Is Radical Prostatectomy a Useful Therapeutic Option for High-Risk Prostate Cancer in Older Men?

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ABSTRACT

Prostate cancer affects a high proportion of men over 70 years of age, who are likely to have high-risk disease and a substantial risk of prostate-cancer-specific death. With life expectancy increasing worldwide, the burden of prostate cancer is also expected to rise. Thus, effective management of this high-risk senior patient group is increasingly important. Radical prostatectomy can increase survival and decrease the risk of metastatic progression. Postsurgery complications are affected more by comorbidity than by age. In patients without comorbidities, surgery is associ-

ated with a low risk of mortality. Advanced age may increase the likelihood of incontinence following radical prostatectomy, but patients with higher risk disease are no more likely to experience this complication compared with lower risk groups. Treatment decisions should be made after considering the health status and life expectancy of the individual patient. If eligible, the patient should be offered radical prostatectomy as a potentially curative treatment, without a rigid restriction to a certain chronological age. *The Oncologist* 2012;17(suppl 1):4–8

INTRODUCTION

There is increasing evidence that older patients (≥ 70 years) have more aggressive prostate cancer than their younger counterparts. In an autopsy study of men with no diagnosed history of prostate cancer, prostate cancer was identified in 45% of the men aged 70 years or over, and they were more likely to have higher stage and more poorly differentiated tumors than younger men [1]. In a retrospective analysis of 2,048 consecutive patients who underwent laparoscopic radical prostatectomy for localized prostate cancer in a single institution, men ≥ 70 years of age showed significantly higher pathologic stages (T3–T4, 30%) and tumor grades (Gleason ≥ 7 , 67%) than younger men (21% and 54%, respectively) [2]. Higher pathologic stages and tumor grades, as well as a higher risk of upgrading, in patients aged 70 or older were also reported by other institutions [3, 4].

Older men with high-risk prostate cancer (i.e., prostate-specific antigen 20 ng/mL, a biopsy Gleason score of 8–10, or

an American Joint Committee on Cancer category of T2b or greater [5, 6]) have a substantial risk of dying from the disease. A nationwide study in Sweden has shown that patients aged 75–84 years with Gleason scores ≥ 7 who are treated conservatively have a higher death rate from prostate cancer than from any other cause (Fig. 1) [7]. In a long-term follow-up of a population-based cohort with localized prostate cancer between 1971 and 1984, men aged over 70 years with Gleason scores of 8–10 who were managed conservatively had a 64% chance of dying of their disease [8]. With the aging of the population and the increasing life expectancy worldwide [9–11], these figures are expected to increase in the future.

In practice, however, few men aged 70 years or older undergo curative therapy for high-risk prostate cancer. Analysis of different age groups according to the initial treatment received for prostate cancer (brachytherapy, radiotherapy, radiotherapy plus brachytherapy, and radical prostatectomy) in the U.S. between 1998 and 2002 showed that men aged ≥ 75 years

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Figure 1. Mortality among men with locally advanced prostate cancer not given curative treatment. Adapted from Akre O, Garmo H, Adolfsson J et al. Mortality among men with locally advanced prostate cancer managed with noncurative intent: A nationwide study in PCBaSe Sweden. *Eur Urol* 2011;60:554–563, with permission.

were not treated with radical prostatectomy, including those with medium- or high-risk disease [12]. Indeed, less than half of these men received any form of aggressive treatment, compared with 90% of patients aged ≤ 74 years.

A study of the U.S. Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database reported that, of the 11,790 men included in the analysis, 14.5% were over 75 years old at the time of treatment, and the likelihood of high-risk disease increased significantly with increasing age [13]. Regardless of their risk score, older men were more often treated with androgen-deprivation therapy (ADT) than their younger counterparts. The authors suggest that underuse of potentially curative local therapy among older men with high-risk disease may, in part, explain the higher cancer-specific mortality rates that were observed with increasing age.

