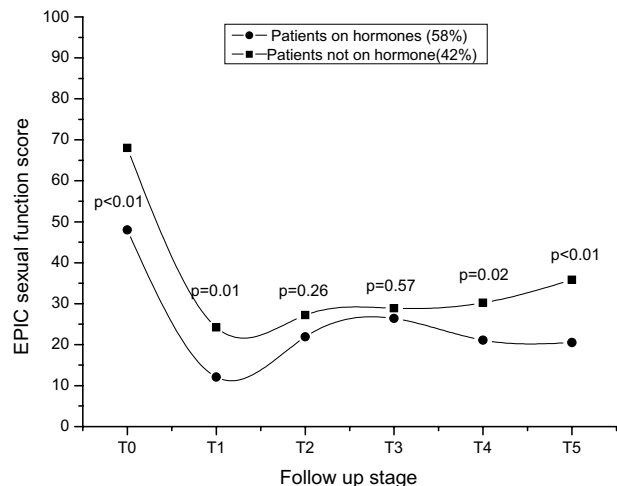


Fig. 7. EPIC sexual function scores for patients depending on whether they underwent neo-adjuvant hormone treatment or not.

Discussion

This prospective longitudinal study demonstrates that after an initial period of mild to moderate urinary symptoms prostate brachytherapy is well tolerated with relatively little deterioration in long-term QoL. Rates of incontinence after brachytherapy are often quoted of the order of 2–3% [7]. Our patient derived QoL data reveal higher levels of incontinence, but only in the first few months after brachytherapy. Urinary incontinence is associated with initial treatment related irritative symptoms and by one year the score for urinary incontinence has returned to the pre-treatment level, remaining unchanged in the second year.

The correlation between initial IPSS score and the score five years after brachytherapy is likely to be due to the effect of established benign prostatic hypertrophy (BPH). While some shrinkage of the prostate can be expected after brachytherapy, those subjects with reduced outflow initially have more symptoms after five years than those who start out with lower IPSS scores. Patients presenting with urinary

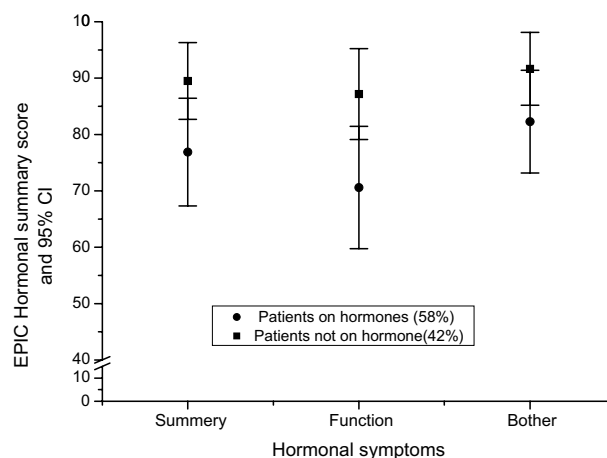


Fig. 8. The influence of hormones on pre-treatment EPIC hormonal score. As expected, patients on hormonal treatment experience more symptoms and note a significant deterioration in quality of life.

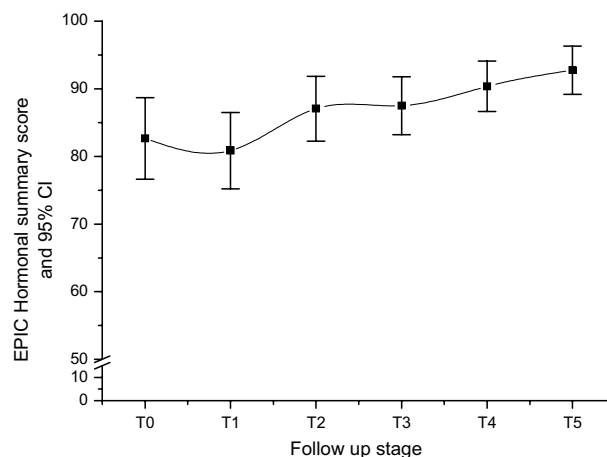


Fig. 9. The mean change in EPIC hormonal summary score in the two years following brachytherapy. Hormonal symptoms gradually resolved over the time course.

symptoms keen to undergo brachytherapy should be made aware that in the long-term they may be troubled by persistent urinary symptoms.

Over 50% of our patients have received hormone therapy mostly to shrink the gland before brachytherapy. This short-term use of hormones appears to have a significant effect on long-term hormonal and sexual function. In both groups, sexual function deteriorated immediately following treatment but then improved. Despite the short-term duration of hormone manipulation, the magnitude of the improvement was less in the neo-adjuvant group. This may reflect a delayed return to pre-treatment testosterone levels. Pinkawa et al. [14] found neo-adjuvant hormones had a similar impact on their cohort of patients assessed at a median of 29 months after brachytherapy. The general reduction in sexual function with time may be due to late effects of brachytherapy and/or age related decline.

In a separate analysis of sexual function after brachytherapy we have shown that 74% of patients have recorded themselves as potent before treatment and this has fallen to only 34% after brachytherapy. Many, however, are subsequently helped by medication.

Our study demonstrates that patient derived QoL data uncover more morbidity than is revealed by solely physician derived data, particularly in the realms of incontinence and impotence as has been demonstrated by others [9].

It is well known that the effects of radiation may continue for several years after treatment. Miller et al. [13] evaluated QoL using EPIC at a median of 6.2 years after treatment for prostate cancer. In the four to eight years after brachytherapy, urinary irritation and bowel symptoms improved but urinary incontinence deteriorated. This contrasted to QoL in those men undergoing radical prostatectomy, in whom no significant deterioration was seen after the first two years. Our study demonstrated no significant change in urinary symptoms up to nine years following treatment using the IPSS instrument. The IPSS instrument may be less sensitive than EPIC and, as the follow up for patients completing EPIC questionnaires is only two years, it is possible that further late effects may become apparent over time. We are therefore continuing to monitor QoL scores longer term in this cohort of patients.

This work is limited in that it describes the experience of a single centre. Morbidity may vary from centre to centre depending on treatment techniques. An ongoing single arm multi-centre trial (RTOG 98-05) is assessing the efficacy and morbidity of brachytherapy [3]. The results from this trial and others will provide more generalisable information on long-term health-related QoL following brachytherapy.

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Received 27 September 2006; received in revised form 18 April 2007; accepted 15 May 2007

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