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BRACHYTHERAPY OR CONFORMAL EXTERNAL RADIOTHERAPY FOR PROSTATE CANCER: A SINGLE-INSTITUTION MATCHED-PAIR ANALYSIS

TOM PICKLES, M.D., MIRA KEYES, M.D., AND W. JAMES MORRIS, M.D., ON BEHALF OF THE PROSTATE OUTCOMES AND PROVINCIAL PROSTATE BRACHYTHERAPY PROGRAM

Prostate Outcomes and Provincial Prostate Brachytherapy Program, BC Cancer Agency, Vancouver, BC, Canada

Purpose: In the absence of randomized study data, institutional case series have shown brachytherapy (BT) to produce excellent biochemical control (bNED) in patients with localized prostate cancer compared with alternative curative treatments. This study was designed to overcome some of the limitations of case series studies by using a matched-pair design in patients treated contemporaneously with BT and external beam radiation therapy (EBRT) at a single institution.

Methods and Materials: Six hundred one eligible patients treated between 1998 and 2001 were prospectively followed up in our institutional databases and matched on a 1:1 basis for the following known prognostic variables: prostate-specific antigen (PSA) level, Gleason score, T stage, the use and duration of neoadjuvant androgen deprivation therapy, and the percentage of positive tissue core samples. Two hundred seventy-eight perfect matches of patients (139 in each group) with low- and intermediate-risk cancer were further analyzed. bNED (Phoenix definition) was the primary endpoint. Other endpoints were toxicity, PSA kinetics, and the secondary use of androgen deprivation therapy.

Results: The 5-year bNED rates were 95% (BT) and 85% (EBRT) (*p* < 0.001). After 7 years, the BT bNED result was unchanged, but the rate in EBRT patients had fallen to 75%. The median posttreatment PSA nadirs were 0.04 ng/mL (BT) and 0.62 ng/mL (EBRT, *p* < 0.001), which predicted a higher ongoing treatment failure rate in association with EBRT use than with BT use. Late urinary toxicity and rectal/bowel toxicity were worse in patients treated with BT and EBRT, respectively.

Conclusions: BT for both low-risk and selected intermediate-risk cancers achieves exceptional cure rates. Even with dose escalation, it will be difficult for EBRT to match the proven track record of BT seen over the past decade.   © 2010 Elsevier Inc.

Prostate cancer, Brachytherapy, Conformal radiation, Outcomes, Toxicity.

INTRODUCTION

Attempts to compare outcomes by treatment modality in patients with prostate cancer have generally been unproductive to date because of the absence of randomized data. One attempt at a randomized trial in this setting was the United States/Canadian ACOSOG-Z0070 trial, in which patients were to be randomized to undergo either brachytherapy (BT) or surgery. However, the trial was closed as a result of poor accrual. In the United Kingdom, the ProtecT trial is still ongoing; in that trial, patients are being randomized to undergo radical prostatectomy, active surveillance, or external beam radiation therapy (EBRT). However, the results of this trial will not be available until at least 2014 (http://www.epi.bris.ac.uk/protect/). Other trials for which we still are awaiting results are comparing a BT boost with EBRT to EBRT alone, but we have been unable to identify in a search

of controlled-trial databases any completed randomized trials directly comparing EBRT and BT. To shed light on the reasons for the lack of such trials, several groups, including our own, are performing feasibility studies (NCT00407875) to test whether patients are willing to be randomized between BT and another treatment. In the meantime, lower-level evidence may be helpful to both patients and physicians in choosing treatment.

Single-institution cohort data have already shown excellent outcomes from BT, with 5-year biochemical control (bNED) rates of 95% for low-risk and 82% for intermediate-risk patients [1]: rates that are similar to those achieved with modern ultra-high-dose intensity-modulated radiation therapy (IMRT) [2]. However, the extent to which case selection is responsible for these results is uncertain. Indeed, nonmatched comparisons of IMRT and BT have shown similar prostate-specific antigen (PSA) outcomes in some series [3] and superior PSA outcomes for BT in others [4]. This study was designed to overcome some of the limitations of case series studies by using a matched-pair analysis of patients treated contemporaneously with BT and EBRT at a single institution. We have not been able to identify another matched-pair analysis of PSA outcomes with PB and EBRT reported in the literature. Therefore, we have undertaken such a comparison of patients treated at this institution in an attempt to determine which treatment—BT or EBRT—provides best cancer control, and at what price in terms of toxicity.

