Localized Prostate Cancer—What the Medical Oncologist Needs to Know

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Abstract

Prostate cancer is the most commonly diagnosed cancer among men and the second leading cause of cancer-related deaths among men in the US. In the post-prostate specific antigen (PSA) era, about 85% of all prostate cancers diagnosed are clinically localized prostate cancers. Most cancers are diagnosed in asymptomatic men, and T1c (stage I) is the most commonly diagnosed stage of prostate cancer. Consequently, medical oncologists are increasingly being asked to participate in multidisciplinary prostate cancer clinics and provide recommendations on localized prostate cancer, particularly related to active surveillance as well as neoadjuvant and adjuvant therapies such as androgen deprivation therapy (ADT) and chemotherapy. This article reviews the potential role of the medical oncologist as a team member in the management of localized prostate cancer. The role of active surveillance as well as neo-adjuvant and adjuvant therapies such as ADT and chemotherapy is discussed in detail. The long-term adverse effects of ADT and potential supportive measures are also reviewed.

Keywords

Localized prostate cancer, androgen deprivation therapy, adjuvant, active surveillance, risk stratification

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The Magnitude of Localized Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men and the second leading cause of cancer-related deaths among men in the US. It is estimated that approximately 192,280 new cases of prostate cancer were diagnosed in the US in 2009 alone;[1] this accounts for about 25% of all new cancer diagnoses in men in the US for 2009. It is estimated that one in six men will develop prostate cancer over their lifetime. Thus, prostate cancer is an important public health issue. Prostate-specific antigen (PSA) has revolutionized screening and treatment decision-making in prostate cancer, although recently there has been much controversy regarding the utility of PSA screening.[2,3] Indeed, the widespread use of PSA screening has led to a dramatic shift in the epidemiology of prostate cancer. Based on data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a disease registry of 8,685 men with various stages of prostate cancer, Cooperberg et al.[4] reported that the percentage of men with low-risk prostate cancer increased from 29.8% in 1989–1992 to 45.3% in 1999–2001 ($p<0.0001$). Similarly, a population-based study based on the Surveillance, Epidemiology, and End Results (SEER) Program reported that from 1988 to 2003, the age-adjusted incidence of stage IV prostate cancer significantly declined by 6.4% each year, and the proportion of men diagnosed at younger ages with poorly differentiated tumors or who underwent a radical prostatectomy (RP) significantly increased over time.[5]

Given the impact of PSA, the epidemiology of prostate cancer is broadly divided into the pre-PSA and post-PSA era. In the post-PSA era, about 85% of all prostate cancers diagnosed are in asymptomatic men and are clinically localized prostate cancers (i.e confined to the prostate at the time of diagnosis).[6] Indeed, clinical stage T1c (stage I) is the most commonly diagnosed stage of prostate cancer. It should be noted that while PSA >4ng/ml is considered the traditional cut-off in PSA screening,[7,8] recent studies suggest that there is no PSA threshold below which having the risk for prostate cancer is zero.[9] Another parallel trend with the increase in low-volume, localized prostate cancers in the post-PSA era has been the increase in medical oncology consultation for localized prostate cancer. Medical oncologists are increasingly being asked to participate in multidisciplinary prostate cancer clinics and provide curbside opinions from colleagues related to localized prostate cancer. The medical oncologist is being asked to review data and provide directions in formal consultation, particularly on active surveillance, to provide recommendations on neoadjuvant and adjuvant therapies, and to discuss clinical trials, if available. This article reviews the potential role of the medical oncologist as a team member in the management of localized prostate cancer. We will present four common case scenarios and use them as a platform to discuss how a medical oncologist may affect the care of a patient with localized prostate cancer.

Localized Prostate Cancer—The Role of the Medical Oncologist

Case Study 1

A 70-year-old retired engineer was found to have a rise in PSA on his yearly screenings from 2.8 to 4.1ng/ml in the past year. He was in average health

for his age, and denied any bothersome symptoms. His physical examination, including digital rectal examination (DRE), was unremarkable. A 12-core prostate biopsy was then performed. Pathologic examination showed that two of the 12 cores were involved on the left with Gleason 3+3 (moderately differentiated) and <50% of cores were positive, and no peri-neural invasion was noted. While not routinely recommended, as per patient request imaging studies (computed tomography [CT] scan of the chest/abdomen/pelvis and bone scans) were obtained and were unremarkable. His urologist recommended active surveillance for his prostate cancer. However, the patient was shocked, and said, 'What do you mean? I have cancer and we are going to observe it?' The urologist then explained the rationale of observation. However, the patient was not satisfied and requested a medical oncology opinion for discussion of treatment options.

