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Prostate brachytherapy

Early biochemical outcomes following permanent interstitial brachytherapy as monotherapy in 1050 patients with clinical T1–T2 prostate cancer

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Abstract

***Background and purpose*: Five European centres (France, Finland, Italy, Spain and the UK) have pooled data to generate a large patient series involving 1175 patients treated with prostate brachytherapy. This paper reports preliminary data on PSA outcome up to 4 years.**

***Patients and methods*: Out of 1175 in the database, 1050 patients with localised prostate cancer who had received transperineal seed implantation as monotherapy between May 1998 and August 2003 were stage T1–T2. A total of 668 (63.6%) patients met the low-risk group definition, 297 (28.3%) as intermediate-risk definition and 66 (6.3%) the high-risk group definition. The majority of patients were Gleason score 6 or less ($n = 951$) and disease stage was T1c in 557 patients.**

***Results*: Of the 1050 patients, PSA data up to 4 years were available for 210 patients, while 364 patients with PSA values up to 36 months were evaluable by the Kaplan–Meier method for freedom from biochemical failure. The biochemical progression-free rate at 3 years was estimated to be 91%, with a 93% and 88% rate for low- and intermediate-risk groups, respectively, versus 80% for the high-risk group. PSA kinetics provide encouraging evidence of treatment efficacy.**

***Conclusion*: These data on 4-year PSA follow-up on patients treated with prostate brachytherapy reflect those previously reported in the literature. This patient series will be followed to provide long-term outcome in the future.**
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Keywords: Prostate cancer; Permanent prostate brachytherapy; PSA; 4-year follow-up

Modern brachytherapy has been added over the past decade to the treatment armamentarium for localised prostate cancer. Indeed, a recent American Urological Association policy briefing projects that prostate brachytherapy will soon surpass radical prostatectomy as the treatment of choice [17]. The reasons for this notable attainment are several: effective dose planning provided by new computer-based systems optimising seed distribution and dosimetry; transrectal ultrasound imaging resulting in precise and predictable seed placement; low patient morbidity; and favourable long-term prostate-specific antigen (PSA) outcomes. Another contributory factor is the development of stranded seeds that minimize migration, allowing for improved post-implant periprostatic coverage and therefore better post-implant dosimetry [12,24,29,30].

The stratification of prostate cancer patients into groups at low risk, intermediate risk, or high risk of biochemical failure after radiotherapy has been conducted on the basis of the patient's pre-treatment PSA, Gleason score and stage [11,25]. The development of such risk group stratification has improved the management of patients with localised prostate cancer and excellent results have been reported with the use of brachytherapy alone in men with low- and intermediate-risk disease [2,25,27,31].

The advent of the PSA era has led to the diagnosis and treatment of patients with earlier stages of disease and,

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potentially, higher cure rates. The use of PSA as a follow-up tool after definitive therapy allows early detection of treatment failure. In its initial application, controversy surrounded the use of PSA in defining failure after radiotherapy. In 1997, the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus panel defined the guidelines for PSA failure as three consecutive rises after the PSA nadir [9]. As the ASTRO definition requires at least three consecutive PSA elevations at 3- to 6-month intervals, a follow-up of over 2 years is recommended in calculating the time of failure.

This Prostate Group was originated from five European centres: France, Finland, Italy, Spain and the UK. These centres have pooled data to generate a large patient series involving 1175 patients treated with prostate brachytherapy. Information on patient demographics has been published previously [22]. This paper reports preliminary data on PSA outcome up to 4 years from the series of 1050 T1—T2 patients treated with transperineal brachytherapy, with or without hormonal therapy.

Methods

Out of the 1175 patients in the database, 1050 patients with localised prostate cancer who had received transperineal seed implantation as monotherapy between May 1998 and August 2003 were stage T1—T2. Patients were stratified into risk groups based on that developed by the Seattle group [5]. Low risk was classified as PSA ⩽ 10 ng/ml, Gleason score 2—6 and stage T1—T2b; intermediate risk as PSA > 10 ng/ml or Gleason score ⩾7 or stage T2c; and high risk as two or more risk factors: PSA > 10 ng/ml, Gleason score ⩾7 and stage T2c.