METHODS AND MATERIALS

Patients were treated at the British Columbia Cancer Agency (BCCA), which is the sole provider of radiation therapy to the residents of British Columbia, Canada (population, 4.5 million). Although currently cancer treatment is delivered at five centers, in the era of this study, eligible patients received their EBRT treatment at one of three centres and their BT treatment at one of two centres. All patients were treated in a generally uniform manner according to cancer management guidelines (http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/default.htm).

Patients were accrued from two databases that collected data in a prospective manner: the Prostate BT database and the Prostate Cohort Outcomes Initiative (PCOI) databases. The Prostate BT database contains clinical, technical, and outcomes data on all consecutive patients treated at the BCCA and now contains 2,500 patient records. The PCOI database was started in 1994 and likewise contains clinical, treatment, and outcomes data for more than 2,000 EBRT patients treated at the BCCA. Both databases were designed with future outcome analyses in mind. Eligible patients were treated from the start of our BT program in July 1998 through closure of the EBRT outcomes database to new accrual in January 2001. The sole selection criteria for inclusion in the PCOI database were local proximity (a maximum of a 2-hour drive to a cancer center) and patient willingness to comply with follow-up requirements. During the period 1994 to January 2001, the PCOI database captured data for 50% of all patients treated with radical EBRT. Follow-up expectations in patients recorded in both databases were an initial 6-week visit, followed by visits every 6 months for 3 years, annual visits until year 6, and biannual visits until year 10. At each visit, toxicity was scored, PSA and testosterone levels were measured, and digital rectal exam-

ination was carried out where appropriate. In 2008, institutional ethics board approval was granted to conduct case-matching and specifically to conduct our retrospective case-matching study of BT and EBRT in patients with prostate cancer.

The nature of treatment with BT depended on the patient's risk level. Patients with low-risk cancer (PSA ≤10 ng/mL, T stage ≤2c, and Gleason score <7) were treated with BT alone. Intermediate-risk patients were treated with BT plus 6 months of androgen deprivation therapy (ADT) (3 months neoadjuvantly and 3 months concurrently with BT) as long as they had either a PSA of ≤15 ng/mL with a Gleason score of ≤6 or a Gleason score of 7 and a PSA of ≤10 ng/mL. Patients with larger prostate glands (>40 cc the first year of the program and >50 cc thereafter) were also treated with 3 months of neoadjuvant ADT and 3 months of concurrent ADT plus BT for a total of 6 months. All patients treated with BT were treated with ^{125}I, low-dose-rate BT, as described in detail previously [5]. This involved the use of a real-time transrectal ultrasonography–guided transperineal technique, as described by the Seattle group [6], using 0.33 mCi (NIST99) of ^{125}I sources (model 6711; Oncura, Arlington Heights, IL). The minimum peripheral dose was 144 Gy. Computed tomography scans were obtained on day 30 as a quality assurance measure. One patient in the final dataset who showed suboptimal initial dosimetry underwent a revision implant [7].

Patients treated with EBRT were planned using computed tomography imaging, without daily image guidance, and were treated with three-dimensional conformal radiation therapy using radiation doses that ranged from 52.5 to 72 Gy. Typical gross tumor volume to planning target volume margins were 1–1.5cm, and rectal doses were limited such that the 95% isodose line did not cover more than 50% of the rectal cross-sectional area. Dose-volume histograms were not generated, and pelvic irradiation was not utilized. Two patients had been randomized to the low-dose arm of the NCIC PR5 study of hypofractionated EBRT (52.5Gy in 20 fractions vs. 66Gy in 33 fractions) [8], and 3 patients were treated with this dose off study. Secondary *post-hoc* analyses that excluded patients receiving EBRT doses of less than 66 Gy were also performed.

