The Management of Clinically Localized Prostate Cancer: Guidelines from the American Urological Association

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Overview

A report on the management of clinically localized prostate cancer, the result of the work of the Prostate Cancer Clinical Guidelines Panel of the American Urological Association, has recently been published.\(^1\)\(^,\)\(^2\) The panel conducted an exhaustive and comprehensive survey of all published medical literature relating to the outcomes of treatment of clinically localized prostate cancer. This study focused on stage T2 cancer but also included stage T1c tumors (nonpalpable but detected by biopsy because of an elevated prostate-specific antigen [PSA] serum level). Many studies indicate that T1c tumors are similar in volume and significance to T2 or palpable localized cancer.

A major goal of the panel’s activities was to make recommendations for treatment based upon scientific data from the literature on prostate cancer. Abstracts of 12,501 articles were reviewed. There were 1,453 articles selected initially that seemed to relate to treatment outcomes. The panel found 396 articles that specifically dealt with stage T2 prostate cancer. However, 231 of these ultimately were rejected because meaningful outcome data could not be extracted. The panel’s efforts finally focused upon 165 scientific articles from which outcome data were extracted and tabulated. The outcomes of patients with T2 prostate cancer treated by radical prostatectomy, external-beam radiation therapy, brachytherapy (or interstitial radiation), and surveillance were studied. It seemed clear that five-year outcomes were not too useful; localized prostate cancer grows somewhat slowly, and evaluation five years after treatment is too soon to assess benefits of the therapeutic effort. Ten-year outcome data are more significant, and even better would be 15-year survival data, but there is simply too little 15-year outcome information available.

As reported experiences were tabulated, it became clear that patterns of outcome data could be gathered for the four treatment modalities, but it was not possible to compare results from a radical prostatectomy series with outcomes for radiation treatment or surveillance. (Tables 1 and 2). Patients who underwent the varying treatments were not selected in a uniform way. Series reporting radical prostatectomy outcomes contained younger patients than those in the literature reporting on radiation therapy. Patients in surveillance protocols were on average 7.3 years older than patients who had surgery and 4.1 years older than patients who had radiation therapy. Tumor grades were significantly different as well. Sixty-two percent of patients on surveillance had low-grade tumors, while 41 percent...
of patients receiving radiation therapy had low-grade tumors, and only 23 percent of patients in radical prostatectomy series had low-grade prostate cancer. Poorly differentiated tumors (or high grade) occurred in 20 percent of patients undergoing surgery, 18 percent of those having external-beam radiation therapy, 10 to 15 percent of brachytherapy series, and only three percent of surveillance series. Pelvic lymph node status was also drastically different in the different treatment groups. Of patients who had radical prostatectomy, 83 percent had staging pelvic lymphadenectomy. Only 26 percent of those treated by external-beam radiation therapy had a staging lymph node dissection; no patient in the surveillance group had node assessment. Their staging was far from uniform.

A major goal of this study was to recover data concerning patient survival: crude, progression-free, metastasis-free, and disease-specific. The literature on prostate cancer survival is almost totally calculated, that is, actuarial or projected survival, by the Kaplan-Meier statistical method. A disturbing discovery was that of all the survival articles dealing with patients who had radical surgery or radiation therapy only, 13 percent (one in seven) were actually followed for five years; survival for the remainder is all projected. Far fewer patients reported in 10- and 15-year survival articles are actually followed to these milestones.

Panel Conclusion
The panel found the data inadequate for valid comparisons of treatment, stating in the report: “Differences were too great among treatment series regarding such significant characteristics as age, tumor grade, and pelvic lymph node status.” There may be differences in treatment outcomes, but the published literature on localized prostate cancer is inadequate to demonstrate these differences. Improvements in our data on prostate cancer outcomes may be seen in the future if we can develop standard methods for selecting and staging patients for treatment and if there can be agreement on methods and time intervals for following patients.

Prostate Cancer Panel Recommendations
1. As a standard, an assessment of the patient’s life expectancy, overall health status, and tumor characteristics is necessary before any treatment decision can be made.
2. As a standard, a patient with clinically localized prostate cancer should be informed about the commonly accepted initial interventions, including, at a minimum, radical prostatectomy, radiation therapy, and surveillance. A discussion of the estimates for benefits and harms of each intervention should be offered to the patient.
3. As a standard, the patient’s preference, based on his attitude toward the course of the disease and the benefits and harms of the different interventions, should be considered in determining his treatment.

