Neoadjuvant and Adjuvant Hormone Therapy: How and When?

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Abstract

Context: A significant proportion of patients with prostate cancer (PCa) will experience clinical or biochemical failure after local treatment with radical prostatectomy (RP) or radiotherapy (RT). It is still a matter of debate whether hormone therapy (HT) in either a neoadjuvant or adjuvant setting can offer a survival benefit for these patients.

Objective: This review paper discusses how and when neoadjuvant and adjuvant HT could be applied for treatment of PCa. Furthermore, the paper outlines the optimal duration of adjuvant HT to RT for treatment of patients with high-grade localised or locally advanced PCa.

Evidence acquisition: This paper is based on a presentation given at a satellite symposium held at the European Association of Urology (EAU) 2008 annual congress in Milan, Italy. Data were retrieved from recent review articles, original articles, and abstracts on neoadjuvant or adjuvant HT in PCa.

Evidence synthesis: Luteinising hormone-releasing hormone agonists have become the standard of care in HT. Neoadjuvant androgen deprivation therapy (ADT) to RP seems to have potential to downstage PCa disease but does not offer a survival benefit over RP alone in patients with localised PCa. On the other hand, short-term neoadjuvant ADT to RT appears to improve treatment outcomes compared with RT alone in patients with locally advanced PCa but seems to be specifically indicated in patients with Gleason score 2–6. Adjuvant ADT with RT seems to offer a survival benefit over RT alone in high-risk localised and locally advanced PCa. Recent data indicate that 6-mo ADT is inferior in terms of survival to 3-yr adjuvant ADT after RT for patients with locally advanced PCa. The role of immediate ADT for men with node-positive PCa after RP should be further investigated.

Conclusions: Neoadjuvant and adjuvant ADT to local treatment may be indicated in carefully selected patients with PCa.

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1. Introduction

Despite early detection and local treatment with radical prostatectomy (RP) or radiotherapy (RT), a significant proportion of patients with cT1–T2 prostate cancer (PCa) will experience clinical or biochemical failure with variable prognoses. The inaccuracy of clinical staging might be a possible explanation for this [1].

Hormone therapy (HT) was originally introduced as a treatment option for patients diagnosed with metastatic PCa [2]. Currently, HT is being used in earlier stages of PCa to increase the likelihood of cure after local treatment. However, it is still a matter of debate whether HT really prolongs survival in all clinical settings, for example, localised or locally advanced PCa. Furthermore, the timing of initiating HT—for example, in a neoadjuvant or adjuvant setting—and the type of HT have become crucial factors in the appropriate treatment of patients with PCa.

In this review paper, we focus on hormone therapy with luteinising hormone-releasing hormone (LHRH) agonists and discuss in which cases neoadjuvant and adjuvant androgen deprivation therapy (ADT) to local treatment can offer a potential benefit in patients with PCa. Furthermore, this paper outlines recent trials evaluating the optimal duration of adjuvant ADT with RT for treatment of patients with high-grade localised or locally advanced PCa.

2. Evidence acquisition

This paper was based on a presentation given at a satellite symposium on PCa that was held during the 23rd annual congress of the European Association of Urology (EAU), 26 March 2008, in Milan, Italy. Data were retrieved from recent review articles, original articles, and abstracts on neoadjuvant and adjuvant ADT in PCa.

3. Evidence synthesis

3.1. Types of hormone therapy

Although many different types of HT are currently available, only a few are recommended by the EAU guidelines for the treatment of PCa [2]. ADT slows the growth of PCa by lowering the levels of androgens, and it has been the mainstay of treatment of advanced and metastatic PCa. Androgen deprivation can be achieved either by surgical (orchidectomy) or medical castration (eg, oestrogens, LHRH agonists, LHRH antagonists) or by inhibiting the action of circulating androgens at the level of their receptor in prostate cells using competing compounds known as antiandrogens (eg, bicalutamide, flutamide). Alternatively, these therapies can be combined in what is called complete androgen blockade. From the recent literature, complete androgen blockade appears to provide only a small survival benefit over monotherapy. On the other hand, minimal androgen blockade (eg, 5α-reductase inhibitors) is still regarded as investigational and seems to be a treatment option for older patients for whom quality of life is of paramount importance [2].