Matching was done in the following manner. Because our management guidelines for patients suitable for BT are more stringent than those for EBRT, the BT guidelines were applied to EBRT patients in producing a list of potential matches for the BT patients. Patients were matched according to the following known prognostic factors: the same era (1998–2001), the same PSA level (within 1 ng/mL), the same Gleason score (categorized as ≤6 or 7), the same T stage (T1 or T2), the same percentage of positive biopsy core samples, when those data were available (> or ≤50%), and the same use and duration of ADT (Yes/No, duration within 3 months). When matches could not be obtained, the patients were discarded from the analysis. Matching was done with no knowledge of outcomes and was accomplished in a semiautomated manner using an Access (Microsoft Corporation) database.

The bNED, defined according to the Phoenix definition of PSA control, was the primary outcomes endpoint [9]. Both databases employ algorithms to detect anomalies in bNED data. In addition, the PSA failure calculation algorithm has been checked against others and found to be accurate [10]. To further ensure the quality of the data, a database quality assurance committee audits PSA failures in men treated with prostate BT to determine whether they represent true failures or PSA bounces. The latter are defined as nonfailures associated with a PSA rise that previously triggered the Phoenix bNED definition but then fell spontaneously to a level of <0.5ng/mL upon further follow-up. The EBRT failures were also audited,

but there were no bounces that triggered the Phoenix definition. Direct linkage to the Provincial Tumour Marker laboratory allowed us to obtain PSA results not otherwise captured in the database and thereby to correct any clerical coding errors (<1%). Other endpoints included the PSA kinetics in relapsers and nonrelapsers. The PSA doubling time was calculated assuming that exponential growth occurred between the first PSA of >1ng/mL during follow-up and the last PSA before any secondary intervention (11). The nadir PSA level at the last follow-up, overall survival, and cause-specific survival were also examined.

The secondary study endpoint was treatment toxicity. This was prospectively assessed using a modified Radiation Therapy Oncology Group toxicity scale (12), and toxicity data were captured in both databases. For BT, late toxicity was defined as that occurring at least 1 year from the implant date; for EBRT, late toxicity was defined as that occurring at least 6 months from the completion of treatment. The prevalence rate of toxicity (that is, the number of patients experiencing toxicity of a given grade during a specified follow-up interval, as a proportion of the total number of patients followed up during that time interval) was calculated for each year of follow-up 4after the first year.

The use of secondary ADT was a third endpoint. The use of secondary ADT was left to the discretion of the treating oncologist. In general, the practice was to intervene only in patients with rapid PSA doubling times or high PSA levels or in patients who developed metastatic disease (13).

Descriptive statistics were used to compare baseline factors between patients using appropriate categoric or noncategoric statistical tests. Actuarial comparison of bNED was performed using the Kaplan-Meier method. Differences in proportions were assessed by chi-square tests. The significance of toxicity grade was tested using the Mann-Whitney test for serial measurements (MedCalc http://www.medcalc.be). All other statistical tests were carried out using SPSS version 14 software.

RESULTS

During the study accrual period, 394 men with T1–2 tumors were treated with BT, and 1,369 were treated with EBRT. Of the latter group, 667 (49%) were followed up prospectively in our PCOI database, and 460 of these did not meet the BT selection criteria, leaving 207 EBRT patients suitable for matching. All 394 men treated with BT were eligible for study entry. Of these men, 139 were successfully matched in a 1:1 manner to 139 men treated with EBRT, using the method described above. The tumor and treatment characteristics of these 139 patients are summarized in Table 1. There were no significant differences between the groups in terms of any prognostic factors. Nonetheless, patients treated with BT were younger than those treated with EBRT (median age, 65 vs. 71 years).

Men treated with BT had superior outcomes in terms of bNED. Specifically, the 5-year bNED rates were 95.2% in the BT group and 84.7% in the EBRT group (log-rank test, $p < 0.001$) (Fig. 1A). Similar results were seen when patients were subdivided into low- and intermediate-risk groups, for which the 5-year bNED rates were 94% (BT) vs. 88% (EBRT) in the low-risk group ($p < 0.001$) and 100% vs. 78% in the intermediate-risk group ($p \leq 0.016$) (Fig. 1B–C). Despite the similar follow-up frequency in both groups, the failure rate

