Editorial

De-Implementation of Primary ADT/Skolarus et al

Castration Remains Despite Decreasing Definitive Treatment of Localized Prostate Cancer in the Elderly: A Case for De-Implementation

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In their important study, Yang and colleagues used the National Cancer Data Base to examine definitive therapy (prostatectomy or radiotherapy) among 400,000 patients who were diagnosed with intermediate-risk or high-risk prostate cancer between 2004 and 2012.[1] By using multivariable regression to adjust for patient and sociodemographic factors, those investigators observed that patients decreasingly received definitive treatment with increasing age and worsening comorbidity. Indeed, greater than 40% of patients aged >80 years did not receive definitive treatment with radiation or surgery. Moreover, one-half of patients aged 80 years with high-risk prostate cancer who did not receive definitive treatment went on to undergo receive primary androgen-deprivation therapy (ADT) instead. In this editorial, the authors conclude that significant under treatment of unfavorable-risk prostate cancer in the elderly puts them at up to 20% risk of prostate cancer-related death at 10 years.

On the 1 hand, less use of definitive prostate cancer treatment among patients who are least likely to benefit (ie, elderly, comorbid patients) argues against the widely held belief that we are overtreating patients with prostate cancer. Indeed, compared with men who received definitive treatment, those who did not receive such treatment were more likely to die within 1 year of diagnosis, regardless of age or prostate cancer disease risk, suggesting that decision making was reasonably aligned with life expectancy. An increasing comorbidity score also was associated with a lower likelihood of receiving definitive treatment, such that men who had 2 or more Charlson-Deyo comorbidity points had approximately one-half the odds of receiving definitive treatment compared with men who had no comorbidities.[2] The finding that sicker patients were less likely to receive definitive treatment for localized prostate cancer after taking into consideration other factors (eg, demographics) was encouraging.

Conversely, Yang et al observed overtreatment of elderly patients through a different mechanism—a high rate of chemical castration with ADT as the primary treatment for many elderly patients with localized prostate cancer who were not treated definitively with radiation or surgery. With increasing age, patients were less likely to receive definitive treatment but more likely to be treated with primary ADT. Although receipt of primary ADT was more pronounced

among patients with high-risk, localized disease who did not receive definitive prostate cancer treatment (41%), 1 in 5 men with intermediate-risk disease who did not undergo definitive treatment also received primary ADT. Because the benefits of castration are associated primarily with advanced rather than localized disease, and because safer, effective treatment approaches, such as observation (ie, watchful waiting) or radiation therapy exist, the authors point out that these findings are *troubling*, citing decreased overall survival with primary ADT for localized prostate cancer and its notable harms (eg, metabolic syndrome, fractures, and cognitive, cardiovascular, and sexual dysfunction).[3]

In patients who do not undergo definitive treatment for localized disease, the early versus delayed castration dilemma has been studied in randomized trials. For example, European Organization for Research and Treatment of Cancer trial EORTC 30891 randomized 985 men with newly diagnosed T0-T4 N0-N2 M0 prostate cancer who were not candidates for local therapy, or who declined definitive therapy, to receive ADT either immediately or upon symptomatic disease progression or serious complications (ie, pathologic fracture, paralysis).[4] The median age was 73 years (range, 52-81 years), and the median prostate-specific antigen (PSA) level was 16 ng/mL (range, 0.2-1306.7 ng/mL). That study excluded men aged ≥80 years and those with regional lymph nodes or ureteral obstruction, and deferred treatment was not reflexively initiated based on rising PSA or alkaline phosphatase levels, new bone scan hot spots, or soft tissue metastases. Patients were followed with rectal examinations, and PSA and alkaline phosphatase levels obtained at 6-month intervals for 2 years and then annually until death, with further evaluation for suspected progression. After a median follow-up of 7.8 years, 541 of 985 men died (52.2% immediate treatment vs 57.6% deferred treatment; hazard ratio, 1.25; 95% confidence interval, 1.05-1.48). There were no differences in time to progression to castration-resistant disease or prostate cancer-specific survival, the median time to the start of deferred treatment was 7 years, and 25.6% of deferred patients never needed treatment. It is noteworthy that, within the first 5 years, there were 187 deaths in the deferred treatment group (38%; 62 prostate cancer-related) versus 153 deaths in the immediate treatment group (31%; 42 prostate cancer-related), indicating that greater than one-third of the cohort had died within 5 years. These rates are higher than current survival estimates for localized prostate cancer and indicate a broad range of disease severity other than localized (eg, PSA >1000 ng/mL). A 12-year update of that trial demonstrated no differences in the time to castration resistance or prostate cancer-specific mortality, with the exception of those

