Urological Oncology

Brachytherapy has become a very popular way of treating prostate cancer worldwide, and increasing attempts are being made by radiation oncologists to find the exact type of patient for whom this treatment is the most suitable. One of the largest series has come from Leeds, and the authors present the PSA relapse-free survival in 667 patients with localised prostate cancer treated by brachytherapy in their department.

Authors from Canada report on the value of taking a repeat prostate biopsy after an initially negative one, but point out that the practice pattern of repeat biopsies is unknown. They decide what factors were important influences in deciding whether a patient would have a repeat biopsy, and particularly those factors which were helpful in predicting prostate cancer at the repeat biopsy.

Prostate-specific antigen relapse-free survival in patients with localized prostate cancer treated by brachytherapy

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Accepted for publication 8 July 2004

OBJECTIVE

To report the clinical outcome after permanent implantation of ^{125}iodine seeds (brachytherapy) for early prostate cancer, after 8.2 years of follow-up.

PATIENTS AND METHODS

Between March 1995 and December 2001, 667 men (mean age 63 years, range 42–77) were treated with brachytherapy at the one cancer centre; 346 (51.9%) had a short course of neoadjuvant hormone therapy. The prescribed minimum peripheral dose was 145 Gy. No patient received external beam radiation.

RESULTS

The median (range) follow-up was 31 (18–98.2) months; 41 patients were lost to follow-up. The actuarial biochemical relapse-free survival was 74.9%; 100 patients had biochemical relapse (international definition). In all, 20 patients had clinical relapse, and 24 died (10 from prostate cancer). The prostate-specific antigen (PSA) relapse-free survival was 78.3%, 66.5% and 56.4% for patients with Gleason scores of <7, 7 and >7, respectively, and was 81.4%, 69.8% and 36.3% for those with PSA levels of <10, 10–20 and >20 ng/mL, respectively (both $P < 0.001$). There was a strong cohort effect depending on year of implant, with progressive annual improvements in relapse-free survival ($P < 0.001$). Hormone therapy, tumour stage, prostate volume before implantation, age and D90 dose had no significant effect on the outcome.

CONCLUSION

The overall relapse-free survival for all patients was 75%; the initial PSA, Gleason score and risk group were significant factors predicting the outcome. Increasing clinical experience was associated with a better outcome but neoadjuvant hormone therapy had no effect.

KEYWORDS

brachytherapy, ^{125}iodine, prostate cancer, outcome, PSA, Gleason score

INTRODUCTION

Although the ultrasonographic- and template-guided technique for permanent seed implantation for prostate cancer was described in the early 1980s [1] it has taken some years for long-term reports of studies

with many patients to become available [2–4]. So far there have been relatively few reports from Europe, because the technique was adopted there more recently [5,6].

Prostate brachytherapy started in Leeds in 1995; after a slow start with <50 patients treated each year, there are now 250 patients treated annually, with a total of >1300 recorded. In all, 667 patients have been analysed with an 18-month minimum follow-up to identify factors which are related to PSA relapse-free survival (PSA-RFS). These include the impact of prognostic factors, the use of adjuvant hormone therapy, the effect of delivered dose and of increasing experience. Side-effects and complications are a critically important part of outcome analysis but are dealt with in a separate paper. Herein we report the clinical outcome after permanent implantation of ^{125}iodine seeds (brachytherapy) for early prostate cancer

PATIENTS AND METHODS

In all, 667 patients were treated between March 1995 and December 2001 (mean age 63 years, range 42–77); the distribution of Gleason score, PSA level and T stage is shown (Table 1). The median (maximum) follow-up for censored patients was 31 (98.2) months and 41 were lost to follow up.

Very few patients presented after PSA screening because this is not generally available in the UK. Many patients therefore presented with LUTS arising from BPH. The mean (range) prostatic volume at implantation was 35 (12–65) mL; 52% of patients received neoadjuvant hormone therapy to reduce the gland and 48% did not.

