High-Risk Prostate Cancer: Role of Radical Prostatectomy and Radiation Therapy

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Keywords

Prostate cancer · Prostatectomy · Radiation

Summary

Up to 12% of European men aged 55–69 years diagnosed with prostate cancer have high-risk disease and thus are at increased risk of mortality. There remains a lack of consensus on definitive treatment for prostate cancer, although both radiation therapy and radical prostatectomy are frequently utilized. Furthermore, the different types of radiation and surgical options also increase the complexity of deciding on a single treatment, as does the use of multimodal treatment plans. Here, we provide an overview of radiation therapy and radical prostatectomy in treating high-risk prostate cancer.

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Introduction

High-risk prostate cancer (PC) is defined by the D'Amico criteria as being bilaterally clinically palpable, extending beyond the prostatic capsule, and having serum prostate-specific antigen (PSA) levels of ≥ 20 ng/ml or a Gleason score of ≥ 8 [1]. Up to 12% of newly diagnosed PC cases in Europe [2] and 13–29% in the United States have been categorized as high-risk depending on whether the cT2c definition was classified as high- or intermediate-risk [3]. Furthermore, there is concern that high-risk PC will see an increasing incidence as a result of the 'D' rating given to PSA screening by the 2012 US Preventative Services Task Force [4]. Today, high-risk PC has a 10-year PC-specific mortality (PCSM) rate of up to about 20% [5]. However, it is currently unclear what the optimal treatment of high-risk PC is, given the lack of any randomized controlled trials (RCTs) comparing surgery and radiation. 2 popular options for treating PC are radiation therapy (RT) and

radical prostatectomy (RP), both as initial therapy and as part of a multimodal treatment plan. In this article, we explore the roles of RT and RP in the treatment of high-risk PC.

Lack of Definitive Research on Treatment

Current research has yet to determine the best treatment for high-risk PC. No large RCT comparing RP versus RT has been completed to date, primarily due to a lack of patient accrual [6]. The ongoing Prostate testing for cancer and Treatment (ProtecT) trial is a phase III trial in 9 cities in the United Kingdom that has randomly assigned 1,643 patients to either active surveillance, RT, or RP (fig. 1) [7]. Nevertheless, this remarkable effort has provided plenty of fodder for the critics regardless of outcome, such as the low numbers of participants with Gleason ≥ 8 on biopsy (37/1,643; 2.3%), PSA ≥ 10.0 ng/ml (166/1,643; 10.1%), and clinical stage T2 or higher (394/1,643; 24.0%), as well as racial homogeneity (Caucasian 1,606/1,643; 97.7%). Retrospective reviews directly comparing RT and RP have yet to come to a collective consensus (table 1). They also may be subject to biases in patient selection, disease and outcome classification, changes in treatment-era techniques, use of nomograms as proxy for true patient outcomes, inaccuracies in nomograms used, and more. Finally, the use of androgen deprivation therapy (ADT) or RT as adjuvant therapy may especially confound the results of studies attempting to isolate the efficacy of RP or RT in high-risk PC patients who are at increased risk of clinical and biochemical recurrence (BCR) which would ethically oblige physicians to offer further treatment.

Radiation Therapy

Men with high-risk PC are more likely to undergo RT plus ADT than to undergo RP [8]. This preference is buttressed by 2 RCTs that showed RT plus ADT to be superior to ADT alone in high-risk

Fig. 1. Simplified study design for the Prostate testing for cancer and Treatment (ProtecT) phase III randomized clinical trial [7]. Patients with prostate-specific antigen (PSA) ≥ 20.0 ng/ml were ineligible for the study. All eligible patients had prostate cancer clinical stage T1c or T2.

Table 1. Selected studies comparing prostate-specific mortality (PCSM) of radiation therapy (RT) with that of radical prostatectomy (RP)

Study (year, type) [ref.]	High-risk definition	High-risk patients, total, n	High-risk patients per treatment, n	Median follow-up, years	PCSM, %	Significance
Narang et al. (2015, retrospective) [11]	1 of following: multiple NCCN high-risk features primary Gleason $5 \geq 5$ core biopsies of Gleason ≥ 8	214	RP = 114 RT/ADT = 100	10 10	RP = 38 RT/ADT = 24	no p value
Sooriakumaran et al. (2014, retrospective) [21]	cT3 N0/Nx M0/Mx and Gleason ≥ 8	7,649	RP = 2609 RT = 5040	5.16 5.76	RP = 4.5 RT = 8.3	$p < 0.001$
Hoffman et al. (2013, prospective cohort) [22]	PSA > 10 or Gleason ≥ 8	437	RP = 381 RT + ADT = 56	15 15	RP = 6.6 RT + ADT = 21.4	HR = 0.36 95% CI 0.20–0.64
Westover et al. (2012, retrospective) [44]	Gleason ≥ 8	657	RP = 285 RT + ADT = 372	7.6 3.6	RP = 5.3 RT + ADT = 1.6	$p = 0.16$

NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; ADT = androgen deprivation therapy; HR = hazard ratio; CI = confidence interval.