men who died within 3 to 5 years.[5] The average patient time on ADT was 27 months versus 87 months for the deferred versus immediate treatment groups ($P < .001$), respectively, indicating approximately 5-year differences in ADT exposure. Fractures were rare in both groups. There was an overall survival advantage to immediate treatment, particularly for men with PSA levels >50 ng/mL and PSA doubling times <12 months.[6] This finding suggests that immediate ADT may be a preferred option in these very-high-risk patients who decline or are not candidates for local treatment.[5] However, most observational studies of primary ADT use for localized prostate cancer have demonstrated no survival advantage for primary ADT in localized disease[7-9]; and, in some patients (eg, those with longer life expectancy and low-risk disease), worse overall survival has been reported among those who received primary ADT.

Elderly men who are not able to undergo or who refuse definitive treatment for intermediate-risk and high-risk, localized prostate cancer have decisions to make in consultation with their providers. Specifically, are the risks and benefits of castration with ADT worth it? Should they pursue an observational approach with delayed treatment for symptomatic and/or metastatic progression that is unlikely to occur in their lifetime? As highlighted in the article, current management options offer minimal support for using ADT as the primary treatment in localized prostate cancer. The National Comprehensive Cancer Network guidelines indicate that<zaq;2> patients who have clinically localized prostate cancer should not receive ADT as monotherapy, perhaps except in cases of very high-risk disease among patients who are not eligible for other treatments as an alternative to observation (ie, watchful waiting).[3]

The disconnect between the greater use of primary ADT in patients who have the least to gain (or lose) with respect to life expectancy may signify a lack of tools to enable providers to effectively counsel patients about the misperception that ADT monotherapy is of value in their care. If we examine reasons for ADT initiation among patients in the deferred group from the EORTC 30891 trial, then symptomatic progression with or without objective evidence accounted for over one-half (55%), whereas asymptomatic rises in markers (26.5%) and asymptomatic objective evidence (10.2%) accounted for much less.[4] Arguably, it is likely that most patients with localized prostate cancer who received primary ADT in the current National Cancer Data Base study were asymptomatic and thus unlikely to have symptomatic progression given US screening practices and lead times. Therefore, primary ADT was probably received to avoid “doing nothing” among asymptomatic men with localized prostate cancer and provided them more harms than benefits.

For elderly men whose combination of life expectancy and prostate cancer risk favors treatment, an alternative to primary ADT to avoid doing nothing is to offer definitive radiotherapy. Radiotherapy has proven efficacy in high-risk patients,[10] as pointed out by the authors, and referral to a radiation oncologist for counseling[11] among men who might otherwise receive primary ADT may simultaneously decrease low-value primary ADT use and increase appropriate treatment for men who may otherwise die of their disease.

The de-implementation of low-value castration among men with localized prostate cancer continues to pose significant challenges rooted in the history of ADT and the concept that "less is more." Since the discovery that prostate cancer cells depend on androgens by Huggins and Hodges in the 1940s,[12] castration strategies have become the primary choice of initial therapy for men with advanced and symptomatic prostate cancer, with spillover effects into the treatment of asymptomatic, localized disease in which little to no benefits exist. Although the harms of ADT are increasingly recognized,[13] they may be underappreciated by providers and patients seeking to treat localized disease in lieu of definitive treatments, helping to drive the observed treatment patterns. In other words, competing *beliefs about consequences* of treating men who have localized prostate cancer using primary ADT—the consequences of both receiving and not receiving ADT—may be playing a significant role in the observed treatment patterns.