Table 1. Pretreatment and treatment characteristics of each group

Characteristic	Brachy	EBRT	p
n	139	139	
Age (y)			
median (range)	64 (48–79)	71 (54–84)	
PSA			
median	5.6	6.4	ns
Gleason score			
6	87.8%	87.8%	
7	12.2%	12.2%	ns
Risk group			
Low risk	77.7%	77.7%	
Intermediate	22.3%	22.3%	ns
T stage (2002)			
1a–c	38.8%	41.7%	
2a	54%	50.4%	
2b	7.2%	7.9%	ns
Percent positive			
cores ≤50%	87.8%	87.8%	ns
(33% of patients)			
ADT use			
Used	31.7%	30.2%	ns
Duration	6 mo	5.8 mo	ns
RT dose			
Median (range)	144 Gy (144 Gy)	68 Gy (52.572 Gy)	
Dosimetrics	144 Gy (100%)	<66 Gy (5%)	
	D90 < 90% (18%)	66 Gy (23%)	
	D90 < 80% (6%)	68 Gy (46%)	
		>68 Gy (25%)	
Technique	^{125}I	3-D conformal	
Median follow-up (mo)	68	67	ns
No. of PSA in follow-up	10	8	
(% obtained according to follow-up schedule)	113%	91%	

Abbreviations: Brachy = brachytherapy; PSA = prostate-specific antigen; ADT = androgen deprivation therapy; RT = radiotherapy; ns = not significant; 3-D = three-dimensional.

The *p* values refer to chi-square tests for categorical variables and the Kruskall-Wallis test for continuous variables. Only 45 patients in each group had information on percentage of positive cores available. The remaining patients were not matched for this variable.

beyond 5 years was very low in the BT group, with only 1 failure beyond 5 years, whereas an additional 14 patients treated with EBRT showed failure, for a projected failure rate in excess of 50% at the maximum follow-up. For those patients who showed no biochemical relapse, the last PSA recorded was a median of 0.04 ng/mL in the BT group and a median of 0.62 ng/mL in the EBRT group ($p < 0.001$). However, the PSA doubling time in those who showed a biochemical relapse was a median of 6 months in the BT group and 24 months in the EBRT group ($p = 0.01$).

In secondary *post-hoc* analysis in which patients receiving EBRT doses of less than 66Gy were excluded, the exclusion of these patients did not affect the bNED results (5-year bNED rate of 84.6%). We also conducted a comparison of all 601 (207 EBRT and 394 BT) patients suitable for
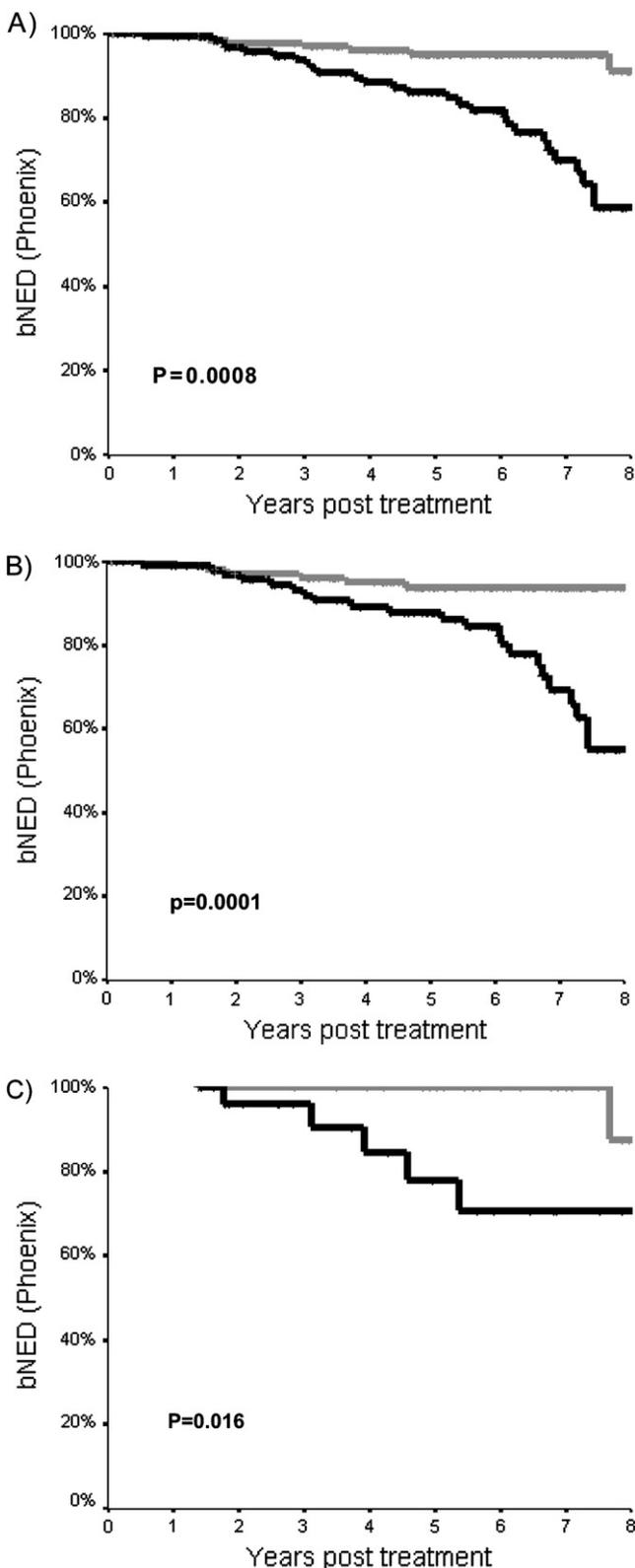
Fig. 1. Kaplan-Meier plots of biochemical control by treatment and risk group. Biochemical control rates at 5 years are as follows: (A) all patients: brachytherapy 95%, external-beam radiation therapy 85%; (B) low risk: brachytherapy 94%, external-beam radiation therapy 88%; (C) intermediate risk: brachytherapy 100%, external beam radiation therapy 78% Log rank test *p* values are shown in the figures. Gray = BT; black = ERBT.

