Radiation therapy for high-risk prostate cancer – a review

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The term high-risk prostate cancer has been coined to encompass a group of patients with a poor prognosis (clinical stage T3/T4, or T1/T2 with PSA > 20 ng/ml or GS ≥ 8). It is estimated that 20% of patients in Canada present with high-risk disease, which translates into approximately 4000 new cases each year. The optimal management approach is unclear but the standard of care in North America for this group of patients is radiation therapy (RT) with prolonged adjuvant hormonal therapy. Current clinical trials are evaluating the role of local therapy, the value of RT dose escalation, the potential benefit of regional lymph node irradiation, the appropriate duration of adjuvant hormonal therapy, as well as the possible impact of adjunctive chemotherapy.

The high-risk group of patients contains a wide spectrum of disease, ranging from patients with aggressive localized disease to those with widespread occult distant metastases. The current challenge facing clinicians is appropriate treatment selection for individual patients. Information from novel biomarkers and improved imaging, as well as more effective local and adjunctive systemic therapies is necessary to improve outcomes for men with this aggressive disease.

Key Words: prostate cancer, radiation therapy, hormone therapy, review

Introduction

Prostate cancer is the commonest malignancy among men in Canada and is the third most common cause of cancer death.[1] In the modern era more than 90% of patients present with clinically localized disease and 15%-20% of these patients fall into the subset of high-risk disease. In the past, the term locally advanced prostate cancer referred to clinical stage T3-T4 disease, but within the past decade the term high-risk prostate cancer has been coined to encompass this group of patients as well as patients with T1/T2 disease with poor prognostic features (either a high prostate specific antigen or high Gleason score).[2,3]

High-risk prostate cancer is an aggressive disease with a poor prognosis and significant morbidity and mortality. In one study close to 50% of men with high risk tumors died of prostate cancer within 10 years of diagnosis, as compared with 6% and 0% of patients with intermediate and low risk disease respectively.[4]

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While there has been a significant decrease in the proportion of patients presenting with high-risk disease in the United States in the past 15 years (41% in 1991 to 15% in 2001), the absolute numbers of patients presenting with this risk category has largely remained unchanged.[5-7]

In Canada, where the rates of PSA screening are somewhat lower than in the United States, it is estimated that 20% of patients present with high-risk disease, which translates into approximately 4000 new cases each year. In this manuscript we will discuss risk categorization in localized prostate cancer and review the role of radiation therapy (RT) in high-risk disease.

Risk categorization

The primary purpose of a risk stratification system is to accurately estimate the probability of treatment failure and to facilitate the selection of the optimal therapeutic approach. Risk stratification systems are also helpful in ensuring prognostic uniformity in clinical trials and in the evaluation of treatment outcomes. The most widely used system is the UICC/AJCC TNM staging system but this does not incorporate two important prognostic factors: pre-treatment PSA level and Gleason score.

In December 2000, the Genitourinary Radiation Oncologists of Canada (GUROC) met in Vancouver to review the available evidence on risk stratification in prostate cancer and reached a consensus on the appropriate classification system to use Table 1.[2] In this system high-risk prostate cancer was defined as the presence of any one of these factors: clinical stage T3/T4, PSA > 20 ng/ml or GS ≥ 8. This model has recently been demonstrated to be internally consistent and to predict prostate cancer specific mortality in patients treated with surgery or radiation therapy.[3,8] For patients treated with RT, the relative risk of prostate cancer specific mortality was 14.2 for those patients with high-risk disease relative to those patients with low-risk disease Table 2.[8]

TABLE 1. **Risk categories**

Risk group	PSA (ng/ml)	Gleason score	UICC T category
Low (all of)	≤10	≤6	≤T2a
Intermediate (any of, if not low risk)	≤20	7	T1/T2
High (any of)	>20	≥8	≥T3

TABLE 2. **Prostate cancer specific mortality after RT**

Risk group	Relative risk	95% CI	PCox
Low	1.0		
Intermediate	5.6	2.0-9.3	.0012
High	14.3	5.2-24.0	<.001

Radiation therapy

Radiation therapy has been the primary treatment modality in the management of patients with high-risk disease for the past 30 years. However, results with RT alone have been poor and in most series the 10 year biochemical freedom from disease (bNED) rate has been approximately 20%.[9,10] The benefit of local therapy in this disease is unclear as many patients are felt to harbor sub-clinical metastases at presentation. The overall survival rates seen with RT alone are similar to those reported with hormonal therapy (HT) alone.[11] The British Medical Research Council (MRC) phase III trial of orchiectomy alone, RT alone and combined orchiectomy and RT in patients with T2-3 disease, closed in 1988 after accruing 277 patients. While this trial was not powered to detect a difference between the three treatment arms, nevertheless, there was no indication that orchiectomy alone compromised survival.[12] The NCIC-CTG/CUOG PR-3 phase III randomized trial is currently ongoing and is powered to detect a small benefit in overall survival from the addition of RT to primary hormonal therapy. The trial will close to accrual in the summer of 2005 having accrued 1200 patients and in addition to assessing the benefit of RT on overall survival, it will also evaluate the impact of loco-regional RT on symptomatic local control of disease and quality of life.

As the results with RT alone have been disappointing a number of strategies including adjunctive hormonal therapy have been used to improve treatment outcome.

