Multimodal approaches to high-risk prostate cancer

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ABSTRACT

Widespread use of testing for prostate-specific antigen (PSA) has led to a migration in the stage and grade of prostate cancer (pca), with most men presenting with localized disease. However, 20%–35% of patients still present with high-risk disease (PSA > 20 ng/mL, biopsy Gleason score 8–10, or clinical stage T3). Despite advances in various treatment modalities, patients with high-risk disease have a significant chance of recurrence and death after surgery, often because of the presence of early occult metastasis at time of diagnosis. The optimal management of high-risk pca remains controversial. The present article aims to discuss the traditional approaches and the more recent evolution toward multimodal therapies.

KEY WORDS

Urology, prostate cancer

1. INTRODUCTION

Widespread use of testing for prostate-specific antigen (PSA) has led to a migration in the stage and grade of prostate cancer (pca), with most men presenting with localized disease¹. However, 20%–35% of patients still present with high-risk disease [PSA > 20 ng/mL, biopsy Gleason score 8–10, or clinical stage T3 (cT3)]². These patients pose a significant treatment challenge, but do not uniformly have a poor prognosis. Historically, for example, up to 40% of cases presented with cT3 disease, and 7.9%–49% of patients had lymph node involvement³. However, overstaging also occurs in up to 27% of cases^{4,5}. Of biopsy-detected Gleason 8–10 cancers, 31% have organ-confined disease, and up to one third will be pathologically downgraded in the radical prostatectomy (RP) specimen⁶. Furthermore, although previous reports of patients with PSA values above 20 treated with RP show PSA failure rates of 44%–50% at 5 years^{7,8}, more recent reports of patients with PSA values above 50 show biochemical progression-free survival (bPFS) rates

of 83% at 10 years and overall cancer-specific survival (CSS) of 87%⁹. Yet despite advances in various treatment modalities, patients with high-risk disease have a significant chance of recurrence and death after surgery¹⁰, often because of the presence of early occult metastasis at time of diagnosis¹¹.

The aim of multimodal therapy is to layer multiple treatment options to improve long-term outcomes by lowering the local tumour burden and eradicating micrometastatic disease¹². In other high-risk localized cancers, notably breast and colorectal, surgery followed by neoadjuvant, adjuvant, or salvage treatments are either recommended or commonly used (guidelines from the National Comprehensive Cancer Network). Such an approach can result in a complete pathologic response at the time of surgery—an important determinant of subsequent CSS^{13,14}.

A multimodal approach is not unique to other surgical specialities; there are several examples from urologic cancers. For example, retroperitoneal lymph-node dissection was the traditional treatment for metastatic testicular cancer. However, with the advent of platinum-based chemotherapeutics, a combination strategy of chemotherapy followed by surgery for residual disease achieves excellent long-term cure rates.

The optimal management of high-risk pca remains controversial. The present article aims to discuss the traditional approaches and the more recent evolution toward multimodal therapies.

2. DISCUSSION

2.1 Radiation Therapy

In several randomized trials involving patients with advanced pca, radiotherapy (RT) in combination with androgen deprivation therapy (ADT) has demonstrated improved clinical disease-free and overall survival (OS) over RT alone^{15–18}. Moreover, experimental data indicate that androgen ablation is a potent radiation sensitizer, in part by reducing tumour hypoxia^{19,20}. As a result, epidemiology data from the United States demonstrate that most men with clinically

advanced pCa who are treated with local therapies receive external-beam RT (EBRT) in combination with long-term ADT²¹. Traditionally, brachytherapy is offered to patients with low-risk disease²², and previous reports of its use in high-risk patients have been discouraging²³. However, emerging data show that low-dose-rate brachytherapy combined with EBRT or ADT (or both) offers results equivalent to those with RT plus ADT.

Dattoli *et al.*²⁴ examined the role of three-dimensional conformal RT plus a ¹⁰³Pd boost with generous brachytherapy margins in 243 intermediate- and high-risk patients. The authors reported a 14-year bPFS of 81% (87% for intermediate-risk and 72% for high-risk patients). In addition, the Seattle group published 15-year results of transperineal interstitial permanent prostate brachytherapy combined with moderate-dose neoadjuvant EBRT in 223 patients with clinical T1–T3 prostate pCa²⁵. The bPFS for the overall group was 74%, and when analyzed by risk group, it was 85.8% for low-risk, 80.3% for intermediate-risk, and 67.8% for high-risk patients. In a further study by Stock *et al.*, 181 pCa patients with Gleason scores of 8–10 were treated with a ¹⁰³Pd implant, 45 Gy EBRT, and 9 months of ADT²⁶. The 8-year bPFS, metastasis-free survival, CSS, and OS were 73%, 80%, 87%, and 79% respectively (Table 1). Multivariate analyses performed in each of the foregoing studies found that pre-treatment Gleason score and then PSA were the strongest predictors of recurrence. These studies provided important data for the use of brachytherapy in combination with EBRT in this cohort of patients, and

it appears this type of multimodal approach is a viable option for selected patients with high-risk pCa.

