TREATMENT OPTIONS IN PROSTATE CANCER STAGE BY STAGE *

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O. Dillioğlugil, M.D.* / P.T. Scardino, M.D.****

** *Professor, Baylor College of Medicine, Scott Department of Urology, Houston, Texas, USA.*
*** *Clinical Fellow, Baylor College of Medicine, Scott Department of Urology, Houston, Texas, USA.*

SUMMARY

In summary, as longevity has improved and mortality from cardiovascular and other diseases has declined, the risk of death from prostate cancer has increased steadily. Though slow growing, prostate cancer is not a benign disease. Nearly 10 % of men will be diagnosed with prostate cancer and 3 % will die of the disease. The prospects for long term control of prostate cancer diminish rapidly once it has spread beyond the immediate periprostatic tissue. The 5 year survival rate for men with metastases is less than 30 % . A simple blood test is available, PSA, which - when used in conjunction with ultrasound-guided systematic needle biopsy of the prostate - will detect potentially lethal prostate cancers earlier than the digital rectal examination. Definitive treatment, especially with radical prostatectomy, can eradicate the tumor in 90% of patients if it is still confined to the prostate pathologically, regardless of the grade of the cancer. Randomized, prospective clinical trials are now underway to demonstrate conclusively whether screening or early surgical therapy will substantially reduce the mortality rate from this disease. Until the results of these trials are available, we recommend that healthy men over age 50, who have a life expectancy of 10 years or longer, have a regular annual PSA and DRE to detect prostate cancer while it is still curable.

INTRODUCTION

Although prostate cancer is responsible for the deaths of 3% of men in most developed countries, the management of this disease has generated considerable controversy. With the availabilitiy of prostate specific antigen (PSA), we are now able to detect the disease earlier, when it is still confined within the prostate in most patients. Modern treatment, especially with radical prostatectomy, is able to eradicate the disease completely in over 70% of the patients overall and, 90% if the cancer is confined to the prostate pathologically. Yet this cancer can not be cured once it has metastasized, conservative management of localized prostate cancer is appropriate in elderly men or those with a life expectancy shorter than 10 years. But it is now clear that treatment offers substantial benefit, in both length and quality of life, for otherwise healthy men with a life expectancy of 10 years or longer who have a clinically localized cancer. This article will review the current staging and management of prostate cancer as practiced in the United States.

Staging

The staging system most commonly used for prostate cancer by American urologists, the ABCD system, was introduced by Whitmore in 1956 (1) and subsequently was modified by Jewett in 1975 (2). This system offered useful categories to define the nature and extent of the local tumor but was unable to provide, simultaneously, information about the presence of cancer in the regional lymph nodes and distant sites. In 1986 the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) agreed upon a uniform staging classification, based on the TNM (tumor, nodes, metastases) system (3).

In 1990, a constructive dialogue was initiated between representatives of the UICC and the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary (GU) Group on one side, and the AJCC and American Society of Urological Oncology on the other. These discussions resulted in the development of the 1992 UICC/AJCC TNM staging system for prostate cancer (Table I) (4, 5). This system was developed with three major goals: (1) The TNM system should be useful in the daily practice of urologic oncology; (2) preserve the logical designation of the primary tumor established in the Withmore that has withstood the test of time, should be preserved; and (3) the system should be flexible enough to incorporate information from emerging technology by utilizing the principal of "telescopic ramification (optional subdivision of the existing T, N, and M categories)" (6). The general categories in the TNM system reflect the anatomic extent of the disease: T1 clinically inapparent; T2 clinically apparent, but localized within the prostate; T3, clinically apparent with local extension outside the prostate; and N+, nodal or M+, distant metastatic spread. The new TNM classification, for the first time, incorporated transrectal ultrasound (TRUS) and PSA into the system.

