Clinical and biochemical outcome of conventional dose radiotherapy for localized prostate cancer

Charles Catton, MD,[1] Mary Gospodarowicz, MD,[1] Jimmy Mui, MD,[1] Tony Panzarella, MD,[2] Michael Milosevic, MD,[1] Michael McLean, MD,[1] Pamela Catton, MD,[1] Padraig Warde, MD[1]

[1]Dept of Radiation Oncology, The Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada
[2]Dept of Biostatistics, The Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada

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Purpose: *To retrospectively review the results of conventional dose radical radiotherapy for clinical stage T1 and T2 prostate cancer, and to identify the factors that predict the biochemical relapse-free rate.*

Methods: *The records were reviewed of 706 hormonally-naïve men with clinical stage T1T2 prostate cancer treated with radical radiotherapy (RT) between 1987-1994 at the Princess Margaret Hospital.*

The median prostate RT dose was 65 Gy in 35 fraction (range 52 Gy in 20 fractions to 67 Gy in 37 fractions). Pelvic lymph nodes were included in the treatment volume and treated to a median dose of 45 Gy in 25 fractions for 283 cases (40%).

The primary end-point was biochemical relapse-free survival from RT using the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus criteria.

Favourable, intermediate and unfavourable pre- treatment prognostic groupings were derived from the initial PSA, T-category, and Gleason score using Cox regression analysis.

Secondary end-points included survival, metastases-free survival and clinical local control.

Results: *The overall biochemical relapse-free rate at 2 and 5 years was 63% and 45% respectively. Overall survival at 5 years was 87%, and metastases-free survival was 86%. Local control by DRE was 72% at 5 years. Multivariate analysis of variables associated with time to biochemical failure after RT showed that pre-RT PSA, T-category and Gleason score were significant independent predictors with hazard ratios of 1.33 ($P = 0.0001$), 1.22 ($P = 0.01$) and 1.33 ($P = 0.029$) respectively.*

PSA nadir was an early indicator of biochemical failure. The biochemical failure rate at 3 years was 20% for a PSA nadir $\leq$ 0.5 ng/ml and 85% for a PSA nadir $\geq$ 2.0 ng/ml ($P < 0.0001$).

Conclusion: *The results of conventional dose RT were unsatisfactory for all risk categories, and overall, less than half of the treated patients remained in biochemical remission at 5 years. These men require more aggressive therapy, that may include dose escalation with conformal techniques, and neoadjuvant/adjuvant androgen deprivation therapy.*

These results highlight the need to support new and on-going clinical trials for management of localized disease.

Key Words: prostate cancer, conventional radiotherapy, outcome

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Address correspondence to Dr. Charles Catton, Dept of Radiation Oncology, The Princess Margaret Hospital, 610 University Avenue, Toronto, ON M5G 2M9 Canada
Tel: (416) 946-2121 Fax: (416) 946-2111

Introduction

Radical external beam radiotherapy of 70 Gy or less in 1.8 Gy- 2.0 Gy fractions (conventional RT) to the prostate with or without pelvic nodal irradiation has a long history in the treatment of clinically localized prostate cancer.[1-3] The early studies that reported the benefit of conventional RT for localized disease predated routine prostate specific antigen (PSA) screening, and the

patients treated in these studies were often selected for RT because of bulky tumors, or because they were not deemed medically fit for surgery. Despite the tendency towards preferential selection and treatment of patients with adverse factors, retrospective studies with 15 years or more follow-up reported survival rates equal to those of age-matched cohorts of the normal population[1,3] following conventional RT for localized disease. However, these reports also show that 30%-40% of treated patients died from prostate cancer.

Evaluating the contribution of RT towards patients' longevity from these reports is confounded by other factors such as advanced age, the use of androgen ablation therapy (AAT), the long natural history of prostate cancer, and the lack of details concerning the pattern of recurrence and late events following treatment. There are few randomized trials addressing the issues in organ-confined disease and a too short median follow-up in these trials to provide long-term survival comparisons.

The introduction of routine serum prostate-specific antigen (PSA) testing in the past decade has significantly altered the way in which prostate cancer is diagnosed, treated, and response to treatment is measured.