LHRH agonists (eg, goserelin, leuprorelin, triptorelin) have become the method of choice in HT because these agents have a good efficacy profile, without the physical and psychological discomfort associated with surgical castration and with less pronounced cardiotoxicity than with oestrogens [2].

3.2. Neoadjuvant and adjuvant androgen deprivation therapy to radical prostatectomy

The EAU guidelines recommend RP as standard treatment for patients diagnosed with stage T1b–T2 PCa and a life expectancy >10 yr who accept treatment-related complications (level of evidence 1b) [2]. Surgery is often not recommended for patients with locally advanced PCa, as this often leads to incomplete tumour excision. However, RP for locally advanced PCa has gained renewed interest since clinical stage T3 PCa is overstaged in about 20% of cases. Although still controversial, good results have been obtained after surgery on patients with cT3a PCa and a life expectancy >10 yr [3]. Most debate is related to whether these patients should receive additional ADT in either a neoadjuvant or adjuvant setting.

Neoadjuvant ADT to RP seems to induce pathological downstaging and decrease the number of positive surgical margins and rate of lymph node involvement in patients with localised PCa [1]. On the other hand, according to a Cochrane meta-analysis [4], neoadjuvant ADT to RP does not seem to provide a significant advantage in overall survival and progression-free survival over prostatectomy alone in patients with predominantly localised T1 and T2 PCa. To date, the effect of neoadjuvant ADT to RP in patients with locally advanced PCa has not been well studied. A retrospective study presented at the EAU 2008 annual congress demonstrated that in patients with initially unresectable (cT3), locally advanced, and high-risk PCa (Gleason score ≥8 or prostate-specific antigen [PSA] ≥20 ng/ml), the
multimodality approach of neoadjuvant HT (median 6 mo) and RP provided a significant chance for long-term disease-free status without major peri- or postoperative complications [5]. Randomised controlled clinical trials are needed to further assess the role of neoadjuvant HT to RP in these patients.

Messing et al [6] performed a prospective randomised trial and compared immediate ($n = 47$) versus deferred ($n = 51$) ADT in patients with node-positive PCa after RP and pelvic lymphadenectomy. At a median follow-up of 11.9 yr, men treated with immediate ADT had a significant improvement in overall survival ($p = 0.04$), PCA-specific survival ($p = 0.0004$), and progression-free survival ($p < 0.0001$) compared with deferred ADT. Most patients, however, had high-burden disease (eg, seminal vesicle involvement, positive surgical margins, Gleason score 8–10), and we still do not know whether patients with minimal node involvement would demonstrate the same results.

### 3.3 Neoadjuvant and adjuvant androgen deprivation therapy to radiotherapy

According to the EAU guidelines, short-term adjuvant ADT to RT for patients with high-risk localised PCa (T2c or Gleason score >7 or PSA >20 ng/ml) may result in increased overall survival (level of evidence 2b). The role of neoadjuvant ADT to RT in patients with high-risk disease is more controversial. Adjuvant ADT to RT is recommended for patients with locally advanced PCa (level of evidence 1) [2].

The Radiation Therapy Oncology Group (RTOG) 8610 trial was the first major, phase 3 randomised trial investigating the effect of short-term neoadjuvant ADT to RT in patients with locally advanced PCa [7]. The trial included 471 patients with bulky T2–T4 disease, with or without pelvic lymph node involvement, who received 2 mo neoadjuvant and 2 mo concomitant ADT combined with RT versus RT alone. At 8 yr, neoadjuvant ADT was associated with an improvement in local control (42% vs 30%, $p = 0.016$), disease-free survival (33% vs 21%, $p = 0.004$), biochemical disease-free survival (24% vs 10%, $p < 0.0001$), and a reduction in the incidence of distant metastases (34% vs 45%, $p = 0.04$) and PCA-specific mortality (23% vs 31%, $p = 0.05$). Subset analysis showed that the beneficial effect of short-term neoadjuvant ADT appears preferentially in patients with Gleason score 2–6. Recently, Roach et al [8] demonstrated the long-term follow-up results of the RTOG 8610 trial and confirmed the important clinical benefits of adding short-term neoadjuvant ADT to RT in patients with locally advanced PCa (Fig. 1). The role of neoadjuvant ADT to RT in patients with localised PCa has not been demonstrated yet.

