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EDITORIAL

Does the Benefit Justify the Risk?

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The past two decades have witnessed a dramatic increase in the number of men who have been diagnosed with prostate cancer. Since the introduction of prostate-specific antigen (PSA) testing, approximately 90 000 additional men have been diagnosed annually and large numbers of these men have received treatments, such as radical prostatectomy, radiation therapy, or androgen deprivation therapy (ADT). Before the widespread use of PSA screening, an American man had an 8.7% lifetime risk of being diagnosed with prostate cancer and a 2.5% risk of dying from this disease (1). By 2005, the lifetime risk of being diagnosed had increased to 17%, whereas the lifetime risk of dying from prostate cancer remained virtually unchanged (2).

PSA screening has dramatically changed the type of patient presenting with newly diagnosed disease. Men now rarely present with symptoms. Between 1996 and 2004, most men (91%) were diagnosed with local or regional disease (2). The rational for treating these men is no longer to relieve symptoms but rather to prevent prostate cancer progression. Unfortunately, data from randomized trials are sparse concerning the efficacy of this approach.

In 2008, the Scandinavian Prostate Cancer Group updated their trial comparing radical prostatectomy with watchful waiting (3). After 12 years of follow-up, the overall survival rate for the two groups appears comparable. Surgery offered some advantage in preventing prostate cancer mortality, but this advantage appears to have been limited to men who were younger than 65 years at diagnosis. Competing medical hazards, as opposed to prostate cancer, were a much more common cause of death during follow-up in both arms of this trial.

Similar data are unavailable for radiation therapy, but it is unlikely that outcomes are dramatically different. Radiation therapy is frequently offered to older men who more commonly have competing medical hazards. Bolla et al. (4) have demonstrated that men with clinically advanced localized disease have a survival advantage when ADT is added for a period of 3 years, but it is unclear whether this survival advantage can be generalized to all men with localized disease.

The increasing use of surgery and radiation to treat localized disease has led to another problem—biochemical recurrence during long-term follow-up. An increasing PSA level does not cause overt symptoms but does command attention. As a consequence, physicians frequently initiate ADT despite the known adverse impact on quality of life. Hot flashes, weakness, fatigue, cognitive impairment, and depression have all been associated with medical or surgical castration. These outcomes were a readily accepted trade-off when treatment was offered to men with widely metastatic disease. It is less clear that contemporary patients gain from this approach.

Adverse outcomes from ADT have been recognized for decades. The Veterans Administrative Cooperative Urological Research Group clearly showed that ADT could dramatically relieve obstructive urinary symptoms or pain from metastases but could also lead to lethal cardiac side effects (5). Patients receiving 5 mg of diethylstilbestrol experienced a 37% increase in non–cancer-related mortality. Smith et al. (6) have shown that ADT can lead to osteoporosis. As a consequence, many men are now placed on bisphosphonates.

What are the consequences of using ADT in contemporary patients? As primary therapy for men with T1 disease, ADT does not appear to offer a survival advantage when offered early in the course of the disease (7). Conversely, early use of ADT appears to exacerbate other medical conditions, such as cardiovascular disease and diabetes. Some geriatricians have described these changes as "androgen deprivation syndrome" (8).

The literature describing the impact of ADT in older men is mixed. Several studies (9–13) have linked ADT with cardiovascular disease, increased lipid profiles, diabetes mellitus, and myocardial infarction. Others (14,15) have found no relationship with between ADT and fatal cardiac events. Although many of these studies are reasonably large, the follow-up period is often short with a limited number of outcome events.

The article by Keating et al. (16) in this issue of the Journal adds to this growing literature. They identified more than 37 000 men who were diagnosed with local or regional prostate cancer between 2001 and 2004, and they tracked their medical outcomes through the Veterans Healthcare Administration. Unlike medical claims data, the Veterans Healthcare Administration tracks both inpatient and outpatient encounter data, including data on medications provided. Patients were observed for up to 5 years.

Their data offer a rare glimpse into the extent of ADT therapy among contemporary patients. Almost one-quarter of the men who were younger than 55 years of age and more than half of the men who were older than 75 years of age received ADT. Although ADT was more common among men with poorly differentiated disease, more than 25% of the men with well-differentiated disease (Gleason 2–4) and more than 30% of men with moderately differentiated disease were treated. We do not know whether these treatments have prolonged survival, but Keating et al. confirm that this approach has the potential for substantial unintended side effects. Almost 25% of the men treated with ADT developed diabetes and 20% developed coronary heart disease. These rates are considerably higher than those found among men who did not receive ADT.

Although the study design used by Keating et al. precludes a definitive statement of a cause and effect relationship, their findings raise important hypotheses that should be tested in randomized trials. The authors said it well in their discussion: "Although the risks associated with androgen deprivation therapy remain incompletely defined, the potential for harm from this treatment underscores the importance of better understanding the benefits." Before the advent of PSA screening, clinicians primarily used ADT to relieve the symptoms of advanced prostate cancer. Now we use ADT primarily to treat patients with a rising level of PSA. With the growing number of men wrestling with rising PSA values after treatment, we should organize appropriate trials and reflect carefully about the anticipated benefits and harm before initiating ADT treatment. Many older men especially those with low-grade disease may not live long enough to benefit, and we may hasten their demise from a competing medical problem.

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