Panel Treatment Recommendations
Radical prostatectomy, radiation therapy, and surveillance are considered optional therapeutic approaches. In its report the panel stated: “The panel considered these interventions to be options because data from the literature do not provide clear-cut evidence for the superiority of any one treatment.” In general the patient who is most likely to benefit from a radical prostatectomy is a healthy man with a relatively long life expectancy, no significant risk factor, and a preference to undergo surgery. It is the panel’s recommendation that radiation therapy is appropriate for a man with a relatively long life expectancy, no significant risk factors for radiation toxicity, and also a preference to undergo radiation therapy. The panel recommended that surveil-
| Series Characteristic | Radical Prostatectomy | External-Beam Radiotherapy | Brachytherapy | Surveillance |
|----------------------|-----------------------|---------------------------|--------------|--------------|
| Mean patient age (range) | 62.7 (34-84) | 65.9 (26-92) | 64.5 (36-91) | 70 (38-90) |
| Number of patients | 9,263 | 14,205 | 4,891 | 913 |
| Number follow-up (%) | | | | |
| 5 years | 1,188 (13) | 1,802 (13) | 642 (13) | 400 (44) |
| 10 years | 759 (8) | 110 (1) | 100 (2) | 46 (5) |
| 15 years | 530 (6) | 0 | 0 | 33 (4) |
| Mean months (range) | 70.2 (1-372) | 70.3 (1-264) | 56.5 (1-219) | 111.6 (3-298) |
| % tumor grade (no./total no.)* | | | | |
| Well differentiated | 23.1 (376/1,631) | 41.2 (517/1,256) | 38.3 (427/1,116) | 62.2 (250/402) |
| Moderately well differentiated | 56.9 (928/1,631) | 40.6 (510/1,256) | 51.3 (572/1,116) | 34.8 (140/402) |
| Poorly differentiated | 20 (327/1,631) | 18.2 (229/1,256) | 10.5 (117/1,116) | 3 (12/402) |
| % pelvic lymphadenectomy (no./total no.) | 83 (910/1,093) | 26 (463/1,756) | 87 (1,743/1,997) | 0 |

Series denotes groups of patients stratified by parameters such as primary treatment modality; one article may include more than one series (data are from 169 series in 165 articles).

*Categorization of degree of differentiation is based either on series reports of good, moderate, or poor differentiation or on the division of Gleason sums of 2-4 (well differentiated), 5-7 (moderately well differentiated), or 8-10 (poorly differentiated).

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lance is probably most suited to the patient with a shorter projected life span and/or a low-grade tumor.

Methods of Staging Prostate Cancer
On the basis of reported evidence and the panel’s opinion, some commonly employed staging methods may not be necessary when dealing with localized prostate cancer. Computerized tomographic scanning and magnetic resonance imaging studies may not be required on most patients with clinically localized prostate cancer. Also, radioisotope bone scans can be omitted for those patients with localized prostate cancer and a PSA concentration of less than 10 ng/ml with associated low-grade tumors. The panel also found evidence to suggest that pelvic lymphadenectomy for staging has an extremely low yield in patients with a PSA under 10 ng/ml and a low-grade tumor.

Complications of Treatment
There are definitely complications that occur following the treatment of localized prostate cancer, but the panel found the literature to be significantly lacking in defining the incidence of various complications. Rather than attempting to quantitate the likelihood of a complication, the panel has presented ranges from the sporadic reporting of complications that appear in the literature. Clearly, the most common complications for radical prostatectomy are impotence and stress inconti-
The most common complications of radiation therapy are cystitis and proctitis. The reported range for these common complications is so wide that the precise incidence is difficult to determine.

Considerations for the Future
A major deficiency detected by the prostate cancer panel was the quality of outcomes data as commonly reported in the medical literature. More uniform methods for assessing and staging patients prior to therapy are needed. Investigators need to present precise data at definite milestones. Five-, 10-, and 15-year outcomes are preferred. There may be a place for actuarial or projected survival data, but the literature as it stands is vastly overweighted with patients who have been followed for extremely short periods of time. Actual survival data are also needed. With the availability of PSA, the process of determining efficacy of treatment may be streamlined in the future, but uniform methods of evaluating and following patients will still be vital.

References
1. Middleton RG, Thompson IM, Austenfeld MS, et al: Report on management of clinically localized prostate cancer. Baltimore, American Urological Association, 1995.
2. Middleton RG, Thompson IM, Austenfeld MS, et al: Prostate Cancer Clinical Guidelines Panel summary report on the management of clinically localized prostate cancer. J Urol 1995;154:2144-2148.

|                | Brachytherapy | Surveillance |
|----------------|--------------|--------------|
|                | Minimum (%)  | Maximum (%)  | Minimum (%)  | Maximum (%)  |
| 5-year survival|              |              |              |              |
| Overall        | 8            | 57.0         | 93.0         | 7            | 67.0         | 92.0         |
| Progression-free| 14          | 38.0         | 90.0         | 1            | 68.0         | 68.0         |
| Metastasis-free| 0            | 0            |              |              |              |              |
| Disease-specific| 3           | 92.0         | 100          | 3            | 89.0         | 99.0         |
| 10-year survival|             |              |              |              |
| Overall        | 0            | 0            |              | 5            | 34.0         | 70.7         |
| Progression-free| 7           | 50.0         | 90.0         | 1            | 53.0         | 53.0         |
| Metastasis-free| 0            | 0            |              |              |              |              |
| Disease-specific| 0           | 0            |              | 3            | 84.0         | 85.0         |
| 15-year survival* |           |              |              |              |
| Overall        | 4            | 39.0         | 67.0         |              |              |              |
| Progression-free| 0           | 0            |              |              |              |              |
| Metastasis-free| 0            | 0            |              |              |              |              |
| Disease-specific| 0           | 0            |              |              |              |              |

*There were no data for survivors of brachytherapy at 15 years.