PSA screening identifies men with prostate cancer much earlier than before. Patients have smaller tumors, and a larger proportion have organ-confined disease. They are less likely to have treatment constraints imposed upon them by coexistent illnesses or disease extent, and the treatment options are wider for those who choose to undergo curative therapy.

The pre-treatment PSA level has become a useful surrogate for disease extent and is an independent factor for predicting the biochemical relapse-free rate after brachytherapy and external beam radiotherapy.[4-6] A rising post-treatment PSA indicates the presence of prostate cancer, is an indication of failure of RT to eradicate the disease, and is a surrogate end-point that predicts for future clinical local and metastatic failure. It may pre-date the clinical failure by 3 or more years.[5,6] Guidelines for the appropriate use of PSA as an end-point after RT have been established by the ASTRO Consensus Committee to promote consistency and comparability in end-point reporting.[7]

Co-incident with the introduction of PSA testing, technical improvements in external beam radiation planning and delivery have been introduced resulting in reduced toxicity of RT for prostate cancer,[8] and allowing 15%-25% higher RT doses to be delivered without an increase in acute and late toxicity.[9] The initial phase II dose escalation trials have shown improved biochemical control rates compared to historical data. The benefit of RT dose escalation was observed mainly for men with one or more intermediate prognostic factors such as T2 tumor, Gleason 7 disease and pre-treatment PSA > 10 ng/ml.[10-12]

The preliminary results of the only completed randomized trial of conventional versus escalated dose RT for localized and locally advanced prostate cancer showed a significant improvement in biochemical control for the intermediate risk subgroup, and support the findings of the earlier phase II trials.[13] The 70 Gy control arm of this study falls in the upper range of conventional radiation doses, and the results of this and other ongoing dose escalation trials may not be readily generalizable to centres that traditionally used even lower radiation doses to treat localized prostate cancer.

Outcome analyses of large cohorts of men treated with conventional RT dose/fractionation schemes for localized prostate cancer continue to provide useful baseline comparisons for the standard arm of the randomized RT dose escalation trials. They also provide useful insights into the optimal patient selection for escalated dose therapy, and provide the data necessary for planning future clinical trials.

Doses in the range of 65 Gy-70 Gy administered with four fields as described in this report remains standard practice in many North American centres. This report provides the outcome and an analysis of the prognostic factors for a large contempory cohort of men treated for localized prostate cancer at a single centre with conventional RT, in the era since the introduction of PSA as a standard means of following patients after RT.

Methods

Seven hundred ninety three men were treated with external beam RT at the Princess Margaret Hospital (PMH) between 1987 and 1994 for clinically localized adenocarcinoma of the prostate (T1T2, NXN0, M0). Patients who received pre-RT hormone therapy (84) or palliative local RT (3) were excluded, leaving 706 who are the subjects of this study.

Diagnosis and staging

Diagnosis was made on transrectal needle biopsy in 581 cases, and on transuretral resection of prostate (TURP) in 121 cases. In four cases the method of obtaining tissue was not recorded. A further 31 cases had a TURP following the needle biopsy and before RT for treatment of obstructive symptoms.

Pathology was reviewed at PMH in 551 cases. Staging investigations included a technesium bone scan

in 678 (96%), a CT scan of the abdomen and/or pelvis in 664 (87%), a bipedal lymphogram in 210 (30%). Lymph node biopsy or sampling was obtained in 126(18%). All patients had a digital rectal examination (DRE) recorded prior to therapy, and according to the practice of the time, 290 (41%) underwent cystoscopy and examination under anaesthesia. The T category was recorded prospectively according to the 1987 UICC classification.[14] Patient entry into this study pre-dated the use of PSA screening, and only 30% of cases were identified this way, although 606 men (86%) had a serum PSA recorded prior to treatment.

Treatment of primary disease

All patients were treated with radical external beam radiotherapy. Treatment was planned with CT scan in 535 (76%) cases, or else with orthogonal simulator films and contrast in the bladder and rectum. A four-field box technique was used in 644 cases (91%), and in 62 cases a three-field oblique technique was used.

All patients were treated 5 days a week on high-energy linear accelerators. Radiation doses were prescribed to the isocentre.

