Clinical Oncology xxx (2014) 1–9

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Primary Radical Therapy Selection in High-risk Non-metastatic Prostate Cancer

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Received 22 July 2014; received in revised form 2 October 2014; accepted 7 October 2014

Abstract

As the incidence of prostate cancer rises, the detection and management of men with high-risk non-metastatic prostate cancer is becoming increasingly important. The benefits of radical treatment have been clearly shown in this group from a number of publications. The current mainstays of treatment are radical prostatectomy (with selective use of adjuvant radiation) and radical radiotherapy with concurrent androgen deprivation. The outcomes from these two approaches seem to be remarkably similar and are considered equally valid options for primary treatment. The choice of therapy is critically dependent on a number of factors, but ultimately left to the decision of the patients with advice from clinicians. Clinicians themselves, however, are known to be biased towards their particular skill set and experiences. Attempts at randomised comparisons between these two modalities have so far failed and are confounded by patient–clinician bias, the continual advances in therapy as well as the long natural history of the disease. In the lack of level 1 comparable evidence, this article explores the existing literature as to the key factors that should be considered in radical treatment selection for high-risk prostate cancer. These factors include disease aggressiveness, comorbidity and life expectancy, functional outcomes and the consequences of therapy failure with regards to salvage treatment. We propose that these factors may be useful in developing a decision guide for rationale radical therapy selection in the light of two apparently equally effective treatments. Ultimately, however, there is an urgent need for added clinical and biological markers that can provide a more precise approach to therapy selection.

Key words: Decision algorithm; high risk; prostate cancer; radical prostatectomy; radical radiotherapy; rational therapy selection

Statement of Search Strategies Used and Sources of Information

This overview was written based on a search of the literature pertaining to radical therapy for high-risk prostate cancer. The primary search was through PubMed and other articles were sourced from related papers or from primary research conducted by the authors.

Introduction

The management of high-risk non-metastatic prostate cancer (HR-PC) remains a major clinical conundrum for clinicians and patients. It does, however, have the best evidence base for survival benefit from radical therapy [1]. Using data from the Swedish Cancer Registry, Rider *et al.* [2] recently showed that in men with non-metastatic disease managed with non-curative intent, only those with high-risk disease had a greater risk of death from prostate cancer compared with other causes of death over a follow-up of 15 years.

There is an ongoing debate as to the best primary radical therapy for HR-PC. The main therapy options are between radical prostatectomy or radical radiotherapy [3]. It is also widely accepted that multimodality therapy is the standard

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http://dx.doi.org/10.1016/j.clon.2014.11.004

Please cite this article in press as: Gnanapragasam VJ, et al., Primary Radical Therapy Selection in High-risk Non-metastatic Prostate Cancer, Clinical Oncology (2014), http://dx.doi.org/10.1016/j.clon.2014.11.004

of care for HR-PC, whether radical radiotherapy with concurrent androgen deprivation (ADT) or radical prostatectomy with adjuvant radical radiotherapy [4,5]. Radical radiotherapy also includes the option of high dose rate brachytherapy, which has to date shown comparable outcomes with radical external beam radiotherapy [6]. The gold standard method to compare outcomes between these two modalities is the prospective randomised controlled trial. However, attempts at a trial have not succeeded in the past, although a new Scandinavian Prostate Cancer Group trial has now opened in this area focusing on comparing radical prostatectomy and radical radiotherapy in locally advanced disease [7]. In the light of this lack of randomised trial evidence, there are a number of epidemiological and registry-based studies that have claimed superiority of one treatment over another [8–10]. To date, there are also no molecular biomarkers that have been shown to be helpful in guiding therapy choice in this area [11,12].