This is not an uncommon scenario encountered in medical oncology clinics. In order to make a treatment decision, two key factors need to be considered: risk stratification and life expectancy (age and comorbidities).

Risk Stratification for Prostate Cancer

The risk for disease progression following definitive therapy for localized prostate cancer can be broadly classified into four categories: very low risk, low risk, moderate risk, and high risk, as outlined in *Table 1*.[10] Low risk is defined as T1c–T2a, Gleason score ≤6, and PSA ≤10ng/ml; intermediate risk is defined as T2b, Gleason 7, or PSA 10.1–20ng/ml, and no high-risk features; and high risk is defined as Gleason 8–10, or T2b or greater, PSA >20ng/ml, or pre-treatment PSA velocity >2ng/ml/year. Retrospective studies have reported that the risk for death from prostate cancer after definitive surgery for localized prostate cancer is much higher among patients with high-risk (hazard ratio [HR] 11.5; p<0.0001) or intermediate-risk disease (HR 6.3; p<0.0001) compared with patients at low risk,[11] and this risk stratification is utilized in the National Comprehensive Cancer Network (NCCN) guidelines (www.nccn.org) for prostate cancer as well. Given the concerns of overtreatment of localized prostate cancer, in the 2010 update the NCCN panel added another category: very low risk, defined as T1c, Gleason score ≤6, PSA ≤10ng/ml, fewer than three core biopsies positive, ≤50% in each core, and PSA density <0.15ng/ml/g (such as the patient in this case study).

Life Expectancy (Age and Presence of Comorbidities)

Not all prostate cancers are lethal; in fact, a large number of men with localized prostate cancer die with it, rather than of it.[12,13] It is thus crucial to ascertain whether the prostate cancer in the individual person is likely to become clinically significant or not over his projected life expectancy. The key question is: does the individual have enough life expectancy to die from prostate cancer? Estimating 10- or 20-year life expectancy is important in this decision-making. The Social Security Administration website has tables that can be used to estimate the probable life expectancy (www.ssa.gov/OACT/STATS/table4c6.html). To adjust for comorbidities, a rule of thumb is to add 50% to this estimate for men who are in the best quartile of health, and subtract 50% for those who are in the worst quartile of health (NCCN). The Adult Comorbidity Evaluation 27 (ACE-27) index is another validated comorbidity index that could be used to ascertain the degree of comorbidity among cancer patients (oto.wustl.edu/clinepi/calc.html).

Table 1: Risk Stratification of Prostate Cancer

Risk Category	Definition
Very low risk	T1c Gleason score ≤6 PSA ≤10ng/ml <3 core biopsies positive ≤50% in each core PSA density <0.15ng/ml/g
Low risk	T1c–T2a Gleason score ≤6 PSA ≤10ng/ml
Intermediate risk	T2b or Gleason score 7 or PSA 10.1–20ng/ml
High risk	T2b or greater Gleason score 8–10 or PSA >20ng/ml, or pre-treatment PSA velocity >2ng/ml/year

Given the concerns of overtreatment of localized prostate cancer, in the 2010 update, the National Comprehensive Cancer Network (NCCN) panel added another category: very low risk, as defined in the table. PSA = prostate-specific antigen.

So, our patient had very-low-risk disease and a life expectancy of 10–15 years. Let us now review whether active surveillance is an appropriate option for him or not.

Role of Active Surveillance

PSA screening has led to an increase in overdiagnosis and overtreatment of prostate cancer.[14,15] Some authors have suggested that up to one-third of prostate cancer that is diagnosed is overtreated.[16] Autopsy studies suggest up to one-third of men in the US >50 years of age have prostate carcinoma, with the majority being early-stage, non-palpable, low-volume disease.[6,17] It is estimated that a total of 1,410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer.[2] Thus, a large proportion of prostate cancers that are diagnosed is likely clinically insignificant.

