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Current status of androgen suppression and radiotherapy for patients with prostate cancer ☆

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Abstract

Analogous to the impact of anti-estrogen therapy in breast cancer, anti-androgen therapy may have a greater impact on the castrate male with non-metastatic disease. The use of castration or a LHRH drug alone, does not appear to adequately suppress intra-prostatic DHT (Dihydrotestosterone) levels. Normal prostate elements appear to be more efficient than metastatic elements at converting DHT precursors to active DHT. Thus, blocking this step may be more critical for clinically localized disease. Laverdiere et al. reported a 2 year positive (+) biopsy rate of 65% with XRT alone compared to 28% when 3 months of NHT preceded radiotherapy, but 5% if NHT was continued for a total of 10.5 months of combined androgen blockade (CAB). Bolla et al. incorporated one month of NHT prior to XRT followed by 3 years of an LHRH drug. An improvement in local control, disease free survival and overall survival of nearly 20% was noted at 5 years. Thus far, these important studies demonstrate that a survival benefit may require long term adjuvant hormonal therapy. There is a need for further studies to define the optimal timing and duration of CAB and the role of XRT. Long term data recently provided by the Radiation Therapy Oncology Group (RTOG) may provide insights into criteria for defining which patients are likely to benefit the most from long term CAB.

1. Introduction

Prostate cancer is the most common non-cutaneous cancer in men and the number two cancer killer men. With the exception of a single small early clinical trial using neutron irradiation, only prospective randomized trials including androgen suppressive therapy have demonstrated an improved survival in men with clinically localized prostate cancer [1–5]. What remains to be determined is which men require the use of hormonal therapy (HT) alone, who should receive HT with local therapy and who should receive local therapy alone. This review focuses on the results of studies completed to date and the need for future studies using androgen suppressive therapy. Selection criteria that might be used for directing therapy tailored for the individual needs of men with prostate cancer will be discussed.

2. Radiotherapy vs surgery: PSA failure and long term survival

Most men seem to be willing to assume that they will not die of something else and undergo treatment to reduce the risk of death due to prostate cancer. Despite the beliefs by many urologists, there is no clear-cut evidence that surgery results in a higher likelihood of survival than radiotherapy. This is a very difficult comparison to make because of differences in the age, the general condition of patients chosen for each treatment, and differences in the extent of disease at the time of treatment [6,7].

In the early 1990 s it became clear that many patients declared as 'cured' by digital rectal exam, in fact had persistent disease [8]. Using the serum marker

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Table 1
Pretreatment PSA and the risk of failure following selected surgical or radiotherapy series

Pre-treatment PSA	5-year freedom from PSA failure[a] after prostatectomy	5-year freedom from PSA failure[b] after radiotherapy	Notes
0–4	85–95	80–86	Patients treated by surgery usually excluded node + patients, and tended to have had lower grade, and stage tumors than those treated with radiotherapy
4.1–10	55–93	42–67	
10–20	56	30–75	
>20	–	45	

[a] Most series exclude node + patients failure PSA > 0.2–0.6.
[b] Clinical staging only includes node positive and T3/4 patients, failures PSA > 1.0–4.0 or rising. Modified from ref. [7].

prostate specific antigen (PSA) to determine the status of disease appears to be the next best thing to having long term follow-up [9]. Due to the sensitivity and its ease of measurement, PSA has become accepted as a valid endpoint. Table 1 compares selected surgical and external beam radiotherapy series [7]. On average, patients treated with radical prostatectomy had lower PSAs, Gleason scores and stages. When matched for any of these factors the results appeared to be similar. These data suggests that regardless of the type of treatment chosen, once the pre-treatment PSA exceeds ~10 ng/ml most patients experience a biochemical failure.

The 'gold standard' for determining the effectiveness of treatment for prostate cancer should be disease specific survival (DSS). An analysis of the long term results of patients treated with radiotherapy alone on Radiation Therapy Oncology Group (RTOG) trials has recently been reported [10]. A multivariate analysis of 1500 men with localized prostate cancer treated on prospective phase III randomized trials between 1975–1992, revealed that centrally reviewed Gleason score was the single most important predictor of death due to prostate cancer. Clinical stage, and pathologic lymph node status were able associated with overall and DSS. These three risk factors combined by these investigators to define four prognostic subgroups that predicted the risk of death from prostate cancer.

The 5-, 10-, and 15-year disease-specific survivals for each prognostic group is summarized in Table 2. Prognostic Group 1 included patients with a Gleason score of 2–5 any stage; or stages T1–2Nx and a Gleason score of 6. Prognostic Group 2 consisted of men with clinical stages of T3Nx, Gleason score 6; or N+, Gleason score 6; or T1–2Nx, Gleason score = 7. Prognostic Group 3 consisted of men with clinical stages of T3Nx, Gleason score 7; or N+, Gleason score = 7; or T1–2Nx, Gleason score = 8–10. Prognostic Group 4 consisted of men with clinical stages of T3Nx, Gleason score = 8–10; or N+, Gleason score = 8–10. As is shown in Table 2, the 5 year survivals were 97%, 91%, 82%, and 66%, for risk groups 1–4, respectively.

