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Urologic Oncology: Seminars and Original Investigations 24 (2006) 51–57

UROLOGIC ONCOLOGY

Seminar article

Expectant treatment with curative intent in the prostate-specific antigen era: Triggers for definitive therapy

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Abstract

Expectant treatment with curative intent for treatment of low-risk prostate cancer faces 3 challenges in the PSA era: (1) appropriate patient selection, (2) adequate surveillance strategies, and (3) identification of triggers for definitive intervention when cure is still possible. Men 65 years or older with T1c disease, prostate-specific antigen density <0.15 ng/ml/cm^3, and favorable biopsy characteristics per the Epstein criteria currently appear to be the safest candidates for expectant treatment. Changes in biopsy characteristics are the most objective trigger for definitive therapy currently in use. Outcomes data are still required to determine the safety of expectant treatment for localized disease.

Keywords: Expectant management; Prostate cancer; Curative intervention

Introduction

Despite the fact that prostate cancer is the most common noncutaneous cancer in men, substantial controversy regarding its treatment persists. Much of this controversy stems from the fact that in reality, "prostate cancer" may be more accurately described as a group of very heterogeneous diseases with long and uncertain natural histories. Before widespread prostate-specific antigen (PSA) screening, we became aware of prostate cancer well along in its natural history because most men were diagnosed with advanced or metastatic disease, and few men were cured with definitive surgery. Furthermore, before the improvements in surgical therapy, such as the identification of the neurovascular bundles by Walsh and Donker [1], treatment was fraught with severe morbidities such as incontinence and impotence in the majority of patients, as well as severe bleeding and a mortality rate reported as high as 5% [2–4]. In such an environment, observation with palliative intervention only with the presentation of symptomatic disease was a common and logical treatment strategy for prostate cancer, so-called "watchful waiting."

In the current era of PSA screening, most men are diagnosed with nonpalpable clinically localized disease, approximately 10 years earlier in the natural history of the disease compared to digital rectal examination (DRE) detected tumors [5,6]. This has resulted in a prostate cancer incidence that is now 49% higher than when PSA testing was not available [7], and estimates of over-diagnosis (i.e., detection of cancer that would otherwise have not been detected in the absence of screening) are between 30% and 50%, depending on age [6,8]. This result suggests that there are many men who will be diagnosed with prostate cancer who may not require treatment and would ultimately die "with prostate cancer" and not "from prostate cancer" if left untreated. Furthermore, despite the advances in the definitive treatment of prostate cancer, both surgery and radiation therapy affect quality of life, thus conservative therapy for some men is still relevant in the PSA era. The concept of "watchful waiting" as practiced in the past (i.e., observation until patients become symptomatic and then the initiation of palliative therapy) has evolved into a more proactive strategy called "expectant management with curative intent" (EMCI) or "active surveillance." Given the opportunity to diagnose men earlier in the natural history of the disease, our current challenge is to differentiate accurately between those patients who will require definitive therapy early enough to cure them and those in whom we can safely delay or avoid the morbidities of treatment.

There are 3 fundamental questions that EMCI programs must address: (1) Which patients are appropriate candidates for EMCI? (2) How will patients in the EMCI program be

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1078-1439/06/$ – see front matter
doi:10.1016/j.urolonc.2005.07.004

followed? and (3) What will be the triggers for intervention in these patients? The answers to these questions are not currently clear and, in fact, may vary with a given subset of patients with prostate cancer. The goal of this article is to review the literature on EMCI in the PSA era with particular emphasis on the triggers for intervention.

Patient selection

The ability to identify accurately men with small volume disease is critical for the implementation of EMCI. To be able to intervene and "cure" men after an initial period of observation, they must first have curable disease to begin with. Herein lays one of the most challenging issues related to EMCI. In the era before PSA, when most patients were diagnosed with locally advanced or metastatic disease, many older men were candidates for watchful waiting because their cancers were too far advanced to cure with locally directed therapy. However, in current EMCI programs, in which the goal is to cure with definitive intervention at the appropriate time if necessary, "success" will largely be determined by selecting appropriate patients with low-volume, low-risk disease. The potential criteria for selection of men for whom expectant treatment would be safe include age, stage, needle biopsy findings (grade and extent), and PSA criteria.

