A Structured Literature Review of Treatment for Localized Prostate Cancer

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Objective: We performed a structured literature review to define the clinical course of localized prostate cancer, the effectiveness of radical surgery and radiation therapy, and treatment complications.

Article Selection: We identified more than 1600 English-language, MEDLINE referenced articles for 1966 through 1991. All but 144 were excluded because they lacked primary data, involved fewer than 15 patients, or described neither the course of the disease nor treatment complications.

Data Synthesis: In these 144 articles, persistent genitourinary complications were more common after radical surgery than after external-beam radiation. Radiation resulted in a higher incidence of bowel problems. The median annual risks for the development of distant metastases and cancer-related death were 2.6% and 1.0%, respectively. Because tumor grade was correlated with metastases (Spearman correlation r=.56) and cancer mortality (r=.31), controlling for grade was necessary before we could compare the effectiveness of treatments for these outcomes. However, stratification by grade of malignancy was available in only nine of the patient series describing metastatic rates and in seven describing cancer-related mortality. Furthermore, in the patient series that described prostate cancer–related metastatic rates, 48% neglected to identify patients unavailable for follow-up, 92% did not stratify patients by age, and only 48% stratified patients by the extent of disease at treatment.

Conclusions: Although we were able to compare complications of treatments, we were unable to determine treatment effectiveness for localized prostate cancer because of methodologic inadequacies in the literature we reviewed. Until better scientific evidence is available, patients and their physicians cannot make informed choices based on knowledge of the benefits of radical prostatectomy, radiation, or watchful waiting.

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As many as 60% of elderly men have prostate cancer, but most do not know it.[1] As a result of new screening tests, increasing numbers of older men are learning that they have prostate cancer. These men and their doctors must make decisions about the treatment options for cancer in the face of a great deal of uncertainty about its natural history and the effectiveness of therapy.

We have only general information about the prognosis of localized cancer. The histologic features of a tumor (tumor grade) is the best predictor of spread of the disease and eventual cancer-related death.[2-5]

Much less is known about the effect of currently available alternative treatments: radical prostatectomy, radiation, and watchful waiting followed by active treatment only if the cancer spreads beyond the prostate. Randomized clinical trials are the gold standard method for testing hypotheses about treatment effects. By randomly assigning patients to treatment, randomized clinical trials effectively reduce the risk that an apparent benefit of treatment is in reality caused by differences among treatment groups in such critical factors as age and, in the case of prostate cancer, grade and stage of tumor. Unfortunately, for this condition, only one clinical trial has been performed comparing surgical treatment

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METHODS

SELECTION OF ARTICLES

For 1966 through 1991, we identified English-language titles and key words in MEDLINE satisfying any of the following criteria:

1. Reports describing therapy of prostate neoplasms: "surgery" or "radiotherapy."
2. Reports with titles containing "natural history," "untreated," "deferred treatment," or "expectant treatment."
3. Reports with titles containing "localized."

We also used these criteria to identify references listed in the citations that did not appear in MEDLINE. From more than 1600 titles identified by any of the search criteria, we excluded all but 144 for one or more of the following reasons:

- Neither the treatment complications nor the course of cancer was described.
- Fewer than 15 patients with localized (stage A or B) cancer were included.
- The report was a review article and did not contain primary data.
- The data were replicated in subsequent publication(s).

Of the 144 selected articles, two described randomized clinical trials[6,7] and five compared patient series of treatments.[8-12] Counting each arm of these studies as separate cohorts, we had 151 separate descriptions of treatment outcomes: 52 for radical surgery, 68 for radiation therapy, and 31 for watchful waiting.

ABSTRACTION OF INFORMATION FROM THE SELECTED ARTICLES

Two reviewers (J.H.W. and C.C.C.) each used a standard form to abstract, compare, and verify data from the 144 articles. Disagreements were resolved by conference. We extracted event rates (death and distant spread of disease) at a single time of follow-up for each report and divided by the number of years of follow-up to obtain a crude annualized rate. Because many reports did not provide an adequate description of the number of subjects observed after the mean follow-up time, we generally used the mean follow-up time. However, if fewer than 15 patients were observed at the mean follow-up, we used a shorter period that would include at least 15 patients.