Various epidemiologic studies have reported results of immediate versus delayed therapy (active surveillance) among men with localized prostate cancer. A SEER-based cohort study reported the results of follow-up of older men (≥65 years of age) with stage T1 or T2 disease managed without any therapy for at least six months after diagnosis.[18] After a median of 8.3 years the authors reported that the 10-year prostate-cancer-specific mortality was 8.3, 9.1, and 25.6% for well-differentiated tumors, moderately differentiated tumors, and poorly differentiated tumors, respectively. The 10-year mortality for prostate cancer for men with moderately differentiated disease declined significantly (6%) in the contemporary PSA era (1992–2002) compared with the pre-PSA era (15–23%). A study by Warlick et al.[19] compared the outcomes of expectant management with delayed RP (median delay 26 months) with immediate RP among patients with small, lower-grade prostate cancer seen at Johns Hopkins. The authors reported that the risks of non-curable cancer associated with delayed and immediate intervention did not differ statistically significantly (relative risk [RR] 1.08, 95% confidence interval [CI] 0.55–2.12; p=0.81). Similar results were reported recently from the Swedish section of the European Randomized Study of

Screening for Prostate Cancer, in which men diagnosed with low-risk prostate cancer were randomized to immediate RP or expectant management with delayed RP.[20] The authors reported that the frequencies of Gleason score >6, capsular penetration, or biochemical progression rates were similar between the two groups. Data from the CaPSURE database suggest that about 50% of men who choose active surveillance for localized prostate cancer do not need any active treatment at five years.[21] Men who are of younger age, have higher PSA, and have a higher Gleason grade were more likely to receive active treatment. Other studies have reported similar results.[22–25]

Finally, a large population-based study comparing androgen deprivation therapy (ADT) and observation among elderly patients (≥66 years of age) with low-risk prostate cancer (clinical stage T1–T2) reported no overall survival benefit with ADT compared with observation (30.2 versus 30.3%, HR 1.00) for this age group.[26] Thus, a significant number of prostate cancers that are diagnosed, particularly among the elderly, are clinically insignificant and will likely not pose a significant health problem. In such cases, no treatment with active surveillance and close follow-up is appropriate.

Various statistical models and nomograms have been developed that can predict the presence of 'clinically insignificant' or 'indolent cancers,' i.e. small, organ-confined prostate cancer.[27–33] It is suggested that PSA velocity rather than absolute value of PSA might be helpful in predicting presence of aggressive prostate cancer.[34,35] Recent studies have also suggested that besides age, PSA, and initial Gleason score, the results of the first repeat prostate biopsy are also an important predictor of disease progression.[36–39]

Another key factor that should be considered in decision-making is patient preference and beliefs. Often the fear of the word 'cancer' is out of proportion to the real threat of cancer. The patient may have a loved one who experienced a terrible death from cancer and consequently he is afraid he is going to have a painful death as well. Listening carefully to the patient, understanding his concerns, and addressing them in an effective and rational fashion is thus of paramount importance in decision-making.

The NCCN recommends that active surveillance is appropriate for men with very-low-risk prostate cancer and a life expectancy of less than 20 years, or those with low-risk disease and a life expectancy of less than 10 years. The recommended follow-up includes PSA checks every three to six months, DRE every six to 12 months, and prostate biopsy after 18 months if initial biopsy had greater than 10 cores, or if any abnormality is noted on PSA or DRE. Prostate cancer progression warranting treatment is to be considered if PSA doubling time is less than three years, a primary Gleason score of 4 or 5 is found on repeat biopsy, or carcinoma is detected to a greater extent or in greater number in repeat biopsies. The advantages of active surveillance include reduced time spent away from work and family due to therapy as well as avoidance of potential side effects of a therapy that was not needed.[40]

For example, RP can have a significant impact on urinary and sexual function, while ADT can lead to osteopenia, weight gain, and increased risk for cardiovascular events.[41,42] The disadvantages of active surveillance include the potential for greater progression of disease than anticipated, the chance that the subsequent treatment may be more complex and invasive, increased patient anxiety, and the need for close follow-up, including prostate biopsies.

In summary, risk stratification of prostate cancer and the life expectancy of the individual person in consideration, along with patient preference, are crucial in clinical decision-making for low-risk localized prostate cancer. Our patient (case study 1) has very-low-risk prostate cancer and a life expectancy of about 10–15 years. Thus, the prostate cancer is most likely clinically insignificant and will not pose a significant health problem. Therefore, active surveillance with regular PSA, DRE, and prostate biopsy would be appropriate and is the recommended treatment.