All patients were treated by implantation with ^{125}iodine seeds as monotherapy; a dose of 145 Gy was planned to a volume encompassing the prostate capsule plus a 2–5 mm margin. Most patients were treated using a two-step pre-planning technique [7], using the Seattle method, with prostate volume estimated by TRUS to plan the implant. Some were treated with a single-step technique. In 413 patients, detailed dosimetry 6–8 weeks after implantation was obtained using CT data. Patients were followed up with 3-monthly PSA assays for the first 2 years and then 6-monthly. Biochemical relapse followed the American Society for Therapeutic Radiology and Oncology (ASTRO) definition [8].

Actuarial survival curves were calculated by the Kaplan-Meier method [9] and the log-rank test used to evaluate differences in survival curves. Cox proportional-hazards multivariate analysis was used to assess the influence of different covariates on the results [10].

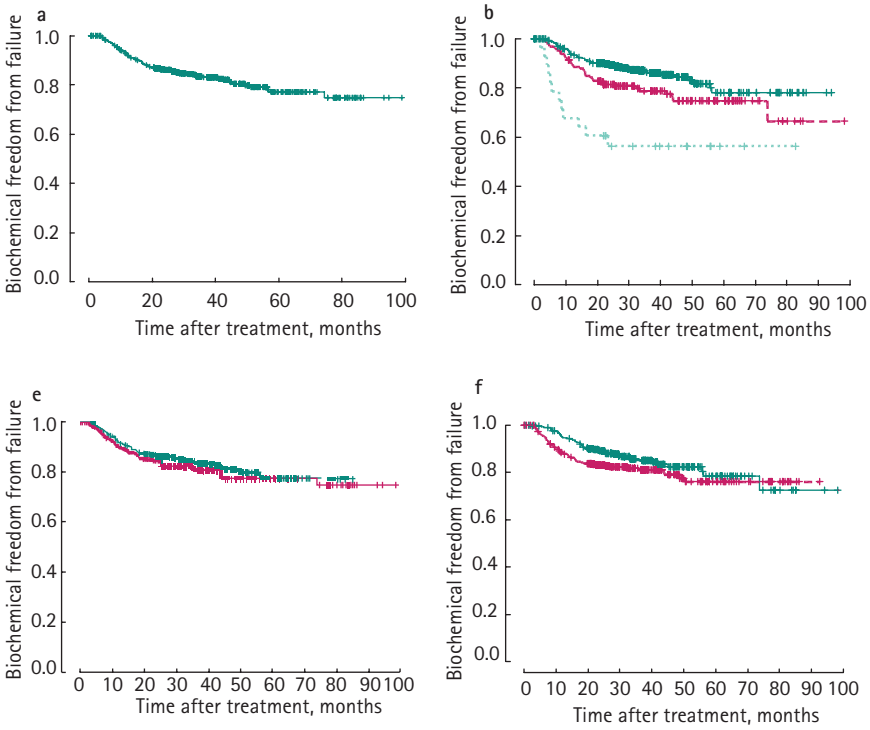
RESULTS

For the entire cohort of 667 men, 110 had evidence of biochemical relapse, 20 had a clinical relapse and 10 died from prostate cancer; 15 other patients died from other causes. Figure 1a shows the actuarial PSA-RFS for all patients; at 8.2 years the PSA-RFS

TABLE 1 The patients' characteristics

Characteristic	N (%)
PSA, ng/mL	
≤10	421 (63.1)
10–20	201 (30.1)
>20	44 (6.6)
Unknown	1 (0.1)
T stage	
T1c	284 (42.6)
T2a	234 (35.2)
T2b	47 (7.0)
T2c	101 (15.1)
Gleason score	
2–5	159 (23.8)
6	303 (45.4)
7	171 (25.6)
8–9	28 (4.1)
Unknown	6 (0.9)

