Low-risk prostate cancer patient: active treatment

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We currently lack a prospective, randomized, multicenter trial, to reassure low-risk prostate cancer patients, especially younger ones, that watchful waiting is a legitimate treatment. To better manage these patients, we need to: first, confirm that the patient has low-risk prostate cancer; second, adapt the treatment to the risk (i.e., if therapy is chosen over watchful waiting, it should be monotherapy not multiple therapy); third, be aware of age migration; fourth, know that radical prostatectomy and radiation were shown to be very effective for these patients at 10-year follow-up; and lastly, make an effort to better define watchful waiting and embrace it more, to avoid overtreatment.

Key Words: prostate cancer, watchful waiting, low-risk

Introduction

When counseling a patient who is newly diagnosed with low-risk prostate cancer, we are faced with a lack of hard data to prove that watchful waiting is the best strategy to follow. Since we do not have prospective, randomized, multicenter trials for watchful waiting we are not currently in a position where we can reassure young men that watchful waiting is a legitimate alternative for early-stage prostate cancer.

In the United States, some high-profile men who were diagnosed in the last decade with prostate cancer became the prostate cancer "poster boys," and have probably "fueled the fire" for active treatment, since this is the type of treatment they pursued. These men include Senator Bob Dole, whose high PSA screening test was followed by a radical prostatectomy; golf legend Arnold Palmer, who had a radical prostatectomy with PSA recurrence; former New York mayor Rudolf Giuliani, who received multi-pronged treatment with hormones, brachytherapy, and external beam radiation; and General Norman Schwarzkopf, who was diagnosed with low-risk prostate cancer in 1994 when he was 59 and chose to have a radical prostatectomy rather than follow watchful waiting.

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Discussion

Risk stratification

D'Amico et al studied 7316 patients who were treated for T1c or T2 prostate cancer. The investigative group looked at prostate-cancer-specific mortality during 10 years after the patients were treated with either surgery (n = 4946) or radiation (n = 2370).[1] The study period was 1988 to 2002, during the prostate-specific antigen (PSA) era, with data from two-multi-institutional databases: the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) and the Center for Prostate Disease Research (CPDR). Patients were stratified into low-, medium-, or high-risk groups based on their pretreatment PSA levels, Gleason scores, and clinical stages, as shown in

TABLE 1. **D'Amico study: risk stratification**[1]

Risk category	PSA (ng/mL)	Gleason score	Clinical stage*
Low	≤ 10	≤ 6	T1c, T2a
Medium	> 10 to 20	7	T2b
High	> 20	≥ 8	T2c

*From digital rectal examination (DRE) findings using the 2002 American Joint Commission on Cancer (AJCC) staging system[3]

Table 1. Cox regression analysis was performed to determine the ability of the pretreatment risk groups to predict the time to prostate-cancer specific mortality (PCSM) for patients in the two treatment groups.

The relative risk of PCSM for those in the intermediate- and high-risk groups compared to those in the low-risk group is summarized in Table 2. After radical prostatectomy, prostate-cancer-specific mortality was relatively low, but there still was mortality among the intermediate- and high-risk patients. After radiotherapy, there was a fairly substantial risk of death in 10 years, although this study includes pre-modern-era radiotherapy.

The studies also looked at prostate-cancer-specific deaths stratified by age and risk. In the radical-prostatectomy-treated group, among the low-risk patients there were virtually no cancer-specific deaths in 10 years, regardless of age. There were deaths from other causes, suggesting that while treatment was effective in some cases, there was probably also some overtreatment. In the radiotherapy-treated group, there were many more deaths than in the radical-prostatectomy-treated group. Generally, older, sicker patients are sent for radiotherapy, and more of these patients die of causes other than prostate cancer. Among patients younger than 60 who received conventional radiotherapy, some, even low-risk patients, died from prostate cancer. The radiotherapy dose that was given, however, was probably substandard compared to today.

For men younger than 60, who were at low-risk of dying from prostate cancer (Gleason 6 or less), there were more prostate cancer deaths at 10 years in those who received radiation than in those who received radical prostatectomy. However, this was not a randomized trial. That leads to a debate about the best way to use the paper's findings when you counsel patients in your daily practice. Despite not being a randomized trial, the study does provide some useful information. It examined a large cohort of patients treated in the PSA era — in fact, the largest cohort that exists. Radiotherapy that was delivered 10 years ago, however, may not be as effective as that given today.