We coded histologic profiles of cancer as well differentiated (Gleason grades 2 through 4), moderately differentiated (Gleason grades 5 through 7), and poorly differentiated (Gleason grades 8 through 10). Whenever possible, we used comparable categories for other histologic coding schemes. We also recorded treatment complications persisting more than 3 months.

As a method for assessing the quality of these reports, we coded whether an article listed the patients unavailable for follow-up and whether it described patient age and comorbidity and grade and stage of cancer.

ANALYSIS

We could describe the course of patients with localized prostate disease only by examining the eligible reports. Because few reports provide data about specific patients, we can say very little about what happened to the individual patients. We looked at the reported outcomes of each article and treated them each as a single datum. We summarized the data by using the median as our measure of central tendency. We converted death and metastatic rates to annual estimates. For example, a reported 20% rate of prostate cancer–related death at a mean of 4 years' follow-up would be expressed in this report as an annual rate of 5%. For each relevant outcome (death and metastatic spread), we included all eligible reports and calculated the median of their published rates. We also noted the range and the 95% confidence interval (CI) for the median using the method of Snedecor and Cochran.[13] Correlations were examined using Spearman's Rank Correlation Coefficient.

General characteristics of the patients known to influence the course of prostate cancer, such as grade of the malignant neoplasm and the extent of the disease at diagnosis, differed among the patient series. Therefore, we cannot recreate a large natural history study with patients as the unit of analysis simply by combining the data sets of the various small studies. However, we had little reason to presume that differences in these variables would have a similarly large influence on complications of surgical or radiation treatment. Therefore, for treatment complications only we provided, in addition to the median, an estimate of the weighted average. Because information was often not available about how many of the originally treated patients were included in calculation of the adverse event rate, we report the data as an estimated weighted average based on the numbers of patients who received the specified treatment. We also show the median complication rate using the patient series as the unit of analysis. Statistical tests of significance were performed for the median rate only. For statistical comparisons, we applied Wilcoxon's Rank Sum Test to the reported rates.

with watchful waiting.[6] While this trial showed no difference in outcome, its small size limits interpretation.

Patient (or case) series are another source of information commonly used to evaluate outcomes. In the typical patient series, the data are for a consecutive cohort treated at a single institution. Patient series are useful for establishing the safety of treatment, for documenting short-term risks, and, rarely, as clear evidence of a medical breakthrough. Patient series may also offer evidence of efficacy that can justify a randomized clinical trial.

Compared with randomized clinical trials, many more patient series for radical prostatectomy, radiation, and watchful waiting are described in the literature. Using meta-analysis, these articles can be combined and synthesized

to obtain more robust estimates of the probabilities for outcomes according to treatment. This results in better estimates of the safety and short-term risks of treatment. The evidence might suggest a treatment advantage with regard to mortality or spread of cancer. To combine case series, however, the individual studies must be given in sufficient detail for stratification by age and stage and grade of cancer.

We present herein the results of a structured review of the English-language medical literature for 1966 through 1991. The primary goal was to estimate mortality, the occurrence of distant metastases for all three treatments, and short-term risks of surgery and radiation. Our secondary goal was to evaluate the quality of the studies as a prerequisite for comparing treatments.

RESULTS

ARTICLE QUALITY

Our five standards of an article's quality were that it enumerated patients who were unavailable for follow-up (standard 1), that it included a description of patient age (standard 2) and comorbidity (standard 3), and that it describe cancer grade (standard 4) and stage (standard 5). Only one of the articles met all five standards; six articles met four, and 24 met three of these five standards of quality. Of the 68 patient series that used cancer mortality as an end point, only nine stratified patients by age, and one by comorbidity. For the 50 patient series that used distant metastases as an outcome, four stratified patients by age, and none by comorbidity. Enumeration of patients unavailable for follow-up was neglected in 48% of the patient series describing metastases and in 35% of those examining cancer mortality. **Table 1** shows the small number of patient series that included stratification by stage of disease or grade of malignant neoplasm. Therefore, in subsequent analyses, we are unable to use patient series stratified by stage and grade of malignant neoplasm when comparing treatments.