This concept—*beliefs about consequences*—is a key domain in the theoretical domains framework[14] of individual behavior change and, more broadly, may be a powerful contributor to the overuse of cancer care by providers and patients. For primary ADT in most men with localized disease, *minimizing beliefs about the harmful consequences of receiving primary ADT* sets up an exchange of temporarily lowering PSA levels, providing false hope to patients and providers that men will live longer and better lives, with near-guaranteed quality-of-life impairments and little to no overall survival advantage. Conversely, *emphasizing beliefs about the positive consequences of not receiving primary ADT* challenges our current belief structures about the inevitability of prostate cancer progression to symptomatic, metastatic disease and the idea that earlier and more effective castration is better. Clarifying this pervasive tension appears warranted to guide the development of effective strategies focused on curbing the overuse of low-value prostate cancer care and working collaboratively with older patients to optimize care and quality of life.

An interesting phase 2 trial recently demonstrated that rapid cycling between high and low serum testosterone concentrations was beneficial for some men with castrate-resistant disease.[15] Rather

than removing testosterone altogether (eg, primary ADT), this “bipolar” approach also challenges dogma that “less is more" with regard to the complex relation between testosterone and prostate cancer. Better understanding patient and provider *beliefs about the consequences* of receiving or not receiving primary ADT in localized disease is needed. Both patients and providers will have to overcome yet unknown psychological barriers to recognize that de-implementation of low-value chemical castration and follow-up with observation can be an appropriate strategy for the preservation of the quality and quantity of life for older men with localized prostate cancer.

In summary, the study by Yang and colleagues demonstrated the potential underuse of definitive surgery or radiation for men with intermediate-risk and high-risk, localized prostate cancer; however, perhaps just as important, the results also highlighted the widespread overuse of primary ADT monotherapy among many of these same men. Maximizing the quality and quantity of life among patients with localized prostate cancer who are elderly and have competing comorbidities may be achieved more effectively either by treating these patients definitively or by opting for observation rather than primary ADT. A better understanding of the optimal ways to de-implement this low-value cancer care appears to be warranted both for elderly patients, who have little to gain by it, and for younger patients, who have more to lose by foregoing definitive treatment with surgery or radiation therapy.

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<H1>CONFLICT OF INTEREST DISCLOSURES</H1>

The authors made no disclosures.

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Cancer

Castration remains despite decreasing definitive treatment of localized prostate cancer in the elderly: A case for de-implementation

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Castration remains despite decreasing definitive treatment of localized prostate cancer in the elderly: A case for de-implementation

Running head: De-implementation of primary ADT

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Precis:
Maximizing quality and quantity of life among patients with localized prostate cancer who are elderly and have competing comorbidities may be achieved more effectively by either treating these patients definitively or opting for observation, rather than using primary ADT. Better understanding optimal ways to de-implement this low value cancer care appears warranted for both elderly patients who have little to gain by it, and

younger patients with more to lose by foregoing definitive treatment with surgery or radiation therapy.

Keywords: Implementation, Low Value, ADT, Castration, Prostate Cancer

In this important study, Yang et al. used the National Cancer Database (NCDB) to examine definitive therapy (prostatectomy or radiotherapy) among 400,000 patients diagnosed with intermediate or high risk prostate cancer between 2004 and 2012.[1] Using multivariable regression to adjust for patient and sociodemographic factors, the investigators found decreasing definitive treatment with increasing age and worsening comorbidity. In fact, more than 40% of patients over 80 years did not receive definitive treatment with radiation or surgery. Moreover, half of patients over 80 years old with high risk prostate cancer who did not receive definitive treatment went on to undergo primary androgen deprivation therapy (ADT) instead. The authors conclude that significant undertreatment of unfavorable risk prostate cancer in the elderly puts them at up to 20% risk of prostate cancer-related death at 10 years.

