Combination of Hormone Therapy and Radiotherapy in Treatment of Locally Advanced Prostate Cancer—Recent Developments and Update

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Abstract

Prostate cancer is the sixth leading cause of cancer death among men worldwide. Risk stratification is used to facilitate the selection of optimal treatment approach; however, there is a lack of consensus in the prostate cancer risk-stratification systems. Furthermore, the term 'locally advanced' is often misused with high-risk disease. This poses problems when interpreting clinical trials and evaluating treatment outcomes. As a result the patients studied in clinical trials represent a heterogeneous population. The current standard care for locally advanced prostate cancer is a combination of radiotherapy (RT) and androgen deprivation therapy (ADT) and this is supported by several large randomized clinical trials. Long-term ADT is recommended but the optimal duration remains to be better defined. The use of newer and more potent hormonal agents appears to be promising, at least in the setting of metastatic castration-resistant disease, but their role in locally advanced disease remains undefined. This article will summarize the available literature concerning the recent development of hormone therapy in reference to locally advanced prostate cancer. As for the future, individualization of treatment and personalized cancer care is the trend. The availability and the use of improved cellular and/or molecular markers to better risk stratify prostate cancer patients will allow us to select the most effective therapy to enhance the overall outcome.

Keywords

Prostate cancer, locally advanced, radiotherapy, hormone therapy, androgen deprivation therapy, risk stratification, androgen receptor inhibitors, androgen synthesis inhibitors, degarelix, abiraterone acetate, enzalutamide, orteronel

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Prostate cancer is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide with an estimated 899,000 new cases and 258,000 new deaths in 2008.[1] Risk-stratification systems are used to assist with treatment selection, ensuring prognostic uniformity in clinical trials, and in the evaluation of treatment outcomes. Based on work by D'Amico et al.,[2] the Genitourinary Radiation Oncologists of Canada (GUROC) developed a classification system for patients with localized/locally advanced disease based on T category, prostate specific antigen (PSA) level at diagnosis, and Gleason score.[3] High-risk disease is defined as the presence of any of these factors: cT3 or cT4 category, PSA >20 ng/ml, or Gleason score >8. The exact definition of high-risk prostate cancer at diagnosis remains controversial and this lack of consensus remains a barrier to comparing clinical outcomes of various institutional series and results of clinical trials. *Table 1* provides a summary of definitions of high-risk disease from different consensus groups.[2–6]

The term 'high-risk disease' is often incorrectly used to describe patients with locally advanced disease. As a result, the patients studied in clinical trials of high-risk prostate cancer represents a heterogeneous group, including those with clinically organ-confined disease (cT1/T2) with Gleason score 8–10 and/or PSA >20 ng/ml, and those with locally advanced disease (cT3/T4). The proportion of patients presenting with locally advanced disease at diagnosis has decreased in the past 20 years, largely as a result of widespread PSA screening; however, this presentation remains a common clinical problem and management remains controversial. Since the discovery of hormone dependence of prostate cancer by Dr Huggins in 1941, hormone therapy has become the mainstay of treatment in metastatic prostate cancer.[7] Hormone therapy now has an increasingly important role in earlier stages of prostate cancer and is the standard of care in locally advanced disease when used in combination with radiotherapy (RT). Over the past few years multiple new

hormonal agents have become available to treat men with metastatic castration-resistant prostate cancer (mCRPC). In this review, we will focus on the possible role of these agents in clinical locally advanced prostate cancer (cT3/T4).

Current Standard of Care for Patients with Locally Advanced Disease

The current standard treatment for men who present with locally advanced prostate cancer is radiotherapy with concurrent and adjuvant androgen deprivation therapy (ADT). This is based on the result from a number of major clinical trials conducted over the last 20 years. Several large randomized clinical trials demonstrated ADT combined with radical RT is associated with significant benefits in local disease control, development of metastasis, disease-free survival (DFS), and overall survival (OS).

