Chapter 47
Management of Locally Advanced Prostate Cancer

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Introduction

Of the nearly 233,000 patients in the United States who will be diagnosed with prostate cancer in 2014, 10 % will have locally advanced disease [1]. Locally advanced prostate cancer is defined as clinically localized stage T3 (extracapsular extension or seminal vesicle invasion) or T4 (fixed tumor or invasion of adjacent structures) disease. Patients with localized T1 or T2 disease with high risk disease features (Gleason 8–10 or PSA >20 ng/mL) are treated similarly. In a study comparing outcomes of immediate vs. deferred treatment in patients with locally advanced prostate cancer, patients who deferred treatment had higher rates of progression to metastatic disease, development of metastatic pain, development of extra-skeletal metastases, cancer related complications (pathological fracture, spinal cord compression, urethral obstruction), and prostate cancer-specific mortality compared with patients who received immediate treatment [2]. Therefore, definitive therapy is recommended for these patients, unless it is not feasible due to age and/or comorbidities and life expectancy is less than 5 years.

A multi-modality approach is generally undertaken for patients with locally advanced prostate cancer [3]. The current treatment options for patients with locally advanced prostate cancer include (1) External beam radiation therapy (EBRT) using either a 3D conformal (3D-CRT) or an intensity modulated (IMRT) technique with image-guided radiation therapy (IGRT) and short-term/long-term androgen deprivation therapy (ADT), given neoadjuvantly, concomitantly and adjuvantly; (2) Shorter course EBRT using either a 3D-CRT or IMRT with IGRT plus a brachytherapy boost and short-term/long-term ADT, given neoadjuvantly, concomitantly and adju-

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vantly; and (3) radical prostatectomy with pelvic lymph node dissection with or without adjuvant radiation therapy or ADT [4]. ADT monotherapy is indicated only if the patient is not a candidate for definitive therapy.

Specific techniques in prostate radiotherapy and brachytherapy have been previously discussed in Chaps. 42 and 43, respectively. This chapter discusses the role of ADT in the context of these combination approaches.

ADT Monotherapy

Androgen deprivation therapy alone is inferior to multi-modality approaches for locally advanced prostate cancer and is only recommended for patients in whom local curative therapies are not feasible due to comorbidities or other factors. In this setting, the optimum timing of ADT (immediate vs. delayed) remains controversial and has been evaluated in two large EORTC trials. The EORTC 30891 trial evaluated 985 patients with localized and locally advanced prostate cancer (T0-4, N0-2, M0) who were randomized to receive immediate or delayed (on symptomatic disease progression or occurrence of serious complications) ADT. The overall survival hazard ratio was 1.25 favoring immediate treatment (noninferiority $P > 0.1$); however, there was no difference demonstrated in prostate cancer-specific mortality or symptom-free survival [5]. In the EORTC 30486 study, 234 patients with pN1-3 disease who did not receive definitive local therapy were randomized to immediate vs. delayed ADT. There was no benefit seen for immediate ADT compared to delayed therapy with respect to overall survival, prostate cancer specific survival, or cancer-independent survival [6, 7]. One exception is that patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy do benefit from immediate ADT [8]. This is discussed in further detail below.

Survival Benefit of Adding Radiation Therapy to ADT

There have been two large trials evaluating the use of ADT or endocrine therapy with or without radiation therapy. The SPCG-7/ SFUO-3 trial randomized 875 patients with locally advanced prostate cancer to receive endocrine therapy (total androgen blockade for 3 months, followed by continuous anti-androgen therapy) alone or endocrine therapy plus radiotherapy. With a median follow up of 7.6 years, the 10-year prostate cancer specific mortality was 23.9 and 11.9 % for the endocrine therapy only group and endocrine plus radiotherapy group, respectively. The 10-year overall mortality was 39.4 and 29.6 %, for the endocrine therapy only group and endocrine plus radiotherapy group, respectively [9]. The NCIC Clinical Trials Group PR.3/Medical Research Council UK PR07 trial randomized 1,205 locally advanced prostate cancer patients to receive lifelong ADT versus lifelong ADT

plus radiotherapy. At a median follow up of 6 years, the overall survival at 7 years was 74 % for the ADT/RT group and 66 % for the ADT alone group (HR 0.77, p = 0.033). The prostate cancer specific survival at 7 years was 90 and 79 % for the ADT/RT and ADT alone groups, respectively [10].