The optimum primary therapy for this group, therefore remains uncertain and polarises opinions between oncologists and urologists [13]. Decision-making bodies currently recommend both radical prostatectomy and radical radiotherapy as therapeutic options for men with HR-PC, although the broad definition of the current classification and the lack of balanced evidence raises the question of how equal these options might be [4,5,14]. Radical radiotherapy outcomes, for instance, have been well studied in large randomised trials, whereas outcomes from radical prostatectomy in HR-PC are derived almost exclusively from retrospective case series or epidemiological studies. In this uncertainty, patients are often left to make a personal decision about their treatment with guidance from their clinician. Indeed, all patients choosing radical therapy irrespective of risk face this choice. This overview explores the key factors that may come into play when considering the choice of radical therapy and proposes an algorithm that may help guide clinicians and patients.

Incidence

HR-PC, as defined by National Institute of Health and Care Excellence (NICE) and D'Amico criteria, covers a wide spectrum and most published studies do not distinguish between high-risk localised (organ confined) and high-risk locally advanced ($\geq$T3) but non-metastatic disease [14,15]. Many surgical series have a majority of the former, whereas radical radiotherapy series have a majority of the latter in their published cohorts. Recent work has attempted to redefine the criteria and introduce further sub-stratifications of risk, but these have as yet not entered widespread clinical or guideline use. The principal differences are sub-stratification of low-risk disease and identifications of a high- and very high-risk group [16]. Based on the original D'Amico criteria, the incidence of HR-PC has been shown to be about a quarter of all new prostate cancer diagnoses. From US data, Meng *et al.* [17] reported a 26% incidence in the CAPSURE database and Abdollah *et al.* [10] reported a 33% incidence in the SEER registry. Data from the UK have shown that HR-PC accounts for about 39% of all presentations and 22% of men aged 50–69 years referred by general practitioners to tertiary clinics [18]. Analysis of trends over time has also shown significant increases in HR-PC in line with the increasing numbers of men diagnosed with prostate cancer [19]. In UK radical treatment series, HR-PC accounts for 17–19% of radical radiotherapy-treated men and 10–13% of surgically treated men [20,21]. HR-PC is thus a significant and growing demographic of men diagnosed with prostate cancer.

Outcomes from Radical Therapy

Data from radical prostatectomy and radical radiotherapy series are hard to compare because of the essentially different therapy types and outcome measures. Moreover, there will be inherent errors in grade and stage assignment, as radical radiotherapy can only rely on biopsy findings and pretherapy imaging for risk stratification. Radical radiotherapy outcomes can also only be properly assessed after the completion of long courses of concurrent ADT, which is the current gold standard in the treatment of HR-PC [4]. The earliest measureable end point is the incidence of biochemical relapse, but this is acknowledged as a poor surrogate of eventual disease progression and death from prostate cancer [22,23]. Prostate cancer mortality is arguably the most robust clinical end point and certainly the most important outcome for patients and clinicians. Available long-term data show very encouraging cancer-specific mortality (CSM) from either radical therapy. In high-risk surgical series, Hsu *et al.* [24] reported a 10 year cancer-specific survival (CSS) of 91%. In a multicentre European collaborative study of 712 men with presenting prostate-specific antigen (PSA) >20, the overall CSS was 89.8% at 5 years and 85% at 10 years [25]. In radical radiotherapy series, D'Amico *et al.* [26] have reported 88% overall survival in men with high-risk disease. Widmark *et al.* [27] reported a 10 year CSS of 88% and progression-free survival of 74%. Most recently, the NCIC CTG/MRC PR07 trial reported a 7 year CSS and progression-free survival rates of 90 and 84%, respectively [28].

There are no prospective randomised controlled trials that have compared radical radiotherapy and radical prostatectomy in high-risk men. Therefore, the only available data come from institutional- or population-based retrospective studies and these have been previously reviewed [29]. Inevitably there are inherent significant differences in patient selection, tumour characteristics and treatment regimens necessitating statistical corrections to make the groups more comparable [8,10,30,31]. In the paper by Zelefsky *et al.* [32], which reported better outcomes from surgery, the radical radiotherapy group had over twice as many high-risk cases and significantly higher numbers of men with locally advanced disease. Both the median presenting PSA and age were also higher in the radical radiotherapy group. In the recently published Prostate Cancer Outcome Study (PCOS) there were significant differences in age, comorbidity and distribution of high-risk cancers

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