RADIATION ONCOLOGY—ORIGINAL ARTICLE

Long-term outcomes in 1121 Australian prostate cancer patients treated with definitive radiotherapy

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Conflict of interest: The authors have declared no conflicts of interest.

Submitted 28 February 2018; accepted 7 August 2018.

doi:10.1111/1754-9485.12797

Abstract

Introduction: Optimal definitive treatment of prostate cancer is controversial, especially in high-risk patients. We report the largest prospective cohort of Australian patients treated with radiotherapy for localised prostate cancer.
Methods: One thousand, one hundred and twenty-one patients with prostate cancer were prospectively registered and treated to a dose of 70–74 Gy. Patients were classified as low, intermediate or high risk based on PSA, clinical staging and Gleason score. Intermediate-risk patients were treated with 0–6 months of hormonal therapy (ADT) and high-risk patients were offered neoadjuvant and adjuvant ADT. Overall survival (OS) and biochemical relapse-free survival (bNED) were calculated using the Kaplan–Meier method.
Results: Median follow-up was 92 months. Eight-year OS and bNED were 78.4% and 68.1% respectively in the entire cohort. OS for the low, intermediate and high-risk groups was 84.5%, 78.4% and 68% respectively. For these risk groups, bNED was 80.3%, 65.7% and 53.7% respectively. In the intermediate and high-risk group, OS and bNED decreased with increasing number of risk factors.
Conclusion: Definitive radiotherapy is an effective treatment for prostate cancer, including in high-risk cases.

Key words: prostate cancer; radiotherapy.

Introduction

Treatment of prostate cancer with definitive radiotherapy has long been an established curative treatment option. In 2003, our group published the results of 480 patients treated between 1993 and 1997 with definitive radiotherapy to a dose of 66 Gy.[1] The 5-year actuarial PSA-recurrence free survival (RFS) was 53% for the whole patient group with rates of 32%, 56% and 75% for high, intermediate and low-risk groups respectively. The dose used in this study was low compared to today's standards, as advances in technology have allowed higher doses to be delivered with acceptable levels of toxicity and improved prostate cancer-specific outcomes.

In August 1999, the radiation oncology departments at Westmead and Liverpool Hospitals, Australia, based on the emerging data, escalated the dose to 70 Gy for all prostate cancer patients using conformal radiotherapy techniques. By late 2002, both centres further escalated their doses to 74 Gy for intermediate and high-risk patients using a 6-field conformal technique as described by Pollack *et al.*[2] Later, the units at Nepean and Campbelltown hospitals, which are linked to Westmead and Liverpool Hospital networks respectively, treated their

patients in an identical manner and were registered on the same databases as the 'home' sites.

This paper reports the 8-year outcomes of this prospectively treated cohort of patients from these four cooperating centres.

Methods

One thousand, one hundred and twenty-one men with histologically confirmed non-metastatic prostate cancer were treated with definitive radiotherapy to a dose of 70–74 Gy at Liverpool, Campbelltown, Westmead and Nepean Hospitals between August 1999 and December 2006.

Bone scans were carried out on all patients with Prostate Specific Antigen (PSA) ≥ 20 ng/mL. Patients with PSA < 20 ng/mL may have also had a bone scan at the discretion of the treating physician. Diagnostic CT scans were used for staging at the discretion of the treating physician.

Staging was based on the sixth edition of the American Joint Committee on Cancer (AJCC) classification system.[3] Patients were classified into the following risk categories based on the NCCN risk groups which take into account the last PSA pre-radiotherapy or neoadjuvant hormone therapy, clinical per rectum examination and Gleason score from biopsies[4]

1. Low risk: T1/2a and PSA < 10 and Gleason score ≤ 6.
2. Intermediate risk: T2b/c and/or PSA 10–20 and/or Gleason score 7.
3. High risk: T3/4 and/or PSA > 20 and/or Gleason score 8–10.

Treatment technique

Radiotherapy

Patients were treated in the supine position with a comfortably full bladder and empty rectum. Patients were treated using a 3D conformal technique with dose constraints as per the Faculty of Radiation Oncology Genito–Urinary Group (FROGG) consensus guidelines.[5] Rectal constraints of V65Gy < 40%/V70Gy<25% were used and the 50% isodose line was not permitted to encompass the posterior rectal wall. Bladder constraints of V50Gy < 50% and femoral V60Gy < 20% were used.