Survival Benefit of Adding ADT to Radiation Therapy

The benefit of combining ADT to radiation therapy, compared with radiation therapy alone, has been demonstrated repeatedly in multiple trials [11–16]. However, the optimum duration of ADT in this setting is still controversial. The RTOG 8610 study randomized 456 patients with T2-T4, N0-1 prostate cancer to receive external beam radiation therapy (EBRT) alone or EBRT plus short-term (4 month) neoadjuvant and concurrent ADT. Ten year overall survival (43 % vs. 34 %, p = 0.12) and median overall survival (8.7 vs. 7.3 years) did not reach statistical significance. However, 10 year disease specific mortality (23 % vs. 36 %, p = 0.01), rate of distant metastasis (35 % vs. 47 %, p = 0.006), disease free survival (11 % vs. 3 %, p < 0.0001), and rate of biochemical failure (65 % vs. 80 %, p < 0.0001) favored the ADT plus EBRT arm, compared with EBRT alone arm [11, 12].

The RTOG 9202 study randomized 1,554 patients with T2c-T4, N0 prostate cancer to receive EBRT plus 4 months of neoadjuvant/concurrent ADT (short-term androgen deprivation, STAD) vs. EBRT plus 2 years of neoadjuvant/concurrent/adjuvant ADT (long-term androgen deprivation, LTAD). Ten-year overall survival was not statistically different for the intent-to-treat population (52 % vs. 54 %, p = 0.36), but was improved in a post-hoc subset analysis of patients with Gleason 8-10 cancer (32 % vs. 45 %, p = 0.0061). There were statistically significant improvements in 10 year disease free survival (13 % vs. 23 %, p < 0.0001), disease specific survival (84 % vs. 89 %, p = 0.0042), local progression (22 % vs. 12 %, p < 0.0001), distant metastasis (23 % vs. 15 %, p < 0.0001), and biochemical failure (68 % vs. 52 %, p < 0.0001) favoring the EBRT plus LTAD arm [13, 14].

The EORTC 22863 study comparing EBRT vs. EBRT plus 3 years of ADT in 415 patients with T1-2 high grade or T3-4 prostate cancer showed statistically significant improvements in 5 year overall survival (62 % vs. 78 %, p = 0.0002), disease free survival (40 % vs. 74 %, p = 0.0001), disease specific survival (79 % vs. 94 %, p = 0.0001), locoregional failures (16 % vs. 2 %, p < 0.0001) and distant metastasis (29 % vs. 10 %, p < 0.0001) all favoring the EBRT plus ADT arm [15].

From these studies, it appears that for cancer specific survival, at least 4 months of ADT is needed for benefit; and for overall survival, at least 3 years of ADT is needed for benefit. Prolonged duration of ADT needs to be balanced with adverse effects of ADT and study of prolonged intermittent ADT (known to provide improved quality of life compared to continuous therapy in advanced disease) has not been studied.

D'Amico and colleagues completed a study of EBRT vs. EBRT plus 6 months of ADT in 206 patients with T1-4, N0 prostate cancer patients with at least one

unfavorable prognostic feature (PSA >10 ng/mL, Gleason ≥7, T3a or T3b disease by MRI) and found an increased overall survival in the EBRT plus ADT arm among patients with no or minimal comorbidity (HR 4.2, $p<0.001$), but not among patients with moderate or severe comorbidity (HR 0.54, $p=0.08$) [16]. Further validation of this finding is needed.

Adverse Effects of ADT

The benefits of ADT are often weighed against the expected adverse effects. The most common adverse events include hot flashes, decreased muscle mass and bone mineral density, metabolic changes, and gynecomastia [17]. There is also a reduction of multiple quality of life measures associated with ADT, including fatigue, depression, cognitive changes, and decrease in sexual libido and function [18, 19].

Among patients receiving ADT, hot flashes may occur as frequently as 80 %, with severe hot flashes occurring up to 30 % of the time [20]. More than half of patients who suffer hot flashes report significant decreases in their quality of life and increase in their distress [21, 22]. The mechanism of hot flashes due to ADT in prostate cancer is incompletely understood; however, it is believed to be caused by negative feedback of plasma sexual hormones upon the hypothalamic secretion of norepinephrine and serotonin [23]. Current approaches to the treatment of hot flashes include hormonal (estrogens and progestins) and non-hormonal (clonidine, serotonin reuptake inhibitors, gabapentin) therapies which have variable activity and side effect profiles [20].

Loss of bone marrow density is seen early after initiation of ADT, with up to 3–4 % loss seen after 12 months of therapy [24]. The loss is ongoing and the risk of osteoporosis increases with the duration of therapy, with reported rates of osteoporosis of 35 % for hormone-naive men with prostate cancer, 49 % after 4 years of ADT and 81 % after 10 or more years of ADT [25]. In addition to vitamin D and calcium supplementation, current approaches to the treatment of ADT-induced osteoporosis include zolendronic acid and denosumab [26, 27].