PSA is now recognized as the most powerful tumor marker in oncology and is the most important test in

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the early detection, staging and monitoring of prostate cancer. The 1992 TNM system includes a new category, T1c, for non-palpable tumors that are detected because of an elevated PSA level. TRUS is also used widely to detect prostate cancer and to guide biopsy needles for accurate samples of the gland. When seen, cancer appears hypoechoic relative to the normal echogenicity of the prostate gland (7, 8). Cancers that can be seen on ultrasound are classified, along with palpable cancers, as T2-4 depending on their extent.

Ultrasound-guided systematic needle biopsies of the prostate are safe, inexpensive and have a higher yield in detecting cancer than directed biopsies of suspicious, palpable or visible lesions (9).

Early Detection of Prostate Cancer

Cancer of the prostate causes no symptoms until it is locally advanced or metastatic. To detect the disease while it is locaiized and potentially curable requires periodic examinations both with DRE and PSA. Both PSA and TRUS add substantially to the detection of cancer compared to DRE alone (10, 11). Because TRUS is subjective, requires special training and is relatively expensive compared to DRE and PSA, it has not been advocated for the routine initial evaluation of men for prostate cancer. Large screening trials with DRE and PSA have shown that PSA nearly doubles the rate of detection possible with DRE alone (Table II) (12). There has been a significant stage migration towards the detection of lower stage prostate cancers by utilizing PSA and TRUS guided biopsies in addition to DRE (13). Before 1990 only about 50% of the cancers detected were confined to the prostate clinically (14). Now, the integration of the new tools (TRUS, PSA) with DRE has improved the detection rate of clinically organ-confined cancer to 90% in screening studies (15, 16). With serial PSA-based screening, the proportion of prostate cancers that are pathologically confined to the prostate is nearly double the proportion in an age-matched group whose cancer was detected in the traditional manner because of abnormal findings on DRE (17).

Both the American Urological Association and the American Cancer Society recommend that healthy men over age 50 have a DRE and PSA annually to detect prostate cancer while it is still curable. Those at high risk for developing prostate cancer, including men with a family history of this disease, should begin regular examination by age 40 (18,19)

Latent Versus Clinically Detected Cancer

When the prostate gland is examined at autopsy in men more than 50 years of age, who have no clinical evidence of cancer, adenocarcinoma is found more than 30 % (20, 21). This remarkable prevalance of histologically recognizable cancer has led some authorities to question the biological significance of prostate cancer detected clinically, especially in screening studies. Most men, it is said will die *with* their cancer rather than *of* it. We examined this issue in detail and calculated that the lifetime risk that a 50 year old man will develop such a histologic malignancy is about 42% (22), yet the lifetime risk that he will delevop a clinically detectable prostate cancer is about 9.5 %, and the risk for him to die of the disease is 2.9 % (23). Thus for every 100 men who harbor cancer in their prostates 23 will be diagnosed with prostate cancer during their lifetime and 7 will die of the disease (22). Clearly we do not want to detect every prostate cancer, but only those that pose a threat to the life or health of the host.

Clinically detected adenocarcinomas of the prostate are similar architecturally and cytologically to those found incidentally at autopsy, but differ in several important pathologic features. They are usually small, well or moderately differentiated, and confined to the prostate (21, 24, 25). Unsuspected prostate cancers found incidentally when the bladder or prostate removed for the treatment of bladder cancer are similar to autopsy cancers (24, 26). We compared the pathologic features of clinically detected prostate cancers with those of prostate cancers in cystoprostatectomy specimens by grouping them into 3 prognostic categories as unimportant, curable, and advanced cancers (Table III) (25). Of 306 cancers detected clinically, only 9% were unimportant, 62% were curable, and 29% were advanced (incurable). In contrast, cystoprostatectomy (or autopsy) cancers were either unimportant (78 %) or curable (22 %) (Figure 1). None were advanced.