Summary for Case Study 1

This was discussed with the patient. The relevant data were reviewed, including the concept that while he did have prostate cancer, the cancer was likely not to have a significant impact clinically, cause bothersome symptoms, or shorten his survival. Moreover, it was emphasized that he would be followed closely to monitor for any progression of disease and/or development of symptoms. The fears and anxiety of the patient were allayed, and he agreed to participate in active surveillance for his localized prostate cancer.

Case Study 2

A 60-year-old pharmacist was found to have a rise in PSA on his yearly screenings from 2.9 to 6.5ng/ml in the past year. He was otherwise in good health. His physical examination, including DRE, was unremarkable. Pathologic examination of the 12-core prostate biopsy showed that eight of the 12 cores were involved on the left with Gleason 4+5, >50% of cores were positive, and peri-neural invasion was noted. CT scan of the chest/abdomen/pelvis was unremarkable, except for possible seminal vesicle invasion. He was then seen by a radiation oncologist who recommended external-beam radiation therapy (RT), and also referred him to a medical oncologist for consideration of neoadjuvant and adjuvant hormonal therapy.

Role of Androgen Deprivation Therapy in Localized Prostate Cancer After Radiation Therapy

While RP or RT is performed with curative intent, about 30–40% of men with localized prostate cancer, particularly those with high-risk disease, have disease recurrence (local recurrence or metastatic disease). Thus, there has been interest in utilizing adjuvant therapies among men with high-risk prostate cancer. The most studied agent has been ADT. Seminal work by Huggins in the 1940s demonstrated that prostate cancer cells are androgen-dependent for growth and proliferation,[43] and the observation was recognized with a Nobel prize in 1966 (shared with Peyton Rous). This discovery led to great interest in the development of ADTs for prostate cancer. These therapies include surgical castration, medical castration with leuteinizing-hormone-releasing hormone (LHRH) agonists such as leuprolide (Lupron®) and goserelin (Zoladex®), and anti-androgen agents such as bicalutamide (Casodex®). More recently there has been interest in identifying other androgen-suppressing agents, including inhibitors of the androgen-regulating enzyme CYP17, such as abiraterone, and androgen receptor antagonists, such as MDV3100.[44,45] ADT is the first-line therapy for metastatic prostate cancer

Table 2: Summary of Randomized Clinical Trials Evaluating the Role of Neoadjuvant or Adjuvant Androgen Deprivation Therapy for Localized Prostate Cancer

