An Overview Cost-Utility Analysis of Prostate Cancer Screening

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The value of prostate cancer screening remains controversial because of the high prevalence of the disease and the fact that many tumors detected through screening are not destined to lead to morbidity or mortality, rendering

Introduction

Cancer of the prostate is now the most common nondermatologic neoplasm in US men, with 240,000 new cases expected to be diagnosed in 1994 and 40,400 men expected to succumb to the disease [1]. Although survivals with localized disease are excellent, in the range of 85% to 90% at 5 years, the prognosis for metastatic disease is quite poor; median survival for metastatic disease is 2 years and has not changed substantially since the introduction of hormonal therapy 50 years ago [1].

Because of this discrepancy between treatment outcomes for localized disease (which parallel survivals of men without prostate cancer) and treatment outcomes for metastatic disease (in which the majority of men will die from prostate cancer), emphasis over the past 10 to 15 years has concentrated on the potential for early diagnosis and treatment. Other management alternatives include prevention—currently being evaluated by the Prostate Cancer Prevention Trial, a 7-year study of prophylactic finasteride (Proscar) [2]—and new agents for the treatment of metastatic disease. Of these new agents, the most promising may be suramin. Although initial results show that it has activity against prostate cancer, evidence that survival is enhanced remains to be demonstrated [3]. Thus, although efforts are in progress to seek out new methods to deal with this pressing public health problem, at present the most promising approach seems to be through secondary prevention, ie, early detection and treatment.

Results of Early Detection Efforts

Prostate cancer screening was first implemented in the 1970s and early 1980s with the use of digital rectal examination (DRE). Results of screening programs employing DRE have varied widely; cancer detection rates range from 0.1% to 7.6%, with generally accepted rates of 1% to 5% [4]. Positive predictive values for DRE range from 6% to 34%, with the most common rates in the 25% range. Because of the poor prognostic implication of extraprostatic disease, perhaps the greatest concern with the use of DRE for early detection has been the detection rates of organ-confined disease. In one of the largest US experiences with a DRE-based screening program, 66% of patients with cancer detected by DRE were upstaged to pathologic stage C (extraprostatic) disease [5].

With the development and application of prostate-specific antigen (PSA) for early detection and screening, many patients will be diagnosed at an earlier stage than with DRE screening alone. Several studies have shown that such is indeed the case. Catalona and associates at Washington University screened 1,653 asymptomatic men over the age of 50 using a PSA cutoff value of 4.0 ng/mL. Among these men, 37 cases of prostate cancer were detected, for a case-finding rate of 2.2% [6]. Subsequent studies have confirmed this finding in larger groups of men and also have demonstrated that with serial screening, the likelihood of detecting organ-confined disease is increased [7].

Although the performance characteristics of PSA are now well-defined through large-scale screening programs, the impact of such early detection and treatment on more significant endpoints, such as disease-specific mortality and overall morbidity, remain undetermined.

Potential Problems With Prostate Cancer Screening

Prostate cancer is unique among solid tumors in its histologic prevalence and natural history, and because of these and other considerations, the seemingly natural application of screening tests to
prevent a lethal disease may have a number of potential hazards that could mitigate the salutary effects.

**Prevalence** - As early as 1935, it was recognized that the histologic prevalence of prostate cancer far exceeded the number of cases in which patients presented with symptoms. Rich [8] and Moore [9] in that year found that microscopic disease could be detected with crude sectioning techniques in 8% to 14% of men aged 50 to 60, and in 11% to 23% of men aged 60 to 70. Subsequent studies in the 1950s and 1960s with more histologic sections found that the rate in men over age 50 was 38%; in men 70 to 80 years of age, 41%; and in men 80 to 90 years of age, as high as 57% [10,11]. Interest in this phenomenon waned for 20 years until Sakr and associates in Detroit analyzed a group of younger men who died due to trauma in that city [12]. The authors found an astounding rate of small prostate tumors: 27% in men aged 30 to 39, and 34% in men aged 40 to 49. The risk of a US male dying of prostate cancer is approximately 3%; thus, if as many as 50% to 70% of men can be expected to develop prostate cancer during their lifetime, it may be the case that some tumors detected through screening are not destined to lead to morbidity or mortality, and therefore treatment is unnecessary.