Between 1966 through 1981 and 1982 through 1991, we observed no change in the percentage of patient series that stratified patients by age, histologic grade, cancer stage, or comorbidity. During the most recent 10-year period, only 62% of series reported using a prostate-specific antigen or acid phosphatase, and 65%, a bone scan, to investigate the extent of tumor spread before treatment.

IMPORTANCE OF AGE, GRADE, AND STAGING IN PREDICTING OUTCOMES

Patient characteristics and outcomes of treatment for clinically localized cancer, given in **Table 2**, illustrate the importance of controlling for age and grade. Patients were oldest in the watchful waiting series and youngest in studies of radical prostatectomy. Grade of tumor appeared worse among patients receiving radiation therapy. Across all patient series, mean age correlated significantly with all-cause mortality rates (r=.61; n=80 series), and proportion of cancer that was poorly differentiated correlated with the annual rate of metastases (r=.56; n=30 series) and cancer-related mortality (r=.31; n=43 series). Therefore, we used multiple regression to investigate further the impact of age and grade on outcome of disease.

We entered mean age, proportion of poorly differentiated cancer, treatment, and whether an article described unavailability for follow-up (as a surrogate for article quality) into the regression model. For overall survival, age was most significant (P=.0003) in 55 patient series. For annual rates of metastases- and cancer-related mortality, the proportion of cancer that was poorly differentiated was most significant in 27 (P=.005) and 38 (P=.004) patient series, respectively. Treatment was not a significant variable in any of the regression models.

In general, stage A cancer discovered on pathologic examination had a lower metastatic rate and cancer-specific mortality rate than palpable, but clinically localized, stage B cancer. However, we observed considerable overlap in the CIs because of the effects of cancer grade. The median annual metastatic rates and 95% CIs were 0.020 (0.010 to 0.043) and 0.044 (0.030 to 0.070) for stage A and B cancer, respectively. For annual cancer mor-

Table 1. Number of Patient Series Describing Prostate Cancer–Related Deaths or Distant Metastases by Tumor Stage and Grade*

	Death			Distant Metastases		
Stratification Method	Surgery	Radiation Therapy	Watchful Waiting	Surgery	Radiation Therapy	Watchful Waiting
Clinical stage						
A	6	10	17	8	8	12
B	7	12	6	6	10	2
Tumor grade						
Well differentiated	1	1	5	3	1	5
Moderately differentiated	1	1	4	2	1	4
Poorly differentiated	0	1	4	3	1	4

*A single patient series may appear more than once in this table.

Table 2. Patient Characteristics and Outcome of Treatment for Clinically Localized Prostate Cancer*

	All Series		Series by Treatment Described					
			Radical Surgery		Radiation Therapy		Watchful Waiting	
	Median (95% CI)	n	Median (95% CI)	n	Median (95% CI)	n	Median (95% CI)	n
Patient characteristics								
Mean age, y	66 (64-67)	99	63 (61-64)	33	66 (64-66)	49	71 (69-73)	27
% of patients with poorly differentiated cancer	13 (10-19)	77	11 (6-25)	22	21 (13-24)	45	7 (6-11)	19
Outcome of disease								
Median annual mortality rate								
All causes	0.045 (0.42-0.52)	99	0.32 (0.020-0.044)	27	0.45 (0.040-0.052)	45	0.060 (0.050-0.104)	27
Cancer-specific causes	0.010 (0.009-0.015)	68	0.009 (0.007-0.013)	230	0.023 (0.010-0.030)	22	0.009 (0.006-0.012)	23
Median annual rate of distant metastasis	0.026 (0.020-0.043)	500	0.023 (0.014-0.025)	18	0.050 (0.030-0.095)	17	0.017 (0.011-0.043)	15

*Some series did not include the patient characteristics and disease outcomes shown here. CI indicates confidence interval.

tality for stage A and B cancer, the rates were 0.006 (0 to 0.009) and 0.012 (0.007 to 0.027), respectively.