The pelvic lymph nodes were included in the initial phase of treatment in 281 cases (40%), and were treated to 45 Gy in 25 fractions (163 cases) or 46 Gy in 23 fractions (117 cases). One patient was treated to the pelvic lymph nodes with a dose of 35 Gy in 14 fractions. The prostate RT dose was 65 Gy in 35 fractions in 472 cases, and 62 Gy in 30 fractions in 204 cases. Thirty patients received other doses, listed in reducing frequency: 60 Gy in 30 fractions (8); 66 Gy in 33 fractions (5); 65 Gy in 33 fractions (4); 67 Gy in 36 fractions (2); 52 Gy in 20 fractions (2); 59 Gy in 32 fractions (1); 61 Gy in 33 fractions (1); 62 Gy in 31 fractions (1); 64 Gy in 32 fractions (1); 65 Gy in 30 fractions (1); 65 Gy in 37 fractions (1); 66 Gy in 35 fractions (1); 67 Gy in 35 fractions (1); 68 Gy in 33 fractions (1).

Follow-up

Normal follow-up practice included a DRE and serum PSA two or more times a year for the first 5 years following RT, and once a year or more thereafter. Bone scans and other imaging modalities were employed only when dictated by suspicion of relapse.

Treatment of relapse

Androgen ablation therapy was given to 158 patients for treatment of recurrent and progressive disease following RT. This included 51 patients with biochemical failure alone, 68 with biochemical and local failure, and 39 with biochemical and distant failure, defined as the development of a positive bone scan.

Statistical considerations

The sample size used for the analysis was based on the available number of subjects who met the study's inclusion criteria within the calendar years under investigation.

The primary endpoint was time to biochemical relapse from the start of radiation therapy (RT). The definition of biochemical relapse was that described by the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel of guidelines for PSA testing following RT.[7] These guidelines define biochemical failure as the occurrence of three consecutive rises in PSA following RT, with the date of failure being the mid-point between the PSA nadir and the first of these rises. Patients who were given hormone therapy after RT for biochemical failure, with less than three consecutive rises in the PSA were classified as biochemical failures at the midpoint between the initiation of RT and the start of hormone therapy. Patients who died before experiencing a biochemical failure were censored at the time of death. Patients alive at last follow-up and free of biochemical relapse were censored at their last follow-up. Patients with stable or falling PSA post RT were censored at the time of last follow-up. Patients with one or two consecutive rises in PSA after a nadir were censored at the mid-point between the nadir and the first rise, as recommended by Lu.[15]

Secondary endpoints included overall survival, clinical local control determined by DRE, metastatic failure determined from a bone scan, though the follow-up practice did not include routine bone scans, and PSA nadir defined as the lowest recorded PSA following RT, and before any biochemical or clinical failure. Each secondary endpoint was calculated from the initiation of RT.

The prognostic groupings were developed by randomly splitting the data in half and using one half to develop the model and the other half to test its ability to discriminate different prognostic groupings. Data splitting avoids the over-optimistic results reported when the same sample is used to develop and test the model.[16] The model was established using Cox proportional hazards regression. The following clinically established explanatory variables were included in the model: pre RT PSA ($\leq$ 4 ng/ml versus 4.1 to 10 ng/ml versus 10.1-20.0 ng/ml versus > 20 ng/ml), Gleason score (< 7 versus 7 versus > 7) and UICC Tumor category (T1 versus T2a versus T2b versus T2c). Variable categorizations were based on commonly used definitions for these variables. The results of the Cox model analysis were summarized by hazard ratios and corresponding 95% confidence

intervals. The assumptions involved with the Cox model (linearity, proportional hazards) were checked and were found not to be in violation.

A prognostic index score was calculated for each combination of variable values using the developed model. A low, intermediate, and a high-risk prognostic group of patients, with approximately equal numbers in each group was defined by ranking scores from lowest to highest. Cut off points at the 33rd percentile and the 66th percentile were used to divide the patients into three prognostic groupings.