Author	Study Population	Sample Size	Treatment	Timing	Follow-up (years)	Results
Schulman, 2000[59]	T2–T3	402	LHRH analog (goserelin) plus flutamide x 3 months then RP versus RP alone	Neoadjuvant	4	OS: 93% in Rx versus 95% in control (p=0.64)
Aus, 2002[60]	T1b–T3a	126	LHRH analog x 3 months then RP versus RP alone	Neoadjuvant	7	OS: 49.8% in Rx versus 51.5% in control (p=0.588)
Klotz, 2003[61]	T1–T2	213	100mg cyproterone acetate 3 times daily x 3 months then RP versus RP alone	Neoadjuvant	6	5-year OS: 88.4% in Rx versus 93.9% in control (p=0.38)
Pilepich, 2001[51]	T2–T4	–	–	Neoadjuvant	8	OS: 53% in Rx versus 44% in control (p=0.10)
Hanks, 2003[54]		1,554	Short-term ADT (goserelin and flutamide for 2 months before and 2 months during RT) versus long-term ADT (short-term ADT + 2 years of LHRH agonist therapy)	Neoadjuvant and adjuvant	5.8	5-year OS: 80% in long-term ADT versus 78.5% in short-term ADT (p=0.73) 5-year PCFS: 46.4% in long-term versus 28.1% in short-term ADT (p<0.0001)
Bolla, 2002[46]	T1–2 and WHO grade 3, or T3–4 and any grade, N0-1, M0	415	RT alone versus RT and ADT (LHRH analog for 3 years)	Adjuvant	5.5	OS: HR 0.51, 95% CI 0.36–0.73 (p=0.0002) PCFS: HR 0.34, 95% CI 0.26–0.46 (p<0.0001)
D'Amico, 2004[47]	T1b–T2b, N0–1, M0, PSA >10ng/ml, Gleason score >7, or radiographic evidence of extraprostatic disease	206	RT alone versus RT and immediate ADT	Adjuvant	4.5	RT + ADT had higher OS (p=0.04) and lower PCM (p=0.02) than RT alone
Lawton, 2005[48]	T1a–T2c, N1, or T3, N0–1	173	RT alone versus RT and immediate ADT	Adjuvant	6.5	OS: HR 1.3 (p=0.001) PCFS: HR 2.2 (p<0.0001)
Messing, 2006[56]	T1b–T2, N1	98	RP alone versus RP and ADT (LHRH or bilateral orchiectomy)	Adjuvant	11.9	OS: HR 1.84, 95% CI 1.01–3.35 (p=0.04) PCFS: HR 4.09, 95% CI 1.76–9.49 (p=0.0004)
McCleod, 2006[62]	T1b–4, N0–NxM0 (N+ not allowed)	3,292	After standard RP or RT, 150mg bicalutamide daily versus placebo for 2 years	Adjuvant	7.7	OS: HR 1.04, 95% CI 0.85–1.26 (p=0.723) PCFS: HR 1.00, 95% CI 0.84–1.19 (p=0.991)
Bolla 2009[55]	T1c to T2a–b, N1–N2, or T2c to T4, N0–N2, M0	970	Short-term ADT (LHRH agonist and anti-androgen) versus long-term ADT (6 months of LHRH agonist and antiandrogen agent + additional 2.5 years of LHRH analog)	Adjuvant	6.4	OM: HR 1.42 (p=0.65) PCM: HR 1.71, 95% CI 1.14–2.57 (p=0.002)

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; LHRH = leutinizing-hormone-releasing hormone; OS = overall survival; OM = overall mortality; PCM = prostate cancer mortality; PCFS = prostate-cancer-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RR = relative risk; RT = radiation therapy; Rx = treatment; WHO = World Health Organization.

and has received considerable attention in the adjuvant setting as well, as outlined below and in *Table 2*.

Timing of Androgen Deprivation Therapy After Radiation Therapy

Immediate versus Deferred Androgen Deprivation Therapy

In the European Organization for Research and Treatment of Cancer (EORTC) protocol 22863412 clinical trial, 415 men with intermediate- or high-risk localized prostate cancer (T1–2 and World Health Organization [WHO] grade 3, or T3–4 and any grade, N0–1, M0) were randomized to RT alone versus RT and ADT (LHRH analog for three years).[46] After a median follow-up of 66 months (5.5 years), the authors reported that the RT + ADT alone group had a higher overall survival (HR 0.51; p=0.0002) and prostate-cancer-free survival (HR 0.34; p<0.0001) compared with the RT alone group. Other randomized clinical trials (RCTs) have also reported that adjuvant ADT after RT is associated with improved overall survival and disease-free survival.[47,48] *Post hoc* sensitivity analyses have suggested that the benefit of immediate ADT is mostly restricted to men with mild or no medical comorbidities, for both intermediate- and high-risk prostate cancer, as was the case in the patient in case study 2.[49,50]

Neoadjuvant Androgen Deprivation Therapy

Few clinical trials have evaluated the role of neoadjuvant therapy before RT. In a large RCT, 471 men with locally advanced prostate cancer (T2–T4) were randomized to neoadjuvant ADT (goserelin 3.6mg every four weeks and flutamide 250mg three times daily) for two months

followed by RT, versus RT alone.[51] After a median follow-up of about eight years, the neoadjuvant arm had higher disease-free survival (33 versus 21%; p=0.004), but not overall survival (53 versus 44%; p=0.10), compared with the RT alone arm. Similarly, the neoadjuvant arm had a higher local control rate (42 versus 30%; p=0.016) and a lower incidence of distant metastases (34 versus 45%; p=0.04). Other clinical trials have also reported improved disease-free survival[52] but not improved overall survival[53] with neoadjuvant ADT before RT.