For patients with clinically localized prostate cancer, their stage of disease was often changed after results were obtained for lymph node dissection and pathologic examination of the prostate capsule removed at surgery. The net effect of such "surgical staging" should be that patients with surgical stage A or B disease will have better outcomes than patients with clinical stage A or B disease. Because patients who receive radiation therapy or pursue watchful waiting usually do not undergo invasive staging before therapy, radical surgical treatment may seem the better treatment. We were able to assess the importance of a surgical staging bias in 16 patient series that reported both clinical and pathologic staging after lymph node dissection and/or examination of the prostate capsule. For all causes of mortality examined in nine patient series, the median annual death rates were 0.044 per 100 patients for clinical stages A and B and 0.022 per 100 patients for surgical stages A and B. For cancer-related mortality, ascertained in seven patient series, the rates were 0.010 and 0.006 deaths per 100 patients for stages A and B, respectively. The pattern of apparent improvement in survival attributable to method of staging is statistically significant ($P=.01$ by Wilcoxon's Rank Sum Test).

SURGICAL REMOVAL OF CANCEROUS TISSUE

For the patient series describing radical surgery, the median rate of cancer present beyond the margin of resection was 25% (95% CI, 19% to 35%; n=22 series). This progression to pathologic stage C disease is a bad prognostic finding. The proportion of cancer confined pathologically to the prostate (organ-confined disease) was 56%.[14-17] Although complete removal of organ-confined disease is generally considered a cancer cure, in these four reports, none,[14] 1%,[15] 5%,[16] and 11%[17] of the men experienced cancer progression outside of the prostate within 5 years of diagnosis.

ADVERSE EVENTS AFTER TREATMENT

Table 3 reports the incidence of adverse outcomes of radiation therapy and radical surgery for articles published between 1982 and 1991. The results show that no treatment is clearly superior to the others in minimizing adverse outcomes. Radical surgery has higher rates of mortality and urinary tract complications than external-beam radiation therapy, but radiation therapy more commonly caused bowel problems. Although interstitial radiation therapy may result in fewer cases of impotence than the other forms of treatment, in all other respects it seems to be worse than external-beam radiation therapy.

In contrast with the very high rate of impotence after typical radical surgery, as few as one third of the men who successfully undergo a nerve-sparing surgery procedure suffer this complication. However, success of this procedure is reported to be adversely impacted by the extent and grade of the malignant neoplasm.[18,19]

COMMENT

We performed a structured literature review to identify relevant treatment outcomes in clinically localized prostate cancer. The treatments examined were radical surgery, radiation therapy, and delayed hormonal treatment (watchful waiting). We had two major findings. First, the literature we reviewed did not provide evidence for the superiority of one form of treatment over another in terms of life expectancy or freedom from distant metastasis. The single controlled clinical trial involving surgery studied

Table 3. Persistent Adverse Outcomes After Treatment of Clinically Localized Prostate Cancer*

	Radical Surgery	Radiation Therapy: External Beam	Radiation Therapy: Interstitial	P†: External-Beam Radiation Therapy vs Surgery	P†: Interstitial Radiation Therapy vs Surgery
Treatment-associated mortality				NS	NS
Weighted mean	1.1	.2	.6		
No. of patients	409	946	587		
Median rate for case series	2	0	0		
No. of case series	6	8	9		
Any incontinence				.01	NA
Weighted mean	20.6	6.1	NR		
No. of patients	301	443	NR		
Median rate for case series	16	6.5	NR		
No. of case series	8	6	NR		
Complete incontinence				.005	NS
Weighted mean	6.8	1.2	5.4		
No. of patients	719	739	195		
Median rate for case series	6	1	2		
No. of case series	11	11	3		
Any bowel injury				.008	.03
Weighted mean	2.7	11.4	14.4		
No. of patients	407	1148	160		
Median rate for case series	1.5	13.5	25		
No. of case series	4	12	3		
Bowel injury requiring long-term treatment or colostomy				NS	.04
Weighted mean	1.3	2.3	3.2		
No. of patients	551	1680	430		
Median rate for case series	1	1	3		
No. of case series	6	17	6		
Stricture requiring long-term treatment				.003	NS
Weighted mean	12.4	4.5	9.8		
No. of patients	542	959	390		
Median rate for case series	9	2.5	9		
No. of case series	9	12	6		
Impotence				NS	NS
Weighted mean	84.6‡	41.4	12.4		
No. of patients	374	415	277		
Median rate for case series	82	44	12		
No. of case series	7	5	4		