The Kaplan-Meier (K-M) method was used to display the association between time to biochemical relapse and each of the variables entered in the Cox model, the resultant prognostic groupings, and PSA nadir. Given the ordinal nature of these variables, the log rank test for trend[17] was used to test these associations. Given that death without a prior biochemical recurrence is a competing risk for each patient the K-M method overestimates the biochemical relapse rate, and in this context the cumulative incidence plot is a preferred alternative to summarize the probability of failure.[18] However, because there were only minor differences in the results of these two approaches, we included only a presentation of the former, to allow comparisons with other series, which quoted K-M estimates. Predicted biochemical relapse-free rate (bNED) curves based on the Cox model were superimposed with the observed K-M bNED rate curves for each prognostic group to provide a sense of the reliability of the model.

All reported P-values were two-tailed. The figures were produced using S-Plus. All statistical analyses were performed in SAS.

Results

The clinical features of the 706 patients at presentation are shown in Table 1.

The median age at presentation was 69 years (range 48-86 years). T-category at presentation was T1 for 22.9% (162) of the patients, and T2 for 77.1% (544) of the patients. Fifty-three percent (377) of the patients presented with a Gleason score of 6 or less, 31% (217) of the patients presented with a Gleason score of 7 and 11% (81) of the patients presented with a Gleason score of ≥ 8. The Gleason score was not recorded for 4% (31) of the patients. The baseline PSA was > 10.1 ng/ml for 48% (337) of the patients (10.1-20 ng/ml for 26% of the patients and > 20 ng/ml for another 22%). It was ≤ 10.0 ng/ml for 38%(269) of the patients, and was not recorded for 14%(100).

The median followup of 613 living cases was 4.3 years (range 0.1- 10.6 years) at the time of analysis.

TABLE 1. **Clinical characteristics of 706 men treated with radical radiotherapy for clinical stage T1 and T2 prostate cancer**

Median age		
69 years (range 48-86)		
Clinical T category (UICC, 1987)		
T1		162
	T1a	10
	T1b	58
	T1c	94
T2		544
	T2a	122
	T2b	200
	T2c	217
	T2x	5
Gleason score		
≤6		377
7		217
8-10		81
Not recorded		31
Pre-RT PSA (ng/ml)		
≤ 4.0		80
4.1-10		189
10.1-20		187
> 20		150
Not recorded		100

The clinical outcomes at 2 and 5 years respectively revealed overall survival 96% and 87%, metastases-free rate 97% and 86%, and clinical local control at DRE 93% and 72%.

A total of 308 patients experienced biochemical failure, and the overall biochemical relapse free rate (bNED) at 2 and 5 years is 63% and 45% respectively. The bNED by the presenting T-category, Gleason score, baseline (pre-RT) PSA, and post-RT PSA nadir are shown in Figures 1-4, and a statistically significant difference ($P < 0.0001$) was observed for each univariate comparison.

Multivariate analysis identified the pre-RT PSA, T-category and Gleason score as independent variables predicting for the time to biochemical relapse, and the hazard ratios and 95% confidence intervals are shown in Table 2. From these results, low, intermediate and high-risk groups for biochemical failure were identified. The bNED for each of these risk groups is shown in Figure 5, and the difference between them at 2 and 5 years is

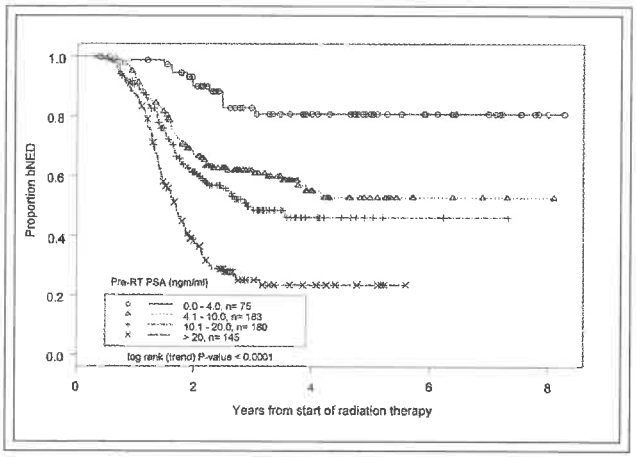

Figure 1. Effect of pre-RT PSA on time to biochemical relapse.