Similarly, a European study investigating the influence of age and comorbidity on treatment, complications, and prognosis for men with prostate cancer determined that significantly fewer men aged 70 years or older received radical prostatectomy or curative radiotherapy than their younger counterparts [14]. These data clearly suggest that older men are undertreated, likely due to the wrong belief that they will not die of their prostate cancer. Life expectancy is highly variable from one individual to another due to differences in health status, but clinicians should keep in mind that a healthy 70-year-old man with no major comorbidities is expected to live another 18 years [15] and thus has significant chances of dying of his cancer in the absence of curative therapy over such a period of time.

IS RADICAL PROSTATECTOMY AN OPTION FOR OLDER PATIENTS WITH HIGH-RISK PROSTATE CANCER?

Compared with observation alone, curative treatment (surgery or radiation therapy) has been shown to improve survival in men aged 65–80 years with low- or intermediate-risk prostate cancer (Gleason score < 7) [16]. In fact, compared with observation, radical prostatectomy can halve the risk of prostate-cancer-specific mortality in patients aged 65 years or over with localized low- or intermediate-risk tumors [17]. Although high-risk patients were not included in this retrospective analysis of the Surveillance, Epidemiology and End Results database, a potentially larger benefit of curative therapy might be expected in such patients who are at high risk of dying from their prostate cancer.

However, these data contrast with a recently published study that also assigned 731 men with localized prostate cancer (33% aged 75 or older; 21% with high-risk disease) to radical prostatectomy or observation [18]. During a median 10-year follow-up, 47.0% of men assigned to radical prostatectomy died, as did 49.9% of men assigned to observation. The percentage of men who died from prostate cancer or treatments was lower among the radical prostatectomy group than the observation group (5.8% vs. 8.4%), with borderline significance for intermediate- and high-risk cancers ($p = .07$) but not for low-risk disease. Furthermore, metastasis-free survival was significantly lower in men who underwent surgery compared to those who were primarily observed, avoiding the need for hormonal therapy and chemotherapy in these men. Overall mortality was high, approaching 50% at a median follow-up of 10 years in this trial, which underlines the importance of in-

Table 1. Summary of published studies comparing prostatectomy, radiotherapy, and androgen-deprivation therapy plus radiotherapy

Study	n of patients	Study design	Endpoint	Results
Paulson et al., 1982 [20]	97	Prospective randomized comparison	Evidence of treatment failure	Prostatectomy: 4/41; radiotherapy: 17/56; $p = .037$
Stokes et al., 2000 [22]	540	Retrospective analysis	One-year nadir prostate-specific antigen ≤ 1 ng/mL (for prostatectomy, undetectable at <0.2 ng/mL)	Prostatectomy: 200/222 (90%); radiotherapy: 198/318 (62%)
D'Amico et al., 2003 [5]	7,316	Retrospective Cox regression analysis	Relative risk of prostate-cancer-specific mortality after treatment compared to that of the low-risk group	<i>Patients with high-risk disease:</i> Prostatectomy: 14.2 (95% CI: 5.0–23.4; $p < .0001$); radiotherapy: 14.3 (95% CI: 5.2–24.0; $p < .0001$) <i>Patients with intermediate-risk disease:</i> Prostatectomy: 4.9 (95% CI: 1.7–8.1; $p = .0037$); radiotherapy: 5.6 (95% CI: 2.0–9.3; $p = .0012$)
Coopenberg et al., 2010 [23]	7,538	Retrospective analysis using parametric survival model	Prostate-cancer-specific mortality	Radiotherapy: HR 2.21 (95% CI: 1.50–3.24; $p = .001$), relative to prostatectomy
Boorjian et al., 2011 [24]	1,238	Retrospective multivariate Cox regression analysis	10-year cancer-specific survival All-cause mortality	Prostatectomy: 92%; radiotherapy: 88%; radiotherapy plus ADT: 92% Radiotherapy: HR 2.04 (95% CI: 1.62–2.56; $p < .0001$), relative to prostatectomy; radiotherapy plus ADT: HR 1.60 (95% CI: 1.25–2.05; $p = .0002$), relative to prostatectomy

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio.

cluding life expectancy and comorbidity status in the treatment decision process.

