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Observation as a management approach for newly diagnosed early prostate cancer may be appropriate for a subset of patients who meet specific selection criteria.

Observation in the Management of Localized Prostate Cancer

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Background: *The widespread use of the prostate-specific antigen test, the availability of ultrasound, and improved techniques for prostate biopsy have led to the diagnosis of organ-confined prostate cancers at an earlier stage. An unknown number of these cancers will be incidental and will not impact the patient's quality or length of life.*

Methods: *The most recent published reports and decision analysis studies on observation management were reviewed. We also analyzed our own series of observed patients.*

Results: *Three contemporary series on observation and three reports on decision analysis for treatment of early prostate cancer define a group of patients who may be treated with observation. Our own preliminary experience, however, demonstrates that a significant number undergo definitive treatment within 3 years from diagnosis. The optimal treatment for men with early prostate cancer is currently unknown.*

Conclusions: *A subset of patients with newly diagnosed prostate cancer may be managed by observation. Standard protocols for selection and follow-up of patients on observation need to be developed.*

Introduction

The majority of patients with newly diagnosed prostate cancer currently present with clinically local-

ized disease. In contrast, until only 10 years ago, most patients presented with more advanced disease. This "stage migration" is a consequence of increased awareness of the disease by physicians and patients, the widespread use of the prostate-specific antigen (PSA) test, and the availability of transrectal ultrasound to more accurately guide prostate biopsies. Management options for clinically localized prostate cancer include surgery, external-beam radiation therapy, cryosurgery, brachytherapy, and observation. In this article, we discuss the most current literature on observation or "watchful waiting," present the clinical parameters of patients who would be most suitably managed by observation, and propose a follow-up schedule for

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Table 1. — Summary of Reported Series of Patients With Localized Prostate Cancer Managed by Observation

Author	Number of Patients	Grade (%)	10-Yr CSS (%)	15-Yr CSS (%)	10-Yr MFS (%)	14-Yr MFS (%)
Chodak et al ²	828	I (59)	87	—	81	—
		II (32)	87	—	58	—
		III (8)	34	—	26	—
Albertsen et al ³	451	I	91	91	—	—
		II	76	72	—	—
		III	54	49	—	—
Johansson et al ⁵	223	I (66)	—	44	—	92
		II (30)	—	83	—	82
		III (4)	—	44	—	53

CSS = cancer-specific survival
MFS = metastases-free survival

patients who elect observation as primary management of their localized prostate cancer.

Rationale for Observation

The finding of prostate cancer in the pathology sample of the prostate in the aging male population is common and exceeds the clinical prevalence of disease 5- to 8-fold. Autopsy series report an incidence as high as 80% in men 80 years and older.¹ With the widespread use of the PSA test as a screen, together with awareness and improvements in ultrasound technology and prostate biopsy techniques, a significant number of men are diagnosed with prostate cancer that might be termed “incidental” and will not affect their survival or quality of life. A significant number of these men will die with their cancer rather than of the cancer. These findings led several investigators to consider observation as a management alternative for some men with newly diagnosed early prostate cancer.

Contemporary Series on Observation

Three studies summarize the majority of experience with observation for prostate cancer during the last 3 decades (Table 1).

The report by Chodak et al² was a pooled analysis of 828 patients from six nonrandomized series (two from the United States, two from Sweden, one from Scotland, and one from Israel) published after 1985. The mean age of men in these series was 69 years, and the distribution of tumor grade was I in 59%, II in 32%, and III in 8% of patients. For grades I, II, and III, 10-year disease-specific survival rates were 87%, 87%, and 34%, respectively, and 10-year metastasis-free survival rates were 81%, 58%, and 26%, respectively.

The report by Albertsen et al³ was a population-based retrospective cohort study of 451 men with clini-

cally localized prostate cancer diagnosed from 1971 to 1976 and identified by the Connecticut Tumor Registry. These men were between 65 to 75 years of age at the time of diagnosis and were either untreated or treated with immediate or delayed hormonal therapy. The mean age was 70.9 years. The most powerful predictor of survival in this series was the Gleason score on pathology. Men with low-grade tumors (Gleason score 2-4) had a life expectancy comparable to a relevant general population. Those with moderate-grade tumors (Gleason score 5-7) had a 4- to 5-year loss of life expectancy, and those with high-grade tumors (Gleason score 8-10) had a 6- to 8-year loss of life expectancy. Ten-year disease-specific survival rates were 91%, 76%, and 54% for low-, moderate-, and high-grade tumors, respectively. Fifteen-year disease-specific survival rates were 91%, 72%, and 49% for low-, moderate-, and high-grade cancers, respectively. The study also found that patient comorbidities as determined by the Index of Coexistent Disease (ICED)⁴ were nearly as potent a predictor of survival as tumor histology.

