Who Benefits from Neoadjuvant or Adjuvant Hormone Therapy?

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1. Introduction

Over the past decade, there has been increasing concern that local treatment with radical prostatectomy (RP) or radiation therapy (RT) alone is often not sufficient to eradicate localised prostate cancer (PCa). It is still questioned whether additional hormone therapy (HT) in either a neoadjuvant or adjuvant setting may improve treatment outcomes (eg, distant metastases, local failure, and overall survival [OS]) in these patients. According to the European Association of Urology (EAU) guidelines, a combination of HT with RT should be recommended in patients with locally advanced T3–4 N0 M0 PCa, as the addition of HT to RT can offer a survival benefit over RT alone [1]. Neoadjuvant HT to RT is currently used to shrink the prostate, therefore enabling optimal radiation doses to the prostate and reducing exposure of surrounding tissue. HT added to RT can also reduce the risk of distant metastases. However, HT...
has been associated with substantial adverse events such as hot flushes, metabolic syndrome, loss of libido, and erectile dysfunction (ED) [1].

As many PCa patients are still young and physically and sexually active, it is of paramount importance to appropriately select patients who may benefit from additional HT. In addition, further research is needed to determine the optimal duration of HT. This paper reviews the current status of neoadjuvant or adjuvant HT to curative treatment for patients with PCa.

2. Evidence acquisition

This paper is based on a presentation given at a satellite symposium on PCa that was held during the 2009 EAU Congress on 18 March 2009 in Stockholm, Sweden. Data were retrieved from recent original articles, review articles, and abstracts on neoadjuvant or adjuvant HT to local treatment for PCa.

3. Evidence synthesis

3.1. What is the benefit of neoadjuvant hormone therapy to radical prostatectomy?

According to a systematic review and meta-analysis of randomised trials of neoadjuvant HT in localised and locally advanced PCa, neoadjuvant HT to RP did not provide a statistically significant survival benefit over surgery alone (pooled relative risk: 1.00; 95% confidence interval [CI], 0.97–1.04; p = 0.95; Table 1) [2]. Moreover, Stephenson et al [3] developed a nomogram, with a concordance index of 0.8, to predict the long-term risk of PCa-specific mortality based on clinical data of 6398 patients who underwent RP from 1987 to 2005 in two US tertiary referral centres. External validation was performed on 4103 patients from a separate institution. Fifteen-year PCa-specific mortality and all-cause mortality were 12% and 38%, respectively. Surprisingly, besides biopsy Gleason grade, prostate-specific antigen (PSA), and year of surgery, neoadjuvant androgen-deprivation therapy (ADT) seems to be statistically significantly associated with PCa-specific mortality.

3.2. What is the benefit of neoadjuvant and adjuvant hormone therapy to radiation therapy?

HT is frequently combined with RT. Already >10 yr ago, Zietman et al [4], using an androgen-dependent breast cancer line (Shionogi tumour model), reported a significant reduction in the radiation dose required to control 50% of tumours when RT was combined with HT compared with RT alone. In addition, neoadjuvant HT resulted in a better efficacy than adjuvant HT to RT. With regard to clinical studies, the Radiation Therapy Oncology Group (RTOG) protocol 8610 was the first randomised phase 3 trial evaluating the effect of neoadjuvant HT to RT in 456 men with bulky (5 × 5 cm) T2–4 N0–M0 tumours between 1987 and 1991 [5]. At a follow-up period of 10 yr, patients who received 2 mo of neoadjuvant ADT plus 2 mo of concurrent ADT combined with RT demonstrated statistically significantly fewer clinical failures (p < 0.0001), distant metastases (p = 0.006), and PCa-specific deaths (p = 0.01) than patients who were treated with RT alone (Table 1) [5]. Although the 10-yr OS was 9% higher among men treated with neoadjuvant HT to RT versus RT alone, the improvement was not statistically significant. No differences in the risk of fatal cardiac events were observed between the treatment groups.