Low-risk disease patients had treatment to the prostate alone. All low-risk patients were recommended to receive 70 Gy in 35 fractions.

Intermediate-risk disease patients were treated using a two-phase technique. Phase one treated the prostate and seminal vesicles to 46 Gy in 23 fractions. Phase two boosted the prostate alone to a total dose of 70–74 Gy in 35–37 fractions. By late 2002, intermediate and high-risk patients were routinely treated to a total dose of 74 Gy.

Men with high-risk disease were treated to 70–74 Gy to the prostate and seminal vesicles, with 74 Gy being standard from late 2002.

Androgen deprivation therapy

Androgen deprivation therapy (ADT) was not commonly used in the low-risk disease group as per the evidence for lack of benefit. It was used on occasion for obstructive urinary symptoms or a bulky prostate making it difficult to meet dose volume histogram (DVH) constraints.

The use of ADT in the intermediate-risk group was individualised according to perceived risk of recurrence (for example, number of intermediate risk factors and degree of core involvement) as well as patient factors (e.g. age, comorbidities and sexual function). If ADT was given, neoadjuvant therapy was preferred and given as per the TROG 96.01 trial protocol.[6]

All high-risk patients were offered both neoadjuvant and adjuvant ADT for a total of 18–36 months according to tolerance as per the EORTC and RTOG trials.[7,8]

In the last 3 years of the study, intermediate-risk patients with T2c disease and all high-risk disease patients were eligible for the RADAR trial[9] randomising between 6 and 18 months of ADT as well as investigating the impact of zoledronic acid. Patients recruited to the RADAR trial were also included in this analysis as the radiotherapy technique parameters were consistent with the centres' standard technique.

Follow-up

Follow-up data including prostate cancer outcomes (PSA) were collected prospectively. Men were seen at 3- to 6-month intervals for the first 2 years following radiotherapy and then at 6- to 12-month intervals thereafter.

Statistical analysis

The primary outcome of the study was biochemical (PSA) disease-free survival and the secondary outcome was overall survival. Time to event outcomes was measured from the last day of completion of radiotherapy.

Biochemical failure was defined according to the Phoenix definition which defines biochemical failure when the level of the PSA has risen by 2 ng/litre above the nadir (defined as the lowest PSA value following irradiation) [13]. The date of biochemical failure was taken as the date of the first PSA reading above this level. Patients developing clinical signs of disease progression or started on ADT for 'relapse' were also recorded as having biochemical failure (irrespective of PSA readings).

Biochemical relapse-free survival (bNED) and overall survival were calculated using the Kaplan–Meier method. A sample size of more than 1000 patients was calculated to have a greater than 90% power with 95% confidence to an absolute increase in 5-year bNED of at least 7% (53% to 60%).

Results

One thousand, one hundred and twenty-one patients were treated between the first of August, 1999 and the end of December, 2006. The total numbers from each centre were: Westmead 387 patients (34.5%), Nepean 248 patients (22.1%), Liverpool 412 patients (36.8%) and Campbelltown 74 patients (6.6%). Median follow-up for the entire cohort was 92 months (0.5–163.8 months).

The median age of men was 69.6 years with a range from 45 to 87 years. Tumour characteristics including T stage, Gleason score, PSA and risk grouping is shown in Table 1. The majority of men had palpable disease (64%) or a Gleason score of 7 (50%). The median PSA (defined as the last PSA prior to radiotherapy or commencement of ADT) was 11.0 ng/ml with a range from 0.7 ng/ml to 253 ng/ml. The majority of patients were either classified as intermediate or high risk (86%).

Androgen deprivation therapy use according to risk group is shown in Table 2. Overall, 61.6% of patients received either neoadjuvant or adjuvant ADT with the higher risk groups more likely to receive hormones. Adjuvant ADT use was more common the higher the risk group.