**Natural History** - A number of series have reported the results of a policy of watchful waiting (surveillance) for localized prostate cancer. It must be recognized that most of these series have used some form of patient selection to determine which patients are eligible for observation, and that the average age in these series is approximately 72, an age at which comorbidity may play a much higher role in mortality rates than prostate cancer. Nevertheless, the results with surveillance have been impressive.

Adolfsson and Carstensen analyzed 61 patients, all under age 70, for a mean follow-up period of 96 months [13]. Although 82% of men had developed local progression at 10 years of follow-up, only 8% died from prostate cancer during that period. The largest US experience was reported from Memorial Sloan-Kettering Cancer Center in 75 patients with localized prostate cancer [14]. Although the median time to local progression was about 7 years (84 months), of patients with stages B1 (T2a), B2 (T2b), and B3 (T2c) cancer, median survivals were 215, 138, and 197 months, respectively. Using individual patient data from 828 patients in six published series, Chodak and associates performed a metaanalysis of results of surveillance [15]. The authors found that disease-specific survival 10 years after diagnosis was 87% for both grade 1 and 2 tumors, and 34% for men with grade 3 disease. The most recent evidence on this subject has been provided by Aus [16]. Of a group of 536 patients, 349 had no evidence of metastatic disease at diagnosis and were followed with surveillance alone. In this observation group, of those who survived beyond 10 years, 50% died of prostate cancer.

These data thus suggest that although many men with prostate cancer who are followed without treatment will die of other diseases, with further passage of time (more than 10 years), the risk of prostate cancer mortality may increase substantially. Because of this uncertainty and the poor quality of existing series of untreated patients, the impact of early detection on prostate cancer-specific survival or morbidity from this disease is unknown.

**Estimates of Benefit From Screening and Treatment**

It is intuitively obvious that in the absence of properly designed, prospective, randomized, controlled clinical trials of prostate cancer screening, the benefit from current screening methods is unknown. Indeed, for this reason, the National Cancer Institute is currently enrolling subjects in a prospective trial in which half of participants undergo screening examinations and the other half have usual medical care within the community (the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, or PLCO) [17]. Because of the unknown effect of screening, the utility of treatment also remains in question. Nevertheless, a number of authors have used the available literature to perform decision analyses to determine the net utility of prostate cancer treatment.

The first of these analyses was conducted by Wasson and Fleming [18,19]. The authors first performed a structured literature review to determine potential outcomes of treatment or surveillance for prostate cancer, and used these data to conduct their decision analysis. Unfortunately, a number of methodological problems have been noted in this analysis:

1. The natural history of untreated prostate cancer patients included four series of patients with T1a (stage A1) disease (which has been recognized as a completely different and significantly less virulent entity than those tumors generally detected by screening). This resulted in rates of metastatic progression as much as 10-fold less than those in Chodak's metaanalysis.
2. Utility factors were determined by the authors and other physicians rather than by patients...
themselves.  
3. Treatment-related mortality was determined from a Medicare-age population rather than the younger male population who would be most likely to benefit from screening and in whom mortality is as much as 20-fold less [20]. Nevertheless, these two series concluded that the estimated benefit of treatment for well, moderately, and poorly differentiated prostate tumors is 0.16, 0.75, and 1.3 years, respectively. Using the authors' derived utility rates, quality-adjusted life years (QALYs) gained by treatment are -0.34, 0.33, and 1.00 years, respectively.

Because of the flaws detected in the methodology of this study, Beck and associates conducted a re-analysis, using what they felt were more appropriate probabilities [21]. Their re-analysis used estimates of survival of untreated prostate cancer from both Chodak's metaanalysis and from data from a series of patients treated with brachytherapy (the authors feel that brachytherapy may have had poor efficacy, but this patient series may portray the natural history of the disease). Table 1 summarizes these comparisons. As can be seen, using either Chodak's data or the brachytherapy data, the gains in both total life expectancy and in quality-adjusted life expectancy may be considerable when prostate cancer is treated.

Cost of Screening and Treatment

To properly determine the costs of prostate cancer screening, it is necessary to go beyond the cost of the screening test itself. For example, a highly automated, dedicated central laboratory may be able to perform PSA analyses for as little as $10 to $15 per assay. This type of analysis, however, is simplistic and ignores the fact that with a 2% to 4% rate of positive screening tests and a 20% to 30% rate of positive biopsies followed by treatment for the detected disease, the primary economic impact of screening becomes the diagnosis and treatment of the disease detected.