FIG. 1. Actuarial PSA-RFS for: ***a,*** *All 667 patients; the 8.2 years (98.2 months) PSA-RFS was 74.9%.* ***b,*** *With biopsy Gleason score (green <7; red 7; light green >7); Gleason score is a predictive factor of PSA control.* ***c,*** *With pretreatment PSA (green ≤ 10, red 10.1–20, light green > 20 ng/mL); initial PSA is predictive of PSA control.* ***d,*** *With ASTRO risk groups (see text); low (green), intermediate (red) and high (light green).* ***e,*** *with tumour stage (T1a–T2a, green; T2b–T2c, red).* ***f,*** *with pretreatment hormone therapy (treated, green; untreated, red); hormone therapy had no effect on PSA control with time.* ***g,*** *with dose level (P = 0.227).* ***h,*** *with type of implant, strand (green) or free (red) seeds.* ***i,*** *with year of implant.*



was 74.9%. The PSA-RFS with Gleason score is shown in Fig. 1b and was 78.3%, 56.5% and 45.4% for patients with Gleason scores of <7, 7 and >7, respectively ($P < 0.001$). Figure 1c shows the correlation with initial PSA; the PSA-RFS was 81.4%, 69.8% and 36.3% for men with a PSA of ≤10, 10.1–20 and >20 ng/mL, respectively ($P < 0.001$). Fig. 1d plots PSA-RFS according to risk groups; the respective PSA-RFS was 84.3%, 73.9% and 52.6% for low (PSA <10 ng/mL, Gleason score of ≤6), intermediate (PSA >10 ng/mL or Gleason 7) and high risk groups (PSA >10 and Gleason ≥7), respectively ($P < 0.001$). There was no correlation between PSA-RFS and stage (Fig. 1e), with PSA-RFS of 74.8% and 77.2% for stages T1a–T2a and T2b–T2c respectively ($P = 0.68$).

In all, 346 patients received hormone therapy before brachytherapy and 321 did not; this therapy was given for 3–4 months for cytoreduction before implantation, and then stopped. The PSA-RFS was 76.1% in patients who received hormones and 72.6% in those who did not (Fig. 1f); when the effect of hormone therapy was analysed with risk group there were no significant differences in any group ($P = 0.107$).

From the dosimetry analysis it was possible to analyse the effect of dose on PSA-RFS; the dose received by 90% of the prostate volume (D90) was taken as the measure of dose received. Figure 1g shows that there was no significant difference in PSA-RFS in cohorts of patients treated with a D90 of 100–160 Gy ($P = 0.227$).

In the first 3 years of treatment, free seeds were implanted and later stranded seeds were used; Fig. 1h shows a significant difference in PSA-RFS between the types of treatment, (91.9% strand and 60.5% free), probably because free seeds were used when patient selection was not as rigorous and the technique not so well established. When evaluated in a multivariate analysis, the risk group and the year of implant remained highly significant ($P < 0.001$ and <0.011), whereas the type of seed used was not ($P = 0.516$).