2.2 Radical Prostatectomy

Traditionally, surgery for high-risk pCa has been discouraged because of concerns regarding the side effects of RP, high rates of positive surgical margins, risk of lymph node metastasis, and high rates of PSA recurrence²⁷. However, surgery has been shown to be more beneficial than watchful waiting in terms of mortality, risk of local progression, and risk of metastasis²⁸, benefits that become evident after 8 years of follow-up. These observations suggest a positive effect for treatment in high-risk pCa patients, because low-risk patients have a more protracted natural history.

As part of a multimodal approach, with the use of adjuvant RT where appropriate^{4–5,29}, recent surgical series have shown rates for bPFS and CSS that are equivalent to or better than those for RT with ADT. Furthermore, several randomized trials have demonstrated that postoperative RT, delivered immediately after RP with adverse pathology, reduces PSA recurrence rates^{30–32} and improves metastasis-free and OS rates³³. In addition, a recent publication from the Memorial Sloan–Kettering Cancer Center examined the effect of RP and EBRT on distant metastasis rates in patients with localized pCa treated with RP or EBRT³⁴. After adjusting for case mix, patients with higher-risk disease treated with RP had a lower risk of metastatic progression and pCa-specific death than did patients treated with EBRT. Multimodal therapy with an initial

TABLE 1 Overall, cancer-specific, and biochemical progression-free survival published in the literature for multimodal approaches in high-risk clinically localized prostate cancer

Reference	Approach	Patients (n)	Survival [% (follow-up)]		
			Overall	Cancer-specific	Biochemical progression-free
Radiation therapy					
Dattoli <i>et al.</i> , 2007 ²⁴	3D-CRT plus ¹⁰³ Pd	243			72 (14 years)
Sylvester <i>et al.</i> , 2007 ²⁵	¹²⁵ I or ¹⁰³ Pd plus EBRT	114			67.8 (15 years)
Stock <i>et al.</i> , 2009 ²⁶	¹⁰³ Pd plus EBRT	181	79 (8 years)	87 (8 years)	73 (8 years)
Surgery					
Ward <i>et al.</i> , 2005 ⁴	RP plus adjuvant or salvage RT	842		73 (10 years)	43 (10 years)
Hsu <i>et al.</i> , 2007 ⁵	RP plus adjuvant or salvage RT	235		85 (10 years)	51.5 (10 years)
Loeb <i>et al.</i> , 2009 ³⁵	RP plus adjuvant or salvage RT	175		92 (10 years)	68 (10 years)

3D-CRT = three-dimensional conformal radiotherapy; EBRT = external-beam radiotherapy; RP = radical prostatectomy; RT = radiotherapy.

RP may therefore offer rates of cancer control that are equivalent to those with RT in these patients, without the need for long-term adjuvant ADT.

In terms of multimodal therapy, the Mayo Clinic has published the largest surgical series to date, involving 842 patients with cT3 disease and a median follow-up of more than 10 years who underwent RP⁴. The bPFS and clinical progression-free survival (cPFS) in that series were, respectively, 58% and 85% at 5 years and 43% and 73% at 10 years. Adjuvant ADT was administered to 51% of patients, and adjuvant RT to 16%. Hsu *et al.*⁵ analysed 235 cT3 PCA patients and found a similar bPFS of 59.5% and 51.5% at 5 and 10 years respectively, and an even higher cPFS than was seen in the Mayo series: 96% and 85% at 5 and 10 years respectively. Adjuvant or salvage RT, or ADT, or both, was given to 56% of these patients. More recently Loeb *et al.*³⁵ examined 175 high-risk patients who underwent RP by a single surgeon. At 10 years, bPFS was 68%, metastasis-free survival was 84%, and CSS was 92% (see Table 1). The 10-year rate of freedom from any hormonal therapy was 71%. Of the high-risk criteria, a biopsy Gleason score of 8–10 (compared with 7 or less) was the strongest independent predictor of biochemical recurrence, metastasis, and PCA death.

Prospective data for 299 high-risk PCA patients from our own centre demonstrate OS, CSS, and bPFS rates of 99%, 99.67%, and 70.23% respectively, at a median follow-up of 4.7 years (data not shown). Those rates appear to afford similar or superior OS and cPFS benefits as compared with the RT-plus-ADT regimens commonly used for these patients; bPFS, on the other hand, is lower in surgical series because of the definitions used for PSA recurrence and because of the uniform use of long-term ADT, which can suppress detection of PSA. In the combination therapy arm of the European Organization for Research and Treatment of Cancer (EORTC) 22863 trial, the 203 patients receiving RT plus 3 years of ADT (91% of whom had clinical T3 disease) had a clinical bPFS of 76% at 5 years¹⁵. However, their definition of PSA recurrence was much less stringent, at 1.5 ng/mL and increasing on 2 consecutive measurements.