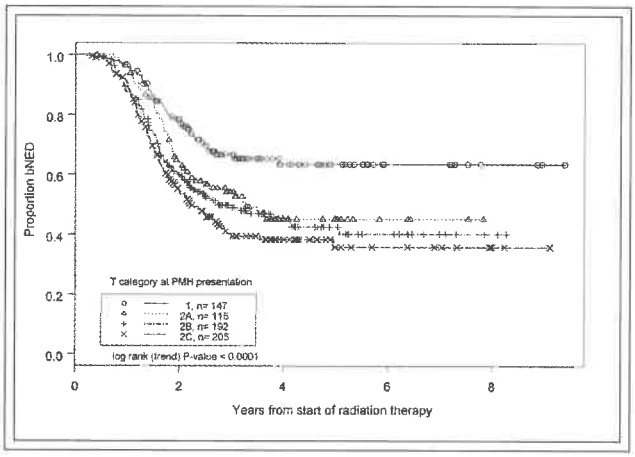

Figure 2. Effect of clinical T-category on time to biochemical relapse.

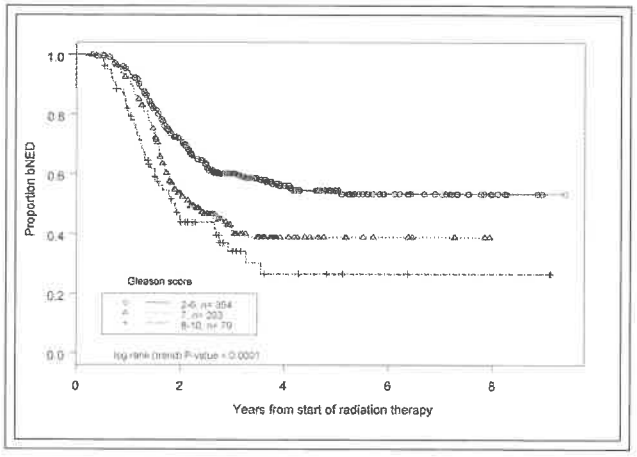

Figure 3. Effect of Gleason score on time to biochemical relapse.

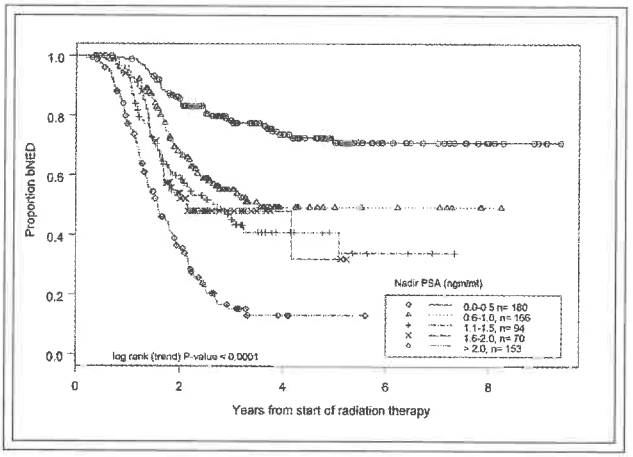

Figure 4. Effect of PSA nadir on time to biochemical relapse.

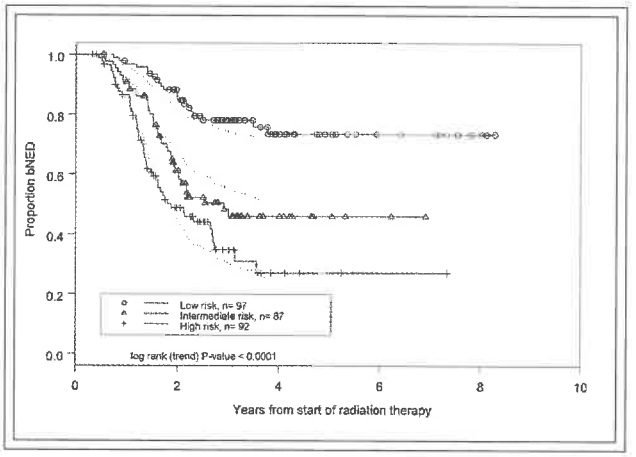

Figure 5. Biochemical relapse-free rates for low, intermediate and high-risk groups determined from the multivariate analysis. Dotted lines adjacent to the KM curves represent the predicted rates for the model based on cut-off points defined at the median, the 33rd and 66th percentile.