The European Organisation for Research and Treatment of Cancer (EORTC) 22863 [9] and RTOG 8531 [10] trials clearly demonstrated that long-term adjuvant ADT with RT improved PCA-specific and overall survival over RT alone in patients with locally advanced PCa. This survival benefit was preferentially noted in patients with Gleason score 7–10. In addition to these trials, equivocal results have been obtained in patients with high-risk localised disease [11,12]. A prospective randomised controlled trial including 206 patients with high-risk localised PCa (PSA ≥10 ng/ml, Gleason score ≥7 or radiographic evidence of extraprostatic disease) compared short-term (6 mo) adjuvant ADT plus...
RT with RT alone. After a median follow-up of 4.5 yr, patients receiving 6-mo adjuvant ADT with RT had a significantly higher overall survival rate ($p = 0.04$), higher survival rate free of salvage ADT ($p = 0.002$), and lower PCa-specific mortality rate ($p = 0.02$) [11]. A more recent retrospective study confirmed that 6-mo adjuvant ADT combined with RT was beneficial in PCa patients with a rapidly increasing pretreatment PSA level. Despite a significantly longer follow-up, younger age at diagnosis, higher proportion of Gleason score 7–10, and advanced T-category cancers, significantly lower estimates of PSA recurrence ($p < 0.001$), disease-specific mortality ($p = 0.005$), and all-cause mortality ($p < 0.001$) were observed in patients treated with ADT and RT compared with RT alone [12].

3.4. Long-term versus short-term adjuvant androgen deprivation therapy to radiotherapy

Although a survival benefit of adjuvant ADT to RT over RT alone has been shown in patients with high-risk localised and locally advanced PCa, some questions remain. What is the optimal duration of adjuvant ADT to RT? After the EORTC 22863 trial [9], 3-yr adjuvant ADT to RT has been regarded as the standard treatment for locally advanced PCa. In a recent study report, the association of short- versus long-term ADT plus RT with prolonged survival for treatment of node-negative, high-risk PCa was evaluated. A pooled analysis of 311 men enrolled in three prospective randomised trials between 1987 and 2000 who received 6-mo or 3-yr ADT with RT for locally advanced or high-grade localised PCa comprised the study cohort. After adjusting for known prognostic factors, the treatment of node-negative, high-risk PCa with 3-yr versus 6-mo ADT plus RT was not associated with prolonged survival in men with advanced age [13].

On the contrary, updated results of the EORTC 22961 trial [14] comparing 6-mo versus 3-yr adjuvant ADT with RT in patients with T1c–2b N1–2 or pN1–2, or T2c–4 N0–2 M0 PCa and PSA < 150 ng/ml showed that 6-mo ADT ($n = 483$) was inferior in terms of survival to 3-yr adjuvant ADT ($n = 487$) after RT (Fig. 2). The noninferiority of 6-mo ADT versus 3-yr ADT could not be confirmed. However, it should be mentioned that most patients in this study had T2c–T3 N0 PCa. Furthermore, there is currently no study available which directly compared the combination of HT and RT with HT alone. This means that it is still uncertain whether the positive effects achieved are due to the combination of both treatments or to HT alone.

4. Conclusions

Although there are many different types of HT available, LHRH agonists are frequently applied. Neoadjuvant ADT can be administered prior to RP to downstage PCa disease in patients with localised PCa, but a survival benefit has not been demonstrated. Further, additional research is needed to define the role of adjuvant ADT for men with node-positive PCa after RP. Neoadjuvant ADT to RT appears to improve treatment outcomes in patients with locally advanced disease, but this beneficial effect has not been demonstrated in patients with localised PCa. Adjuvant ADT with RT seems to offer a clear survival advantage over RT alone in locally advanced and high-risk localised PCa. However, the
optimal duration of adjuvant ADT to RT in these patients remains unclear. The recently updated EORTC 22961 trial showed that survival with short-term adjuvant ADT seems to be shorter than with long-term adjuvant ADT after RT for patients with locally advanced PCa. Despite promising results in carefully selected patients, it is clear that more randomised studies with long-term follow-up are needed to further investigate the value of neoadjuvant and adjuvant ADT to local treatment for PCa.

Conflicts of interest

Prof. Van Poppel received an honorarium for presenting the lecture at the EAU symposium on which this paper was based.

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