The report by Johansson et al⁵ was a prospective, population-based study from Sweden between 1977 and 1984. Of a total of 642 patients with prostate cancer, 223 had localized disease and received no initial treatment. Their mean age at diagnosis was 72 years. Tumors were well, moderately, and poorly differentiated in 66%, 30%, and 4% of cases, respectively. At a mean follow-up of 14 years, metastases occurred in 8%, 18%, and 67%, and death from prostate cancer in 6%, 17%, and 56% for well, moderately, and poorly differentiated tumors, respectively.

Analysis of Observation Management Studies

These three studies reporting outcomes from observation for prostate cancer have been widely criticized in the United States. Steinberg et al⁶ summarized the concerns expressed by various investigators. They noted a predominance of low-grade tumors in all these observation studies. They also observed that some

patients with false-positive diagnoses of prostate cancer might have been included in the Scandinavian series since many diagnoses were made there by fine-needle aspirate. Additionally, the mean age at diagnosis in the observation series is older than the age at diagnosis in many prostate cancer treatment series reported in the United States. The authors expressing caution in considering observation as a management option for all men with newly diagnosed prostate cancer and suggested that most men with prostate cancer with a life expectancy of greater than 10 to 15 years should be treated with curative intent.

Two additional reports from Scandinavia also temper the thrust for recommending observation in the majority of patients with newly diagnosed early prostate cancer. Aus et al⁷ noted that of those patients who failed observation and later died of prostate cancer, 61% required one or more palliative treatments before death. They also reported that an average of 5 weeks were spent in the hospital as a direct consequence of the cancer. Grönberg et al⁸ reported that age at diagnosis was a strong predictor of prostate cancer death. Patients who were diagnosed before age 60 had an 80% risk of dying of prostate cancer, while those over 80 years of age had less than 50% risk.

Decision Analysis for Management of Early-Stage Prostate Cancer

The optimal treatment for individuals with localized prostate cancer is unknown. One structured review of the medical literature⁹ did not support benefit from treatment by surgery or radiation therapy over observation.

Fleming et al¹⁰ have developed a decision analysis program that modeled three management strategies (surgery, external-beam radiation therapy, and observation) for men with localized prostate cancer. The model analyzed expected outcomes by tumor grade for men 60 to 75 years of age. The main benefit of treatment was defined as a reduction in the chance of death or disability from metastatic disease. These benefits were offset in the model by the risks of treatment-related morbidity and mortality. They determined that, in most cases, the potential benefits of therapy were sufficiently small that the choice of therapy should be sensitive to the patient's preferences for different outcomes. Observation could be a reasonable alternative to invasive local treatment for many men with localized prostate cancer. Others have come to different conclusions.

Beck et al¹¹ performed a decision analysis using data from the Chodak pooled analysis on observation and

Table 2. — Clinical Parameters Favoring Observation in Newly Diagnosed Localized Prostate Cancer

Gleason score	≤6
Number of cores involved in sextant biopsy	≤2
% involvement with cancer in any core	≤50%
PSA density	≤0.15
Life expectancy	≤10 yrs

from more contemporary data from radical prostatectomy series. Conflicting with conclusions from Fleming and associates, this model supported treatment for all grades of prostate cancer for 65-year-old men with newly diagnosed clinically localized prostate cancer of any histologic grade. The authors recommend more quality of life studies with actual prostate cancer patients and collaboration between decision analysis scientists and academic urologists to refine these models. More recently, Yoshimura et al¹² performed a decision analysis to evaluate the usefulness of pretreatment prediction of clinically significant or insignificant tumors in patients with PSA-detected stage T1c prostate cancer. Analysis was performed on healthy subjects with a life expectancy of 20 years. Test characteristics for detecting significant cancer were derived from the data reported by Epstein et al¹³ for clinical T1c prostate cancer. These characteristics include a PSA density of >0.15 or adverse needle biopsy pathology variables such as Gleason histologic pattern (not score) 4 or 5, three or more of the six biopsies involved by tumor, and any core with more than 50% cancer involvement (Table 2). This study confirmed that selecting observation over treatment for patients with clinical T1c presumably insignificant tumors might be appropriate. They encouraged further efforts to achieve more precise preoperative staging in patients with early-stage prostate cancer.