Adjunctive hormonal therapy

In the past 15 years four large randomized trials have assessed the benefit of neoadjuvant and adjuvant hormonal therapy in patients with high-risk disease.[9,13-15] Table 3 In two of these studies there was a clear benefit in overall survival with the use of prolonged adjuvant hormonal therapy (HT).[9,15] In the RTOG 85-31, a study of 977 patients randomized to

TABLE 3. **Benefit of adjunctive hormones in high-risk disease (% absolute benefit)**

Study	**RTOG 85-31**	**RTOG 86-10**	**EORTC 22863**	**RTOG 92-02**
HT duration	Indefinite	4 months (neoadjuvant and concurrent)	3 years	2 years
Overall survival	15% (10 yrs)		16% (5 yrs)	
OS Gleason 8-10	17%		11%	
Distant mets free	10%	11%	19%	5.5%
Local control	14%	12%	14%	6%
bNED	24%	14%	31%	27%

RT alone or RT and indefinite hormonal therapy the 10 year survival was 53% with RT and HT as compared to 35% in those patients treated with RT alone (p <0.0043).[15] In the EORTC 22863 study reported by Bolla et al there was a 16% overall benefit in 5 year survival (78% versus 62%) with the use of 3 years of adjuvant HT.

The optimal duration of adjuvant hormonal is unclear. The RTOG 92-02 study randomized 1554 patients to 4 or 28 months of HT and, on preliminary subset analysis, there was an overall survival benefit (81% versus 70.7%, p=0.044) seen with the use of prolonged HT in patients with Gleason 8-10 tumors. These results, along with the updated report of the EORTC 22863 study (which used 3 years of adjuvant HT) has made RT and prolonged (2-3 years) adjuvant HT the standard of care in North America for patients with high risk prostate cancer. The EORTC 22961 trial comparing 6 versus 36 months of adjuvant HT has accrued 966 patients and closed in May 2002. This trial, along with mature results from the RTOG 92-02 study should establish whether prolonged adjuvant HT is necessary in this setting.

Dose escalation

In patients with low and intermediate risk disease there is now clear evidence from phase III randomized trials that RT dose-escalation using 3D conformal RT or intensity modulated techniques (IMRT) improves bNED outcomes.[16,17] Pollack et al have reported the mature results of a phase III study of 305 predominantly intermediate risk patients from the M. D. Anderson Cancer Center.[16] Overall there was a 6% improvement in freedom from failure (mostly biochemical failure) and in patients with a pre-treatment PSA of > 10 ng/ml, there was a 10% improvement in distant metastasis rates at 6 years and a 19% improvement in Freedom From Failure (FFF) rates (62% versus 43%, p = 0.01). While there are no randomized trials of dose escalation in high-risk disease, various institutional retrospective studies have suggested that dose escalation in this sub-group of patients may also have substantial benefits.[18,19]

Regional lymph node irradiation

Patients with high-risk prostate cancer have a moderate to high-risk of occult lymph node metastatic disease.[20,21] Prophylactic nodal irradiation using conventional dose RT with neoadjuvant HT has been shown to improve progression free survival in one randomized phase III trial, while other trials have produced negative results.[22,23] Using IMRT, it is now possible to escalate the dose to the pelvic lymph nodes with minimal acute bladder and small bowel toxicity.[24] A typical dose distribution is shown in Figure 1

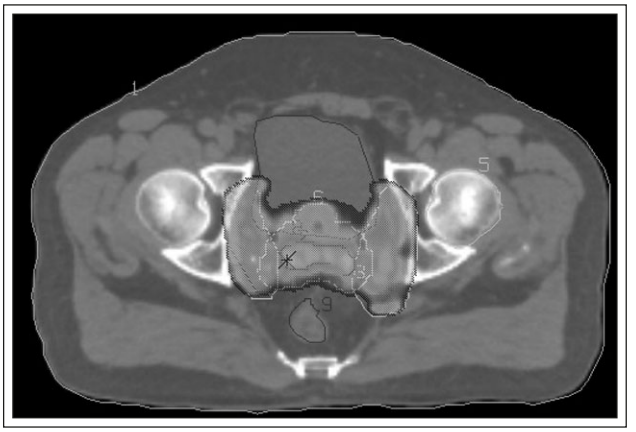

Figure 1. Isodose wash IMRT dose distribution for prostate and pelvic lymph nodes.

Figure 2. Wire frame rendering of IMRT dose distribution for prostate and pelvic lymph nodes.

demonstrating that the bladder and adjacent small bowel can be excluded from the high dose area. A wire frame rendering of an IMRT dose distribution for the prostate and pelvic nodes of a recent case treated at Princess Margaret Hospital is shown in Figure 2. The long term efficacy and toxicity of this approach is not known and randomized clinical trials will be necessary to evaluate this strategy.

Adjunctive chemotherapy

Recent data showing improved survival in patients with hormone refractory prostate cancer treated with Docetaxel containing regimens has raised the possibility that adjuvant chemotherapy might be effective in patients with localized disease.[25,26] A Canadian phase II study assessing the safety of neoadjuvant chemotherapy is currently accruing patients and a national Phase III study through NCIC-CTG is being considered. A phase III trial in high-risk prostate cancer comparing RT alone to RT and adjuvant paclitaxel, estramustine and etoposide is currently being performed by the Radiation Therapy Oncology Group (RTOG 99-02). However, given the recently demonstrated lack of activity of estramustine in prostate cancer it is likely that this trial will have problems in completing its target accrual.[27]

Conclusion

The standard of care for patients with high-risk prostate cancer is RT with adjuvant HT.[2,28] The optimal duration of HT is currently being assessed in two randomized clinical trials which will report in the next few years. Dose escalation to the primary tumor and regional lymph nodes remains experimental as does neoadjuvant and adjuvant chemotherapy.

The high-risk group of patients contains a wide spectrum of disease, ranging from patients with aggressive localized disease to those with widespread occult distant metastases. The current challenge facing the clinician is appropriate treatment selection for each individual patient. Additional information from novel biomarkers and improved imaging, as well as, more effective local and adjunctive systemic therapies is necessary to improve outcomes for men with this aggressive disease. □

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