matching, from which a total of 278 patients (46% of 601 patients) were successfully matched for the primary analysis. This showed similar results. Specifically, the 5-year bNED rates were 95.3% and 81.0 % in the complete datasets (matched and unmatched cases, total *n* = 601, difference in bNED = +14.3%) and 95.2% and 84.7%, respectively, in the 139 matched-pair cases (difference in bNED = +10.5%).

In the toxicity analysis, acute genitourinary (GU) toxicity was more frequent in the BT group than in the EBRT group. In addition, 15% of patients in the BT group required catheterization, whereas none of the patients in the EBRT group required catheterization (*p* < 0.001). Of those BT patients requiring a catheter, 52% required it for a week or less and 42% for more than a month. Acute grade 3 GU toxicity was seen in 2.9% of BT patients and in only 0.7% of EBRT patients. There was no difference in the frequency of acute gastrointestinal toxicity between the EBRT and BT groups. Specifically, grade 2 toxicity was seen in 5% of EBRT and 4% of BT patients; grade 3 toxicity did not occur in either group.

Late toxicity scores were available for only 59% of EBRT and 83% of BT follow-up data collection points, inasmuch as some of the follow-up data consisted of PSA data only. The mean worst late toxicity grade recorded was 0.51 in the BT group and 0.16 in the EBRT group (*p* < 0.001). The prevalence rates of late grade 2–4 and grade 3–4 toxicity are shown in Fig. 2. Late GU toxicity was more prevalent in BT patients than in EBRT patients (*p* < 0.001), whereas late gastrointestinal toxicity was more prevalent in EBRT patients than in BT patients (*p* = 0.0183). Note that many patients who developed late toxicity had improvement in their symptoms with time. Patients treated with EBRT who also received ADT had worse late urinary toxicity than did those not treated with ADT (grade 2–3 urinary toxicity: 22% in those treated with ADT vs. 2.4% in those not treated with ADT, *p* = 0.003), but this was not seen in BT patients.

Actuarial use of secondary ADT after relapse was 8% in the EBRT group and 5% in the BT group (*p* not significant). All BT patients with a PSA doubling time of <12 months have received secondary ADT; the comparative figure with EBRT is 50%. Only 2 patients have died of prostate cancer, 1 from each group. Non-prostate cancer–related death rates were lower in the BT group than in the EBRT group (4% vs. 18% projected at 8 years; *p* = 0.001).