Table 1. Baseline demographics for the patient cohort

	n	%
T stage†		
T1	398	35.5
T2	570	50.8
T3/T4	150	13.3
Gleason Score‡		
≤6	354	31.6
7	552	50.8
8–10	212	18.9
PSA§		
<10	484	43.2
10–20	389	34.7
20–50	206	18.4
>50	41	3.7
Risk stratification		
Low risk	157	14.0
Intermediate risk	545	48.1
High risk	419	37.4

†Three patients unable to have T stage assigned. ‡Three patients unable to have Gleason score assigned. §One patient pre-operative PSA unknown.

Table 2. Use of androgen deprivation therapy stratified by risk group

Risk group	Neoadjuvant hormonal therapy, *n* (%)	Adjuvant hormonal therapy, *n* (%)	Any hormonal therapy, *n* (%)
Low	13 (8.3)	0 (0)	13 (8.3)
Intermediate	271 (49.7)	37 (6.8)	274 (50.3)
High	398 (95)	319 (76)	403 (96.2)

The 8-year overall survival for the entire cohort was 75.7% with a median survival time of 157.1 months. Overall survival was significantly lower in the high-risk group compared to the low-risk group as shown in Figure 1 ($P < 0.01$). The 8-year biochemical relapse-free survival for the entire cohort was 64.8% with a median time to biochemical failure of 76 months. Biochemical relapse-free survival was lower in the high-risk group compared to the low-risk group and on breakdown of the intermediate and high-risk group by number of risk factors, a lower biochemical relapse-free survival was evident with an increasing number of risk factors. Within each risk group, the estimates of risk for patients with two factors present were consistently lower than those with only one factor although these differences were not statistically significant, suggesting that classification by risk group is a much stronger correlate of outcome than the number of factors present. The sample sizes in each of these groups however were modest; in 80, 26 with one factor and 36, 19 with two factors in the intermediate and high-risk groups respectively.

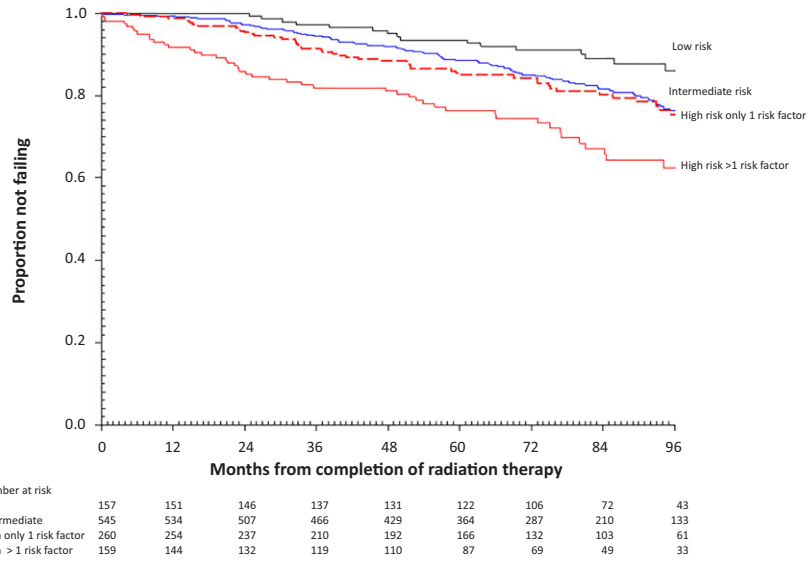
Biochemical relapse-free survival by risk group is shown in Figure 2, with the high-risk group separated into those with one risk factor and those with greater than one risk factor.

Discussion

To our knowledge, this is the largest prospective cohort of Australian prostate cancer patients treated with radiotherapy. Furthermore, the study has a long median follow-up time of 92 months. Our overall findings are consistent with that reported in the international literature.[10–14]

Comparing the current cohort treated to 70–74 Gy to our previously reported series of 480 patients treated to 66 Gy, the improvement in 5-year biochemical control (82% versus 53%) supports the use of dose escalation in prostate cancer treatment.[10–14] Other Australian series which have used higher doses have shown similar results at the 5-year mark. Choong *et al*.[15] reported on a cohort of 301 Australian patients treated with doses of 78 Gy with fiducial marker image-guided radiotherapy and found a 4-year freedom from biochemical failure rate of 88.8%.