Addition of Androgen Deprivation Therapy to Radiotherapy is Beneficial

In the landmark European Organization for Research and Treatment of Cancer (EORTC) 22863 trial, 415 patients were randomized to RT alone (50 Gy to the whole pelvis with an additional 20 Gy to the prostate and seminal vesicle), or RT with androgen suppression (3 years of goserelin). Most patients (91 %) had locally advanced disease (cT3/T4).[8,9] With a median follow up of 9.1 years, the 10-year OS rate was 39.8 % in patients treated with RT alone and 58.1 % in those receiving combined modality therapy (hazard ratio [HR] 0.60; p=0.0004). The 10-year DFS was 22.7 % and 47.7 %, respectively (HR 0.42; p<0.0001). The 10-year prostate cancer mortality rate was significantly reduced from 30.4 % to 10.3 % with the addition of ADT to RT (HR 0.38; p<0.0001).[10] Similar results were seen in the Radiation Therapy Oncology Group (RTOG) 85-31 trial in which patients were randomized to either RT and lifelong ADT or RT alone. With median follow up of 7.6 years, the 10-year OS, disease specific survival (DSS), local failure, distant metastases, all favored the combination therapy arm.[11]

The Optimal Duration of Androgen Deprivation Therapy

Long-term ADT of 2–3 years is the current standard of care in patients with locally advanced disease; however, the optimal duration of ADT remains to be defined. The EORTC 22961 trial, using a non-inferiority design, compared RT with either short- (6 months) or long-term (3 years) ADT in patients with locally advanced disease. With median follow up of 6.4 years, this trial showed an inferior OS with the use of short-term ADT.[12] The RTOG 9202 trial randomized patients with locally advanced prostate to either long-term (28 months) or short-term (4 months) ADT with radiation therapy. Long-term ADT led to improvement in DFS and on subgroup analysis an OS benefit was observed in men with Gleason score of 8–10 (31.9 % versus 45.1 %; p=0.0061).[13,14] A recent American Society of Clinical Oncology (ASCO) abstract from Nabid et al., presented the results of a randomized trial that compared intermediate-term ADT (18 months) to long-term ADT (36 months), and found no difference in 5-year OS and DSS between the two approaches.[15] The authors suggested that long-term ADT could be 'safely' reduced to intermediate-term ADT without compromise of outcome. However, the result of this study should be interpreted with caution as this study was designed as a superiority trial and not powered sufficiently as a non-inferiority trial. A current phase III randomized trial by the Tran-Tasman Radiation Oncology Group TROG 03-04 (RADAR) trial investigating short-term ADT of 6 months versus intermediate term ADT of 18 months. This trial has closed to accrual and results are awaited.[16]

Table 1: Definition of High-risk Prostate Cancer

Source	Definition
GUROC[3]	CS ≥T3a OR GS 8–10 OR PSA ≥20 ng/ml
D'Amico[2]	CS ≥T2c OR GS 8–10 OR PSA ≥20 ng/ml
RTOG[4]	CS≥T2c OR GS 8–10 AND PSA <100 ng/ml OR any clinical stage AND GS 8–10 AND PSA 20–100 ng/ml
NCCN[5]	CS ≥T3a OR GS 8–10 OR PSA≥20 ng/ml OR any two of: CS T2b/c, GS 7, PSA 10–20 ng/ml
EAU[6]	CS ≥T3 OR GS 8–10 OR PSA ≥20 ng/ml

CS = clinical stage; EAU = European Association of Urology; GS = Gleason score; GUROC = Genito-Urinary Radiation Oncologist of Canada; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RTOG = Radiation Therapy Oncology Group.

Radiotherapy is an Essential Part in Management of Locally Advanced Prostate Cancer

Three large phase III trials have shown that RT treatment in addition to ADT improves outcome, including OS, in locally advanced prostate cancer (see *Table 2*). In the National Cancer Institute of Canada (NCIC) PR3/Canadian Urologic Oncology Group (CUOG)/Medical Research Council (MRC) UK PR07 study, 1,205 patients with locally advanced prostate cancer patients were randomized to ADT treatment alone or ADT in combination with RT. Eighty-seven percent of the patients had locally advanced (T3/4) disease. With a median follow up of 6 years, the combined modality treatment resulted in a 23 % reduction in overall mortality (HR 0.77; p=0.03) and a 46 % reduction in disease-specific mortality (HR 0.54; p=0.0001)[17] (see *Figure 1*). A recent update presented at the ASCO annual meeting, with median follow up of 8 years showed sustained and significant OS and DSS benefit for the combined ADT and RT group.[18]