Because of the remarkable performance of PSA in screening programs, some authorities have raised the question of the clinical significance of nonpalpable T1c cancers detected because of an elevated PSA. But the vast majority of such cancers have pathologic features (tumor volume and grade) similar to but less extensive than cancers detected by the traditional DRE. These cancers are more likely to be cured with definitive therapy. In our own series and in that published recently from the Johns Hopkins Hospital, only 13-16% of T1c cancers were found to be clinically unimportant (similar to cancers found at autopsy) compared to 2-8% of the palpable, T2 cancers (Table III) (25, 27, 28).

MANAGEMENT OF PROSTATE CANCER

Localized Prostate Cancer (T1-2)

Prostate cancer grows slowly. Traditionally definitive therapy has been reserved for otherwise healthy men with a life expectancy of 10 years or longer. Expectant management was the most common form of initial therapy recommended in the American College of Surgeons survey in 1990 (18). Definitive therapy includes radical prostatectomy (perineal or retropubic), external beam irradiation therapy, or brachytherapy (interstitial radiotherapy) alone or in combination with external beam therapy. Sophisticated computer models of this disease (decision analysis models) have attempted to assess the impact of therapy (29), since there are no satisfactory controlled clinical trials that have established, beyond reasonable doubt, that treatment

Table I- The T categories of the 1992 TNM classification for prostate cancer adopted by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC)

Stage	Definition or Criteria for Inclusion
T1	Clinically inapparent tumor, not palpable, nor visible by imaging
	T1a Tumor an incidental histologic finding; ≤ 5 % of tissue resected
	T1b Tumor an incidental histologic finding; > 5 % of tissue resected
	T1c Tumor identified by needle biopsy (e.g. because of elevated serum PSA)
T2	Confined within the prostate
	T2a Tumor involves half of a lobe or less
	T2b Tumor involves more than half of a lobe but not both lobes
	T2c Tumor involves both lobes
T3	Tumor extends through the prostate capsule
	T3a Unilateral extracapsular extension
	T3b Bilateral extracapsular extension
	T3c Tumor invades seminal vesicle (s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles
	T4a Tumor invades bladder neck and/or external sphincter and/or rectum
	T4b Tumor invades levator muscles and/or is fixed to pelvic wall

From, Ohori, M. et. al., Cancer, 74:104,1994.

Table II- Value of DRE and PSA in early detection of prostate cancer (n = 6,630) (12).

DRE	PSA	Positive Predictive Value	Confined to Prostate Pathologically (p T 1 - 2)
Abnormal		21%	70%
	Elevated	32%	67%
Normal	Elevated	24%	74%
Abnormal	Normal	10%	88%
Abnormal	Elevated	49%	59%

From, Catalona, W. J. et. al, J. Urol., 151: 1283, 1994.

Table III- The distribution of incidental cystoprostatectomy prostate cancers and nonpalpable radical prostatectomy cancers detected by elevated PSA among the three prognostic groups.

		Group %		
Patient Population	**No.**	**Unimportant**	**Curable**	**Advanced**
1. Cystoprostatectomy series	90	78	22	0
2. Radical prostatectomy series Nonpalpable, elevated PSA	55	13	76	11

Modified from, Ohori, M. et. al. J. Urol, 152:1714. 1994.