TABLE 2. **Multivariate (Cox) analysis of variables associated with time to biochemical failure after radical RT for localized prostate cancer. All variables were defined as being linearly increasing. PSA <4.1; 4.1-10; 10.1-20; >20. T-category T1; T2a; T2b; T2c. Gleason score <7;7;>7.**

Variable	Hazard ratio	95% CI	P-value
Pre-RT PSA	1.37	1.14-1.66	0.001
T-Category	1.22	1.05-1.41	0.01
Gleason score	1.33	1.03-1.77	0.029

statistically significant (P <0.0001). Each risk group is categorized in Table 3.

Discussion

The ASTRO consensus definition

A rising PSA after external beam RT for adenocarcinoma of the prostate is a useful surrogate endpoint that can predict both local and systemic failure.[19,20] The ASTRO consensus panel definition[7] of biochemical failure is recommended to standardize the reporting of biochemical failure in prostate cancer treated with RT, although it does slightly underestimate the failure rate when the follow-up is short.[21] A potentially more serious source of error was recently described[15] that arises when the ASTRO consensus definition is used to perform actuarial estimations of relapse. According to the ASTRO definition, relapses are back-dated to the point half way between the nadir and the first PSA rise, after three consecutive PSA rises have been identified. Kaplan-Meier estimations of relapse rates censor unrelapsed patients at the time of the last observation. If the median follow-up for a cohort is relatively short, it may contain a significant proportion of patients with one or two PSA rises that are "impending failures", and censoring these patients at the last observation may result in a substantial underestimation of the true actuarial biochemical relapse rate. Lu recommends that unrelapsed patients with a rising PSA be censored halfway between the nadir and the first PSA rise to minimize the effect of impending failure on the calculation of the actuarial relapse rate. This strategy was employed to estimate biochemical relapse rates in the current report.

PSA nadir

The post-RT PSA nadir is an early indicator of response to RT. Figure 4 shows that patients who achieved a nadir $\leq$ 0.5 ng/ml had a 5-year bNED rate of 71% compared to 49% for those with a nadir of 0.6-1.0 ng/ml, and 13% for those with a nadir of >2.0 ng/ml (P<0.0001). This may only reflect an early separation of those with a rapidly rising PSA from those with a slowly rising PSA, but Hanlon et al[22] have shown with long term follow-up that the 5-year bNED rate approximates the eventual cure rate for prostate cancer treated with RT.

Our results are similar to those reported by Shipley et al,[23] with 5-year bNED rates of 83%, 68% and 28% for PSA nadirs of $\leq$ 0.5 ng/ml, 0.6-0.9 ng/ml and $\geq$ 2.0 ng/ml respectively, and support the contention of Critz et al[24] that a PSA nadir of < 0.2 ng/ml predicts for a high likelihood of eventual biochemical control after radical RT for localized prostate cancer.

TABLE 3. **Prognostic groupings developed by randomly splitting the data in half and using one half to develop the model and the other half to test its ability to discriminate different prognostic groupings. A prognostic index score was calculated for each combination of variable values using the developed model. Low, intermediate, and high-risk prognostic group of patients, were defined by ranking these scores from lowest to highest. Cut off points at the 33rd percentile and the 66th percentile were used to divide the patients into three approximately equal sized prognostic groupings. The bNED for each grouping is shown in Figure 5.**

Favourable prognosis (n=97)		
PSA (ng/ml)	T-category (UICC 1987)	Gleason score
0-4	1 or 2A or 2B	2-6 or 7
0-4	2C	2-6
4.1-10	1	2-6 or 7
4.1-10	2A or 2B	2-6
Intermediate prognosis (n=87)		
PSA (ng/ml)	T-category (UICC 1987)	Gleason score
0-4	2B or 2C	8-10
4.1-10	1	8-10
4.1-10	2A	7 or 8-10
4.1-10	2B	7
4.1-10	2C	2-6 or 7
10.1-20	1	7 or 8-10
10.1-20	2A	2-6 or 7
10.1-20	2B	2-6
> 20	1 or 2A	2-6
Unfavourable prognosis (n=92)		
PSA (ng/ml)	T-category (UICC 1987)	Gleason score
4.1-10	2B or 2C	8-10
10.1-20	2A	8-10
10.1-20	2B	7 or 8-10
10.1-20	2C	any
> 20	1 or 2A	7 or 8-10
> 20	2B or 2C	any

Overall survival, distant and local control, and bNED

The 5-year metastases-free rate was 86%. Overall 5-year survival was 87%, and very similar to our earlier reported 5-year survival rates of 88% and 83% for patients with T1 and T2 disease treated with radical

RT,[2] and to the 85% reported from a large pooled series of men treated with radical RT for organ confined prostate cancer.[23]

These results are not unusual for a relatively short median follow-up, and the early introduction of AAT for biochemical rather than clinical relapse, and do not indicate cure.