In high-risk prostate cancer, radical prostatectomy is highly effective. A large number of patients are cured with surgery alone. Data from a study of biochemical recurrence-free survival showed that 40% of patients had no evidence of disease 10 years after surgery for high-risk disease [5, 19]. Because there is only one trial comparing radical prostatectomy with radiation therapy [20], no formal conclusions can be drawn on the relative benefits of the two therapies [21]. Nevertheless, the data from several large retrospective trials comparing prostate cancer treatments suggest that surgery may be more effective than radiotherapy (Table 1) [5, 20, 22–24].

A retrospective study of long-term biochemical disease-free survival of 540 men with prostate cancer determined that, although there is little difference for men with low- or intermediate-risk disease, for those with high-risk disease there is a significant improvement in biochemical disease-free survival with radical prostatectomy compared with radiation therapy [22]. Another retrospective study of 7,316 men with prostate cancer treated with radiation or surgery between 1988 and 2002 in the U.S. showed higher rates of non-prostate-cancer-specific mortality among men treated with radiation therapy compared with those treated with surgery [5]. The data also showed higher rates of prostate-cancer-specific mortality among men with high- or intermediate-risk disease treated with radiation therapy compared with radical prostatectomy. In addition, analysis of risk-adjusted cancer-specific mortality outcomes in 7,538 men with localized disease showed a two- to threefold increased risk of cancer-specific mortality among

men who received ADT or radiotherapy for localized prostate cancer compared with men who were treated with surgery [23].

Another study investigating the effect of radiotherapy or radical prostatectomy on distant metastases in 2,380 patients with localized disease concluded that men with high-risk prostate cancer (defined by cT3, Gleason 8–10, or prostate-specific antigen >20 ng/mL) treated with surgery had a lower risk of metastatic progression and cancer-specific mortality compared with those who received radiotherapy [25]. Additionally, a comparison of the long-term survival of men with high-risk prostate cancer treated with surgery ($n = 1,238$), radiotherapy ($n = 265$), or ADT plus radiotherapy ($n = 344$) showed that the ADT/radiotherapy combination was as effective as surgery in terms of long-term cancer control, but that overall survival was higher among the men treated with surgery [24].

Caution is needed in the interpretation of these comparisons between surgery and radiation therapy because they are based on nonrandomized retrospective analyses of large databases, with the caveats associated as such in terms of patient recruitment and characteristics, treatment allocation, and subsequent management. It is possible, for example, that patients who received ADT/radiotherapy were deemed to be unfit for surgery because of older age and associated comorbidities, explaining a shorter overall survival rate compared with the surgery arm. There is a need for randomized controlled trials with long-term follow-up to unambiguously establish the superiority of surgery over radiation therapy in terms of prostate-cancer-specific mortality and overall survival.

Surgery may also have symptomatic benefits. Men with

obstructive and/or irritative symptoms have been shown to derive improvement in function after surgery [26]. Indeed, in our experience, the presence of obstructive symptoms is often a reason to counsel the patient to consider undergoing surgery. Furthermore, we find that those who have been taking a 5 α -reductase inhibitor for obstruction are able to stop the medication after the operation. Among patients who go on to receive adjuvant radiation therapy, prior radical prostatectomy brings an increased risk of urinary stricture and incontinence, but only minimal moderate or severe acute and late toxicity and no detriment to quality of life [27].

COMPLICATIONS OF SURGERY FOR HIGH-RISK PROSTATE CANCER

Although there may be concern surrounding the use of surgery in senior adults, it has been shown that the complications of prostatectomy are related more to comorbidities than to the age of the patient. For otherwise healthy men, the risk of postoperative mortality following radical prostatectomy is relatively low. Alibhai et al. found that, for a 75-year-old man with no comorbidities, the predicted 30-day mortality was 0.74% [28]. However, analyzed by age and the Charlson comorbidity index, increasing comorbidity was a stronger predictor than age of early postsurgery complications (Fig. 2). Similarly, among 11,522 men who underwent radical prostatectomy, the Charlson index was also identified as a significant predictor of surgery-related death, postoperative complications, and late urinary complications [29]. In addition, analysis of the effect of age and comorbidity on treatment outcomes in 2,048 men treated by laparoscopic radical prostatectomy also concluded that the occurrence and severity of short-term postoperative complications were more strongly related to comorbidity than to chronological age [2].