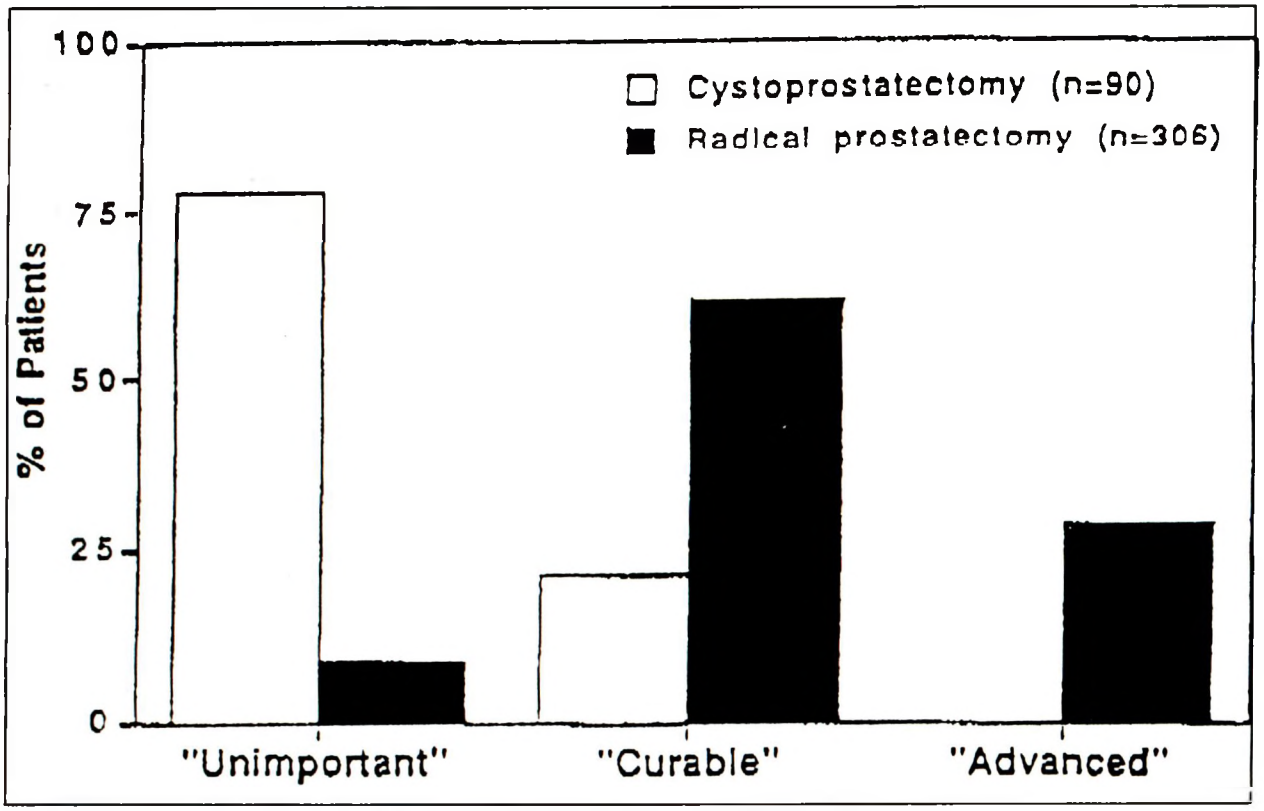

Fig 1. Distribution among the 3 prognostic groups of 90 cancers found incidentally in cystoprostatectomy specimens compared with 306 cancers detected clinically and treated by radical prostatectomy (From, Ohori, M., et. al., J. Urol., 152:1714, 1994).

of early stage disease reduces the mortality rate from the disease. Recently published data, however, strongly support the benefit or definitive therapy for appropriate patients (30).

Watchful Waiting (Expectant Management)

Studies of the natural history of localized prostate cancer managed expectantly show that within 10 years most cancers grow locally but few patients will die of the disease (31, 32). The best information about the natural history of clinically localized prostate cancer managed expectantly comes from a recently published pooled analysis of 828 cases from six nonrandomized studies (33). The outcome (metastasis-free survival, cancer-specific survival) was analyzed by the grade (I, II, III) of the cancer (Table IV). They concluded that watchful waiting may be a reasonable option for men with grade I or II cancer, especially if their life expectancy is 10 years or less. Men with grade III cancer did poorly. Although few men with grade I or II tumors died of their cancer within 10 years, 19% of the patients with grade I, 42 % with grade II and 74% with grade III developed metastases within 10 years. This study provides strong evidence that clinically localized prostate cancer, while slow growing, is no "toothless lion". The disease grows steadily, eventually metastasizes, and ultimately kills the patient if he does not die prematurely from some other cause.