PC. Widmark et al. [9] randomized 875 patients between an ADT only cohort and an RT plus ADT cohort, and showed that RT plus ADT had superior PCSM compared with ADT only (11.9 vs. 23.9%) as well as overall mortality (29.6 vs. 39.4%) at 10-year follow-up. Warde et al. [10] randomized 1,205 patients between RT plus ADT and ADT only, and showed that RT plus ADT improved overall survival at 7-year follow-up compared with ADT only (74 vs. 66%). A number of retrospective studies have shown results that favor RT over RP, with Narang et al. [11] showing lower PCSM (24 vs. 38% in a total of 214 patients) (table 1) and Stephans et al. [12] indicating lower BCR rates (46 vs. 53% in a total of $> 1,500$ patients). Moreover, concerns about side effects, positive margins, and inadequate disease control in high-risk patients may contribute to a ‘therapeutic nihilism’ that sways physicians away

from recommending RP and towards RT plus ADT for patients with high-risk PC [13].

Clinical trials have shown that higher RT dosages (78–80 Gy) have superior clinical and biochemical outcomes compared to lower RT dosages (66–70 Gy). The transition from 2D radiation to 3D-external beam radiotherapy (EBRT) in the mid-1990s and further refinement of 3D-EBRT into intensity modulated radiotherapy (IMRT) in the early 2000s were instrumental in facilitating higher RT dosages without excessive risk of side effects to the organs surrounding the prostate [14]. For high-risk PC, certain recent literature suggests that combined EBRT/IMRT and brachytherapy is superior to EBRT alone [15], IMRT alone [16], or brachytherapy alone [17], although the exact radiation dosages varied among the studies despite all being in the ‘high-dosage’

Table 2. Selected studies comparing prostate-specific mortality (PCSM) of combined radiation therapy (RT) and androgen deprivation therapy (ADT) with that of RT only

Study (year, type) [ref.]	High-risk definition	High-risk patients, total, n	High-risk patients per treatment, n	Length of ADT, months	Median follow-up, years	PCSM, %	Significance
Bolla et al. (2002, RCT) [45]	cT3/T4 N0/N1 M0 cT1/T2 and World Health Organization grade 3	415	RT + ADT = 207 RT = 208	36	5.5	RT + ADT = 6 RT = 21	p = 0.0001
Pilepich et al. (2005, RCT) [46]	cT3 positive regional lymph node	977	RT + ADT = 488 RT = 489	indefinite ^a	7.6 (all) 11 (survivors)	RT + ADT = 16 RT = 22	p = 0.0052
Granfors et al. (2006, RCT) [47]	locally advanced disease stratification for T and N stages	91	RT + ADT = 45 RT = 46	indefinite ^b	9.7 (all) 16.5 (survivors)	RT + ADT = 36 RT = 57	p = 0.03 (overall) p = 0.005 (N1 only)
Horwitz et al. (2008, RCT) [41]	cT2c–T4, N0, with PSA < 150 ng/ml	1,554	RT + short-term ADT (sADT) RT + long-term ADT (lADT)	4 28	11.31 11.27	RT + sADT = 16.1 RT + lADT = 11.3	p = 0.0042

^aContinuous drug application.

^bOrchiectomy.

RCT = Randomized controlled trial; PSA= prostate-specific antigen.

range. In a literature review, Grim et al. [18] suggested that combined EBRT and brachytherapy had improved PSA-free progression results compared to single-modality RT in high-risk PC, although they indicated brachytherapy was superior to other RT modes in low-risk PC and combined therapy had similar outcomes to brachytherapy only in intermediate-risk PC.

Radical Prostatectomy

Many studies have suggested that RP is also a viable treatment for high-risk PC. Retrospectively reviewing patients whose lymph nodes were positive for PC, Steuber et al. [19] showed that RP plus adjuvant ADT had superior 10-year cancer-specific survival (CSS) rates compared to ADT alone (76 vs. 46% in a total of 158 patients), while Ghavamian et al. [20] showed that RP, pelvic lymph node dissection (PLND), and orchiectomy had superior 10-year CSS rates compared to PLND and orchiectomy (79 vs. 39% in a total of 461 patients). Evidence of lower PCSM from high-risk PC with RP than with RT have come from a retrospective study by Sooriakumaran et al. [21] (4.5 vs. 8.3% in a total of 7,649 patients) and a prospective observational study by Hoffman et al. [22] (6.6 vs. 21.4% in a total of 437 patients) (table 1). Several studies utilizing Kattan nomograms to estimate PC-specific survival curves have also concluded that patients undergoing RT have higher PCSM [23] and higher probability of metastasis [24] than patients undergoing RP, although many RP patients received salvage radiation after surgery. Proponents of RP in high-risk PC argue that RP provides more accurate pathological staging to guide disease management and prevent overtreatment with ADT, eliminates the PC

‘source’ to prevent cancer ‘seeding’ that promotes metastasis [13], and causes a rapid decrease in PSA after surgery that allows for quicker detection of persistent or recurrent PC and thus application of adjuvant therapy than other treatment modalities [25].