The clinical primary tumor control at 5 years was 72%. This is closer to the 65% local control reported by Crook et al[25] for T1 and T2 tumors assessed by post-RT biopsy, than to our earlier experience of 86%-92% clinical local control for organ confined disease.[2] Similar RT treatment techniques were used in both series, and the differences in clinical outcome may reflect an increased sensitivity in later years for recording adverse changes.

The overall bNED rate was 45% at 5 years, and is comparable to the 50% 5-year bNED rate reported by Pollack et al[11] for all T1-4 tumors treated with conventional dose RT, but less than the 66% 5-year bNED rate reported in the Shipley et al pooled analysis of T1 and T2 tumors.[23]

The current series contains 42% of patients with Gleason score 7-10 disease compared to 26% for Shipley et al, which may account for the differences in the outcomes.

Univariate and multivariate outcome analysis, and prognostic subgroups

The univariate analysis presented in Figures 1-4 showed significant differences in the time to biochemical failure for men presenting with T1 versus T2 disease, a Gleason score of ≤ 6 versus 7 versus 8-10, and a pre-RT PSA level of ≤4.0 versus 4.1-20.0 versus >20.0, that agrees with the findings of others.[10-12,23,26]

The multivariate analysis shown in Table 2 also yielded the three prognostic groups shown in Figure 5 and categorized in Table 3.

The 5-year bNED rate for the favourable group is 73% and consists of patients with two or more favorable factors of PSA ≤ 10.0 ng/ml, T1 or T2a tumor, or Gleason score ≤ 6, and no unfavorable factors.

The 5-year bNED rate for the intermediate group is 46% and consists of patients presenting with one unfavorable factor of Gleason score 8-10, T2c tumor, or PSA > 20.0 ng/ml; or two intermediate factors of Gleason score 7, or T2b tumor or PSA 10.1-20.0 ng/ml. This category also included patients with two unfavorable factors and a very low PSA (≤ 4.0 ng/ml).

The 5-year bNED rate for the unfavorable group is 27%, and consists of patients presenting with two or more unfavorable factors, or with one unfavorable and one intermediate factor, or with three intermediate factors.

Zelefsky et al[12] also identified three prognostic categories for organ confined prostate cancer treated with conventional and dose-escalated RT. Favorable factors were PSA ≤ 10.0 ng/ml, Gleason ≤ 6 and stage T1, and the intermediate and unfavourable risk patients had one or two unfavorable characteristics respectively. The 3-year bNED rate for each risk group was 80%, 60% and 40% for patients treated with <70.2 Gy. D'Amico et al[27] reported 3-year bNED rates of 95%, 80% and 40% respectively for low, medium and high risk patients treated with radiotherapy for organ confined prostate cancer.

It is interesting to observe that for our patients the 1987 UICC classification[28] of T2-category into a, b and c sub-categories discriminated between low, intermediate and high risks for biochemical relapse when adjusted for the Gleason score and pre treatment PSA. D'Amico et al[26] made the same observations using the very similar 1992 AJCC classification.[29] The more recent UICC classification[28] collapses the T2a and T2b categories into T2a, and it is likely that useful prognostic information has been lost as a result.

Clinical significance of results

Despite the clear stratification of our patients into favourable, intermediate and unfavourable prognosis categories the results of conventional RT for each category were disappointing.