A standard approach to seed implant was used across the five centres [22]. Seeds were applied using a transperineal approach under transrectal ultrasound guidance. The planned prescribed dose was 145 Gy to cover the whole gland and the prostate volume receiving 150% of this dose was <55%. A pre-implant prostate volume study was conducted using ultrasound with subsequent computerised dosimetry planning and post-implant dosimetry. A total of 1001 (95.3%) patients received I-125 seed implants (Rapid Strand®, Oncura) and 49 (4.7%) patients received loose Pd-103 seeds (Mod 200, Theragenics). Prior hormonal therapy with an anti-androgen or a luteinising hormone-releasing hormone (LHRH) analogue was used either for prostate cytoreduction or whilst treatment options were being considered.

Patient follow-up post-implantation included serial PSA measurements every 6 months, digital rectal examination (DRE) and side-effect monitoring. PSA values at baseline, months 12, 18, 24, 30, 36, 42 and 48 were summarised for all patients. Biochemical failure was defined according to the ASTRO Consensus definition [9] as the midpoint between the PSA nadir and the first of three consecutive rises in PSA or the time when second-line therapy was given. PSA values after initiation of second-line therapy or after biochemical failure were excluded from subsequent evaluations. Patients with at least three post-implant PSA measurements prior to month 24 and at least one PSA measurement on or after month 24 were evaluated for time to biochemical failure.

Results

Mean (SD) patient age was 64.8 (6.5) years and median PSA (range) at implantation was 7.3 (0.4—50.0 ng/ml). A mean (SD) prostate volume of 33 (12.2) ml was reported. The majority of patients were Gleason score 6 or less (n = 955) and disease stage was T1a/b (n = 2); T1c (n = 561); T2a/b (n = 382); and T2c (n = 105). Overall, 668 (63.6%) patients met the low risk group definition, 297 (28.3%) as intermediate risk definition and 66 (6.3%) the high risk group definition. Gleason scores were not available for 19 patients (insufficient biopsy material in certain cases) and consequently their risk group status could not be determined. With regard to prior therapy, 18 patients (1.7%) had undergone a transurethral resection of the prostate and 405 patients (38.6%) had received hormonal therapy; 644 (61.3%) had not received hormonal therapy and the status of one patient (0.1%) was unknown.

The PSA kinetic profile was studied for all patients; relapses were censored at the time of event. Median (range) PSA follow-up time was 30 months (1—72 months) based on 1050 patients. Median PSA values excluding patients who had previously failed therapy stratified according to age, prostate volume at implant, prior hormonal therapy and risk group status are shown in Table 1. Box plots of PSA values up to 48 months are shown in Fig. 1.

Table 1
Summary of median PSA levels up to 4 years stratified according to risk factors excluding patients who previously failed therapy

	PSA level (ng/ml) at month								
	0 (n)	6 (n)	12 (n)	18 (n)	24 (n)	30 (n)	36 (n)	42 (n)	48 (n)
All	7.3 (1050)	0.8 (786)	0.7 (751)	0.6 (517)	0.5 (670)	0.4 (400)	0.3 (397)	0.2 (142)	0.2 (210)
Age ⩽65 y	6.9 (540)	0.9 (409)	0.9 (396)	0.7 (281)	0.6 (360)	0.5 (207)	0.3 (214)	0.2 (69)	0.2 (108)
Age >65 y	7.8 (510)	0.6 (377)	0.5 (355)	0.4 (236)	0.3 (310)	0.3 (193)	0.2 (183)	0.2 (73)	0.2 (102)
Prostate size ⩽35 ml	7.3 (650)	0.7 (465)	0.6 (451)	0.6 (306)	0.5 (402)	0.4 (248)	0.3 (235)	0.2 (86)	0.2 (125)
Prostate size >35 ml	7.4 (397)	0.8 (319)	0.7 (299)	0.6 (210)	0.5 (267)	0.4 (152)	0.3 (162)	0.2 (55)	0.2 (85)
No prior hormonal tx	7.0 (644)	1.0 (480)	0.8 (449)	0.7 (277)	0.6 (397)	0.4 (216)	0.3 (213)	0.2 (89)	0.2 (119)
Prior hormonal tx	8.0 (405)	0.5 (305)	0.5 (301)	0.5 (239)	0.4 (273)	0.3 (184)	0.3 (184)	0.2 (53)	0.2 (91)
Low risk	6.5 (668)	0.7 (482)	0.6 (454)	0.6 (335)	0.5 (419)	0.3 (253)	0.2 (241)	0.2 (96)	0.2 (119)
Intermediate risk	10.6 (297)	0.9 (231)	0.8 (232)	0.6 (150)	0.5 (194)	0.4 (118)	0.3 (119)	0.2 (37)	0.2 (68)
High risk	12.4 (66)	1.0 (58)	0.8 (49)	1.0 (31)	0.6 (45)	0.7 (28)	0.4 (30)	0.5 (9)	0.3 (20)

