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Original Article

Hormone and Radiotherapy versus Hormone or Radiotherapy Alone for Non-metastatic Prostate Cancer: A Systematic Review with Meta-analyses

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Abstract

Aims: Radiotherapy is standard treatment for localised prostate cancer and is often combined with hormone treatment to prevent androgen stimulation of prostate cancer. Hormone therapy carries significant morbidity and can only be justified in the radical treatment of localised disease if it can be balanced against a significant gain in disease control and survival.

Materials and methods: We searched Medline, Premedline, Embase, Cochrane Library, Web of Science (SCI & SSCI) and Biomed Central for randomised controlled trials published in English comparing radiotherapy or hormone therapy alone with radiotherapy and hormone therapy in combination as first-line treatment in patients with non-metastatic prostate cancer reporting overall survival, disease-free survival, distant metastases-free survival, biochemical survival, adverse events (including cardiovascular) and/or health-related quality of life.

Results: Fourteen trials were included and showed that combination therapy was associated with better or similar survival and disease-free outcomes compared with single-modality treatment, and that this may particularly be the case for patients with higher risk disease. The results also suggested that combination therapy is associated with more and worse adverse events and quality of life, although this was not always the case. Some of the results are at risk of reporting bias.

Conclusion: The published data support the use of combined treatment with androgen deprivation and radiotherapy for intermediate- and high-risk localised and locally advanced prostate cancer. Optimal timing, duration, formulation and the management of side-effects remain important questions for further research.

Key words: First-line treatment; hormone therapy; locally advanced; prostate cancer; prostate neoplasm; radiotherapy

Introduction

High-dose external beam radiotherapy delivered using modern intensity-modulated and image-guided techniques is a standard treatment for localised prostate cancer. It is usually combined with a period of androgen deprivation therapy (ADT), using drugs that prevent androgen stimulation of prostate cancer by blocking the luteinising hormone releasing hormone (LHRH) release controlling the hypothalamic–pituitary axis release of follicle-stimulation hormone (FSH) and luteinising hormone (LH), which stimulate the testes to produce testosterone. This simulates the effect of surgical castration. Alternatively anti-androgen drugs acting as competitive antagonists of androgen receptor activity may be used. In the metastatic setting, combinations of these two approaches achieve maximal androgen blockade. Although most trials of hormone therapy used in association with radiotherapy have used ADT, some have used anti-androgens. Hormone therapy carries significant morbidity and can only be justified in the radical treatment of localised disease if it can be balanced against a significant gain in disease control and survival.

The mechanism of androgen suppression synergy with radical local radiotherapy is uncertain, but may include both sensitisation of the cancer cell to radiation and modification of the metastatic process [1]. Initial response in terms of

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prostate-specific antigen (PSA) reduction is almost universal, apart from very poorly differentiated tumours, which may not be considered for radical local treatment. Thus, a reduction in the number of viable tumour cells at the primary site might be expected, and so ablative local therapy would have a higher chance of eradicating sufficient cell numbers to achieve cure. In addition, hormone therapy is a systemic treatment and could affect micrometastases, which may be more important when seeking a survival effect. It has been suggested that within a short time of starting ADT there is significant vascular shutdown within the tumour [2], which theoretically could invoke radioresistance through hypoxia, but this has never been shown to affect clinical outcome of combined treatment.

Radiotherapy is a defined event within a specific timeframe, typically 7–8 weeks. Hormone therapy may be given for a variable length of time and may precede radiotherapy (neoadjuvant treatment, NAH), be given during radiotherapy and for a period after radiotherapy. The optimal timing and overall duration is uncertain; typically, patients with 'intermediate- to high-risk' localised disease receive NAH for 3–6 months before radiotherapy, whereas patients with 'high-risk' or locally advanced cancers might receive hormone treatment for 2 years or longer, with NAH often, but not always, part of that treatment. Which patients should receive hormone therapy, when, what type and for how long have not been clearly defined.

The aim of this study was to compare the outcomes of patients who have received external beam radiotherapy and hormone therapy, singly or in combination, as first-line treatment for prostate cancer, and to examine whether certain patient risk groups benefit from any of the treatment strategies.

Materials and Methods

Criteria for Considering Studies in this Review

Randomised controlled trials published in English comparing radiotherapy or hormone therapy alone with radiotherapy and hormone therapy in combination as first-line treatment in patients with non-metastatic prostate cancer reporting overall survival, disease-free survival, distant metastases-free survival, biochemical survival, adverse events (including cardiovascular) and/or health-related quality of life were considered.

Search Methods for Identification of Studies

The search strategy consisted of two searches; one updating the Cochrane review by Kumar *et al.* on this topic [3]; thus conducted from 2006 to 16 May 2013 for Medline, Premedline, Embase, Cochrane Library, Web of Science SCI & SCII and Biomed Central and an additional full search for orchiectomy (Medline [1946 to 16 May 2013], Premedline [15 May 2013], Embase [1974 to 16 May 2013], Cochrane Library [16 May 2013], Web of Science [SCI 1899 to 16 May 2013 and SSCI; 1956 to 16 May 2013] and Biomed Central [as per database]) using the OVID Medline search strategy (adapted to each database) detailed in Table 1.

Data Analysis

One author screened the results of the computerised search and imported all potentially relevant papers into a database, which was screened for relevant studies by another author. The inclusion of potentially relevant studies was confirmed by consensus between three of the authors

Table 1
OVID Medline search strategy (adapted to each database)

1	exp Prostatic Neoplasms/
2	Prostatic Intraepithelial Neoplasia/
3	(prostat$ adj3 (cancer$ or carcinoma$ or adeno$ or malignan$ or tum?r$ or neoplas$ or intraepithelial$)).tw.
4	PIN.tw.
5	1 or 2 or 3 or 4
6	exp Radiotherapy/
7	Radiotherapy, Adjuvant/
8	radiotherap$.tw.
9	(radiation adj (therap$ or treatment$)).tw.
10	external beam irradiation.tw.
11	external beam therap*.tw.
12	external beam treatment*.tw.
13	(EBRT or XRT).tw.
14	(CRT or 3DCRT or IMRT).tw.
15	conformal irradiation.tw.
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	5 and 16
18	exp Antineoplastic Agents, Hormonal/
19	exp Androgen Antagonists/
20	antiandrogens.mp.
21	((androgen$ or hormon$) adj3 (ablat$ or block$ or withdraw$ or depriv$ or supress$)).mp.
22	gonadotrophin releasing hormone analogue$.mp.
23	(luteinizing hormone releasing hormone or LHRH).mp.
24	grha.tw.
25	(zoladex or decapeptide).mp.
26	(eligard or leuprorelin or enatone or a-43818 or lupron or tap-144).mp.
27	exp Gonadotropin-Releasing Hormone/
28	exp Cyproterone/
29	(bicalutamide or casodex).mp.
30	exp Estrogens/
31	oestrogen.mp.
32	exp Flutamide/
33	(niftolid$ or eulexin).mp.
34	(nilutamide or nilandron$).mp.
35	exp Diethylstilbestrol/
36	exp Progestins/
37	exp Finasteride/
38	proscar.mp.
39	adjuvant hormon$ therap$.tw.
40	(neoadjuvant or neo-adjuvant hormon$ therap$).tw.
41	17 and 40
42	limit to 2006 onwards
43	exp Orchiectomy/
44	(orchiectom$ or orchidectom$).tw.
45	43 or 44
46	17 and 45
47	42 or 46