An important difference to note between our two cohorts is the pattern of hormonal therapy use. In this study, 60.3% of patients received either neoadjuvant or adjuvant hormonal therapy, which is substantially more than the 18.3% of patients in the previous cohort receiving hormonal therapy, predominantly in the neoadjuvant setting. This reflects clinical practice changes since our initial study, in the light of the evidence from randomised trials[6–8] including pivotal Australian studies. These include the TROG 96.01 study, which investigated the impact of neoadjuvant ADT with radiotherapy to doses of 66 Gy. Neaodjuvant ADT improved biochemical free survival, and 6 months of ADT was found to be better than



Number at risk

Low	157	151	146	137	131	122	106	72	43
Intermediate	545	534	507	466	429	364	287	210	133
High only 1 risk factor	260	254	237	210	192	166	132	103	61
High > 1 risk factor	159	144	132	119	110	87	69	49	33

Fig. 1. Eight-year overall survival and biochemical relapse-free survival stratified by risk group and number of risk factors.

3 months. The recently reported results of the RADAR trial showed that adjuvant ADT improved prostate cancer-specific survival and time to PSA failure.[9]

The overall survival for our entire cohort was high, at 75.66%. There was a trend for lower overall survival with increasing risk group, with the difference significant between the low and high-risk group. The intermediate group showed higher overall survival than the low-risk group and lower overall survival than the high-risk group as expected, however the difference was not statistically significant. With biochemical relapse-free survival, there was a greater separation between risk groups especially for the high and low-risk groups which would indicate comparatively worse biochemical control with higher risk groups, as expected. On breakdown of biochemical control in the high-risk group based on the number of risk factors, those with only one risk factor versus more than one risk factor performed better as expected. Although this difference was not statistically significant, this trend in the high-risk group population would support the current move in further subdividing the original high-risk D'Amico classification group. More recently, a Very High Risk (VHR) subgroup has been defined which encompasses those cancers with multiple risk factors or Gleason pattern 5 or greater than 5 cores with Gleason score 8–10.[16] This subgroup, regardless of treatment modality, has poorer outcomes compared to the non-VHR high-risk group patients.

An interesting finding of our study is that high-risk patients with only one risk factor appear to have similar biochemical control as intermediate-risk patients. The main difference between the two would be the use of ADT, with the intermediate group more likely to receive neoadjuvant ADT alone, whereas the high-risk patients were more likely to have both neoadjuvant and adjuvant ADT.

Our long-term results of a cohort treated with older techniques combined with current improvements in radiotherapy delivery and doses support definitive radiotherapy as an effective treatment for prostate cancer. Interestingly, though the use of radiotherapy as primary treatment has decreased in recent years. Ruseckaite *et al.* analysed the Victorian and South Australian prostate cancer registries between 2009 and 2013 and found that the radiotherapy rates had decreased from 25.6% to 15.6%. At the same time, intermediate and high-risk disease rates had increased from 45.9% to 47.7% and 22.4% to 25.7% respectively.[17]

Within the literature, there is a lack of randomised data directly comparing the treatment options of radiotherapy and radical prostatectomy for prostate cancer. The only published randomised trial comparing these two modalities is the ProtecT trial by Hamdy *et al.*[18] In this trial, 1643 men were randomly assigned to either radiotherapy, prostatectomy or active monitoring. The majority of men had low to intermediate-risk disease.[19] At 10 years, prostate specific mortality was equal across all three groups. Both radiotherapy and prostatectomy resulted in lower rates of disease progression and metastasis than active monitoring, which is to be expected. Comparing radiotherapy to prostatectomy, there was a trend towards improved disease-specific survival in favour of radiotherapy and hormonal therapy; however, this was not statistically significant. Our overall survival results are lower than that achieved in the ProtecT radiotherapy arm; however, our cohort included a higher proportion of men with intermediate and high-risk disease (86%). It is these men who were more commonly present for definitive treatment of their prostate cancer.