Radical Radiotherapy

Radiotherapy offers several advantages for the treatment of localized prostate cancer, principally because morbidity is minimal when modern, high energy linear accelerators are used (Table V). Reported 10 year overall survival rates after radiotherapy appear to be comparable to other forms of management. However, the major limitation of radiotherapy is its inability to completely eradicate the cancer in a high proportion of cases (34). With the availability of PSA to closely monitor the response to therapy, radiotherapy has come under even closer scrutiny (35). Some 36 - 59% of patients with clinical stage T1-2 prostate cancers will have a rising PSA level within 5 years of treatment (36 - 38). PSA levels rise some 4-5 years before the appearance of clinically overt disease (37).

Cancer - specific survival rates for stages T1-2 have been reported as 86 - 96% at 5 years, 67-86% at 10 years, and 46-67% at 15 years. While survival rates parallel the general population for 5-8 years (39), the high rate of late recurrence, and the greater risks of distant metastases in patients whose local tumor is not controlled (40, 41), substantially reduce the long term survival rates of patients treated with radiotherapy. If the tumor recurs locally after definitive radiotherapy, it is difficult to detect while it is still confined to the prostate and treatment (for example,

Table IV- Cancer specific and metastasis free survival 5 and 10 years after conservative management of localized prostate cancer.

	5 Year %	10 Year %
Cancer specific survival		
Grade I	98	87
Grade II	97	87
Grade III	67	34
Metastasis free survival		
Grade I	93	81
Grade II	84	58
Grade III	51	26

Chodak et. al. N. Engl. J. Med. 330: 242, 1994.

Table V- Pertinent advantages and disadvantages of radical prostatectomy and radical external beam radiotherapy.

Radical Prostatectomy

Advantages

a- High probability of cure (80 % undetectable PSA at 5 yr, 76 % at 10 yr).
b- Treatment completed promptly.
c- Remarkably reduced morbidity in past 10 years.

Disadvantages

a- Necessity for hospitalization (5 days).
b- Mortality 0.1 - 0.3 %; serious morbidity (MI, PE, pneumonia) 2-3 %; risk of transfusion (< 10%).
c- Risk of incontinence (94 % continent at 1 year, 4-5 % stress incontinence, 1-2 % severe incontinence; age related; highly treatable with collagen injections or artificial urinary sphincter).
d- Risk of impotence (10-100 % depending on location and extent of tumor, preoperative quality of erections, skill and experience of surgeon).

Radical Radiotherapy

Advantages

a- No hospitalization.
b- Rare incontinence, unless cancer recurs.
c- Impotence develops slowly (50 % at 7 years).
d- Rare complications with modern linear accelerators (> 15 MeV).

Disadvantages

a- Long treatment course (7 weeks) with daily visits.
b- Proctitis in 25-30 % acutely (usually controlled with medicines).
c- Cancer may not be eradicated locally (20-90 % have positive biopsy of the prostate at 2 years; 50 % have rising PSA level at 5 years) and local recurrence is difficult to treat.

with salvage radical prostatectomy) carries substantial risks (42).

Radical Prostatectomy

While radical prostatectomy carries greater risks of serious complications than radiotherapy (Table V), its major advantage is the high rate of cure that can be obtained, especially if the cancer is confined to the prostate pathologically. The 15 year cancer-specific survival rates range from 86 % to 93% (43-46). PSA levels have proven to be especially sensitive in detecting recurrence of cancer after radical prostatectomy. Because the prostate is completely removed, there should be no detectable PSA in the circulation. PSA levels become detectable 3-6 years before clinical recurrence, so that the proportion of patients with an undetectable PSA level at 5 years reflects closely the proportion that will live out their lives free of recurrent prostate cancer (37, 47).

In a series of 955 patients (mean age 59 years) with T1-2 cancer, treated with radical retropubic prostatectomy at the Johns Hopkins Hospital, 83% remained free of disease at 5 years and 70% at 10 years (48). If the cancer was confined to the prostate pathologically, corresponding figures were 97% and 85%. Five and 10 year cancer-specific survival rates in this series were calculated as 96% and 93%, respectively.