Neoadjuvant and Adjuvant Androgen Deprivation Therapy

A large randomized clinical trial (Radiation Therapy Oncology Group [RTOG] Protocol 92-02) tested the efficacy of short-term versus long-term ADT among 1,554 men with locally advanced prostate cancer (T2c–T4).[54] Eligible men received ADT (goserelin 3.6mg monthly and flutamide 250mg three times/day) for two months before and two months during RT, and were then randomized to receive no additional therapy (short-term ADT) versus two years of LHRH agonist therapy (long-term ADT). After a median follow-up of 5.8 years, the authors reported that the men in the long-term ADT arm had higher five-year disease-free survival (five-year rate 46.4 versus 28.1%; p<0.0001) but not overall survival (80 versus 78.5%; p=0.73). However, sensitivity analysis revealed that among men with Gleason 8–10 prostate cancer, but not Gleason 7 or lower, men in the long-term ADT arm had higher overall survival as well (81.0 versus 70.7%; p=0.044). Thus, ADT before and/or after RT should be considered for men with high-risk prostate cancer, such as our patient (NCCN).

Duration

While adjuvant ADT appears to be beneficial after RT among select patients with intermediate- or high-risk prostate cancer, the next question is how long the therapy should be continued for. The EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group reported results on an RCT in which men with locally advanced prostate cancer (T1c–T2a–b and N1 or N2, or T2c–T4 and N0–N2, M0) receiving RT (n=970) were randomized to short- or long-term ADT (six months of LHRH agonist and anti-androgen agent + an additional 2.5 years of LHRH analog).[55] After a median follow-up of 6.4 years, while there was no difference in the five-year overall mortality rate for short- and long-term suppression (HR 1.42; p=0.65), the five-year prostate cancer mortality rate was higher in the short-term ADT group compared with the long-term ADT group (HR 1.71; p=0.002). However, the incidence of hot flashes and sexual dysfunction was higher in the long-term ADT group.

Summary for Case Study 2

In summary, adjuvant ADT (LHRH agonist with/without anti-androgen therapy) before, during, and/or after RT is associated with better outcomes among selected men with high-risk, locally advanced prostate cancer, such as this patient. While long-term ADT (two to three years) is associated with better outcomes among men with high-risk disease, long-term ADT is also associated with increased adverse effects. The use of shorter-course (four to six months) adjuvant ADT before/after RT may be appropriate among men with intermediate-risk prostate cancer. We reviewed the benefits and adverse effects of ADT with this patient, and he agreed to receive long-term ADT (two to three years) after his RT.

Case Study 3

A 55-year-old attorney was seen by a urologist for localized prostate carcinoma involving eight of the 12 cores, Gleason 4+5, and >50% of cores positive. PSA was 23ng/ml. CT scans of the chest/abdomen/pelvis were unremarkable, except for borderline lymph-node enlargement. He then underwent RP and pelvic lymphadenectomy. Surgical pathology showed the presence of adenocarcinoma of the prostate, Gleason 4+5=9, involving both lobes, no seminal vesicle invasion, and negative surgical margins. However, five pelvic lymph nodes were noted to be positive. Given the presence of positive lymph nodes, he was then referred by his urologist to a medical oncologist for consideration of adjuvant hormonal and/or chemotherapy.

Androgen Deprivation Therapy for Lymph-node-positive Localized Prostate Cancer

Given the success of adjuvant therapies in other cancers such as colon cancer and breast cancer, there has been interest in adjuvant therapies for prostate cancer, particularly high-risk types. In the RCT Eastern Cooperative Oncology Group (ECOG) 3886, men with lymph-node-positive prostate cancer after RP and pelvic lymphadenectomy were randomized to immediate ADT (bilateral orchiectomy, or goserelin continually) versus deferred ADT, i.e. ADT only on detection of distant metastases or symptomatic recurrences.[56] After a median follow-up of 11.9 years, the authors reported that men assigned to immediate ADT (n=47) had a significant improvement in overall survival (HR 1.84; p=0.04) and prostate-cancer-specific survival (HR 4.09; p=0.0004) compared with those assigned to deferred ADT (n=51). It should be noted that the duration of ADT was not optimally defined in the study (goserelin was recommended to be used continually), and the study results do not address the appropriateness of adjuvant ADT in lymph-node-negative, high-risk localized prostate cancer. When first published, this study received criticism for its small sample size and poor methodology.[57] Moreover, the long-term effects of ADT on bone or cardiovascular risk were not ascertained prospectively in a systematic fashion, as the trial was conceived in the 1980s and at that time these adverse effects (osteopenia and cardiovascular risk) were not well recognized.