The incidence of metabolic syndrome is higher in patients receiving ADT for their prostate cancer. Multiple studies have shown increases in weight, body fat, total and low-density lipoprotein cholesterol, as well as, increased rates of hypertriglyceridemia, abdominal obesity, and hyperglycemia [28, 29]. There is a substantial amount of data demonstrating that ADT adversely affects these traditional cardiovascular risk factors, and recent studies have reported a relationship between ADT and an increased risk of cardiovascular disease. However, different studies both have and have not reported an increased risk of cardiovascular death. The decision regarding whether or not to initiate ADT in patients with cardiac disease should consider the benefits of therapy against any possible risks. It is recommended that patients in whom ADT is initiated undergo periodic follow-evaluation of blood pressure, lipid profile, and glucose level. However, there is no need for specific cardiac evaluation in asymptomatic patients [30].

Surrogate Endpoints for Prostate-Cancer Specific Survival After RT Plus ADT

Given that the small survival benefit of LTAD compared with STAD is often associated with increased toxic effects from longer term ADT, there is much interest in the development of predictive biomarkers and surrogate endpoints for survival. D'Amico and colleagues reviewed the data from two randomized controlled trials (the Dana Farber Cancer Institute (DFCI) trial and the Trans-Tasman Radiation Oncology Group (TROG) trial) [16, 31] to try to identify men in whom radiotherapy and STAD was insufficient for cure. In this retrospective study of 734 men with localized and locally advanced prostate cancer who received radiotherapy and 6 months of ADT, they found that end of treatment PSA value >0.5 ng/mL and PSA nadir >0.5 ng/mL were both validated as potential surrogate markers for prostate cancer specific mortality. Men who do not achieve end of treatment or nadir PSA of ≤0.5 ng/mL was recommended to be considered for additional ADT therapy or participation in clinical trials [32].

Role of Radical Prostatectomy in Locally Advanced Prostate Cancer

Radical prostatectomy with extended lymph node dissection remains an option for select patients with locally advanced prostate cancer with no fixation to adjacent organs. The role of radical prostatectomy for high risk and locally advanced prostate cancer was evaluated by Lau and colleagues from the Mayo Clinic. Among 6,419 patients who underwent radical prostatectomy between 1987 and 1996, 407 patients had pathologic Gleason score ≥8. Among these patients, 26 % had localized disease and 27 % had lymph node positive disease. Notably, 45 % of these high-risk patients received some form of adjuvant therapy (ADT and/or radiotherapy). The 10-year overall survival was 67 %, progression-free survival was 36 % (53 % for those who received adjuvant therapy and 23 % for those who did not get adjuvant treatment), and disease specific survival was 85 % [33].

A nonrandomized, retrospective analysis comparing 1,318 patients treated with radical prostatectomy and 1,062 patients treated with EBRT with elective nodal irradiation at Baylor Medical College and Memorial Sloan Kettering Cancer Center showed an 8-year probability of freedom from metastatic progression was 97 % for radical prostatectomy patients and 93 % for EBRT patients. Surgery was associated with a lower risk of both distant metastasis (HR 0.35; $p < .001$) and prostate cancer–specific mortality (HR 0.32; $p = 0.015$). Differences in the rates of metastatic progression were more pronounced with higher risk disease (8 % in 8-year metastatic progression), compared with intermediate risk (3 %) or low risk (2 %) disease [34].

Role of Neoadjuvant ADT Prior to Radical Prostatectomy

Previous studies have evaluated the role of neoadjuvant hormonal therapy prior to radical prostatectomy. While none of these studies demonstrated improvements in overall survival, there were reductions in positive margin rates; and improvements in lymph node involvement, pathological staging, rate of organ-confined disease, and disease recurrence rates. However, most of these studies included patients with low-risk or intermediate risk disease [35–41].

In a Cochrane Database Systemic Review of these neoadjuvant androgen deprivation therapy trials for localized and locally advanced prostate cancer, neo-adjuvant hormonal therapy prior to prostatectomy did not improve overall survival (OR 1.11, $p=0.69$). However, there were significant improvements in the positive surgical margin rate (OR 0.34, $p<0.00001$) and other pathological variables such as lymph node involvement, pathological staging and organ confined rates. The use of longer duration of neo-adjuvant hormones, that is either 6 or 8 months prior to prostatectomy, was associated with a significant reduction in positive surgical margins (OR 0.56, $p=0.002$) [42].