Watchful waiting programs have typically involved older men. However, in the PSA era, with more younger men being diagnosed, EMCI is being offered to younger men as well. As such, dissimilarities in the likelihood of different aged men in expectant treatment programs to undergo treatment have been noted. Younger aged men tend to be treated with definitive therapy more often than older men. Meng et al. [9] found that men older than 75 years were less likely to receive treatment than men younger than 75 years when examining the Cancer of the Prostate Strategic Urological Research Endeavor database. Likewise, Zietman et al. [10] found that men younger than 75 years were more likely to undergo definitive treatment in their cohort of patients with a mean age of 71. In addition, men older than 75 years were more likely to undergo hormonal therapy. Similarly, El-Geneidy et al. [11] found that age $<$75 years was predictive of curative intervention on both univariate and multivariate analysis. Furthermore, Johansson et al. [12] noted a decrease in the progression-free survival, survival without metastases, and prostate cancer-specific survival when patients with T1−T2 disease were followed beyond 15 years as compared to the rates observed up to 15 years, suggesting that age should be an important factor in selecting patients for expectant treatment because the length of follow-up is predictive of progression.

In addition to age, comorbidities that may decrease life expectancy are also important to consider before embarking on expectant treatment. Although Albertsen et al. [13] found that comorbidities influenced the decision to pursue watchful waiting, Wu et al. [14] failed to note any effect of comorbidities on secondary treatment-free survival for patients in their cohort when observed to 5 years. The differences in observations between these 2 studies may be related to the difference in the length of follow-up; the study by Wu et al. [14] looked at men to 5 years, while the study by Albertsen et al. [13] had a mean follow-up of 15.5 years. Because there is no uniformity in how EMCI programs are conducted, the predilection to treat younger, otherwise healthy men versus older men or those with significant comorbidities is likely reflective of the biases of both physicians and patients, many of whom are less comfortable withholding definitive treatment in younger healthy men who may have a longer lifespan and, thus, may be more likely to be affected clinically by their prostate cancer. Until we are able to more confidently predict who is likely to have progression and show the efficacy of the EMCI strategy, this bias seems prudent.

Clinical stage is a very important criterion in selecting patients for expectant treatment. Bill-Axelson et al. [15] found in their cohort of untreated men (nearly 3/4 of whom had palpable disease) that at 10 years of follow-up, more than 44% of the untreated men had evidence of local progression, while 25% had evidence of metastases. These rates were significantly lower in patients who received surgery. Similarly, the Partin tables predict that 75% of patients diagnosed with stage T1c disease, Gleason 5−6, and PSA from 6−10 ng/ml are likely to have organ confined disease [16]. For T2a disease, Gleason 5−6, and PSA 6−10 ng/ml, organ confined status decreases to 58%, while in those patients with T2b disease, the rate decreases to 50%, suggesting that clinical stage T2 disease is significantly less likely than T1c disease to be organ confined. Thus, definitive treatment seems logical for those patients with palpable disease because surgery has proved to reduce prostate cancer death in these men.

The effect of tumor grade on outcome is also profound and is, in fact, the most important aspect of biopsy characteristics. Johansson et al. [12] showed that patients with grade 3 disease (similar to Gleason sum 8−10) had a 56% chance of distant metastases developing compared to a 24% chance in patients with grade 2 disease (similar to Gleason sum 5−7). Furthermore, Albertsen et al. [13] showed in a recent study on watchful waiting with 20-year follow-up that patients with Gleason 8−10 disease had a mortality rate of 121/1000 patient-years; those patients with Gleason 6 disease died at one fourth that rate, with only 30 deaths per 1000 patient years.

It is known that the extent of tumor found on biopsy generally correlates to the amount of tumor found at prostatectomy. Epstein et al. [17] established a set of PSA and needle biopsy findings (the Epstein criteria) that were found to be predictive of small volume disease in patients diagnosed with clinical stage T1c prostate cancer. Studies applying these criteria found that 79% of patients with PSA density $<$0.15 ng/ml/cm^3 and favorable needle biopsy char-