Similar results were seen in the Scandinavian Prostate Cancer Group (SPCG)-7 study in which 875 patients with locally advanced prostate cancer were randomized to hormonal therapy alone (3 months ADT and then anti-androgen therapy until progression or death) or combination of hormonal therapy and RT. Approximately 80 % of patients in this study had locally advanced disease. With a median follow up of 7.6 years, prostate cancer-specific mortality and overall mortality were significantly reduced by the addition of RT to hormonal management. Overall mortality at 10 years was reduced from 39.4 % in the endocrine alone group to 29.6 % in the combined ADT and RT group (relative risk [RR] 0.68; p=0.004).[19] A French study by Mottet et al. reported the results of a randomized phase III trial in which 264 patients with locally advanced prostate cancer were randomly assigned to ADT alone for 3 years or ADT combined with RT. With a median follow up of 67 months, a significant difference was found in favor of the combined approach with regards to loco-regional progression (p<0.0001), metastatic progression (p=0.018), and progression-free survival (PFS) (p<0.001). While there was no improvement demonstrated in OS, this is likely due to the fact that follow up was short (median OS was not reached in either group at the time of analysis). In addition the power of the trial to detect a survival difference was limited due to the small sample size.[20]

Table 2: Summary of Results from Three Large Randomized Trials Assessing the Benefit of Radiotherapy in Combination with Androgen Deprivation Therapy

Reference	No. of Patients	Median Follow-up (Years)	Progression-free Survival	Disease-specific Survival	Overall Survival
			ADT versus ADT+RT	ADT versus ADT+RT	ADT versus ADT+RT
NCIC-PR3[17]	1,205	6	–	79 % versus 90 %	66 % versus 74 %
			HR 0.3 (p=0.0001)	HR 0.54 (p=0.0001)	HR 0.77 (p=0.033)
SPCG-7[19]	875	7.6	26.3 % versus 74.1 % (p<0.0001)	76.1 % versus 88.1 % (p=0.004)	60.6 % versus 70.4 % (p<0.0001)
Mottet et al.[20]	264	5.6	8.5 % versus 60.9 % (p<0.0001)	86.2 % versus 93.2 % (p=0.0586)	71.5 % versus 71.4 %*

**Median overall survival not reached in either treatment arm at the time of analysis. ADT = androgen deprivation therapy; HR = hazard ratio; NCIC = National Cancer Institute of Canada; RT = radiotherapy.*

The Optimal Sequencing of Treatment

The optimal timing of ADT treatment in relation to RT is unclear. The RTOG 9413 trial randomized 1,323 patients with localized prostate cancer, in a 2 by 2 design, to either neo-adjuvant and concurrent versus adjuvant hormone therapy, or either whole pelvis RT versus prostate-only RT.[21] With median follow up of 7 years, this study did not find any significant difference in PFS or OS between neo-adjuvant and adjuvant hormone.[22]

New Hormonal Agents

Gonadotropin-releasing Hormone Antagonist

The initial testosterone surge and subsequent microsurges seen with gonadotropin-releasing hormone antagonist (GnRH) agonists prompted the search for alternative ADT strategies. GnRH antagonists bind directly to and block GnRH receptors and are not associated with any increase in testosterone on treatment. The third-generation GnRH antagonist degarelix has been extensively studied and is increasingly being used in advanced prostate cancer. Initial data suggest degarelix is at least as effective as GnRH agonist.[23,24] Klotz et al., comparing degarelix with leuprolide, found more rapid suppression of testosterone and PSA with the use of degarelix.[25] This study also suggested that degarelix therapy improved PSA PFS but this needs confirmation in other trials.[26] The advantage of degarelix is its monotherapy approach without the need for anti-androgen to prevent the initial testosterone flare. The other potential clinical advantage is its use in highly symptomatic patients when rapid testosterone suppression is favored. However, the main clinical drawback in its use is monthly administrations unlike most of the GnRH agonists, which are given at 3 or 4 monthly intervals. In addition, there is an increased risk for injection-site reactions and chills with degarelix compared with leuprolide.