On the one hand, less use of definitive prostate cancer treatment among patients who are least likely to benefit (i.e., elderly, comorbid patients) argues against the widely held belief that we are overtreating patients with prostate cancer. Indeed, compared with men undergoing definitive treatment, those men who did not receive definitive treatment were more likely to die within one year of diagnosis, regardless of age or prostate cancer disease risk, suggesting that decision-making was reasonably aligned with life expectancy. Increasing comorbidity score was also associated with a lower likelihood of receiving definitive treatment such that men with two or more Charlson-Deyo comorbidity points had approximately half the odds of receiving definitive treatment compared to men with no comorbidities.[2] The fact that sicker patients were less likely to receive definitive treatment of localized prostate cancer after taking into consideration other factors (e.g., demographics) was an encouraging finding.

On the other hand, the authors found overtreatment of elderly patients through a different mechanism—a high rate of chemical castration with ADT as the primary treatment for many elderly patients with localized prostate cancer who were not treated definitively with radiation or surgery. Patients with increasing age were less likely to receive definitive treatment, but more likely to be treated with primary ADT. While being treated with primary ADT was more pronounced in patients with high risk localized disease who did not receive definitive prostate cancer treatment (41%), one in five men with intermediate risk disease not undergoing definitive treatment was also treated with primary ADT. Given the fact that the benefits of castration are primarily associated with advanced rather than localized disease, and safer, effective treatment approaches such as observation (i.e., watchful waiting) or radiation therapy exist, the authors point out that these findings are 'troubling' citing decreased overall survival with primary ADT for localized prostate cancer, and its notable harms (e.g., metabolic syndrome, fractures, cognitive, cardiovascular, and sexual dysfunction).[3]

In patients not undergoing definitive treatment for localized disease, the early versus delayed castration dilemma has been studied in randomized trials. For example, EORTC 30891 randomized 985 men with newly diagnosed T0-4 N0-2 M0 prostate cancer who were not candidates for local therapy, or declined definitive therapy, to receive ADT either immediately or upon symptomatic disease progression or serious complications (i.e., pathologic fracture, paralysis).[4] The median age was 73 years (range 52-81) and PSA 16 (range 0.2-1306.7) This study excluded men ≥80 years, those with regional lymph nodes or ureteral obstruction, and deferred treatment was not reflexively initiated based on rising PSA or alkaline phosphatase, new bone scan hot

spots, or soft tissue metastases. Patients were followed with rectal exams, PSA and alkaline phosphatase levels obtained at 6 month intervals for 2 years, and then annually until death with further evaluation for suspected progression. After a median follow up of 7.8 years, 541 of 985 men died (52.2% immediate vs. 57.6% deferred, hazard ratio 1.25, 95% CI 1.05 to 1.48). There were no differences in time to progression to castration-resistant disease or prostate cancer-specific survival, with the median time to start deferred treatment of 7 years, and 25.6% of deferred patients never needing treatment. Interestingly, within the first five years, there were 187 deferred treatment group deaths (38%, 62 prostate cancer-related) vs. 153 immediate treatment group deaths (31%, 42 prostate cancer-related) indicating that over one-third of the cohort had died within 5 years. These rates are higher than current survival estimates for localized prostate cancer, and indicate a broad range of disease severity other than localized (e.g., PSA >1,000). A 12-year update of this trial demonstrated no differences in time to castration resistance or prostate cancer-specific mortality, with the exception of those men dying within 3-5 years.[5] The average patient time on ADT was 27 months vs. 87 months for the deferred vs. immediate groups ($p<0.001$), respectively, indicating approximately 5 year differences in ADT exposure. Fractures were rare in both groups. There was an overall survival advantage to immediate treatment particularly for men with PSA>50 ng/mL and PSA doubling times <12 months.[6] This finding suggests that immediate ADT may be a preferred option in these very high risk patients who decline or are not candidates for local treatment.[5] However, most observational studies of primary ADT use for localized prostate cancer have demonstrated no survival advantage for primary ADT in localized disease,[7-9] and in some cases (e.g., longer life expectancy and low risk disease), worse overall survival among those treated with

primary ADT.