RP is typically divided into open radical retropubic prostatectomy (RRP) and robot-assisted laparoscopic prostatectomy (RALP). While RALP has become increasingly popular, there is much debate as to whether it has improved oncologic outcomes compared with traditional RRP. Both Masterson et al. [26] and Magheli et al. [27] concluded that RRP and RALP have similar BCR rates at 48–60 months. Positive surgical margins are an independent risk factor for BCR, and there is no consensus on whether RALP has lower rates of positive surgical margins [28] or if the rates are similar to RRP [29, 30]. Moreover, there have not been any RCTs comparing RRP and RALP, nor have there been any long-term follow-up studies on actual patient survival rates. Finally, there is no consensus if one type has superior functional outcomes or complication rates when surgeon experience and surgical volume are accounted for [28, 31].

Multimodal Therapy

Both RT and RP can be used in conjunction with each other or with other treatment modalities if one therapy is not satisfactory. Post-RP RT is frequently initiated if RP alone is deemed insufficient for cancer control, and is divided into adjuvant RT (RT provided before diagnosis of BCR from rising PSA levels) and salvage RT (RT provided after confirmation of BCR by PSA). While adjuvant RT has been shown to lower BCR, improve local control, decrease me-

tastases, and improve overall survival compared with no post-RP treatment [32], there is a debate as to when to best provide post-RP RT. While D'Amico et al. [33] indicated that adjuvant and salvage RT had comparable all-cause mortality in pT3R0 or pT2R1 men with slow PSA doubling times, a meta-analysis of 41 studies over the past 20 years by King [34] indicated that every PSA = 0.1 ng/ml was associated with a 2.6% loss of relapse-free survival (rise in PSA $\geq$ 0.2 ng/ml) after salvage RT and suggested it is desirable to initiate adjuvant RT when PSA is undetectable. Until the 3 ongoing RCTs investigating the outcomes of adjuvant versus salvage RT (RADICALS, GETUG-17, and RAVES) publish their results, post-RP salvage versus adjuvant RT will continue to be debated [35].

ADT is frequently used in conjunction with post-RP RT. Retrospective reviews indicate that combined luteinizing hormone-releasing hormone agonists plus post-RP RT have superior disease- and PSA relapse-free status compared to post-RP RT alone [36, 37], while the initial results of the RTOG 96-01 phase III trial indicate that post-RP RT and bicalutamide also have improved PSA progression-free status compared to post-RP RT alone [38]. Ultimately, the 4 ongoing RCTs (GETUG-16, RTOG 96-01, RTOG 05-34, and RADICALS) should provide more decisive answers on the efficacy of combined post-RP RT and ADT [35].

ADT in combination with RT has been shown to be superior to RT alone as primary treatment of high-risk PC. Pollack et al. [39] reviewed that some RCTs in the 1990s comparing combined RT and ADT with only RT had shown survival benefits of combined treatment in high-risk PC. Since then, multiple RCTs have confirmed that including ADT reduces PCSM in patients initially treated with RT for high-risk PC (table 2). Current research focuses on optimizing the duration of ADT, with 2–3 years of adjunct ADT recommended as having improved outcomes over short-term adjunct ADT (< 6 months) for high-risk PC [40, 41].

Finally, clinical trials have begun investigating the outcomes of combination treatment with RT, ADT, and chemotherapy as compared with standard RT and ADT. Rosenthal et al. [42] showed that RT, ADT, and combination chemotherapy with paclitaxel, estramustine, and etoposide did not improve rates of overall survival, disease-free survival, BCR, or disease progression as compared with RT and ADT only in a phase III trial. However, early data suggests that combined RT, ADT, and docetaxel and prednisone had a 4% overall survival improvement over RT and ADT only at 4-year follow-up (93 vs. 89%) [43]. The addition of chemotherapy presents another exciting new area of research at the forefront of PC treatment.

Conclusion

A substantial proportion of PC is still initially diagnosed as high-risk PC with elevated mortality rates. However, the most appropriate treatment for high-risk PC remains unclear. Enough research that supports either RT or RP as the primary, initial treatment exists for proponents of either treatment to advocate their therapy of choice. In addition, multimodal treatments incorporating RT and RP are frequently utilized since single-modality treatment may not be sufficient for cancer control. For the foreseeable future, treatment options for high-risk PC will continue to be refined yet remain controversial.

Disclosure Statement

Mr. Qi does not report any conflicts of interest. Dr. Moul reports no conflicts of interest related to the subject matter of this article.

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