Low and intermediate risk prostate cancer – role of hormonal therapy with external beam radiation therapy

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Risk categorization based on pre-treatment PSA, clinical stage and Gleason score is now widely used in the management of patients with localized prostate cancer. In patients with low-risk disease (cT1-T2a, PSA < 10 ng/ml and Gleason score ≤ 6) there is no role for the routine use of adjunctive hormonal therapy. In intermediate-risk patients (T1-T2, PSA < 20 ng/ml and Gleason ≤ 7) there is some evidence to suggest improved outcomes with neo-adjuvant hormonal therapy when low-dose external beam radiation therapy (EBRT) is used. However, with appropriate modern dose EBRT there is little data to support the use of routine adjunctive hormonal therapy and this should be done only in the context of a clinical trial.

Key Words: prostate cancer, radiation therapy, hormones, risk categorization

Introduction

Androgen deprivation is a well-established treatment strategy for patients with metastatic prostate cancer. However, its role in patients with localized disease is unclear. In surgical studies, androgen deprivation has been shown to downstage tumors but randomized trials have not shown any improvement in clinically relevant outcomes .[1-3] However several studies over the past 2 decades have suggested that androgen deprivation improves outcome in patients with locally-advanced disease treated with external beam radiation therapy.[4-9]

In the modern era more than 90% of patients present with clinically localized disease and > 80% of these patients fall into the subsets of low and intermediate-risk disease.[10] High-risk disease is now routinely approached with combined

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hormonal-radiotherapy based on randomized studies that have shown improvements in overall survival.[4-7] Treatment strategies for low and intermediate-risk prostate cancer include watchful waiting, hormone therapy (e.g. androgen deprivation or AD), radical prostatectomy, brachytherapy, and external beam radiotherapy (EBRT). However, based on the data from high-risk disease, the use of neo-adjuvant and adjuvant hormonal therapy in patients treated with EBRT has risen substantially over the past decade despite the toxicity of this strategy and the lack of proven benefit. The applicability of the high-risk trial data is further confused by the fact that the dose of radiation used in these studies was sub-optimal. In this manuscript we will discuss risk categorization in localized prostate and review the role of adjunctive hormonal therapy with EBRT.

Risk categorization

The primary purpose of a risk stratification system is to accurately correlate the probability of treatment failure and to help facilitate the selection of the optimal therapeutic approach. Risk stratification systems are also helpful in ensuring prognostic uniformity in clinical trials and in the evaluation of treatment outcomes. The most widely used system is the UICC/AJCC TNM staging system but this does not incorporate two important prognostic factors: pre-treatment Prostate Specific Antigen (PSA) level and Gleason Score (GS).

In December 2000, the Genitourinary Radiation Oncologists of Canada (GUROC) met in Vancouver to review the available evidence on risk stratification in prostate cancer and reached a consensus on the appropriate classification system to use, Table 1.[11] In this system low-risk prostate cancer was defined as the presence of all of these factors: clinical stage T1-T2a, PSA < 10 ng/ml and Gleason score ≤ 6; high-risk disease was defined as the presence of any of these factors: T3-T4; PSA > 20 ng/ml or Gleason score ≥ 8. All other cases of localized disease fall into the intermediate-risk category. This model has recently been demonstrated to be internally consistent and to accurately predict prostate cancer specific mortality in patients treated with surgery or radiation therapy.[12,13]

Recent data from the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) registry indicate that there has been a stage migration of prostate cancer over the last 15 years since PSA (prostatic specific antigen) screening became widely available in the United States.[10] According to the CaPSURE registry, between 1989 and 2002, the proportion of patients presenting with low-risk disease increased from 31% to 47% and presenting with intermediate-risk disease increased from 34% to 37%. Therefore, more than 80% of all new patients now present with low or intermediate-risk disease and less than 20% present with high-risk tumors.

Low-risk disease

The results of treatment of patients with low-risk with external beam radiation therapy alone are excellent with biochemical freedom from disease (bNED) rates of more than 80% with the use of modern radiation techniques and appropriate RT doses. Kupelian et al have reported a 93% 5-year bNED rate in 217 consecutive patients treated at the Cleveland Clinic in patients treated with ≥ 72 Gy.[14] These excellent results with EBRT were confirmed by Zietman et al in a randomized dose-escalation trial with > 80% of 116 low-risk patients free of disease at 5 years.[15] A number of consensus conferences have discussed androgen deprivation with EBRT in these patients and it is clear that there is no role for the routine use of hormonal therapy.[11,16,17] However, it is distressing to note that 57% of patients with low-risk disease being treated with EBRT receive neo-adjuvant hormonal therapy in community practice in the United States.[18] While low-risk patients should be entered onto clinical trials to assess the role of adjunctive hormonal therapy with radiation therapy, unless a subpopulation of patients with a poor prognosis can be identified, it is unlikely that meaningful results will be found.