Elderly men not able to undergo or refusing definitive treatment for intermediate and high risk localized prostate cancer have decisions to make in consultation with their providers. Namely, are the risks and benefits of castration with ADT worth it? Should they pursue an observational approach with delayed treatment for symptomatic and/or metastatic progression that is unlikely to occur in their lifetime? As highlighted in the article, current management options offer minimal support for using ADT as the primary treatment in localized prostate cancer. The National Comprehensive Cancer Network guidelines state: "ADT should not be used as monotherapy in clinically localized prostate cancer," perhaps except in cases of very high risk disease among patients not eligible for other treatments as an alternative to observation (i.e., watchful waiting).[3]

The disconnect between the higher use of primary ADT in those patients with the least to gain (or lose) with respect to life expectancy may signify a lack of tools to enable providers to effectively counsel patients about the misperception that ADT monotherapy is of value in their care. If we examine reasons for ADT initiation among patients in the deferred group of EORTC 30891, symptomatic progression with or without objective evidence accounted for over half (55%), while asymptomatic rises in markers (26.5%) and asymptomatic objective evidence (10.2%) accounted for much less.[4] Arguably, it is likely that most patients with localized prostate cancer treated with primary ADT in the current NCDB study were asymptomatic and thus unlikely to have symptomatic progression given US screening practices and lead times. Therefore, primary ADT was probably given to avoid 'doing nothing' among asymptomatic men with localized prostate cancer and provided them more harms than benefits. For elderly

men whose combination of life expectancy and prostate cancer risk favors treatment, an alternative to giving primary ADT to avoid 'doing nothing' is to offer definitive radiotherapy. Radiotherapy has proven efficacy in high risk patients,[10] as pointed out by the authors, and referral to a radiation oncologist for counseling[11] among men who might otherwise receive primary ADT may simultaneously decrease low value primary ADT use, and increase appropriate treatment of men who may otherwise die of their disease.

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This concept, *beliefs about consequences,* is a key domain in the Theoretical Domains Framework[14] of individual behavior change, and may be a powerful contributor to overuse of cancer care by providers and patients more broadly. For primary ADT in most localized disease, *minimizing beliefs about the harmful consequences of giving*

primary ADT sets up an exchange of temporarily lowering PSA levels providing false-hope to patients and providers that men will live longer and better lives, with near-guaranteed quality of life impairments and little to no overall survival advantage. Conversely, *emphasizing beliefs about the positive consequences of not giving primary ADT* challenges our current belief structures about the inevitability of prostate cancer progression to symptomatic metastatic disease, and that earlier and more effective castration is better. Clarifying this pervasive tension appears warranted to guide development of effective strategies focused on curbing overuse of low value prostate cancer care, and working collaboratively with older patients to optimize care and quality of life.

Interestingly, a recent phase II trial demonstrated that rapid cycling between high and low serum testosterone concentrations was beneficial for some men with castrate-resistant disease.[15] Rather than removing testosterone altogether (e.g., primary ADT), this 'bipolar' approach also challenges dogma that 'less is more' in the case of testosterone's complex relationship with prostate cancer. Better understanding patient and provider *beliefs about the consequences* of giving or not giving primary ADT in localized disease is needed. Both patients and providers will have to overcome yet unknown psychological barriers in order to recognize that de-implementation of low value chemical castration, and follow up with observation, can be an appropriate strategy for the preservation of the quality and quantity of life of older men with localized prostate cancer.

In summary, this study demonstrated the potential underuse of definitive surgery or radiation for men with intermediate and high risk localized prostate cancer, but

perhaps as important, also showed the widespread overuse of primary ADT monotherapy among many of these same men. Maximizing quality and quantity of life among patients with localized prostate cancer who are elderly and have competing comorbidities may be achieved more effectively by either treating these patients definitively or opting for observation, rather than using primary ADT. Better understanding optimal ways to de-implement this low value cancer care appears warranted for both elderly patients who have little to gain by it, and younger patients with more to lose by foregoing definitive treatment with surgery or radiation therapy.

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