DISCUSSION

This nonrandomized matched-pair comparison of BT and EBRT showed superior cancer control outcomes in patients treated with BT, but at the cost of a substantial increase in the incidence of acute urinary toxicity and a much smaller increase in the incidence of late urinary toxicity. In a previous report from our institution, the bNED rates in patients treated with BT were 96% at 5 years, which mirrored the excellent results in the present study (14). The outcome in patients treated with EBRT, however, was poor in comparison, with a 25% projected 7-year relapse rate for those patients who had a relatively good prognosis.
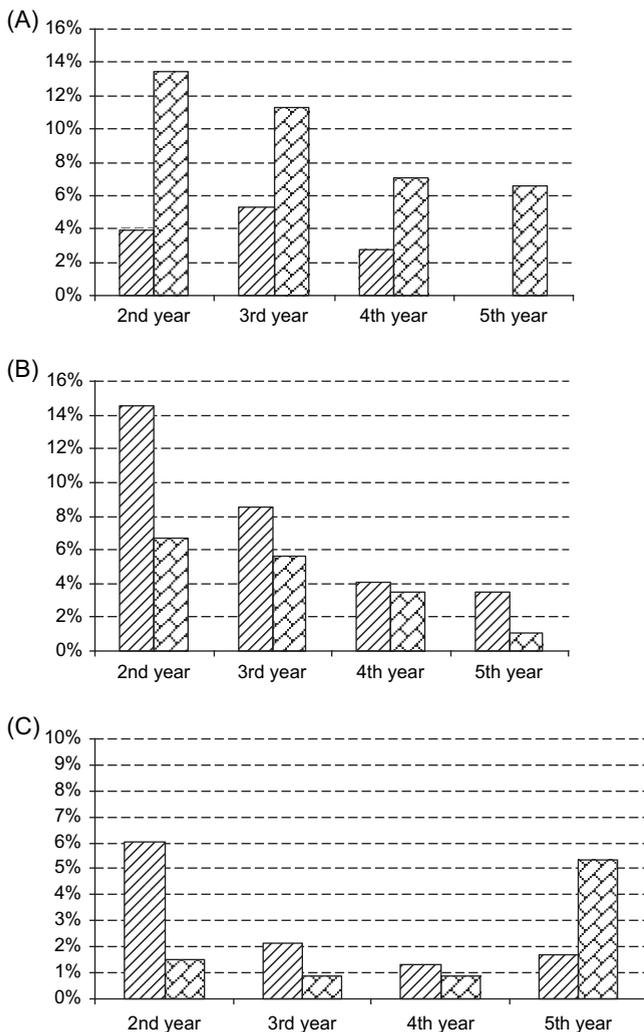
Fig. 2. Prevalence rates of (A) late grade 2 genitourinary (B) late grade 2 gastrointestinal. (C) late grade 3–4 genitourinary or gastrointestinal toxicity by treatment modality. Genitourinary toxicity ($p < 0.001$) is greater with brachytherapy, and gastrointestinal toxicity with external-beam radiotherapy ($p = 0.0183$). Fine hatching = external-beam radiotherapy; bricks = brachytherapy.

The observed lower median PSA nadir in patients treated with BT is interesting. It has been argued that such lower PSA values are to be expected after BT because the very high radiation dose delivered by BT causes metabolic atrophy, which is not the case with conventional doses of EBRT; therefore, comparisons of PSA nadirs may not accurately reveal future trends in bNED rates (15). However, there is also substantial evidence showing that the PSA nadir is correlated with the relapse rate, implying that further relapses may be seen during longer follow-up in our EBRT group but not in the BT group (16, 17). The slower PSA doubling time in EBRT patients likely reflects occult local persistence/relapse caused by relative underdosage with EBRT (18). Conversely, the rapid PSA doubling times in the (few) men who experienced relapse after BT likely reflects failure outside the radiation field resulting from occult metastatic disease that was present at diagnosis (19). Nonetheless, the actual rates of metastases are currently low (1 in each group)

because of the early institution of secondary ADT in those showing a fast PSA doubling time.