In addition to equivalent or better bPFS outcomes, RP as primary treatment may offer several other advantages over primary RT. As many as 27% of patients identified as having cT3 disease are downstaged to pT2 disease⁴. Only RP can provide pathology staging to discern these patients, in whom monotherapy maybe the only treatment required, thereby avoiding overtreatment with RT plus 3 years of ADT, a regimen that is associated with worse outcomes across multiple quality-of-life domains³⁶.

Pelvic lymph node dissection should be performed during RP for high-risk PCA, because 15%–40% of those nodes will be positive³⁷. If positive nodes are found, ADT can be started, which has been shown (albeit in the pre-PSA era) to improve survival³⁸.

High-risk PCA patients may subsequently experience local treatment failure and require adjuvant or salvage therapies³⁹. The rate of long-term complications can be affected by the order in which treatments are given. Surgery as the primary local treatment is associated with a lower complication rate and smaller impact on quality of life when compared with salvage RP after RT⁴⁰. Rates of urinary incontinence and stricture after salvage RP have been reported at 30%–66% and 28% respectively⁴¹. Patients receiving adjuvant RT after RP demonstrate rates of total urinary incontinence and urethral stricture of 6.5% (vs. 2.8%) and 18% (vs. 10%) respectively³³. Furthermore, the morbidity for RP in patients with high-risk disease appears no greater than that in patients with localized disease⁴. However, the maintenance of erectile function in these patients is low^{4,5} as a result of the wide resection required in high-risk disease. Still, those rates compare favourably with the rates after RT for cT3 disease⁴².

A further benefit of primary RP in patients with high-risk clinically localized PCA may be in the subsequent development of metastatic disease. The Southwest Oncology Group (SWOG) 8894 trial compared orchiectomy with orchiectomy plus flutamide in patients with metastatic PCA. Based on the improved survival seen in patients with metastatic renal and ovarian cancer whose primary tumour was removed, Thompson *et al.*⁴³ re-analyzed data from that trial. Although their findings were hypothesis-generating only, they noted that the risk of death was reduced in patients with metastatic disease that had undergone prior RP as compared with those that had received no previous definitive therapy [hazard ratio (HR): 0.77]. Conversely, patients that had undergone prior RT had an increased risk of death (HR: 1.22).

2.3 Neoadjuvant Therapies

As previously discussed, the use of ADT with RT is reported to improve rates of survival and local control. The administration of neoadjuvant and adjuvant ADT in conjunction with surgery has been disappointing. A Cochrane review published in 2006 concluded that neoadjuvant ADT improves organ-confined rates, pathologic downstaging, positive surgical margins, and rate of lymph node invasion⁴⁴, but neither neoadjuvant nor adjuvant ADT before RP provides a significant OS or DFS advantage over RP alone. However, in a randomized study of 3 months compared with 8 months of neoadjuvant ADT before RP, rates of biochemical “no evidence of disease” were significantly lower in the 267 men enrolled at the 3 top-recruiting “high volume” sites (24%) than in the 238 men enrolled at the remaining 8 “low volume” sites (40%, $p < 0.001$)⁴⁵.

The roles of other neoadjuvant therapies before surgery continue to be examined. Docetaxel has been shown to improve OS in patients with castrate-resistant

pca⁴⁶. Neoadjuvant docetaxel administered for 6 months before RP has demonstrated good tolerability and can lead to PSA declines of more than 50% and decreased tumour volume on endorectal magnetic resonance imaging⁴⁷. A subsequent phase II multi-centre study examined the use of docetaxel with ADT in newly diagnosed patients with untreated clinically localized high-risk pca⁴⁸. Of 72 patients enrolled, 64 completed the protocol therapy with a median follow-up of 42.7 months. Although the median PSA recurrence-free survival was not reached, it was estimated to be 65.1 months, with 19 patients (30%) experiencing a PSA recurrence.

Several phase III trials have commenced evaluating neoadjuvant and adjuvant chemo-hormonal approaches in conjunction with prostatectomy or RT. The Cancer and Leukemia Group B 90203 trial is a randomized study of neoadjuvant docetaxel and ADT before RP, compared with immediate RP in 750 patients with high-risk, clinically localized pca.

3. SUMMARY

Patients with high-risk pca are more likely to succumb to their disease, and they therefore represent a significant treatment challenge. The traditional approach of RT plus ADT is being complemented by evolving multimodal approaches such as newer radiation therapies and RP as primary treatment with adjuvant or salvage therapies (or both) when appropriate. To make a significant impact in this cohort of patients, clinicians must learn from the experience of other cancers and begin to layer treatment options to improve outcomes.

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