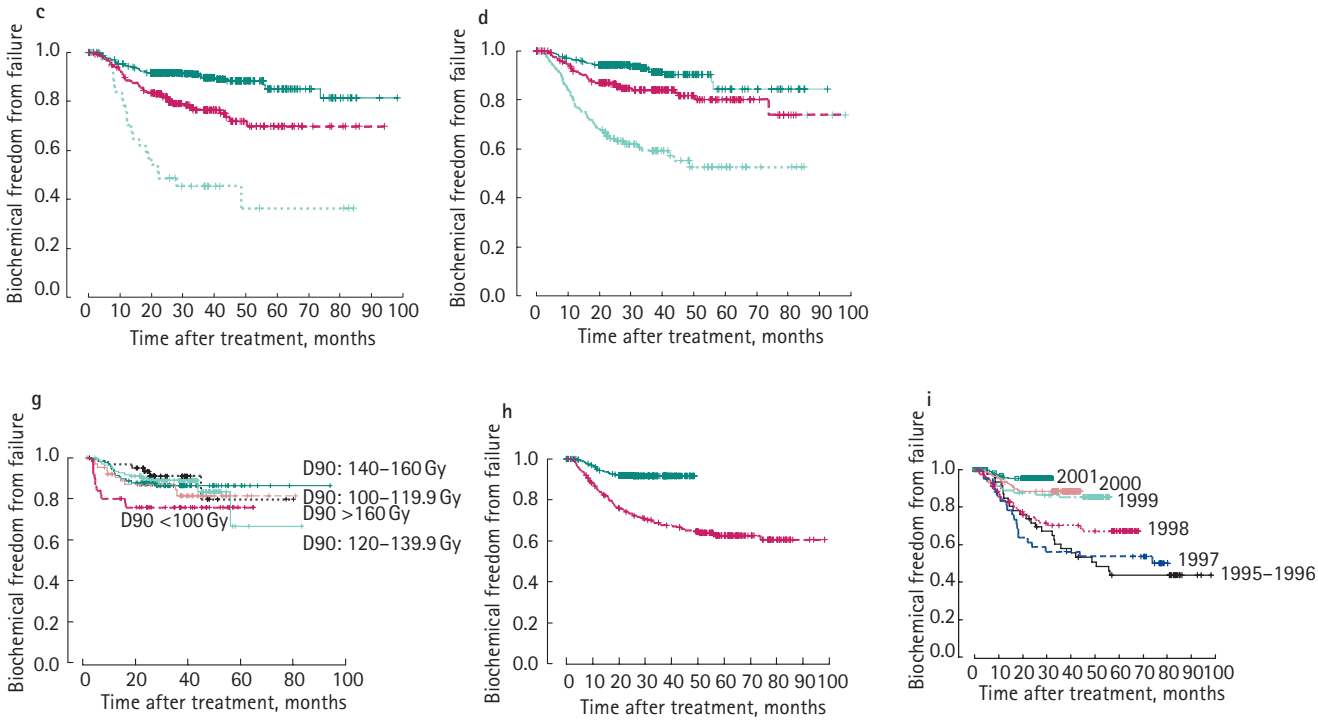
The PSA-RFS with year of implant is shown in Fig. 1i, and shows annual improvements, with a PSA-RFS of 95.3%, 88.4%, 85.3%, 67.1%, 50.1% and 43.6% for patients implanted in 2001, 2000, 1999, 1998, 1997 and 1995–6. Some of this effect is an artefact created by the decreasing follow-up, but some is probably because there was better patient selection and improvements in technique. This is reflected in a steadily improving D90, although the dose alone did not appear to be a significant factor for outcome. Nevertheless, the actuarial PSA-RFS for patients implanted between 1998 and 2001 was 86.3% at 5 years, compared with 74.9% for all patients and 31% for those treated between 1995 and 1998.

DISCUSSION

The results show similar PSA-RFS to those reported from other centres [3–6,11] but comparison is difficult because of differences in case mix and in length of follow-up. The effect of the key prognostic factors of PSA, Gleason score and risk group were confirmed, as in other studies. Although clinical tumour stage is a prognostic factor on univariate analysis, it rarely remains significant when PSA and Gleason score are considered. The present results showed no significant correlation between PSA-RFS and clinical stage.

Unlike external beam radiation [12], the addition of hormone therapy had no

FIG. 1. Continued



significant effect on PSA-RFS. This could be because hormone therapy was given for only a few months and because the risk-group profile differed for brachytherapy and external beam irradiation; this was confirmed by others [13,14].

In contrast to the study of Stock and Stone [15] and Potters *et al.* [16], the present study showed no significant effect of D90 on the probability of achieving biochemical control. This could be because the site of low dosage does not coincide with the position of tumour, and/or because some PSA relapses are not a result of local recurrence but distant dissemination.

The cohort effect has been reported by others and confirms that there is a significant effect of increasing experience [16]. New developments in ultrasonography and planning software, plus the availability of better mentoring, should allow experience and training to be gained more easily for those who have recently started or are about to start an implant programme. However, the results for patients treated between 1998 and 2001 are comparable with those reported elsewhere.

ACKNOWLEDGEMENTS

This research was supported by the Cookridge Hospital Prostate Cancer Research and Education Funds, and Prostate Research Campaign UK. We acknowledge Kathy Gould, Tony Flynn, Carolyn Richardson, Shaun St Clair, Elizabeth Brearley, Heidi Probst and Tony Evans for their valuable contribution to the prostate brachytherapy programme at the Leeds Teaching Hospital NHS Trust.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **PSA-RFS**, PSA relapse-free survival; **ASTRO**, American Society for Therapeutic Radiology and Oncology.