A subsequent publication did address some of the major concerns.[56] It should be recognized that this is the only RCT on adjuvant ADT for lymph-node-positive prostate cancer after RP.[56] Moreover, the treatment of biochemical recurrence (rise in PSA) after RP (or even RT) without radiologic evidence of metastatic disease is currently controversial.[58] Thus, long-term ADT should be considered among men with lymph-node-positive prostate cancer after RP.

Neoadjuvant Androgen Deprivation Therapy Before Radical Prostatectomy

A few studies have also evaluated the role of neoadjuvant ADT before RP. In a large clinical trial, 402 men with localized prostate cancer (T2–T3) were randomized to neoadjuvant ADT in the form of LHRH analog (goserelin) plus flutamide for three months followed by RP, versus RP alone.[59] After four years of follow-up, the authors reported no difference in survival between the two arms. However, the neoadjuvant ADT arm had higher clinical and pathologic downstaging (p<0.01), a lower number of positive margins (p=0.01), and a lower local recurrence for cT2 tumors (p=0.03) but

not for cT3 tumors (p=0.41). Two other RCTs have reported higher pathologic downstaging and a lower number of positive margins with neoadjuvant ADT before RP,[60,61] but no benefit in overall survival has been shown. Thus, neoadjuvant ADT before RP is not routinely recommended.

Adjuvant Anti-androgen Monotherapy

While the results of adjuvant medical castration (LHRH agonist) after RP for lymph-node-positive localized prostate cancer have been 'positive,' as outlined above, the results of adjuvant anti-androgen monotherapy (flutamide or bicalutamide) have been disappointing. In the largest hormonal therapy trial ever conducted in prostate cancer patients, the early prostate cancer program trial,[62] men with localized lymph-node-negative prostate cancer after RT or RP were randomized to receive 150mg bicalutamide daily versus placebo for two years. After a median follow-up of 7.7 years, the authors reported no difference in overall survival or disease-free survival between the two groups. Thus, use of adjuvant anti-androgen monotherapy after RP or RT is discouraged.

Role of Adjuvant Chemotherapy

Currently, docetaxel is the only approved chemotherapy that has been shown to improve survival in metastatic prostate cancer, and is the first-line therapy for metastatic castrate-resistant prostate cancer.[63,64] While no chemotherapy regimen has an established role as adjuvant therapy for localized prostate cancer, a few clinical trials are ongoing, such as the Cancer and Leukemia Group B (CALGB) 90203 trial (neoadjuvant docetaxel-based therapy among men with high-risk, localized prostate cancer).

However, accrual in such trials is difficult, and a few trials had to close early due to poor accrual, such as TAX 3501, or due to increased adverse effects, such as acute myelogenous leukemia (AML) in the patients receiving mitoxantrone in the SWOG 9921 study (adjuvant ADT versus ADT and mitoxantrone and prednisone following RP in selected high-risk prostate cancer patients). At this time, there are no data to recommend adjuvant chemotherapy for localized prostate cancer.

Summary for Case Study 3

In summary, adjuvant ADT (LHRH agonist with/without anti-androgen therapy) for two years after RP is associated with better outcomes among men with locally advanced prostate cancer with positive lymph nodes, such as the patient in case study 3. However, long-term ADT can be associated with significant adverse effects and should be discussed with the patient (see case study 4). While currently no chemotherapy regimen has an established role as adjuvant therapy for localized prostate cancer, a few clinical trials are ongoing. We reviewed the data with the patient and recommended long-term adjuvant ADT. The adverse effects of ADT were also reviewed, as discussed below with case study 4.

Case 4

A 65-year-old physician underwent RP for high-risk localized prostate cancer. Surgical pathology showed presence of adenocarcinoma of prostate, Gleason 4+5=9, involving lobes, no seminal vesicle invasion, and negative surgical margins, and five pelvic lymph nodes were noted to be positive. His urologist recommended long-term ADT with LHRH agonist for the positive lymph nodes. However, the patient had a strong family history of osteoporosis and was concerned about the long-term adverse effects of ADT. A dual-energy X-ray absorptiometry (DEXA) scan was obtained that showed presence of osteopenia. He was referred to a medical oncologist for further opinion.