The results reported by the RTOG are likely to be among the most reliable for assessing the impact of radiotherapy alone on DSS. The patients included were well defined, had good follow-up and their outcomes reflected the care delivered by a large number of practitioners from around the country. The survival results observed, reflect a time when hormonal therapy was instituted for symptomatic disease, and not for a rising PSA. Recognition of the wide range of outcomes, such as seen in these four probnostic subgroups, is critical to provide informed consent that is accurate and to the design of clinical trials including patients with clinically localized prostate cancer.

Since the patients with the greatest risk of dying of prostate cancer includes those with high grade disease these groups will be considered first. Recent data suggests that the results following a radical prostatectomy for high grade disease are likely to be similar to the survival following radiotherapy reported by the RTOG. For example, in a large population based

Table 2
DSS by Risk Groups: treated on RTOG randomized trials with radiotherapy alone (1975–1992)[a]

Group	Death/No.	5 Year[b]	10 Year[b]	15 Year[b]
1	63/474	97% (95–99)	85% (81–89)	71% (61–81)
2	69/335	91% (88–94)	75% (69–81)	59% (49–69)
3	89/336	82% (78–86)	60% (52–68)	38% (21–55)
4	138/314	66% (60–72)	34% (26–42)	28% (19–37)

[a] DSS = Disease Specific Survival. Group 1 included patients with a Gleeson Score (GS) = 2–5 any stage; or stages T1–2Nx and a GS = 6; Group 2 clinical stages of T3Nx, G = 6; or N+, GS = 6; or T1–2Nx, GS = 7. Group 3 clinical stages T3Nx, GS = 7; or N+, GS = 7; or T1–2Nx, GS = 8–10. Group 4 clinical stages of T3Nx, GS = 8–10; or N+, GS = 8–10.
[b] 95% confidence intervals in parenthesis. Modified from Roach et al. ASCO proceedings 1998 [10].

study limited to patients with clinical T_{1-2} and high grade tumors Lu–Yao demonstrated identical 5 year survivals with either surgery or radiation [11]. Also of interest, these results were essentially identical to those noted in risk Group 3 (described above) reported by the RTOG. This observation supports the generalizability of the RTOG long term outcome data. Of further interest, roughly 75% of patients with Gleason scores of 8–10 undergoing radical prostatectomy for clinical stages of T1–2 disease have a detectable PSA within 4 years [12–14]. These findings are consistent with the long term survival data reported by Oefelein et al. who noted a 15-year DSS of 40% for patients treated with radical prostatectomy for Gleason scores of 8–10 [15]. These results are virtually identical to the 15-year survival of 38% for RTOG Group 3 patients.

3. The rationale for androgen suppressive therapy and radiotherapy

Elsewhere in the oncologic literature we have learned that chemotherapy combined with radiation results in an improved survival compared to radiotherapy or chemotherapy alone for unresectable non-small-cell lung cancer, small-cell lung cancer, esophageal cancer, anal cancer, nasopharyngeal cancer, and rectal cancer. The unifying features for all of these sites includes: (1) the presence of locally advanced disease not well suited for cure with surgery alone; (2) the availability of chemotherapeutic agents with modest independent activity; (3) a site which can be easily incorporated into a radiotherapy portal; (4) evidence of favorable interactions between the drug in question and radiation.

Available data provides evidence that all of these features are present when androgen suppressive therapy is combined with radiotherapy. As discussed above the vast majority of men with high grade disease are not cured with surgery alone. Surgical series using neoadjuvant hormonal therapy prior to resection confirmed modest anti-tumor activity resulting in a reduction in the incidence of positive margins, and a reduction in prostate tumor volumes [16,17]. The reductions in the volume of the normal prostate improves our ability to incorporate the prostate into a radiotherapy portal by making it smaller and reducing the volume of normal tissues incidentally irradiated [18–20]. This should significantly reduce the probability of complications. These reductions in the tumor volume from associated with neoadjuvant hormonal therapy (NHT) also has the potential to improve the outcome by reducing the amount of cancer requiring sterilization by radiation. Finally, experimental and clinical data suggests that there may be synergistic interaction between hormonal therapy and radiation [21–23]. Zietman et al. concluded that it may be best to administer androgen suppressive therapy until the tumor is maximally suppressed prior to the delivery of radiation. Waiting for regrowth or prior to maximal response appeared to be less effective. The applicability of this observation to the clinic setting remains to be defined in a randomized trial. Radiation induced apoptosis may well explain the synergism noted [22,24].