Furthermore, several randomised phase 3 clinical trials investigated the value of adjuvant HT to RT in patients with high-risk localised or locally advanced PCa [6–9]. Bolla et al

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### Table 1 – Overview of randomised, controlled, phase 3 trials evaluating neoadjuvant or adjuvant hormone therapy to radical prostatectomy or radiation therapy for the treatment of prostate cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study population</th>
<th>Treatment</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane meta-analysis [2]</td>
<td>Localised/locally advanced PCa T2–4 N0–X M0</td>
<td>Neoadjuvant HT to RP vs RP alone</td>
<td>No statistically significant improvement in OS</td>
</tr>
<tr>
<td>RTOG 8610 [5]</td>
<td>Low-risk localised or locally advanced</td>
<td>2 mo of neoadjuvant HT plus 2 mo of concurrent HT to RT vs RT alone</td>
<td>Statistically significantly fewer 10-yr clinical failures, distant metastases, and PCa-specific deaths</td>
</tr>
<tr>
<td>EORTC 22861 [10]</td>
<td>T1–T2 grade 3 or T3–T4 N0–1 M0 High-risk localised or locally advanced</td>
<td>Long-term (3 yr) adjuvant HT to RT vs RT alone</td>
<td>Better 10-yr OS but not statistically significant</td>
</tr>
<tr>
<td>SPCG-7/SFUO-3 [11]</td>
<td>Low-risk localised or locally advanced</td>
<td>HT + RT vs HT alone</td>
<td>Significantly better 10-yr OS</td>
</tr>
<tr>
<td>Canadian trial [14]</td>
<td>Localised T1c–2b N1–2 or pN1–2 or T2c–4 N0–2 M0</td>
<td>8-mo vs 3-mo neoadjuvant HT to RT 3-yr vs 6-mo adjuvant HT to RT</td>
<td>No increased 5-yr DFS, except in high-risk patients</td>
</tr>
<tr>
<td>EORTC 22961 [15]</td>
<td>Locally advanced</td>
<td>28-mo vs 4-mo HT to RT</td>
<td>Statistically significantly improved 10-yr DFS, DSS, local progression, distant metastasis, and biochemical failure</td>
</tr>
<tr>
<td>RTOG 9202 [16]</td>
<td>Locally advanced</td>
<td>No improved 10-yr OS, except in a subset of patients with Gleason score 8–10</td>
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</table>

PCa = prostate cancer; HT = hormone therapy; RP = radical prostatectomy; OS = overall survival; RTOG = Radiation Therapy Oncology Group; RT = radiation therapy; EORTC = European Organisation for Research and Treatment of Cancer; SPCG-7/SFUO-3 = Scandinavian Prostate Cancer Group Study 7 and Swedish Association for Urological Oncology 3; DFS = disease-free survival; DSS = disease-specific survival.
[7] demonstrated that HT starting on the first day of RT and continued for 3 yr was associated with a significantly better 5-yr OS than RT alone (78% vs 62%, p = 0.0002) in patients with T1-T2 grade 3 or T3-T4 N0-1 M0 PCa enrolled in the European Organisation for Research and Treatment of Cancer (EORTC) study 22861 between 1987 and 1995. Even at a longer follow-up period, the OS benefit was maintained in patients receiving long-term adjuvant HT (3 yr) to RT for locally advanced PCa without increasing cardiovascular toxicity (Fig. 1 and Table 1) [10]. It is still not proven whether the benefits are the result of hormone-induced radiosensitisation or of an effect on micrometastases. Recently, Widmark et al [11] performed an open, randomised phase 3 study comparing HT with and without RT to assess the effect of RT. The Scandinavian Prostate Cancer Group Study 7 and the Swedish Association for Urological Oncology 3 (SPCG-7/SFUO-3) trial included 875 men from 47 centres in Norway, Sweden, and Denmark who were treated with life-long antiandrogen therapy alone or antiandrogens plus RT for high-risk localised PCa. Median follow-up was 7.6 yr. The cumulative incidence at 10 yr for PCa-specific mortality was significantly lower for patients who were treated with antiandrogens plus RT than for patients who received antiandrogen therapy alone (11.9% vs 23.9%, p < 0.001; Table 1). This significant difference also translated into improved OS. After 5 yr, urgency, urinary incontinence, and ED were slightly more frequent among patients who received antiandrogens plus RT. However, at a follow-up period of 4 yr, quality of life was comparable between the treatment groups.