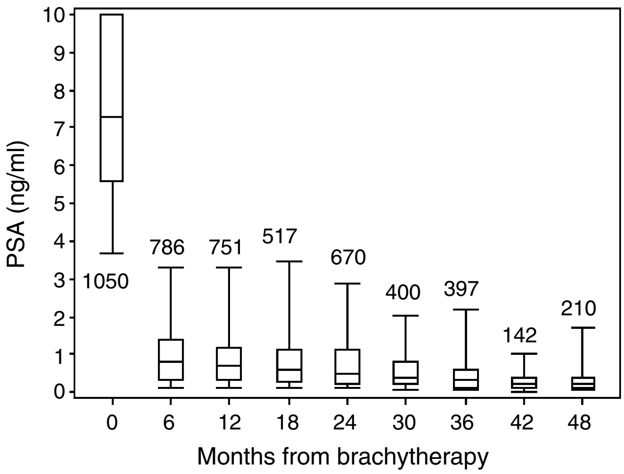

Fig. 1. PSA values up to 48 months. Number of patients at each time point shown. Whiskers extend to 5% and 95%; box represents 1st and 3rd quartile (i.e. 25% and 75%).

Of the 1050 patients, 364 were evaluable by the Kaplan–Meier method for freedom from biochemical failure according to the ASTRO definition up to 3 years. The Kaplan–Meier method assumes that evaluable patients censored before 3 years would have the same chance of failure up to year 3 as the patients who have been followed up beyond year 3. The biochemical progression-free rate at 3 years was estimated to be 91% (95% CI = 88–94%) with a 93% (95% CI = 90–97%) and 88% (95% CI = 82–95%) rate for low- and intermediate-risk groups, respectively, versus 81% (95% CI = 64–98%) for the high-risk group. In the hormone naïve group, the biochemical progression-free rate at 3 years was estimated to be 91% (95% CI = 87–95%) and in the patients who received hormonal therapy the rate was 92% (95% CI = 88–96%). The biochemical progression-free rate in patient with prostate size 35 ml or less was 90% (95% CI = 86–95%) compared with 92% (95% CI = 88–97%) in those with prostate size greater than 35 ml. Finally, with regard to age, biochemical progression-free rate at 3 years was 91% (95% CI = 87–95%) in patients aged 65 years or less and 91% (95% CI = 86–95%) in those over 65 years.

An evaluation of PSA data up to 4 years indicates that 31 patients had a biochemical relapse. Of these, 15 patients were from the low risk group, 12 the intermediate risk group and four the high risk group. Of the same set of 31 patients, 15 were hormone naïve, 20 had a prostate sized 35 ml or less and 17 were aged 65 years or less.

Discussion

This European initiative involving 1050 patients with T1–T2 prostate cancer treated with prostate brachytherapy can now report 4-year follow-up data. These data differ from previously published large series in that patient selection utilised established guidelines and a similar technique throughout the five centres. Also evident is the fact that the treatment delivered as well as follow-up protocols have remarkable homogeneity across countries.