For this reason, in 1990, Optenberg and Thompson conducted the first decision analysis to calculate the cost of screening for prostate cancer in the United States [22]. At the time of the analysis, data on the performance characteristics of PSA were in their infancy, and so estimates were employed. Subsequently, this decision analysis has been updated [23].

The assumptions of this decision analysis were as follows:
1. Men aged 50 to 70 would undergo screening. Men under age 50 have a low likelihood of disease, and men over age 70 have a higher risk of comorbid conditions and may not benefit from identification and treatment of disease.
2. Men with cardiovascular disease would not be screened. This type of comorbid condition would increase the risk of treatment-related morbidity, and the reduced life expectancy would reduce the likelihood of benefit from treatment.
3. Either positive DRE or elevated PSA would prompt prostate biopsy.
4. If prostate biopsy was positive for cancer, staging would be performed.
5. Patients with the following stages of disease would undergo stage-specific treatment: Stage T1a (A1), no treatment; stage T1b-c, T2a-c (A2-B3), radical prostatectomy; stage T3-4 (C), external beam radiotherapy; and stage TxNxM1 (D2), bilateral orchiectomy.
6. Patients would be at risk for the following therapy-related complications that may require treatment: incontinence, impotence, urethral stricture, and rectal injury.

Using the above assumptions, a decision tree was developed. A comprehensive literature search was then conducted to obtain probabilities for each event, based on screening with DRE, PSA, or a combination of the two. Two screening scenarios were then developed. In Scenario 1, all patients with prostate cancer detected through screening underwent treatment. In Scenario 2, only patients with stages T1b, T1c, and T2 disease with grade 2 disease were treated. (This scenario assumed that patients with grade 1 disease did not require treatment and that patients with grade 3 disease or T3-4 disease would not benefit from treatment, as the disease was incurable.) For both scenarios, the cost of screening and treatment was calculated. Table 2 presents the cost of the first year of screening under each of these two assumptions.

Cost-Utility Estimates of Screening and Treatment

Using the above information, estimated ranges of cost utility can be developed for prostate cancer screening and treatment. If it is assumed that such screening is used only for men between the ages of 50 and 70 and that men with cardiovascular disease are not screened, using both DRE and PSA, a total of 1,107,217 tumors would be detected [23]. To develop the most pessimistic estimate of benefit, Scenario 1 costs will be used. Thus, for DRE and PSA screening, the total cost of screening
would be $25.7 billion, and the total cost of each tumor detected and treated would be $23,300. 

Table 3 displays the cost-utility estimates using the data of Fleming [19] and Beck [21]. As can be seen, in the estimates of Fleming, cost per life year gained ranges from a high value of $145,600 to a low of $17,900. Using these same assumptions and adding quality adjustment, the lowest estimate of cost utility is $23,300, but the "highest" estimate is $68,500 for each QALY that is "lost" due to screening and treatment. Quite different results can be obtained using Chodak's and Beck's estimates. These estimates suggest that the cost per crude and quality-adjusted life year gained by screening and treatment ranges from $8,400 to $23,100.

It is appropriate to put these cost-utility estimates into perspective. Smith and colleagues, in their summary of previously reported cost-effectiveness analyses [24], listed the cost per life year saved of several commonly used medical interventions: Liver transplantation, $237,000; screening mammography in women under age 50, $232,000; coronary artery bypass, two-vessel disease with angina, $106,000; captopril (Capoten) for hypertension, $82,600; hydrochlorothiazide for hypertension, $23,500; and smoking cessation counseling, men, $1,300. Thus, if one accepts Beck's contention that QALYs gained from screening range from 1.01 to 2.68, the cost-utility ratio of prostate cancer screening and treatment falls well within (and actually dramatically improves upon) that of common medical practice.

Conclusions

Due to a lack of prospective, randomized studies of screening for prostate cancer, the impact of screening on prostate cancer morbidity or mortality cannot be determined. Nevertheless, using available data (albeit terribly flawed), a number of authors have developed estimates of the benefit of treatment of the disease. If these estimates are merged with estimates of the cost of screening and treatment, a range of cost-utility ratios can be calculated. Using recently refined estimates of benefit, the number of crude life years gained as well as QALYs gained is well within the ranges of those of currently accepted medical therapies. Thus, it can be concluded that screening for prostate cancer may be cost effective and that patients should be given the option to participate in screening programs.

References:


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