Although the addition of HT to RT may prolong disease-specific survival (DSS) and even OS in patients with high-risk localised or locally advanced PCa, there is some evidence suggesting that HT is associated with an increased risk of cardiovascular events [12]. D’Amico et al [13] examined the impact of comorbidities on treatment outcome in 206 men who received RT alone or RT plus 6 mo of HT for localised but unfavourable-risk PCa. At a median follow-up of 7.6 yr, 36% of patients died. The OS was significantly increased in men randomised to RT and HT compared with RT alone (p = 0.01), but this result appeared to apply only to men with no or minimal comorbidities. Among men with moderate or severe comorbidities, OS rates did not differ significantly (p = 0.08).

### 3.3. What is the optimal duration of neoadjuvant and adjuvant hormone therapy to radiation therapy?

Because the optimal duration of neoadjuvant or adjuvant HT has not yet been defined, several randomised trials have been performed to compare different durations of HT. In addition, shortening the period of HT may reduce the therapy’s costs and adverse events. This is the rationale for a Canadian multicentre, randomised, controlled phase 3 trial that evaluated the effect of 3 mo versus 8 mo of neoadjuvant ADT to RT in 378 men with clinically localised PCa between 1995 and 2001 [14]. A longer period of neoadjuvant HT to RT did not improve the 5-yr disease-free survival (DFS), except in a subgroup of high-risk patients (Fig. 2 and Table 1). In the EORTC randomised phase 3 trial 22961, Bolla et al [15] compared 6 mo with 3 yr of concomitant and adjuvant HT to RT in 970 patients with T1c-2b N1-2 or pN1-2 or with T2c-4 N0-2 M0 PCa. Noninferior OS was defined as a mortality hazard ratio (HR) ≤ 1.35 for short-term HT versus long-term HT. At a median follow-up of 6.4 yr, 24% of patients died. The 5-yr OS rate was 81.1% versus 85.1% (HR: 1.47; 95% CI, 1.12–1.94) for patients who received 6 mo of HT compared with 3 yr of HT, respectively. Thus, noninferiority in terms of OS could not be proven in patients receiving 6 mo versus 3 yr of adjuvant HT to RT (Table 1). In addition, at 5 yr, clinical progression-free survival (PFS) and biochemical PFS were significantly worse for patients who were treated with 6-mo adjuvant HT than patients randomised to 3-yr adjuvant HT to RT. In accordance with EORTC trial 22961, updated RTOG study 9202 reported that the addition of long-term HT (24 mo) improved outcomes in patients with locally advanced PCa who were treated with short-term HT (4 mo) before and during RT (n = 758) compared with no further HT (n = 763) in terms of 10-yr DFS (22.5% vs 13.2%; p < 0.0001), DSS (88.7% vs 83.9%; p = 0.0042), local progression (12.3% vs 22.2%; p < 0.0001), distant metastasis (14.8% vs 22.8%; p < 0.0001), and biochemical failure (51.9% vs 68.1%; p ≤ 0.0001; Table 1) [16]. A difference in OS at 10 yr was not
observed, except in a subset of patients with Gleason score 8–10 (45.1% vs 31.9%; \( p = 0.0061 \)) in favour of long-term HT to RT.

4. **Conclusions**

Neoadjuvant HT to RP does not seem to offer a survival benefit over RP alone in patients with localised or locally advanced PCAs. Moreover, besides biopsy Gleason grade, PSA, and year of surgery, neoadjuvant HT before surgery may have a detrimental effect on PCAspecific survival. In contrast, neoadjuvant HT to RT appears to improve treatment outcomes, except OS, over RT alone in patients with locally advanced PCAs. Adjuvant HT to RT can significantly improve OS compared with RT alone in high-risk localised and locally advanced PCAs patients. Furthermore, compared with HT alone, the addition of RT to HT halved the 10-yr PCAspecific mortality in patients with high-risk localised or locally advanced PCAs, with acceptable risk of adverse events. However, the OS benefit may pertain only to patients with no or minimal comorbidities. With regard to the optimal duration of neoadjuvant or adjuvant HT to RT, the EORTC 22961 trial failed to prove noninferiority in terms of OS of 6 mo of HT compared with 3 yr of HT to RT. In line with these data, it has been suggested that long-term HT should be the standard of care, especially in patients with high-risk PCAs.

**Conflicts of interest**

The author has no conflicts of interest.

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**References**