Medical castration prior to RT is often used in patients with locally advanced disease to reduce the size of the prostate prior to RT and also to improve lower urinary tract symptoms (LUTS). There are preliminary data suggesting that degarelix produces a reduction in prostate volume similar to that produced by goserelin acetate while giving better LUTS relief in symptomatic patients.[27,28] While further studies need to be carried out to define the role of GnRH agonists in locally advanced disease, there are sufficient data to suggest that degarelix is a reasonable alternative in 2014 to LHRH agonists in this setting—especially in highly symptomatic patients.

Androgen Synthesis Inhibitors

The role of persistent androgen-axis signaling, which is mediated by intra-tumoral androgen synthesis (in addition to testicular and adrenal synthesis), in driving tumor growth in patients with CRPC is now well established. Abiraterone is a first-in-class inhibitor of the CYP17 enzymes mediating androgen synthesis, both extragonadal and gonadal. It has been shown (in combination with prednisone) to improve OS in patients with mCRPC in patients who were previously treated with chemotherapy and in those who were chemotherapy naïve.[29–31] The reported toxicity has been low, although higher mineralocorticoid adverse effects, such as fluid retention, hypertension, and hypokalemia, were seen in patients who received abiraterone compared with placebo. Abnormalities in liver-function testing are also seen with abiraterone and there is some suggestion of increased cardiac dysfunction in some patients.

Orteronel (TAK-700) is a new CYP17 inhibitor with potentially greater selectivity for androgen as opposed to corticosteroid synthesis than abiraterone and is in phase III development for the treatment of mCRPC. Two phase III trials are currently undergoing: one will evaluate patients who have progressed following taxane-based chemotherapy (NCT01193257; the other will evaluate patients who are chemotherapy naïve (NCT01193244).[32,33] Both studies compare orteronel plus prednisone with placebo plus prednisone.

The role of these agents in the locally advanced non-metastatic and non-hormone resistant setting remains to be determined. There are numerous single institution phase III studies investigating the use of abiraterone in addition to standard ADT + RT in patients with locally advanced disease. The RTOG is conducting a phase III trial (RTOG 1115) in the setting of high-risk localized disease in which the patients receive the ADT with GnRH agonist in conjunction with dose-escalated RT and randomized to receive addition of TAK700 for 2 years or not (NCT01546987).[34] There is no current evidence to support their routine use in the adjuvant/neo-adjuvant setting.

Androgen Receptor Inhibitors

Enzalutamide (MDV 3100) is a novel androgen receptor (AR) antagonist that binds the AR with a higher affinity than bicalutamide. It has no known agonist effects and inhibits nuclear translocation of the AR. Phase I and II studies demonstrated significant antitumor activity in men with CRPC regardless of their prior chemotherapy status.[35,36] On the basis of these findings, two phase III studies were conducted: AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) and PREVAIL (A safety and efficacy study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer). The AFFIRM trial randomized men with CRPC after chemotherapy to either enzalutamide or placebo in a 2:1 ratio. Enzalutamide significantly prolonged median OS, 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR 0.63; p<0.001). All of the secondary endpoints including time to PSA progression (8.3 months versus 3.0 months, HR 0.25; p<0.001), radiographic PFS (8.3 versus 2.9 months, HR 0.40; p<0.001), and time-to-first skeletal event (16.7

months versus 13.3 months, HR 0.69; p<0.001) were all in favor of patients who received enzalutamide.[37] The other phase III trial PREVAIL has a similar study design and investigating efficacy of enzalutamide in chemotherapy-naïve patients (NCT01212991).[38] This trial has recently completed accrual and the results of the first interim analysis are expected shortly.