*Based on case series of complications lasting more than 3 months described in the literature between 1982 and 1991. NA indicates not applicable; NR, not reported; and NS, not significant.

†Statistical difference of unweighted reported rates in case series using Wilcoxon's Rank Sum Test.

‡For nerve-sparing surgery in two patient series the weighted mean was 31.5.

too few patients for its results to constitute definitive evidence that surgery has no advantage over watchful waiting. The substantial methodologic flaws in the remaining literature (which were based on case series methods) did not permit valid comparisons of the end results of treatment. Second, both surgery and radiation therapy have substantial short-term complications. In this respect, watchful waiting, because it is not associated with the complications listed in Table 3, is clearly superior.

Despite the lack of evidence for its efficacy, the rate at which radical prostatectomy is performed is increasing rapidly in many parts of the United States. What explains this growth in popularity? Many clinicians believe that surgical treatment is justified based on the argument that if all cancer is removed, it is impossible for cancer to spread. However, even after radical prostatectomy appears to have removed all disease and pathologic examination indicates that the tumor was confined to the prostate, as many as 11% of men have evidence of spread of cancer within 5 years. Perhaps more discouraging, in about one quarter of

radical procedures, the tumor is found outside of the prostate capsule, already beyond surgical cure at resection.

Another cause of unjustified enthusiasm may be stage migration bias.[20-22] Walsh and Jewett[23] described a dramatic temporal trend for increased survival in patients with stage IB cancer treated at their institution. This more than twofold improvement was attributed to better diagnostic testing and patient selection. Bagshaw[24] made an analogous observation in patients with stage IIB prostate cancer: large stage IIB lesions had an almost twofold worse prognosis than small stage IIB lesions. Results of these two studies indicate that more sensitive testing and categorizing of early-stage prostate cancer can identify patients who will do well. When these patients receive treatment, the treatment may incorrectly be assumed to have caused the improved outcome, but this can only be established by a clinical trial. The opportunity to become fooled is compounded in the present environment, where mass screening programs are discovering small cancerous lesions, creating an unprecedented epidemic in the reported incidence of cancer, even though population-based mortality rates remain virtually constant.[25] Uncritical enthusiasm for screening and aggressive treatment makes the new approach standard practice; the old methods may erroneously become a standard for reference in malpractice suits.

What about the patient? Despite our limited knowledge about the natural history of prostate cancer, some clinicians believe that aggressive screening and therapy for localized prostate cancer offer the only hope for reducing morbidity and mortality associated with this disease.[26] Others[27,28] express concern about the unproven benefits, high costs, and adverse effects of radical surgery or radiation therapy. A consequence of this difference in opinion is a high variation in use of treatment by geographic regions in the United States and between the United States and several other nations.[27-29] In other words, cancer detection and treatment seem to depend more on the happenstance of where a man lives than on the proven merits of a particular approach. A man who is told that he has clinically localized prostate cancer, or a high probability of localized disease as a consequence of the results of a screening test, must make a difficult choice between avoiding the risk of immediate harms of treatment if he elects watchful waiting and possible, but scientifically undocumented, improvement in survival if he chooses surgery or radiation therapy. If he chooses radiation therapy, the organ and periprostatic tissue will be treated at the same time. Whether this approach is as effective as surgical treatment is very controversial.[7,30] If he chooses radical surgery, he confronts a 25% probability of cancer extension through the prostate capsule and beyond the margin of resection. For management of tumor extension, he may be asked to consider adjuvant radiation therapy with its attendant morbidity.

