

Adjuvant Therapy in High Risk Prostate Cancer: The Argument PRO

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Abstract

Most patients diagnosed with localized prostate cancer today are cured with surgery or radiation therapy to the prostate. However, a subset of patients can be defined as having a high risk of failure with standard treatment. This risk stratification for disease recurrence is based on established parameters for T stage, Gleason score and PSA.

Adjuvant therapy after surgery has been applied in other tumors and may improve local control, progression-free survival and survival. In men with extracapsular disease or positive surgical margins after radical prostatectomy, adjuvant radiotherapy is a common treatment option. Placebo controlled randomized studies on adjuvant hormonal therapy have resulted in improved progression-free survival and prolonged survival. Drug toxicity and the impact of treatment on quality of life are important considerations when selecting an adjuvant therapy.

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1. Introduction

The introduction of prostate-specific antigen (PSA) based early detection programs means that prostate cancer is now being detected in younger men and at earlier disease stages than was previously possible [1]. Of the new prostate cancer cases, as many as 85% will be diagnosed at local or regional stages. Management options for early stage patients include radical prostatectomy, radiotherapy, hormonal therapy, and watchful waiting.

Many men who undergo early treatment for prostate cancer have an excellent outcome, however a significant proportion experience disease recurrence and will progress to lethal metastatic disease despite optimal local therapy.

A risk assessment may identify those patients who need adjuvant treatment despite optimal local treatment [2,3]. Approximately one-third of men with clinically localized disease develop PSA progression following radical prostatectomy or radiotherapy [4–6].

However a PSA rise will not detect a recurrence smaller than 10^7 to 10^8 cells, nor does PSA identify the site of recurrence.

D'Amico et al. reported that patients with either biopsy Gleason scores of 8 to 10, prostate specific antigen (PSA) greater than 20 ng/ml or clinical stage T3 or T4 disease are at high risk of treatment failure as measured by biochemical recurrence 5 years after local therapy [7]. However, the distribution of patients with high risk disease has shifted and currently patients with locally advanced disease (T3 or T4) or high PSA values at presentation are rare. Based on recent data from CaPSURE (Cancer of the Prostate Strategic Urological Research Endeavor), the proportion of patients presenting with high, intermediate and low risk disease changed between 1989 to 1990 and 2001 to 2002 from 40.9%, 28.0% and 31.2% to 14.8%, 37.5% and 47.7%, respectively [1].

The incidence of T3–4 tumors decreased from 11.8% to 3.5%, respectively. This reflects a significant downward risk migration. Despite these trends adjuvant treatment options should be offered to patients based on their individual risk assessment according to validated nomograms [8].

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Nomograms may predict the individual pathological stage or outcome in men with prostate cancer scheduled for radical prostatectomy or radiation therapy. A recent study revealed that nomograms were comparable to expert opinions in predicting organ confined disease at surgery, and performed better in predicting 5-year recurrence-free survival in a clinical practice setting [9].

2. Adjuvant hormonal therapy

Randomized studies have shown that castration by bilateral orchiectomy or luteinizing hormone-releasing hormone agonists as adjuvant to radiotherapy resulted in prolonged progression-free and overall survival [3,10,11].

Studies on adjuvant hormonal therapy after radical prostatectomy have also reported significant progression-free and overall survival advantages [5,12–15].

After radical prostatectomy adjuvant hormonal therapy should ideally be offered to patients with disease that has spread to the lymph nodes or extended beyond the prostate since as many as 75% of such patients may have PSA progression within 5 years.

Focally positive margins are associated with a 40% risk of progression at 5 years, while extensive positive margins cause a 65% risk [2,4].

The majority of patients with recognized regional lymph node metastasis have disease progression when not treated. Since lymph node metastasis is due to systemic disease, the goal of treatment is to prolong the duration of freedom from disease.

In a recent prospective randomized study published by Messing et al. the impact of adjuvant hormonal therapy in lymph node positive cases was analyzed [12]. With a median follow-up of 7.1 years the authors could demonstrate a significant survival benefit in men with immediate hormonal therapy after radical prostatectomy in men with positive lymph nodes.

Zincke et al. reported the Mayo clinic experience with adjuvant hormonal therapy in 707 patients treated with radical prostatectomy [5]. In this retrospective analysis with a median follow-up of 8, 7 years adjuvant hormonal therapy resulted in improved progression and cancer death rates.

However, castration is associated with decreased libido, sexual dysfunction, fatigue, hot flashes, loss of bone mineral density and increased risk of osteoporotic fractures [6].

Results of the bicalutamide 150 mg Early Prostate Cancer (EPC) programme evaluated the efficacy of bicalutamide 150 mg once daily as adjuvant antiandrogen treatment [14].