In our own series of 478 consecutive patients from Baylor College of Medicine who had clinically localized (T1-2) prostate adenocarcinoma treated by radical prostatectomy (Figure 2) the overall actuarial progression free probability was 79 ± 5% at 5 years and 76 ± 7% at 10 years. Overall 15% of these patients had seminal vesicle invasion or lymph node metastases (9). The surgical margins were positive in only 16% of the patients in this series. Only 7% of the patients without seminal vesicle invasion or nodal metastases had a positive surgical margin. When the cancer was confined to the prostate pathologically-as it was in half of the patients- 94% were free of progression at 5 years and 90% at 10 years, compared to 61% and 59%, respectively, if the cancer was not confined. Even for patients with poorly differentiated cancers (Gleason grades 7-10), radical prostatectomy can prevent progression of the disease if the cancer is removed while it is still confined to the prostate (49).

Figure 3 shows the pattern of recurrence of radical prostatectomy for each clinical stage. While the follow-up is short, patients with T1c cancers seem to have a very favorable prognosis. We have also operated upon a small group of patients with clinical stage T3 cancer (Figure 3). These patients were substantially more likely to recur within 5 years, even if the pelvic lymph nodes were negative (9). Thus the

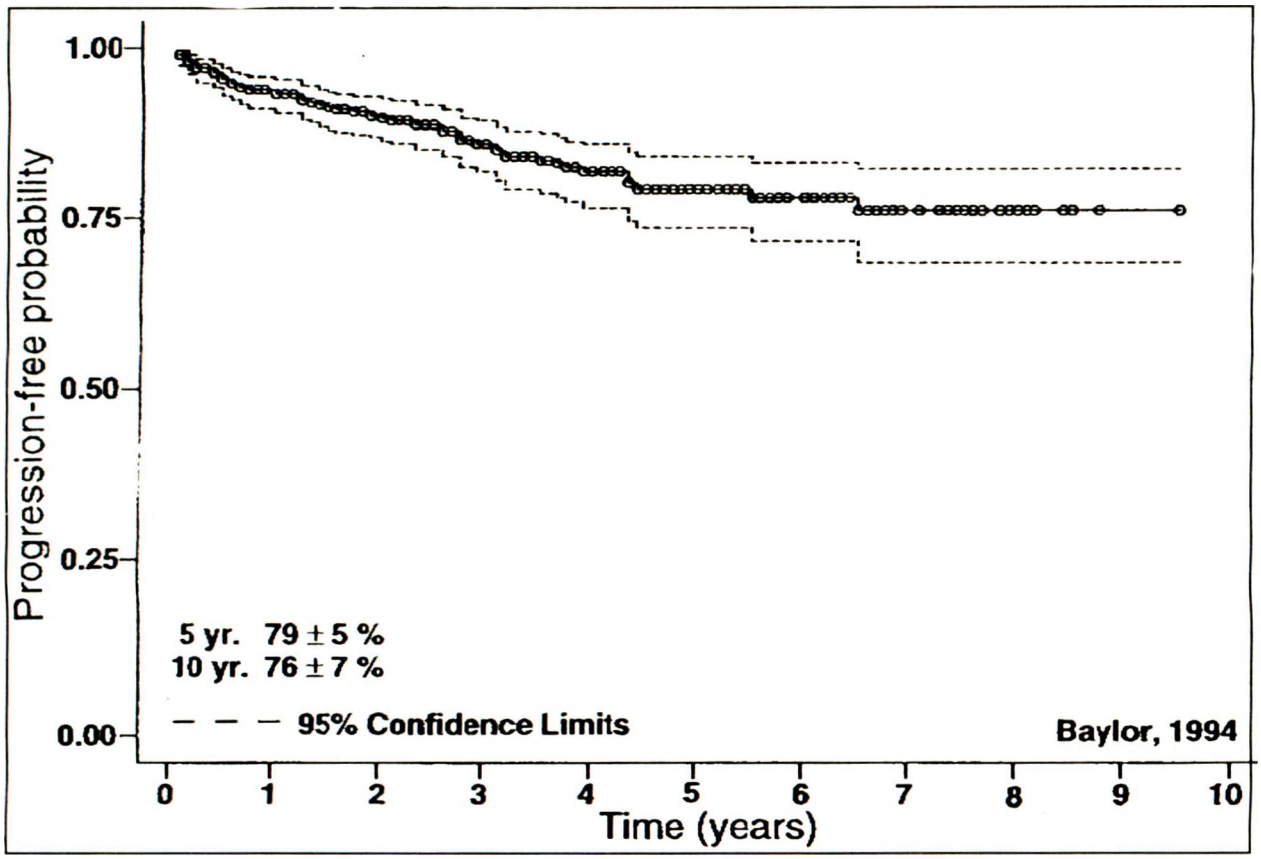

Fig 2. The actuarial probability of freedom from progression for the whole population of 478 patients with clinical T1-2 NO Mo prostate cancer treated by radical prostatectomy. Dotted lines indicate 95 % confidence intervals (Baylor, 1994).