4. Status of clinical trials to date

The randomized trials assessing the impact of hormonal therapy on survival from prostate cancer can be divided into those that use primarily NHT prior to radiotherapy or surgery or those that incorporate long term adjuvant hormonal therapy (AHT). To date all of the trials using NHT prior to surgery have been negative for an improvement in disease free survival [17,25]. In contrast, two prospective randomized trials have shown that the use of neoadjuvant (before and during) hormonal therapy is associated with an improvement in local control, and the disease free survival [26,27]. An update of the first study was recently presented at the meeting of the American Society of Clinical Oncology in Los Angeles [28]. Local control, disease free survival and time to distant failure were all shown to be improved and an 8% higher overall survival was observed among the patients on the experimental arm. However, this difference was not statistically significant ($P = 0.22$) [28]. Laverdiere et al. noted a 65% incidence of positive biopsies at 2 years with radiotherapy alone compared to a 28% incidence when 3 months of neoadjuvant hormonal therapy preceded radiotherapy [27].

The results of trials using AHT have thus far been more impressive than those associated with NHT alone. For example, Laverdiere et al. noted only a 5% incidence of positive biopsies if 3 months of combined androgen blockade (CAB) preceded radiotherapy, and was continued for 6 months after radiotherapy was completed [27]. The EORTC incorporated one month of neoadjuvant anti-androgen blockade prior to radiotherapy followed by 3 years of an LHRH drug and noted an improvement in local control, disease free survival and overall survival was noted for 5 years [4]. Pilepich et al. also noted a improvement in survival in the subset of patients with high grade disease (Gleason score 8–10) with the use of long term adjuvant androgen suppressive therapy [5]. The findings of these three studies should not be surprising. It is well known that hormonal (estrogen) suppressive therapy prolongs survival in the adjuvant setting for women with non-metastatic breast cancer [29–31]. In an analogous fashion adjuvant long term anti-androgen therapy

Table 3
Major randomized trials: comparing long-term androgen blockade x/− XRT[a] with localized prostate cancer (Table based on data from references [3–5,27])[a]

Source	Trial design	Major conclusions
Canadian (1997)	XRT vs neoadjuvant CAB (3 months) + XRT vs neoadjuvant + adjuvant CAB (10.5 months) + XRT	Positive Biopsy rates at 24 months: XRT alone = 65% vs Neoadjuvant × 3 months = 28% vs Neoadjuvant × 3 months + 6.5 months = 5%. Follow-up too short to evaluate survival
British (1997)	Phase III trial comparing early androgen suppression vs no initial treatment	Early androgen suppression improves survival compared to delayed therapy. Less morbidity noted in the intervention groups as well
EORTC (1997)	Phase III trial comparing neoadjuvant × 1 month then adjuvant CAB × 3 years plus XRT vs XRT alone	Experimental to control arm: local control 97% vs 77% ($P < 0.001$); DFS = 85% vs 48% ($P < 0.001$); overall survival = 79% vs 62%, ($P = 0.001$)
RTOG (1997)	Phase III trial comparing adjuvant long term LHRH therapy plus XRT vs XRT alone	Patients with Gleason scores of 8–10 experience a survival advantage if treated with long term adjuvant hormonal therapy

[a] XRT = Radiotherapy. CAB = Combined Androgen Blockade. DFS = Disease Free Survival.

might be expected to have a greater impact on the castrate male with non-metastatic disease, see Table 3.

5. RTOG trials pending analysis

Where are we headed and what new studies are needed? Phase III trials pending analysis by the RTOG are shown in Table 4. RTOG 9202 includes more than 1500 patients and will help and should confirm the findings of the EORTC study. This study uses only 2 years of adjuvant HT and thus it may answer the question of whether 3 years of adjuvant therapy is really required? RTOG 9413 should tell us whether 4 months of hormonal therapy before radiotherapy is more effective than 4 months after radiation and confirm the value of prophylactic pelvic irradiation in high risk patients. RTOG 9406 (a dose escalation study) should form the basis for a future randomized trial that will determine whether higher doses are truly synergistic with CAB. Because of the low risk nature of patients in RTOG 9408 it will be many years before we will be able to assess a survival endpoint but this study should tell us whether low risk patients experience an improvement in PSA failure and local control.

