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Combined hormone therapy and radiation therapy for locally advanced prostate cancer☆

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Abstract

The combination of radiotherapy and androgen suppression with luteinizing hormone releasing hormone agonist has become a standard of care for locally advanced prostate cancer. Phase III randomized trials have shown that for locally advanced prostate cancer a 4-month complete androgen blockade initiated 2 months prior radiotherapy and stopped at the completion of radiotherapy increased overall survival in patients with Gleason score 2–6, meanwhile an adjuvant long term androgen suppression (2.5–3 years) improved significantly overall survival.

Keywords: Locally advanced prostate cancer; Hormonal treatment; External irradiation

1. Introduction

High risk prostate cancers include locally advanced prostate cancer (T3-4 N0-X M0), cancer with high grade disease defined as a Gleason scores of 8–10 (T1-2 N0-X M0) or those with a pretreatment serum PSA > 20 ng/ml [1]. The primary treatment was once androgen suppres-

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sion (AS) with orchiectomy or estrogens [2], and more than 80% of the patients respond favorably with side effects [3], which resulted in a replacement by an agonist analogue of the luteinizing hormone-releasing hormone (LHRH), with the same efficacy [4]. The poor results [5,6] of radiotherapy prompted the advent of phases III randomized trials combining radiotherapy (RT) and AS. Long term HT has become a "standard-of-care" and the local control is better obtained by three-dimensional conformal radiotherapy ± intensified modulated radiotherapy (3D-CRT ± IMRT) which has replaced conventional irradiation without increasing the risk of morbidity [7]. The aim of this review is devoted to published trials with definitive irradiation, excluding adjuvant or deferred radiotherapy after radical prostatectomy.

2. Rationale for combining androgen suppression with radiation therapy

The combination is aiming at decreasing the volume of the prostate, reducing the risk of local relapse within the irradiated volume by inhibiting repopulation during irradiation, decreasing the occurrence of distant metastases, improving the effectiveness of radiation by an additive or supra-additive effect. Animal studies on transplantable androgen dependant tumor, treated by radiation alone, radiation preceded by orchiectomy, radiation followed by orchiectomy ± androgen restauration [8–10], have shown that neoadjuvant AD provides: the greatest effect according to TCD 50, a supra-additive apoptotic response and result in prolonged suppression of tumor growth.

3. Combined hormone therapy and radiation therapy results of the phase III trials

3.1. Very high risk

3.1.1. Concomitant and long-term LHRH adjuvant hormonal treatment

The EORTC study compare radiotherapy with concomitant and adjuvant hormone therapy to radiotherapy alone; 82% of patients were T3, 10% T4, 89% N0. The hormone treatment was cyproterone acetate, beginning 1 week before the start of radiotherapy and subcutaneous injection of Zoladex® for 3 years starting on the first day of radiotherapy. There was a difference in 5-year survival, 78% in favour of the combination versus 62% for radiotherapy alone ($P = 0.001$) [11], confirmed at 10 years: 58.1% vs 39.8% ($P = 0.0004$). The 10-year prostate-cancer mortality was 31.0% with radiotherapy alone and 11.2% with long-term androgen suppression combined with radiotherapy ($P < 0.001$) [12].

3.1.2. Long-term LHRH adjuvant hormonal treatment

The RTOG Trial 85-31 was designed to evaluate the effectiveness of Zoladex® alone, started during the last week of radiation therapy and continued indefinitely or until relapse (arm 1) or started at relapse (arm 2). Fifteen percent of patients had undergone radical prostatectomy in group 1 and 14% in group 2, and 29 and 26% had lymph node involvement respectively. The combined approach has been associated with all 8-year efficacy end-points except overall survival; subset analysis by Gleason score, revealed a significant overall survival ($P = 0.036$) in favor of the adjuvant HT arm for centrally reviewed Gleason 8–10 patients who had not previously undergone prostatectomy [13]; 10-year overall survival was better for the adjuvant HT: 49% vs 39% ($P < 0.002$) [14].

3.1.3. Neo-adjuvant and concomitant short term combined androgen suppression

The RTOG trial 86-10 was designed to test the potential value of a combined androgen suppression (CAS) prior (2 months) and during radiation therapy (2 months) with respect to radiotherapy alone: 7% had a positive nodal status in the combined treatment arm versus 9% in the radiotherapy alone arm. Thirty percent of patients had a T2 tumor, 70% T3–4 and 91% of tumors were node negative [15]. At 8 years, AS has been associated with all efficacy end-points except overall survival, but subset analysis demonstrated that a significant enhancement in overall survival was seen in patients with Gleason score 2–6: 70% vs 52%; $P = 0.015$. These results were maintained at 10-year with a significant difference in disease specific mortality (23% vs 36%; $P = 0.01$), but no difference in 10-year overall survival (43% vs 34%; $P = 0.12$) [16].

The Trans-Tasman Radiation Oncology Group trial compared radiotherapy alone [17], 3-months AS with goserelin and flutamide starting 2 months before radiotherapy; or 6-month AS with the same regimen starting 5 months before radiotherapy. Compared with patients assigned RT alone those assigned 3-months androgen suppression had significantly improved disease free survival ($P = 0.0001$). Six-months AS improved prostate cancer specific survival ($P = 0.04$).

3.1.4. Short term neoadjuvant versus short term adjuvant combined androgen suppression with whole pelvis or prostate only radiotherapy

RTOG 94-13 study is a four arm trial devoted to patients with an estimated risk of lymph node involvement >15%. The first randomization is done between neoadjuvant concurrent hormone therapy (NCHT) – 2 months before and 2 months during RT – and 4-month adjuvant hormone therapy (AHT) after RT; the second randomization took place between whole pelvis radiotherapy (WPRT) followed by a boost to the prostate or prostate only radiotherapy (PORT). WPRT plus NCHT improved the 4-year progression free survival (61%) compared with PORT + NCHT (45%), PORT + AHT (49%)