Similar to the new androgen synthesis inhibitors, the role of enzalutamide in the neo-adjuvant or adjuvant setting is unknown and this remains the direction of future studies. As of January 2014 there is only one phase I study investigating the role of enzalutamide in locally advanced disease (NCT02023463).[39]

Toxicity of Hormone Therapy

ADT is associated with multiple side effects including fatigue, hot flushes, mood lability, depression, sleep disturbance, gynecomastia, and sexual dysfunction.[40–42] Long-term use of ADT can potentially cause more serious side effects such as osteoporosis, cardiovascular morbidity/mortality, and the metabolic syndrome. These adverse effects not only negatively impact on one's health but also quality of life. In general, there is lack of awareness, early screening, and intervention of ADT-associated toxicity. The exact risk and optimal management is far from clear and ongoing research in this field is required.

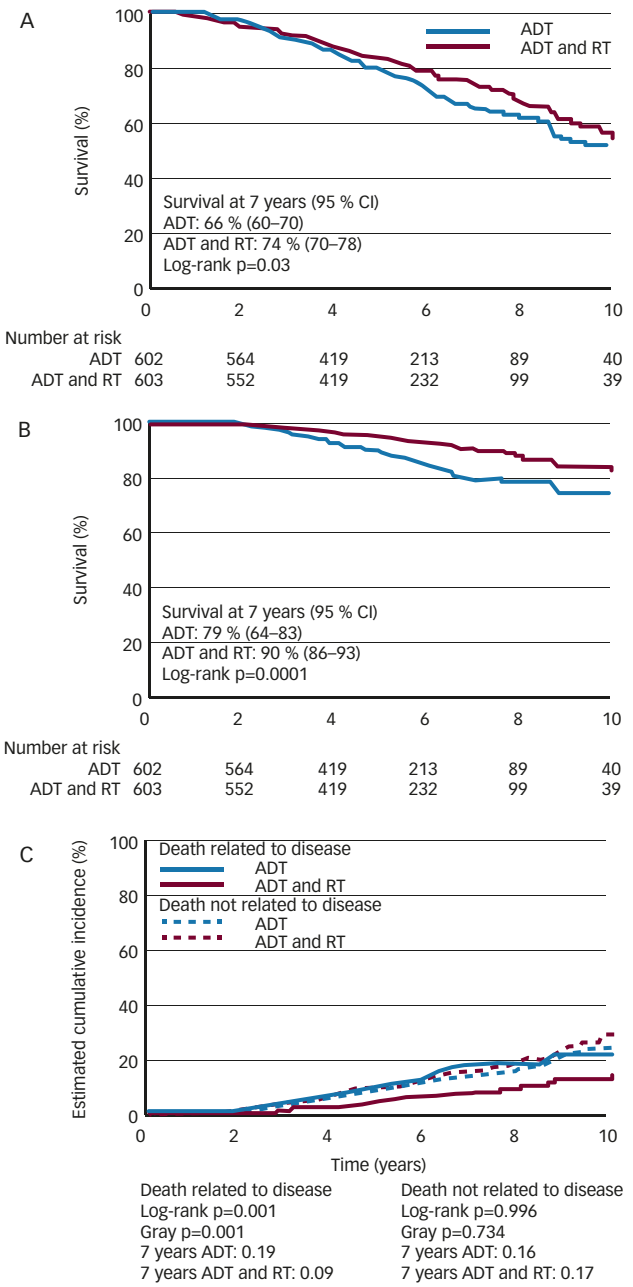
ADT decreases bone mineral density (BMD) and increases risk for bone fracture.[43,44] Bone fractures lead to significant morbidity and have a major impact on mortality.[45] Prevention of bone mineral loss through lifestyle modification (smoking cessation, decreased caffeine intake, and regular weight-bearing exercises) is often advised. Many would recommend vitamin D and calcium supplements although their role in the setting of ADT-induced bone loss remains undefined. These supplements have not been proved consistently to prevent bone loss in men with prostate cancer receiving ADT. A recent review of 12 clinical trials failed to prove their efficacy.[46] Furthermore, a high level of calcium supplement is thought to be associated with increased cardiovascular disease. Future studies are required to address the safety and efficacy of these supplements.