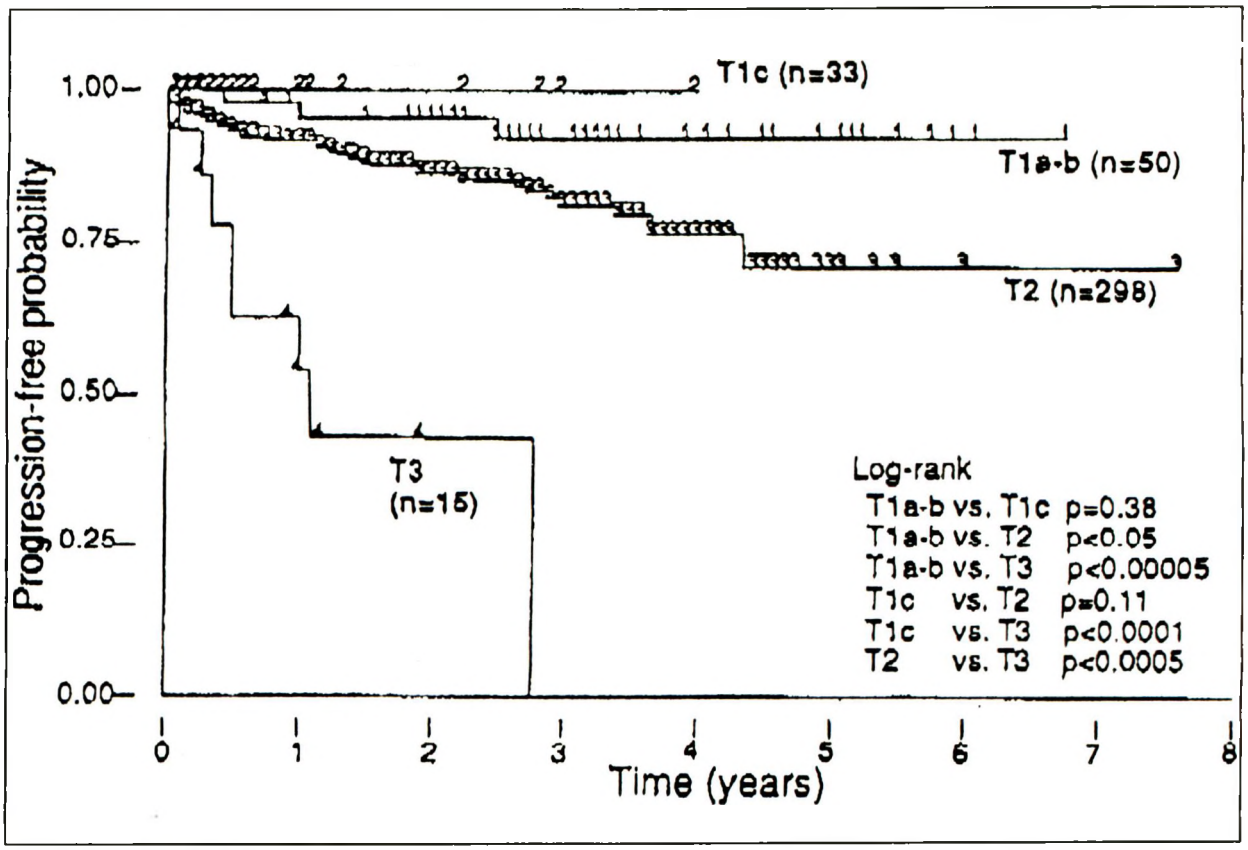

Fig 3. Progression free probabilities of 396 patients after radical prostatectomy by clinical stage (From, Ohori, M., et. al, Cancer, 74:104, 1994).

distinction between T1-2 and T3 cancers can be made with reasonable accuracy using DRE and/or TRUS. The poor outcome for clinical stage T3 cancers also means that delaying the diagnosis until the cancer is locally advanced may reduce or eliminate the chances of cure.

Comparing Treatment Options

Each of the 3 options for the treatment of localized prostate cancer have advantages and disadvantages. For watchful waiting the major disadvantage is the risk of missing the opportunity to cure the cancer, which could then progress and become locally extensive or metastatic. An uncontrolled cancer will eventually lead to a long, complicated and painful death. The major advantage of watchful waiting is that the patient avoids (or postpones) the morbidity (and possible mortality) of definitive therapy. This strategy (watchful waiting) assumes that the patient will die of some other cause before he becomes ill from the cancer (13). The success of this strategy depends on our ability to assess accurately the risk posed by the patient's cancer and the life expectancy of the patient. Unfortunately neither of these parameters can be judged with great accuracy today, although several investigators have made careful estimates based on the best information published in the literature (50).

As Table VI shows, poorly differentiated cancers were more common in the radical prostatectomy series than in the watchful waiting series (16.6% vs. 7.2%), yet the rate of metastatic progression was substantially less in the radical prostatectomy series (12.6 % vs. 25%). Furthermore, death