In the high-risk setting, there has been no randomised trials comparing the two treatment modalities and thus results can only be compared across studies, which have

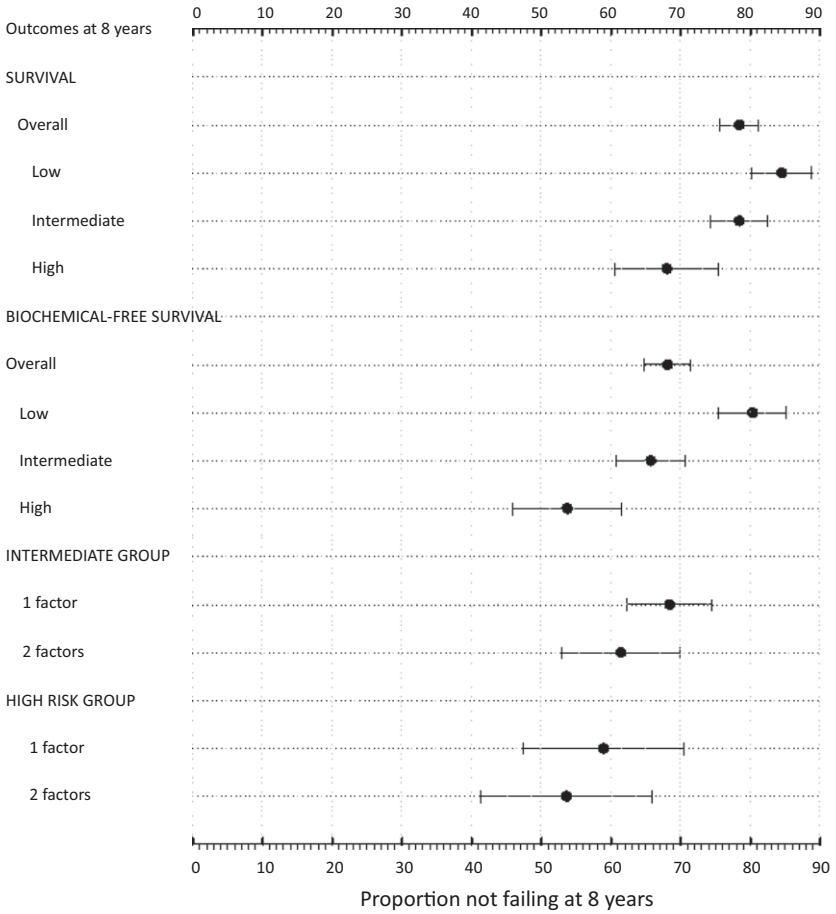


Fig. 2. Biochemical relapse-free survival according to risk group stratified by number of risk factors.

its limitations. Clinically, there has been a shift in the treatment of this patient group. Previously, definitive radiotherapy and hormonal therapy was considered the standard of care,[20] however radical prostatectomy is being increasingly recommended as a part of a multimodal approach with adjuvant or salvage ADT and/or radiotherapy.

The literature on the use of prostatectomy in high-risk prostate cancer patients with at least 10 years of follow-up date is described as follows. Walz *et al.* reported the outcomes of 757 men with high-risk prostate cancer and reported a 10-year biochemical free survival of 37.2% and 17.9% in men with one versus two risk factors respectively.[21] Donohue *et al.*[22] reported on 238 patients with Gleason 8–10 prostate cancer and found a 10-year biochemical free survival of 27%. Loeb *et al.*[23] reported the outcomes in men treated at John Hopkins Hospital with high-risk prostate cancer and found a 10-year biochemical free survival rate of 32%. Pierorazio *et al.*[24] reported long-term outcomes of 1061 patients treated with radical prostatectomy with Gleason scores of 8–10. They reported that 80% of the men experienced a biochemical recurrence by 15 years. Abdollah *et al.*[25] reported on 1100 high-risk prostate cancer patients treated with robotic prostatectomy and found 37% required salvage therapy at 10 years. Ward *et al.*[26] reported the outcome of 842 men with cT3 prostate cancer who underwent radical prostatectomy. They report a freedom from biochemical recurrence of 43% and 38% at 10 and 15 years respectively. These independently conducted studies show a fairly consistent rate of biochemical control with the use of primary prostatectomy of around 30–40% at 10 years.

Some argue that prostatectomy and adjuvant radiotherapy should be the standard of care as studies have shown an improvement in biochemical free survival with the use of adjuvant radiotherapy. Looking specifically at the high-risk population, Thompson *et al.*[27] reported on 425 men with pT3 disease and found that adjuvant radiotherapy led to a median PSA relapse-free survival of 10.3 years. Bolla *et al.*[28] reported a 10-year biochemical progression free survival of 61.8% in patients receiving post-prostatectomy radiotherapy. Swanson *et al.*[29] reported that the addition of post-operative radiotherapy in high-risk patients at 10 years was 52%.