With a median follow-up of 3 years, bicalutamide 150 mg significantly reduced the risk of objective disease progression. Among patients treated with radical prostatectomy, 15% of patients on bicalutamide 150 mg met the criteria for PSA progression (PSA doubling, 262 patients; objective progression, 20 patients; and death, 54 patients) compared with 26% of patients on placebo (PSA doubling, 496 patients; objective progression, 30 patients; and death, 47 patients). With longer follow-up sufficient data on overall survival will be available and may identify risk groups for adjuvant antiandrogen therapy. The most common adverse events were mild-to-moderate gynaecomastia and/or breast pain.

3. Adjuvant radiation

Patients at high risk for local failure following radical prostatectomy and at low risk for distant metastases may be offered immediate adjuvant radiotherapy to improve progression-free survival rates and reduce local relapse.

The pathologic findings at the time of surgery can be used to distinguish patients at risk for local recurrence from patients at risk for systemic progression [2,15–18].

Studies suggest that adjuvant external beam RT for extracapsular extension or positive surgical margins enhances cancer control by maintaining undetectable prostate specific antigen (PSA) and decreasing the risk of local and systemic progression.

Valicenti et al. performed a matched pair analysis in pT3N0 prostate cancer; 36 patients were treated with adjuvant RT and compared with specimens from 36 not treated with RT who were matched with respect to PSA (less than 10 vs. 10 ng/ml or greater), Gleason score (less than 7 vs. 7 or greater), seminal vesicle invasion and surgical margin status [16]. RT was associated with a significant decrease in the 5-year risk of biochemical recurrence from 89% for patients receiving adjuvant RT vs. 55% for those undergoing radical prostatectomy alone.

Adjuvant therapy is less toxic than salvage radiotherapy after radical prostatectomy in patients with positive surgical margins. Severe (grade 3 to 4) gastrointestinal complications are extremely rare [19]. Urinary strictures may occur in 5% to 10% of patients. In a prospective randomized study Van Cangh et al. noted that 60 Gy external RT administered 3 to 4 months after RP for pathologically locally advanced prostate cancer had no significant impact on urinary continence compared with prostatectomy alone [19].

In contrast, salvage radiotherapy may lead to poorer urinary control in 5% to 10% of patients, probably due to the higher doses required for salvage radiotherapy.

Adjuvant radiotherapy is both more effective and safer than salvage treatment, to whom should it be offered? Patients with positive surgical margins after radical prostatectomy have increased 5-year progression rates between 36% and 50%. Postoperative radiation therapy (RT) is often advocated for improving these outcomes. In a retrospective study, Kamat et al. analyzed the response to adjuvant RT given for patients with positive margins after RP and undetectable PSA [8]. Only Gleason grade 4 or greater and pre-RP PSA greater than 10.9 ng/ml were predictive of biochemical recurrence after adjuvant RT.

These patients at high risk for local failure but low risk for distant metastases should be offered immediate adjuvant radiotherapy.

4. Adjuvant chemotherapy

Cytotoxic chemotherapy has demonstrated significant palliative benefit in the treatment of hormone refractory prostate cancer. More recently, the taxanes have been shown a PSA decreases of 50% or more in approximately two-thirds of patients [20].

However the optimal agent or combinations of chemotherapy, duration of treatment, need for androgen deprivation therapy and definition of risk groups remain unknown.

A recent study evaluating adjuvant chemotherapy with mitoxantrone suggested a survival benefit to 4 cycles of mitoxantrone chemotherapy [21].

An intergroup trial sponsored by the NCI is randomizing high risk patients after radical prostatectomy with Gleason scores of 8 to 10, pT3b or pT4 disease or node positive disease to 2 years of adjuvant androgen

deprivation therapy with or without 6 cycles of mitoxantrone plus prednisone [21].

A randomized trial sponsored by the Radiation Therapy Oncology Group is analyzing the combination of paclitaxel, etoposide and estramustine in patients with clinically determined high risk disease treated with external beam radiotherapy and androgen deprivation therapy [21].

More active and less toxic agents may improve systemic therapy in patients with high risk of progression.

In Phase II trials targeted therapy including use of growth factor inhibitors, angiogenesis inhibitors, antioxidants and inducers of apoptosis is analyzed [20].

Most drugs are tested in a neoadjuvant or salvage setting, however some of the reported results may be promising for the use in an adjuvant setting.

5. Conclusion

Despite primary surgery many men with locally advanced, stage pT3b or N+ prostate cancer can have progressive disease with local or systemic recurrence. Unfortunately when patients are treated at progression, the conventional therapies offer only possible palliation of symptoms but no long-term cure. The timing and duration of adjuvant hormonal therapy are controversial and no definitive recommendation can be made regarding immediate or deferred hormonal therapy until more results of prospective randomized trials are reported.

In selected cases adjuvant radiation or hormonal therapy has a significant impact on time to progression and cause specific survival in men with locally advanced prostate cancer.

New treatment options are analyzed in phase II trials and may offer alternative or targeted therapies.

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