Both the 70 Gy and 78 Gy arms of the randomized trial of external beam dose escalation trial reported a 5-year bNED rate of 80% for patients with a pre-RT PSA of <10 ng/ml compared to 55% 5-year bNED rate for our patients with a PSA <10 ng/ml, and 73% 5-year bNED rate for our favourable prognosis category as a whole.[13]

Zelefsky et al and Hanks et al have reported 4-year bNED rates of 73%- 80% for intermediate prognosis categories treated with 75 Gy or more. This compares to our bNED rate at 4 years of 46% for the intermediate prognosis category or for all patients with a pre-RT PSA 10.1-20 ng/ml.[10,12]

Our conventional dose RT 4-year actuarial results show that 54% of intermediate category patients and 27% of favourable category patients experience biochemical failure.

Non-randomized comparisons of conventional and escalated dose RT must be made with caution, as there is a high risk of unrecognized bias being present. However it is clear that more effective treatment is required for these men.

Considering our results, and the compelling phase

II and early phase III evidence that shows low morbidity and possibly improved biochemical control with dose escalation, we recommend that men with low and intermediate risk factors who receive external beam RT alone receive a minimum dose of 70 Gy. Randomized trials remain necessary to determine the dose and fractionation schedule for optimal local control.

Unfavourable category patients

In patients with unfavourable prognostic categories dose escalation is less beneficial than with other patients, presumably because they are more likely to harbor micrometastatic disease. Zelefsky et al[12] reported a 3-year bNED rate of 60% for unfavourable prognosis patients treated with ≥75.6 Gy, and Hanks et al[10] reported a 2-year bNED rate of 30% for patients with a pre-RT PSA > 20.0 ng/ml treated with ≥ 75.75 Gy.

Our unfavourable category patients had bNED rates of 49% and 27% at 2 and 5 years. Considering only the pre-RT PSA level , those men >20 ng/ml had a 3-year bNED rate of 25%.

Androgen deprivation therapy (ADT) may be used as an adjunct to improve local control[30] and/or as an adjuvant systemic therapy to reduce the risk of failure from occult metastatic disease[10] in conjunction with conventional and escalated dose RT.[31]

Bolla et al[32] in a randomized trial of adjuvant hormone therapy following RT showed improvement in local control, disease free survival and overall survival of nearly 20% at 5 years after conventional dose radiotherapy for men with T3-4, or Gleason > 7 tumors who received 3 years of ADT. In a three-arm randomized trial for men with localized prostate cancer, Laverdiere et al[33] reported a 2-year positive biopsy rate of 65% after conventional RT alone compared to 28% when 3 months of ADT preceded radiotherapy, and 5% when the ADT was continued for a total of 10.5 months as total androgen blockade. Ludgate et al[34] showed in a large retrospective series that 8 months of neoadjuvant ADT improved bNED for men with Gleason scores > 4 treated with conventional radiotherapy.

Ongoing and future randomized trials of adjuvant and neoadjuvant ADT are needed to determine the optimal timing and duration of ADT as an adjuvant systemic therapy, and to determine whether ADT may complement conventional and/or escalated dose RT to improve the local control of localized prostate cancer.

Men with adverse prognostic factors treated with conventional or escalated dose radiotherapy should be encouraged to participate in neoadjuvant or adjuvant therapy trials, although they may also still benefit from dose escalation. The role of dose escalation for patients treated with combined modality therapy is not known.

Conclusion

These results confirm the value of careful and prolonged follow-up of patients treated in a standardized manner.

Men treated with conventional dose radical external beam RT for localized prostate cancer were stratified into low, intermediate or high risk groups for biochemical relapse from the pre-RT PSA, Gleason score and 1987 UICC clinical T-category.

The overall results of conventional dose RT were unsatisfactory, and less than half of patients treated remained in biochemical remission at 5 years. The proven value of conformal therapy in reducing late rectal toxicity has made it the standard treatment technique for external beam RT of prostate cancer. The improved results for low and intermediate risk patients with external beam dose escalation support the view that a radiation dose of <70 Gy is inadequate treatment for most men treated with curative intent.

The proper role of ADT in conjunction with external beam RT remains to be defined, although there is evidence that it may improve local control for patients treated with conventional dose RT, and also improve survival for high risk patients.

Questions about the optimal patient selection for dose escalation, the radiation dose and treatment technique employed, and the role of ADT in conjunction with RT for men in all risk categories with localized disease high-light the continuing need to implement and support new and ongoing clinical trials. □

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