Our Observation Series: Preliminary Findings

We are currently evaluating the outcomes of patients who elected observation at our institution. An interim analysis of the first 96 patients with newly diagnosed organ-confined prostate cancer that elected observation as primary management of their cancer was performed. All patients had clinical stage T1c or T2 cancers and a serum PSA level of less than 10 ng/mL. The Gleason score was 2-5 in 35 patients (36%), 6 in 49 patients (51%), and 7 in 12 patients (13%). The mean age at diagnosis was 71 years (range 54-83). This series is not an observation series in the classical sense; patients were actively monitored with periodic PSA determinations, digital rectal examinations, and transrectal ultrasound with prostate biopsies with an intent to institute active treatment if adverse clinical param-

Table 3. — Observation for
Localized Prostate Cancer: Follow-up Protocol

Prostate-specific antigen	q 6 months
Digital rectal ultrasound	q 6 months
Transrectal ultrasound and prostate biopsy	q 12-24 months

ters developed at follow-up (Tables 2-3). At a mean follow-up time of 29 months (range 9-71), 28 patients (29%) have undergone some type of treatment, mostly external-beam radiation therapy. We note that 9 (32%) of the 28 patients who subsequently received treatment had a low (2-5) Gleason score cancer at diagnosis.

Further analysis of the patients in this series will lead to the development of rational guidelines (eg, frequency of PSA determination, digital rectal examination, and transrectal ultrasound and prostate biopsies) for optimal follow-up. Additional study of these patients will also determine the indications for active intervention in men who elect observation as the initial management of their clinically localized prostate cancer.

Future Directions

When completed, the Prostate Cancer Intervention Versus Observation Trial (PIVOT)¹⁴ will provide a more precise definition of the natural history of early prostate cancer. This randomized trial is designed to determine whether surgery or observation provides superior length and quality of life for men with clinically localized prostate cancer. Over 1,000 men will be randomized and then followed for a minimum of 12 years.

Developing techniques in molecular biology may improve the selection of patients for observation. Thus, Borre et al¹⁵ quantified microvessel density by immunohistochemistry in archival tumors obtained at diagnosis in 221 prostate cancer patients who had been followed expectantly. Microvessel density correlated with clinical stage and histopathologic grade, and it was a significant predictor of disease-specific survival. The association between angiogenesis as measured by microvessel density and survival in patients with prostate cancer managed by watchful waiting suggests that the pattern of neovascularization is important in the natural history of prostate cancer.

Borre et al¹⁶ also studied the expression of p53 immunoreactivity of prostate cancer specimens from men undergoing observation. The expression of mutated p53 correlated with tumor stage and grade and was an independent adverse prognostic factor in men undergoing observation.

Conclusions

Our understanding of the natural history of prostate cancer has improved in the last several years. It is now possible to define a subset of men with clinically localized prostate cancer who may be managed by observation. Further research is needed to more precisely identify the individual patients who will be best managed by observation.

References

1. Franks L, Duch M. Latent progression in tumors: the natural history of prostate cancer. *Lancet*. 1956;2:1037-1039.
2. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med*. 1994;330:242-248.
3. Albertsen PC, Fryback DG, Storer BE, et al. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA*. 1995;274:626-631.
4. Imamura K, McKinnon M, Middleton R, et al. Reliability of a comorbidity measure: the Index of Co-Existent Disease (ICED). *J Clin Epidemiol*. 1997;50:1011-1016.
5. Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer: a prospective, population-based study in Sweden. *JAMA*. 1997;277:467-471.
6. Steinberg GD, Bales GT, Brendler CB. An analysis of watchful waiting for clinically localized prostate cancer. *J Urol*. 1998;159:1431-1436.
7. Aus G, Hugosson J, Norlen L. Need for hospital care and palliative treatment for prostate cancer treated with noncurative intent. *J Urol*. 1995;154(2 pt 1):466-469.
8. Grönberg H, Damber L, Jonson H, et al. Prostate cancer mortality in northern Sweden, with special reference to tumor grade and patient age. *Urology*. 1997;49:374-378.
9. Wasson JH, Cushman CC, Bruskewitz RC, et al. A structured literature review of treatment for localized prostate cancer. Prostate Disease Patient Outcome Research Team. *Arch Fam Med*. 1993;2:487-493.
10. Fleming C, Wasson JH, Albertsen PC, et al. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. Prostate Patient Outcomes Research Team. *JAMA*. 1993;269:2650-2658.
11. Beck JR, Kattan MW, Miles BJ. A critique of the decision analysis for clinically localized prostate cancer. *J Urol*. 1994;152:1894-1899.
12. Yoshimura N, Takami N, Ogawa O, et al. Decision analysis for treatment of early stage prostate cancer. *Jpn J Cancer Res*. 1998;89:681-689.
13. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA*. 1994;271:368-374.
14. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). *Oncology (Huntingt)*. 1997;11:1133-1140, 1143.
15. Borre M, Offersen BV, Nerstrom B, et al. Microvessel density predicts survival in prostate cancer patients subjected to watchful waiting. *Br J Cancer*. 1998;78:940-944.
16. Borre M, Stausbøl-Grøn B, Overgaard J. p53 accumulation associated with bcl-2, the proliferation marker MIB-1 and survival in patients with prostate cancer subjected to watchful waiting. *J Urol*. 2000;164(3 pt 1):716-721.