The EBRT doses used in the era of this study were low at a median of 68 Gy, which could account for the less favorable results in association with this modality. Higher doses of EBRT are being used in some more recent studies. For example, the results of a randomized study of dose escalation of 68–78 Gy delivered with three-dimensional conformal EBRT were recently updated and showed that the increased radiation dose of 78 Gy led to an improvement in the bNED rate (Phoenix definition) at 5 years from 60 to 68%. If these findings are extrapolated to our patient population, however, the increase in improvement would still be insufficient to close the gap between EBRT and BT (20). Additionally, the higher EBRT dose came at the cost of a doubling in the incidence of both rectal bleeding and fecal incontinence, though not more serious toxicity. It therefore seems that, to match the excellent results being obtained with BT, doses of radiation higher than 78 Gy would need to be combined with more sophisticated administration techniques to achieve the results we saw for BT. Indeed, results of IMRT done with daily fiducial imaging, such as the results from Memorial Sloan Kettering (21), or of EBRT in combination with a - proton therapy boost (22) have shown that EBRT results can approach BT results, albeit at a much increased financial cost (23).

The toxicity analysis showed significantly worse late urinary toxicity rates in association with BT but worse bowel toxicity rates in association with EBRT. Our findings were in agreement with earlier results of analyses of toxicity in our patient population undergoing BT (12, 24–26) and EBRT (27, 28). Toxicity was not a primary endpoint of this study, however, mainly because patients were not matched for potential predictors of toxicity and also because the numbers of patients were too small to allow for meaningful conclusions. We chose to analyze toxicity as a prevalence rate, as suggested by Peters *et al.* (29), rather than analyzing it using the actuarial method. This is because late toxicity often abates; therefore, it seemed incorrect to score late toxicity as a permanent event.

This study is limited by its nonrandomized design. Thus, there are potential biases in the data that have not been overcome by the stringent matching process. For example, although the BT selection criteria did not change during this study, we were funded to treat only 50 patients in the first year and 100 in the second year of our program before further expansion could occur. We therefore do not know how many patients treated with EBRT were actually suitable candidates for BT and either were not offered it or declined it. In addition, the use of ADT was specified by the protocol in the BT group, but was discretionary in EBRT patients, some of whom were receiving ADT before referral and some of whom were given ADT to reduce prostate size or for unknown reasons. A further limitation of our study was that we were able to match only a minority of the potentially eligible patients on a 1:1 basis. However, *post-hoc* analyses showed that the results for the entire patient group of 601

men were similar to those of the matched group. Further, given that we matched patients according to the main prognostic factors, any expected difference in outcome, such as in the bNED between BT and EBRT patients, would be less, in general, than if we had analyzed cases not so rigorously matched. Clearly, as expected, matching reduced the difference in the bNED outcome by reducing potential bias caused by nonmatching.

These limitations aside, this analysis compared contemporaneously treated patients seen at a single institution, and the results therefore reflect our real experience. Now that we have amassed experience in more than 2,500 BT cases over the past decade and analyzed the outcomes in the first consecutive 1,006 patients (14), and have also conducted several analyses of toxicity (12, 24–26), we are confident that BT provides superior cancer control in men with a low and selected intermediate risk of treatment failure.

It could be argued that striving for high cure rates in all patients is unnecessary, given that most patients with prostate cancer die of other causes, and there is no good evidence that intervention significantly enhances overall survival in those with low- and low- to intermediate-risk prostate cancer. In the case of higher-risk cancers (30), it is reasonable to suppose that younger men with such disease are more likely to develop clinically significant progression and possibly die of their prostate cancer than the elderly because of their increased life expectancy, and thus should be considered for BT. Indeed, our EBRT patients were an average 7 years older than BT patients, although the youngest in both groups had life expectancies of several decades. A further consideration that favors BT use is that the secondary use of ADT, though it protects against many EBRT failures, is associated with a detriment in quality of life; this may outweigh the shorter-term radiation toxicity that accompanies BT. In clinical practice, these issues are considered by physicians and patients in the appropriate selection of treatment.

CONCLUSION

Prostate BT provides superior PSA control over EBRT in patients with low-risk and selected intermediate-risk prostate cancers. Until the results of randomized studies comparing BT with either EBRT or surgery are available within the next decade, nonrandomized comparative studies can provide the yardstick by which patients and physicians can make informed decisions about which treatment is likely to best suit them. For many, that will be prostate BT.

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