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Platinum Priority – Review – Prostate Cancer

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Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review

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Abstract

Context: The relative benefits and harms of hormonal treatment (HT) versus no or deferred HT in patients with nonmetastatic prostate cancer (PCa) relapse after primary curative therapy are controversial.
Objective: To assess the effectiveness of HT for nonmetastatic PCa relapse, prognostic factors for treatment outcome, timing of treatment, and the most effective treatment strategy to provide guidance for clinical practice.
Evidence acquisition: A systematic literature search was undertaken incorporating Medline, Embase, and the Cochrane Library (search ended March 2015). Studies were critically appraised for risk of bias. The outcomes included overall and cancer-specific survival, metastasis-free survival, symptom-free survival, progression to castrate resistance, adverse events, and quality of life.
Evidence synthesis: Of 9687 articles identified, 27 studies were eligible for inclusion (2 RCTs, 8 nonrandomised comparative studies, and 17 case series). The results suggest that only a subgroup of patients, especially those with high-risk disease, may benefit from early HT. The main predictors for unfavourable outcomes were shorter PSA doubling time (<6–12 mo) and higher Gleason score (>7). Early HT may be warranted for patients with high-risk disease. An intermittent HT strategy appears feasible. Most studies had a moderate to high risks of bias.
Conclusions: HT for PCa relapse after primary therapy with curative intent should be reserved for patients at highest risk of progression and with a long life expectancy. The

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potential benefits of starting HT should be judiciously balanced against the associated harms.

Patient summary: This article summarises the evidence on the benefits and harms of hormonal treatment in prostate cancer (PCa) patients in whom the disease has recurred following earlier curative treatment. We found that only a select group of patients with aggressive PCa and a fast rising prostate-specific antigen may benefit from early hormonal treatment (HT), whereas in others HT may be more harmful than beneficial.

1. Introduction

Prostate-specific antigen (PSA) monitoring is the cornerstone of follow-up after curative treatment for prostate cancer (PCa). Elevations in PSA may indicate local or distant disease recurrence. The most widely used definition of biochemical recurrence (BCR) after radical prostatectomy (RP) is two consecutive rising PSA values $\geq$0.2 ng/ml [1], whereas BCR after radiation therapy (external-beam radiation therapy [EBRT] or brachytherapy) is commonly defined as a confirmed rise in PSA 2 ng/ml above the posttreatment PSA nadir [2]. The incidence of BCR at 10 yr posttreatment is 21–47% for RP and 16–52% for EBRT; for brachytherapy, the figure at 15 yr posttreatment is 16–53% [3,4].

Although BCR after radical therapy is seen frequently, the natural course of this biochemical finding is highly variable. It commonly precedes clinical symptoms by years and may not have an impact on survival outcomes [1,3]. Nevertheless, up to 34% of men who develop BCR after RP may eventually develop clinical recurrence, with a median time of 8 yr between BCR and metastatic disease [5]. With the new imaging modalities, metastatic disease may be discovered more quickly. Hormonal treatment (HT) designed to suppress the androgen axis is widely used in patients with PCa relapse but is associated with side effects (including hot flashes, sexual dysfunction, loss of libido, fatigue, anaemia, depression, cardiovascular disease, metabolic syndrome, and osteoporosis), some of which can be severe and associated with an increased mortality and/or impair quality of life (QoL) [6]. The relative benefits and harms of salvage HT in the setting of BCR or local disease recurrence are controversial, and there is uncertainty regarding how, in whom, and when it should be used. It is crucial to identify those patients with disease recurrence who may benefit most from HT.

This systematic review was undertaken by the European Association of Urology (EAU) Prostate Cancer Guideline Panel as part of its guidelines update for 2016 and aimed to assess the clinical effectiveness of salvage HT in patients with BCR or nonmetastatic clinical recurrence after curative treatment for PCa, and to attempt to achieve some clarity regarding prognostic factors that influence treatment outcomes, the optimum timing of treatment, and the most effective treatment strategy.

2. Evidence acquisition

2.1. Search strategy

The protocol for the review has been published (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42015016075), and the search strategy is outlined in Supplement 1. Briefly, databases including Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched systematically in March 2015. All abstracts and full-text articles were screened by two reviewers independently. Disagreement was resolved by discussion or with an independent arbiter. No language restrictions were applied, but only studies published from 2000 onwards were selected to ensure contemporary data with PSA measured at PCa recurrence. The search was complemented by additional sources including the reference lists of included studies and a panel of experts (EAU Prostate Cancer Guideline Panel).

2.2. Types of study designs

All randomised controlled trials (RCTs), quasi-RCTs, non-randomised comparative studies (NRSs) comparing HT with either no HT or deferred HT, and single-arm case series involving HT in this setting were included. Studies with a minimum follow-up of 1 yr (to assess the primary outcome measure of overall survival (OS) at 1 yr) and a minimum of 50 participants were included.

2.3. Types of participants

Men with PCa who underwent one or more primary or salvage local treatments with curative intent, and who subsequently developed nonmetastatic disease recurrence and were considered beyond local salvage treatment, were included in the review. The primary or salvage local treatments included RP, EBRT, brachytherapy, cryotherapy, and high-intensity focussed ultrasound. The definition of disease recurrence was as defined by trialists including either different definitions of BCR, or local or regional clinical recurrence (such as radiographic evidence of positive lymph nodes). No restriction on BCR definitions was imposed due to the expected heterogeneity of the definitions used. Sensitivity analyses based on standard and nonstandard definitions were planned. Patients who had