TABLE 1. **Risk categories**

Risk group	**PSA (ng/ml)**	**Gleason Score**	**UICC T category**
Low (all of)	≤ 10	≤ 6	≤ T2a
Intermediate (any of, if not low risk)	≤ 20	7	T1/T2
High (any of)	> 20	≥ 8	≥ T3

Intermediate-risk disease

The randomized trial data presented in Table 2 show that improvement in local control and/or disease-free or overall survival can be achieved when androgen deprivation is combined with conventional-dose EBRT in patients with high-risk disease.[4,6-8,19] D'Amico et al have recently reported improved survival in 206 patients treated with 70 Gy and 6 months of AD versus 70 Gy alone (88% versus 78%; P<0.04).[20] Approximately 80% of these patients had intermediate-risk disease. There have been a number of concerns raised about this trial including the fact that the difference in survival was based on only six prostate cancer-specific deaths in the control arm, as compared to no prostate cancer-specific deaths in the experimental arm.[21] In addition, data on the primary study endpoint (biochemical progression) was not provided in the manuscript. A small study by Laverdiere et al showed improved PSA-based outcome using 64 Gy plus AD. In this RCT, 70% of patients could be classified as intermediate-risk but further follow-up is necessary to fully evaluate this trial.[5]

Despite these recent data, two issues complicate current decision-making as to the role of AD in intermediate-risk disease. The first concern is that the randomized studies showing benefit to adjunctive AD (either neoadjuvant or adjuvant) combined with EBRT have largely been completed in patients with high-risk disease. As such, their conclusions may not be applicable to any or all intermediate-risk patients. The second issue is that these trials have been completed in the era of conventional dose EBRT (doses less than 74 Gy) and long-term bNED rates with EBRT alone using these dose fractionation schemes were approximately 40% in intermediate-risk patients.[22-24]

Non-randomized, single-institution series have reported clinical outcome data regarding the role of AD in addition to dose-escalated EBRT for intermediate-risk patients. Kupelian et al reported on the treatment outcome in a cohort of 1041 consecutively treated patients with T1-T2 prostate cancer who were treated with radical prostatectomy, EBRT, brachytherapy (permanent seed implantation) or combined brachytherapy and EBRT.[14] Seven hundred and eighty five patients were treated with EBRT (484 given ≤ 72 Gy, 301 > 72 Gy) and 143 of these patients were given neoadjuvant AD (≤ 6 months duration). While AD was a significant predictor of biochemical outcome on univariate analysis for the whole patient cohort, when the group of patients treated to ≤ 72 Gy was excluded, this was no longer significant (p=0.91). Zelefsky et al reported on their cohort of 772 patients (89% T1-T2 disease; treated with IMRT to a median dose of 81 Gy) that AD had no influence on the biochemical freedom from disease (median follow-up of 24 months).[25] Furthermore, a lack of benefit (and a possible detrimental effect) of short-course AD on 5-year metastasis-free survival and cause-specific survival, has been reported by Martinez et al in a large retrospective review of 1260 patients treated with combined EBRT and brachytherapy.[26] Although these studies do not represent definite evidence on the lack of benefit of adjunctive hormonal therapy in these patients, their consistent findings suggest that the addition of AD to dose-escalated EBRT may not be required to optimize biochemical outcome for intermediate-risk patients. The recent RCTs by D'Amico and Laverdiere are of interest, but further data using survival end-points are required before recommending AD in addition to dose-escalated EBRT for the intermediate-risk group.

Toxicity of sort term adjunctive hormonal therapy

The side effects of long-term hormonal therapy are well known but more relevant to the treatment of

TABLE 2. **Benefit of adjunctive hormones in high-risk disease– summary of studies**

Study	**RTOG 85-31**	**RTOG 86-10**	**EEORTC 22863**	**RTOG 92-02**	**TROG 96-01**	
HT duration	**indefinite**	**4 months (neoadjuvant and concurrent)**	**3 years**	**2 years**	**3 months**	**6 months**
Overall survival	15% (10 yrs)	-	16% (5 yrs)	-	-	-
OS Gleason 8-10	17%	-	11%	-	-	-
Distant mets free	10%	11%	19%	5.5%	-	6%
Local control	14%	12%	14%	6%	11%	16%
bNED	24%	14%	31%	27%	14%	16%

intermediate-risk prostate cancer is the toxicity of neoadjuvant androgen deprivation for a period of 3-6 months. Hot flashes occur in about 80% of men.[27] Depression and impairment of cognition have also been linked to short term use of hormones, and decreased libido, erectile dysfunction and fatigue are also experienced in the majority of treated men.[28,29]

A decline in hemoglobin (Hgb) of > 1.0 g/dL was observed in 75% of patients after a period of 2 months in a study involving total androgen blockade.[30] There has been some suggestion that patients who have a significant decrease in hemoglobin with neoadjuvant hormonal therapy have a poor biochemical outcome with EBRT.[31] This possible effect of hemoglobin on outcome is similar to that observed during radical radiotherapy studies in cervix cancer and head and neck cancer.[32,33] These results suggest that caution is warranted when AD and EBRT are used for intermediate-risk prostate cancer patients outside of the context of a clinical trial.

Conclusions

At the present time, there is no evidence to support the use of adjunctive hormonal therapy in patients with low risk prostate cancer. For patients with intermediate-risk disease there is some evidence to support the use of hormonal therapy when low dose radiation therapy (< 72 Gy) is used. With modern doses of radiation therapy androgen deprivation should only be used within the context of a clinical trial. □

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