The use of bisphosphonates or denosumab is recommended in men who have significant BMD loss and are at high risk for fracture. Multiple randomized trials have demonstrated the efficacy of bisphosphonates in prevention of BMD loss associated with ADT use.[47–50] Denosumab has been shown in a large double-blind randomized trial to significantly improve BMD and reduce incidence of fractures in men with non-metastatic, hormone-sensitive prostate cancer receiving ADT.[51,52]

In terms of the impact of ADT on cardiovascular morbidity and mortality, there are conflicting results. Several published reports including two large population-based studies using data from Surveillance Epidemiology and End Results (SEER) reported that ADT is significantly associated with increased incidence of cardiovascular events.[53,54] Retrospective analysis based on prospective randomized trials have been conducted and found no difference on cardiovascular mortality in patients receiving ADT.[55–58] A meta-analysis incorporating data from eight randomized phase III trials showed ADT use was not associated with an increased risk for cardiovascular death compared with no ADT use (11.0 % versus 11.2 %; p=0.41).[59] The results of retrospective analysis have their own limitations; therefore, careful interpretation is advised. Future clinical trials should prospectively assess risk factors for adverse cardiovascular events and mortality.

The use of ADT has been recognized as an independent risk factor of the metabolic syndrome.[60,61] There is evidence linking the use of ADT and development of insulin resistance and diabetes.[62] There is also evidence suggesting ADT negatively affects lipid profile and causes a rise in serum cholesterol and triglyceride.[60] Androgen suppression alters body

Figure 1: Overall and Disease-specific Survival at 7 Years in the NCIC-PR3 Trial



(A) Kaplan-Meier curve for overall survival by treatment group; (B) Kaplan-Meier curve for disease-specific survival by treatment group; and (C) cumulative incidence of disease-specific survival. ADT = androgen deprivation therapy; CI = confidence interval; NCIC = National Cancer Institute of Canada; RT = radiation therapy. Reproduced with permission from The Lancet.[17]

composition by increasing body fat and decreasing lean body mass,[63–65] which results in reduced physical performance and muscle strength.

Prostate cancer patients receiving ADT should be educated and engaged in physical exercise to counteract ADT-induced toxicities. In a recent systemic review of 10 randomized trials, exercise intervention was found to improve a range of ADT-induced adverse effects including muscular strength, cardiorespiratory fitness, functional task performance, lean body mass, and fatigue.[66] The current literature support routine implementation of structured exercise and should be considered in all patients who are receiving ADT.

Conclusion

There are now mature data to support the use of combined ADT and RT in the treatment of locally advanced prostate cancer. Long-term ADT of 2 to 3 years is recommended, although the optimal duration remains to be better defined. Despite this, locally advanced prostate cancer continues to cause significant morbidity and mortality and we need to further refine and improve our management strategies. The use of newer and more potent hormonal agents in metastatic disease has produced good results but their roles in the locally advanced setting remain undefined. The traditional clinical research approach in this setting is to perform randomized phase III trials using combination of ADT and RT ± new agents using OS as the primary trial outcome. This approach, while scientifically valid, will likely take 1 to 2 decades to produce results. This is because of the prolonged survival of patients with locally advanced prostate and the risk for death from other causes. The development of valid surrogate endpoint(s) for survival in this setting is urgently needed and efforts are underway under the auspices of the Prostate Cancer Foundation. This study which is being coordinated by the Dana-Farber Cancer Institute–the intermediate clinical endpoints in cancer of the prostate initiative (ICECaP) aims to perform a meta-analysis using individual patient data of prostate cancer adjuvant trials with goal of identifying a validated intermediate clinical endpoint that will serve as an acceptable surrogate endpoint for OS. (Chris Sweeney, personal communication).

Individualization of treatment and personalized cancer care is the future. In striving for personalized medicine, cellular and molecular tests are needed to better risk stratify prostate cancer patients. The biomarkers, genome sequencing, and genetic signatures may help to predict overall outcome, risk for failure, and treatment response. These tests remain to be prospectively validated before its routine use in clinical setting. Better understanding of the biology of the tumor will allow us to select the most effective therapy to enhance the overall outcome of the patients. ■

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