More recent evidence evaluating the impact of neoadjuvant ADT prior to radical prostatectomy also showed no impact on the incidence of biochemical recurrence. A Korean study of 69 men randomized to receive or not to receive preoperative neoadjuvant hormone therapy showed no differences in positive margin rate or biochemical recurrence rate; however, the mean operative time was significantly higher in the group of men who received preoperative hormone therapy [43]. Thus there is no compelling evidence that neoadjuvant ADT should be used in patients with advanced localized prostate cancer.

Role of Adjuvant Therapy After Radical Prostatectomy

The need for adjuvant therapy after radical prostatectomy depends on pathological factors. Adjuvant radiation therapy may be indicated in patients with T3 disease (extracapsular extension or seminal vesicle involvement) or positive margins, and may be considered for patients with Gleason score ≥ 8, and/ or PSA that does not nadir to undetectable levels. The exact timing of post-prostatectomy radiation therapy (adjuvant vs. early salvage) is still being investigated [44]. Current NCCN guidelines recommend adjuvant radiotherapy for positive margins and adjuvant ADT for lymph node positive disease [4].

In the SWOG S9921 trial, 983 men with high risk prostate cancer (extraprostatic extension or high Gleason grade) received adjuvant therapy with ADT (goserelin and bicalutamide for 2 years) alone or in combination with mitoxantrone chemotherapy after prostatectomy. For the 481 men who received ADT only, the estimated 5-year biochemical failure-free survival was 92.5 % and 5-year overall survival was 95.9 %. This trial was closed to further accrual in January 2007, after three cases of acute myelogenous leukemia were reported in the mitoxantrone treatment arm. The final analysis of the primary endpoint of overall survival comparing the two arms for this trial has not been reported; however, the results seen for this ADT arm

makes a compelling argument to counsel patients with high risk prostate cancer about adjuvant ADT after prostatectomy [45].

Messing and colleagues reported on the results of a multi-institutional trial of 98 men who had undergone radical prostatectomy and had nodal metastases who were randomized to receive adjuvant ADT or to be followed until disease progression. Immediate treatment with ADT was associated with improved overall survival, prostate cancer specific survival, and recurrence rate, compared with observation and treatment at disease progression [8].

Wirth and colleagues evaluated adjuvant flutamide vs. no adjuvant treatment after radical prostatectomy in 309 patients with locally advanced, lymph node-negative prostate cancer. Recurrence-free survival was better in the flutamide group ($p=0.0041$); there was, however, no detectable difference in overall survival ($p=0.92$). Treatment with flutamide was also associated with significant toxicity [46].

The Casodex Early Prostate Cancer Trialists' Group evaluated the efficacy and tolerability of adjuvant high dose bicalutamide versus placebo for 8,113 patients with localized or locally advanced non-metastatic prostate cancer. In locally advanced disease, bicalutamide significantly improved PFS irrespective of standard care (surgery, radiotherapy, or watchful waiting). Adjuvant bicalutamide significantly improved overall survival in patients receiving radiotherapy but there was no survival difference in the prostatectomy subgroup [47].

Role of Chemotherapy in Locally Advanced Prostate Cancer

The role of chemotherapy in high-risk localized prostate cancer has been evaluated in multiple phase I-III clinical trials. It has been evaluated in the neoadjuvant, concurrent, and adjuvant setting in combination with radiation therapy and ADT where some trials revealed markedly increased incidence of severe toxicities, and other trials showing reasonable tolerability [48–54]. To date, there have been no trials demonstrating survival benefit of neoadjuvant or adjuvant chemotherapy; therefore, its use in this setting is still investigational. There is an ongoing trial investigating the role of neoadjuvant hormonal therapy in combination with docetaxel prior to radical prostatectomy (CALGB 90203).

Future Directions and Ongoing Clinical Trials in Patients with Locally Advanced Prostate Cancer

The development of newer agents may also offer a less toxic approach to neoadjuvant therapy [55]. Abiraterone, an inhibitor of extragonadal androgen synthesis approved for castrate resistant prostate cancer in the post-docetaxel setting, is being evaluated in the neoadjuvant setting in addition to LHRH agonist therapy (ClinicalTrials.gov identifier NCT01088529). Similarly, enzalutamide, a potent anti-androgen, is also under investigation in the neoadjuvant setting (ClinicalTrials.gov identifier NCT01547299). Other agents being tested in the neoadjuvant setting include

ipilimumab, an anti-CTLA4 antibody approved for melanoma (ClinicalTrials.gov identifier NCT01194271); OGX-011, a second-generation antisense molecule that blocks production of clusterin (ClinicalTrials.gov identifier NCT00138918); axitinib, a tyrosine kinase inhibitor (ClinicalTrials.gov identifier NCT01385059).

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