For evaluation of literature describing treatments for prostate cancer, our study has two major limitations. First, when describing treatment outcomes, we chose the median rate of outcomes of the studies as our measure of central tendency. The disadvantage of using the median rate of outcomes is that it does not account for the relative sample sizes of the different studies. If we believed that all the studies were estimating the same underlying rate of outcomes (a "fixed effects" model), we would try to attribute differences among the studies to binomial variation (random error). Bigger studies would have less such error and should be weighted more heavily. However, we observed that the variation in rates of outcome between studies (due to occult differences in patients and cancer stage and grade) was so large that it overwhelmed our concerns about adjustment for variation in sample size among studies.

Second, our estimates of complication rates may be misleading if published results lag behind current practice. We tried to minimize this possible source of error by limiting our comparison of treatments to case series published since 1981. Although mortality estimates obtained from the published literature are similar to those reported in Medicare claims,[28] we are not confident that our adverse-event estimates reflect current rates. We also cannot be sure that the observed differences in complications among treatments might not be the result of confounding by unreported patient characteristics. Nevertheless, this literature is probably the best source of information available.

Although we used MEDLINE and a check of article references to find published reports about treatment of localized prostate cancer, we may have overlooked some studies. However, our interpretation of the identified patient series was conservative. We are confident that we did not omit any controlled trials of treatment. We do not believe that the addition of several more patient series would significantly change our findings.

We could not "blind" our two independent reviewers because they had to read every word of the articles to identify important information. By using two reviewers and requiring them to compare results, we believe that we have minimized the likelihood of bias.

The information obtained from this structured review of localized prostate cancer can be used to estimate the median annual cancer-related mortality rate, the probability of death due to cancer, and the complications of treatment reported in the published literature. The outcome expected after treatment for clinically localized prostate cancer depends on at least three variables other than the choice of the treatment itself: the age of the patient, histologic grade of tumor, and anatomic extent of tumor. We have demonstrated that surgery is more often offered to younger patients and that grade of malignancy is not evenly distributed among treatment choices. This phenomenon is the result of intelligent and compassionate physicians tailoring what they consider to be the best treatment to the needs of their individual patients. It has the unfortunate effect of obscuring possible differences among treatment results. The

quality of outcomes studies must be improved. Therefore, we make the following recommendations.

First, factors that have obvious potential to bias or confound interpretation of studies such as age, staging, grade, and comorbidity ought to be reported in a standard way in all reports. For example, although the Gleason system is the most commonly used system for grading prostate cancer in the United States, many other systems exist. Furthermore, the reliability of all grading systems and newer methods for measuring biologic features of tumor need strengthening.[31,32] Unavailability for follow-up and methods used to exclude distant metastases should be fully reported. Measures for reporting treatment complications should also be standardized.

Second, from the patient's perspective, description of a change in health and function as a result of a particular treatment usually outweighs a change in biochemistry or ultrasonography results alone. In all the articles we reviewed, change in patient health or function was ignored. This crucial omission must be remedied in the future.

Third, clinical trials and patient series using standard reporting methods must be performed. We document elsewhere[29] the dramatic growth of prostate cancer treatment. The economic costs to society and the psychological costs to patients of our current screening and treatment patterns ought to be based on better information than currently exists in the published literature.

Until these improvements are realized, clinicians who advocate radical surgery, radiation therapy, or watchful waiting will continue to have a poor foundation to support their opinions.

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A list of all articles included in this review can be obtained from Dr Wasson at the reprint address given below.

Reprint requests to Community and Family Medicine, Center for the Evaluative Clinical Sciences, HB 7250, Strasenburgh Hall, Hanover, NH 03755-3863 (Dr Wasson).

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