Using biopsy results to stratify patients

Gancarczyk et al[2] developed CPDR probability nomograms to predict the pathologic stage at the time of radical prostatectomy, based on pretreatment PSA, highest biopsy Gleason sum, and percentage of biopsy cores positive for cancer. For low-risk patients who have a PSA less than or equal to 4 ng/mL, or greater than 4 but less than 10 ng/mL, using the biopsy quantification is clearly useful. (We can also use biopsy quantification to some degree to help stratify patients who go on watchful waiting.) Unfortunately, none of the active treatment studies have been done prospectively with long-term follow-up. For example, if we have a low-risk patient who has less than one third of his biopsy cores positive, there is so far no data that shows that such a patient can be safely managed by watchful waiting for 10 years. We need to do trials in this area.

TABLE 2. **Relative risk of prostate-cancer specific mortality of intermediate- and high- risk patients receiving surgery versus radiation**[1]

Risk group	Surgery		Radiation	
	Relative risk (95% CI)	P	Relative risk (95% CI)	P
Low	1.0		1.0	
Intermediate	4.9 (1.7 – 8.1)	0.0037	5.6 (2.0 – 9.3)	0.0012
High	14.2 (5.0 – 23.5)	<0.001	14.3 (5.2 – 24.0)	< 0.001

Monotherapy for low-risk patients

For low-risk patients, monotherapy choices include nerve-sparing radical prostatectomy, conformal external beam radiation therapy (EBRT), brachytherapy, or watchful waiting. If, rather than use watchful waiting, we are going to provide active treatment for low-risk patients, we should focus our efforts on monotherapy and certainly not do combined therapy, which has even greater risks of morbidity.

The Holmberg trial favors surgery

Holmberg et al[3] conducted a randomized trial of treatment for early prostate cancer, and concluded that radical prostatectomy significantly reduced disease-specific mortality, but there was no significant difference between surgery and watchful waiting in terms of overall survival. Although most subjects were actually intermediate- to high-risk patients, this was a randomized trial, and it did show that surgery is better than watchful waiting. That is the dilemma we face. There is no better data to help low-risk patients choose watchful waiting or radical prostatectomy.

Age migration

Not only have we had stage migration (as discussed earlier by Dr. Klotz), but Holmberg and colleagues also showed that we have had age migration.[3] We are now seeing low-risk individuals younger than 60. A significant number of patients we see in practice with newly diagnosed prostate cancers are younger than 60. We have the conundrum finding data to reassure younger men that they should go on watchful waiting.

Watchful waiting and secondary treatment

Currently, virtually all papers have shown that about half of the patients on what we call watchful waiting seek active treatment in 3 years. In a study with Wu and colleagues,[4] factors that predicted which men on watchful waiting selected secondary treatment were analyzed. Data on 8390 patients diagnosed with prostate cancer from 1990 to 2001 was obtained from the Department of Defense CPDR database. This was not a randomized trial, but was really ad hoc watchful waiting. A total of 1158 of the patients diagnosed with prostate cancer "started" on watchful waiting and received no active treatment for at least 9 months. This study was probably a mixture of true watchful waiting and patients who could not make up their minds. Nevertheless, we found a 55.2% dropout rate at 5 years. This is a high rate, but maybe we delayed active treatment and prolonged quality of life in some patients.

We found an even higher dropout rate in a subset of 313 low- or intermediate-risk younger patients from the CPDR database.[5] This subset comprised patients age 70 or younger, with a biopsy Gleason score of 6 or less (with no Gleason pattern 4), 3 or fewer positive biopsy cores, clinical stage T2 or less, and pretreatment PSA of less than 20 ng/mL. At 4 years, only 27% of patients remained on watchful waiting. We found that age was a strong driving factor. It seems that since these were younger patients, when their PSA levels went up, either the patients or their doctors "got cold feet," so they were moved to active treatment. We need to learn a better way to do watchful waiting, since this ad hoc approach does not work.

Conclusion

To summarize, there are several take home messages for treating low-risk prostate cancer patients. First, you should assess the patient's risk status to see if he can be defined as a low-risk patient. Second, use a risk-adapted treatment approach, which means that if you are going to do active treatment for low-risk patients, then give monotherapy; we should not be doubly overtreating these patients. Third, because of age migration in the PSA era, watchful waiting as currently practiced in most places is really "temporarily deferred treatment." Most centers do not have a systematic approach, such as that used by Dr. Klotz's group, so watchful waiting is done in a haphazard way. Fourth, radical prostatectomy and radiation are very effective treatments for low-risk patients at 10-year follow-up, as evidenced in several studies. Lastly, we do need to better define how we do watchful waiting in our patients and to embrace it to a greater extent, to avoid overtreatment. □

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