The use of ADT, particularly long-term, is associated with a significant increase in adverse events including increase incidence of hot flashes, sexual dysfunction, cognitive changes, mood swings, osteopenia (bone loss), weight gain, diabetes, and potential for increased risk for cardiovascular disease.[41,42,65,66] The use of long-term ADT, particularly among the elderly and men with baseline osteopenia (such as our patient), has been associated with up to a 50% increase in fracture risk.[67] In such patients, the use of agents that could slow this process or potentially even reverse bone loss should be considered, as discussed below.

Bisphosphonates

A number of small clinical trials have evaluated the role of bisphosphonates, particularly pamidronate and zoledronic acid, in the prevention of bone loss among prostate cancer patients receiving ADT.[68–72] Universally, the studies have reported that bisphosphonates (such as zoledronic acid 4mg every three months intravenously [IV]) can effectively improve bone mineral density (BMD) after one year of treatment.[68–75] However, the ability to reduce fractures is less clear. Moreover, ostenecrosis of the jaw is a rare but serious adverse effect of bisphosphonates, and thus the risks and benefits of bisphosphonates should be carefully weighed before its use.

RANKL Inhibitors

Denosumab is a fully human antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), which plays an important role in osteoclast formation and function.[76] In an RCT, 1,468 men with localized prostate cancer on ADT were randomized to subcutaneous denosumab (60mg every six months) or placebo.[77] The authors reported that the BMD of the lumbar spine at the end of two years was significantly higher in the denosumab group compared with placebo (5.6% increase versus 1.0% loss; p<0.001), and men in the denosumab arm had a lower incidence of vertebral fractures as well (relative risk [RR] 0.39, 95% CI 0.19–0.78; p=0.006). However, denosumab is a relatively new agent and long-term toxicity data are not known. Denosumab is not currently US Food and Drug Administration (FDA)-approved.

Lifestyle Modification

Lifestyle modification, including regular physical activity, prevention of weight gain, and smoking cessation, can slow bone loss and improve bone density, and should be recommended. These interventions also have a beneficial role in prevention of other adverse effects associated with ADT such as weight gain, diabetes, and cardiovascular risk. The use of calcium (1,200–1,500mg per day) and vitamin D (400IU per day), as per National Osteoporosis Foundation (NOF), National Institutes of Health (NIH), and Food and Nutrition Board (FNB) recommendations, should be encouraged.[78]

Summary for Case Study 4

In summary, osteopenia can be a significant adverse effect of ADT, particularly long-term ADT. Therefore, a baseline DEXA scan can be

obtained and repeated every one to two years among men on ADT. For men who have baseline osteopenia (such as our patient) or who show signs of reduced BMD during follow-up, agents that can improve bone density, such as bisphosphonates, might be considered. Our patient was interested in receiving long-term ADT, and thus use of bisphosphonates to prevent/reduce osteopenia was recommended. We also recommended lifestyle modification (physical activity, calcium, and vitamin D supplementation) as these not only can reduce bone loss, but may have other beneficial effects as well.

Key Points About Localized Prostate Cancer a Medical Oncologist Should Know

- The majority of prostate cancers diagnosed are clinically localized prostate cancers, with clinical stage T1c being the most common.
- Medical oncologists are increasingly being asked to provide input on localized prostate cancer, particularly related to active surveillance and neoadjuvant and adjuvant therapies, such as ADT and chemotherapy.
- Active surveillance is appropriate for men with low-risk disease and a life expectancy less than 10 years.
- Adjuvant ADT after RT is appropriate for men with high-risk disease and a life expectancy greater than 10 years.
- Adjuvant ADT after RP is appropriate for men with high-risk disease and positive lymph nodes after RP.
- The management of men with biochemical recurrence (rising PSA) after RP or RT and no radiological evidence of metastatic disease is controversial.
- Long-term ADT therapy can be associated with adverse effects including hot flashes, sexual dysfunction, weight gain, diabetes, cardiovascular disease, and bone loss. Lifestyle modification (such as physical activity) should be encouraged among all patients, and in men who have osteopenia or osteoporosis (at baseline or during follow-up), bone agents such as bisphosphonates should be considered.
- Men with high-risk, locally advanced cancers should be encouraged to participate in clinical trials. ■

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