In view of the short follow-up time, crude data in the form of median PSA for the entire group and defined subgroups are reported. Serum PSA levels have been reported to follow a gradual decline following I-125 brachytherapy [18]. Previous series have established that PSA levels continue to decrease for at least 48 months after brachytherapy [4]. Henderson et al. report median PSA levels of 0.5, 0.4 and 0.1 ng/ml at 1, 2 and 3 years, respectively, in a series of 255 patients treated with I-125 prostate brachytherapy; patients were predominantly T2 with Gleason score 6 or less [15]. Grimm et al. [13] similarly report a slow PSA decline in a series of 124 patients with Gleason 6 or less prostate tumours; 85.6% were also stage T2a or less. Median PSA levels at 1, 2 and 3 years were 0.8, 0.55 and 0.3 ng/ml, respectively. A PSA nadir of 0.1 ng/ml was achieved at 5 years, while at 10 years, 81% of patients had a PSA level <0.2 ng/ml. It has been argued that low PSA nadirs are associated with a greater probability of success following prostate brachytherapy plus EBRT. In a series of 489 men, those who had a nadir of 0.2 ng/ml or less had a 92% non-rising PSA rate ($P = 0.001$) at 10 years after treatment compared with a rate of 41% for men with a nadir of 0.3–1.0 ng/ml. All men whose nadir was greater than 1.0 ng/ml had recurrence [10]. Data reported by Grimm et al. [13] indicate a similar finding, although his group does not go so far as to define a single PSA nadir cut-off point. Potters et al. [25] also performed a multivariate regression analysis for PSA nadir post-implant in a series of 717 patients. Hazard risk ratios using a PSA nadir definition of $\leqslant$1.0 and $\leqslant$0.5 ng/ml were each significant predictors of biochemical outcome, with the 0.5 ng/ml level being only slightly better than the 1.0 ng/ml level: 3.57 vs. 2.78.

Although the optimal treatment for organ-confined prostate cancer remains controversial, prostate brachytherapy seems comparable in terms of oncological results to both EBRT and radical prostatectomy when patients are stratified on the basis of pre-treatment prognostic factors [20,26]. For low-risk, intermediate-risk and high-risk disease, Kwok et al. [21] reported 5-year biochemical control rates of 85%, 63% and 24%, respectively. Potters et al. [25] reported 5-year PSA-relapse free survival rates for favourable-, intermediate- and unfavourable-risk patients of 92%, 74% and 55%, respectively. Beyer et al. [3] report cancer specific survival rates at 10 years of 91–98% and 66–69% for patients with low- and high-risk disease, respectively, following brachytherapy as monotherapy. A PSA progression-free survival rate of 87% at 10 years has also been proven in low-risk patients by Grimm et al. [13]. Future analyses will allow comparison to these data.

Some series have documented that younger patients have a significantly higher rate of organ-confined disease than older men [28]. Carter et al. [7] reported that age at diagnosis may be a stronger predictor of prostate cancer curability than differences in pre-treatment PSA. Herold et al. [16] have also documented that older patients have an increased incidence of extra capsular extension, higher Gleason scores, and a greater propensity for distant metastases than younger patients. Not all studies support these findings, however, and Catalona et al. [8] reported that age was not a predictor of recurrence after radical prostatectomy. In the current series, mean age at implant was 64.8 years and although it is too early to definitively establish the effect of age on outcome, early analysis of PSA outcome has not revealed differences in biochemical progression free survival.

Approximately 39% of patients in the present series had previously undergone hormonal therapy, used either for prostate cytoreduction or from the point of diagnosis until brachytherapy was applied. There are many issues that remain controversial concerning the use of hormonal therapy in patients treated with brachytherapy including efficacy, selection criteria, duration of use and optimal drug choice. The Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) trials have demonstrated improvement in various disease endpoints, including local control, metastasis free-survival and overall survival, with the use of hormonal therapy in trials of external beam radiotherapy [6,14]. A single study by the Mt Sinai Group suggested that hormonal therapy may improve outcome in higher-risk patients treated with implant alone and in those patients receiving less than optimal quality implants, although this study suffered from different length of follow-up in the hormone treated vs. hormone naïve patients [23]. A more recent report by Ash et al. [1] suggests that hormonal therapy did not have a significant effect on outcome in men with localised prostate cancer receiving 3 months neoadjuvant hormonal therapy with an LHRH agonist. This study also reported a benefit of adding 5–6 months of hormonal therapy to brachytherapy alone for high-risk patients. The role of hormonal therapy as adjuvant therapy in low or intermediate risk is less clear. Kollmeier et al. showed no benefit in a group of mostly low-risk patients treated with implant alone, with a minimum follow-up of 5 years [19]. The effect of androgen manipulation will be examined in future analyses of the current database.

Conclusion

The 4-year PSA follow-up on patients treated with prostate brachytherapy reflects those previously reported in the literature. These data establish an excellent early baseline in a European population of prostate cancer patients. Patient selection for brachytherapy was appropriate with the majority of patients being in the low and intermediate risk categories.

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