In centers of excellence for the treatment of prostate cancer, patients with high-risk disease do not have an increased risk of postsurgery incontinence compared with other risk groups [30]. Nevertheless, long-term follow-up from the Prostate Cancer Outcome Study, a cohort of unselected population-based patients in the U.S., suggests that older men have a significantly higher decline in urinary function following radical prostatectomy compared to younger ones [31]. Overall, after a 2-year follow-up, lack of urinary control and frequency of incontinence greater than two episodes per day were reported by 13.8% of men aged 75–79 years compared with 0.7–3.6% of younger men, but, regardless of age, only a minority (8.7%) were bothered by it [31].

In a series of 3,477 radical prostatectomies performed by one surgeon, return to continence (i.e., no need for pad or protection) at 18 months after radical prostatectomy also significantly decreased with age from 95% in men aged <60 years to 86% in those aged ≥ 70 years [32]. In another series of 2,048 men (including 297 aged ≥ 70 years) who underwent laparoscopic radical prostatectomy in a single institution, postoperative continence also significantly declined with age, ranging from 87% in men aged <60 years to 67.5% in those aged ≥ 70 years [2].

In the Scandinavian Prostate Cancer Group 4 trial, which

Figure 2. Rate of any complication within 30 days following radical prostatectomy among men who underwent this surgery in Ontario, Canada, between 1990 and 1999, as a function of age group and number of comorbid conditions (diagnosis count). Adapted from Alibhai SM, Leach M, Tomlinson G et al. 30-day mortality and major complications after radical prostatectomy: Influence of age and comorbidity. *J Natl Cancer Inst* 2005;97:1525–1532, with permission.

randomized 695 men (median age, 65 years) with localized prostate cancer to radical prostatectomy or watchful waiting, urinary leakage was more common in men treated by surgery. The average level of self-assessed quality of life was similar to those treated with watchful waiting, who also experienced side effects due to tumor growth, lower urinary tract symptoms, and ADT [33].

No randomized trial evaluated quality of life after surgery and radiation therapy. Nevertheless, external beam radiation therapy also impairs quality of life due to urinary and bowel side effects, and this may be exacerbated in case of combination with ADT [34]. In our own experience, although the use of urinary continence pads is more frequent in men aged >70 years following prostatectomy, there is no significant difference in the proportion who rate their quality of life as good/excellent, compared with those aged ≥ 70 years (unpublished data). The order in which treatment is provided can help to reduce the risk of incontinence. Among men who receive surgery followed by salvage radiotherapy, the risk of incontinence is far lower (13% vs. 56%) compared with men who receive radiotherapy followed by salvage prostatectomy [35].

CONCLUSION

Although there is a lack of data from prospective randomized trials directly comparing radiotherapy and radical prostatectomy, retrospective studies and registries suggest that surgery may offer benefits in terms of biochemical recurrence-free survival, metastasis-free survival, prostate-cancer-specific mortality, and overall survival. Regardless of whether radical prostatectomy or radiotherapy is used, it is clear that curative therapy needs to be offered to these patients, and the use of ADT monotherapy is not acceptable in light of the outcomes

that are achievable with more aggressive treatment. Postsurgery complications are affected more by comorbidity than by age; in patients without comorbidities, surgery is associated with a low risk of mortality.

Treatment decisions should be made after considering the health status of the individual patient. Selected patients (i.e., those with high-risk tumors and minimal comorbidity) should

be offered radical prostatectomy as a potentially curative treatment, without restriction to a certain chronological age.

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