In comparison, studies looking at the use of radiotherapy as the primary definitive treatment are summarised here. Kuban *et al.*[12] showed an 8-year biochemical free survival of 63% in those treated to 78 Gy. Of note, these patients did not receive ADT. Peeters *et al.*[30] reported a 7-year biochemical free survival of 56% with 78 Gy in 664 patients, of which 55% were high risk. Dearnaley *et al.*[31] reported 55% 10-year biochemical free survival in 843 patients, 43% of which were high risk. Narang *et al.* reported on 288 high prostate cancer patients, investigating the VHR subpopulation of this group. At 10 years, biochemical free survival was 37.3% for the very high-risk population versus 55.2% in the non-VHR high-risk patients.[32] Wilcox *et al.* reported on an Australian cohort of 782 with intermediate and high-risk prostate cancer treated with ADT and dose-escalated radiotherapy (71.3 Gy to 78 Gy). They reported a biochemical free survival of 88% at 5 years.[33]

The 8-year biochemical free survival of 53.7% in our cohort of 419 high-risk patients is comparable to these findings. This is in spite of a limitation of our study which would be the relatively low doses used comparative to current practices. At the time of the study, doses of 70–74 Gy were considered high. Interestingly, two Australian series have even reported at least in the early follow up, that there was no benefit in doses above 74 Gy.[34,35] More recently, with improvements in technology including the use of Intensity-Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), higher doses of radiation are able to be delivered resulting in improved prostate outcomes.[36] Thus, our results on the largest Australian cohort with long follow up, despite what may be considered as a lower dose in the current clinical landscape, contributes strong evidence for radiotherapy as primary treatment for prostate cancer.

Overall when radiotherapy results are compared to the surgical series, it appears to demonstrate a trend towards higher biochemical free survival. The results are not as marked when definitive radiotherapy is compared to a combined approach of prostatectomy plus post-prostatectomy radiotherapy. Disadvantages of this approach are the potential combined toxicities of two treatment modalities. Additionally, there are no standardised guidelines regarding the optimal timing of adjuvant radiotherapy, as demonstrated by Kishan *et al.* They reported the results of a survey of 1253 radiation oncologists and urologists, which included Australian respondents, and found statistically significant differences in their approach. Radiation oncologists preferred treatment in the adjuvant setting and salvage in lower PSAs, compared to urologists.[37] It is anticipated that the Australian led RAVES trial may help clarify this question.

As stated, comparing results across trials has its limitations. Multiple retrospective series have been carried out comparing the two modalities in this high-risk population with widely varying results.[38–43] Additionally, the impact of upstaging after surgery in the lower risk groups needs to be taken into account, raising the issue of stage migration.

In context of the evidence from the studies discussed above, if similar efficacy of either treatment modality was assumed, other factors may be more relevant in the decision-making. A recently published study by Dorth *et al.* examined the cost effectiveness of radiotherapy versus surgery for intermediate and high-risk prostate cancer. They reported a higher quality adjusted life expectancy and cost effectiveness for radiotherapy.[44] These results are in the American context however may also be applicable to Australian patients. A further interesting consideration is the concept of long-term decision regret, which was researched by Shakespeare *et al.*[45] Eighty-three percent of patients reported regret over their decision on surgery due to toxicity, and 33% reported regret of not being adequately informed about radiotherapy as an alternative. These are complex issues, which require detailed discussions with patients by all specialists.

Given this lack of randomised evidence, by directly comparing definitive radiotherapy ± hormonal therapy versus radical prostatectomy in high-risk prostate cancer, along with the results of the ProtecT trial, we would advocate that all prostate cancer patients have detailed discussions about both treatment options. This is timely given the current debate surrounding the optimal treatment for prostate cancer. The Australasian Faculty of Radiation Oncology has recently released a position statement regarding patient informed decision-making in this context.[46]

In conclusion, radiotherapy is an effective form of initial treatment for prostate cancer. This study reports on the outcomes of the largest prospectively recruited cohort of Australian prostate cancer patients treated with definitive radiotherapy provides further evidence to this. It is important that patients be aware of their treatment options.

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