6. Do we really need combined androgen blockade?

Most prospective randomized trials suggest that there is a modest improvement with the use of CAB compared to mono-therapy (i.e. LHRH drugs alone). For example, NCI 0036 demonstrated a longer survival among patients who received leuprolide and flutamide compared to leuprolide alone [32]. Of note the greatest benefit was seen in patients with minimal disease raising the possibility that more benefit still might be experienced in patients with even earlier (non-metastatic disease). The more recent SWOG study demonstrated no improvement in survival with the addition of flutamide to orchiectomy [33]. The differences between these two studies may reflect short follow-up, or may be explained by the 'flair' phenomena that may occur in patients treated with an LHRH drug which is not seen following orchiectomy. However other studies suggests that orchiectomy combined with an anti-androgen results in a survival advantage over orchiectomy alone complicating this explanation [34,35]. When using an LHRH drug it appears to be particularly prudent to block the possibility of a 'flare' occurring with an anti-androgen.

Neither castration nor LHRH drugs alone, appear to adequately suppress intraprostatic DHT (Dihydrotestosterone) levels [36–42]. Patients with metastatic disease progress and die due to hormone refractory disease. This metastatic phenotype does not appear to be efficient at producing DHT from precursors, so blocking this step may not be as critical in this setting [43]. In contrast, CAB may be more critical for treating clinically localized prostate cancer, because normal prostate elements appear to be more efficient than metastatic elements at converting DHT precursors to active DHT. Significant levels of DHT within the gland may prevent maximal suppression of tumor within the prostate, making it more important to block this source.

7. Implications and conclusions

It is likely that if all men with prostate cancer were castrated at diagnosis fewer would die of prostate cancer. However, since men belonging to RTOG Group 1 have relatively long disease specific survival and thus

Table 4
Phase III RTOG trials including androgen suppression pending analysis

RTOG studies pending final evaluation
9202: Neoadjuvant Goserelin and Flutamide 2 months before and during XRT x/− adjuvant Goserelin × 2 years (>1500 patients entered).
RTOG prostate cancer trials in progress (as of 1998)
9406: 3-DCRT, phase I-II limited participation dose escalation study (neoadjuvant androgen suppression optional).
9408: Early stage disease (PSA < 20 ng/ml, <T2c disease Goserelin and Flutamide 2 months before and during XRT vs XRT alone.
9413: ('two by two design'), Goserelin or Leuprolide and Flutamide 2 months before and during XRT vs Goserelin or Leuprolide and Flutamide for 4 months following the completion of XRT. Prostate only XRT vs prostate and whole pelvic irradiation.
Future directions
Long term use of neoadjuvant therapy prior to local therapy? XRT and Chemotherapy with combined androgen suppression as neoadjuvant +/- adjuvant therapy in high risk patients (see Table 2).

most would not benefit. For example at 5 years at most 3%, and at 10 years at most 15% would have a survival benefit. Since many men belonging to this risk group are much more likely to die of other causes than prostate cancer, the absolute benefit that is likely to result from castration would be substantially less than either 3% or 15%. At the other extreme patients belonging to Group 4 are more likely to show survival benefits to treatments that are more aggressive than radiotherapy alone.

There are several reasons to believe that radiotherapy should continue to be used for patients with clinically localized prostate cancer [44]. First, as with other solid tumors, radiotherapy is potentially curative for patients with localized disease. Based on completed RTOG trials many patients are rendered disease free for many years with radiotherapy alone. Furthermore, hormonally refractory disease is still almost always responsive to radiotherapy. This suggests that the mechanisms of activity for hormonal therapy and radiation are different. The literature discussed suggests that some prostate cancer patients benefit from combined modality therapy analogous to the numerous studies that demonstrate a survival advantage with the use of chemotherapy plus radiation compared to radiotherapy alone or chemotherapy alone for other solid tumors [45]. But which patients should be selected for CAB in addition to radiotherapy?

Based on the available data, patients presenting with clinically localized and low grade disease (RTOG groups 1 and 2), who wish to retain potency should probably be managed with either local treatment (surgery or radiotherapy) or 'watchful waiting'. These conclusions must be considered tentative because the follow-up among patients treated with short term NHT is less than 10 years. Perhaps with longer follow-up a significant difference in survival will be noted. Patients with more aggressive disease (RTOG Groups 3 and 4) should probably be treated with long term androgen suppressive therapy in conjunction with radiotherapy. These conclusions must again be considered tentative because the follow-up among patients treated with long term CAB is less than 10 years. Patients with high pretreatment PSA values (e.g. >20 ng/ml) but who would otherwise appear to be low risk might also fall into this category. Again longer follow-up is required before we will be able to define the relative value of PSA for predicting death due to prostate cancer.

The future is bright for patients diagnosed with prostate cancer. Patients with very early disease can find comfort in the fact that their DSS is likely to be excellent and they probably can be spared castration. Patients with high risk diseases can find comfort in the fact that we can significantly improve their survival compared to conventional treatment used only two short years ago. Patients with hormone refractory disease are likely to benefit from recent and future lessons learned through the successful completion of clinical trials [46,47].

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