from prostate cancer was also lower (7% vs 16.8%). The 10 year cancer-specific survival rates (weighted means) for each treatment option was calculated as 74% for radiotherapy, 84% for watchful waiting and 93% for radical prostatectomy (50). Disregarding possible selection biases and differences in the follow-up, these authors concluded that at 10 years there appears to be a positive treatment effect for radical prostatectomy, and at 15 years there may be an even greater advantage.

Decision Analysis. The outcome after the various treatment options for prostate cancer have been modelled with a computer program known as decision analysis. The Dartmouth Prostate Patient Outcome Research Team (PORT) of the Agency for Health Care Policy published a detailed analysis of the benefits of treatment, and the well documented rate of death from cancer for patients with distant metastases (51). The benefits of therapy in reducing the rate of developing distant metastases was offset somewhat by the complications of the treatment, and

Table VI- A comparison of three management options utilized in the treatment of patients with clinical stage T1-T2 prostate cancer.

	Watchful Waiting	Radiation Therapy	Radical Prostatectomy
Age; mean (years)	71.3	65.9	61.8
Poorly differentiated tumor	7.2 %	14.0 %	16.6 %
Metastatic progression (10 year)	25.0 %	29.0 %	12.6 %
(95 % CI)	(20 - 31)	(25 - 33)	(10.3 - 15.3)
Prostate cancer death (10 year)	16.8 %	38.2 %	7.0 %
(95 % CI)	(13 - 21.4)	(23.3 - 59)	(5.4 - 8.9)

Modified from Adolfsson et. al. Cancer. 72: 310, 1993.

the results were reported in "quality - adjusted life years". For example, the risk of urinary incontinence after radical prostatectomy was estimated as 6%, and a year lived as an incontinent man was taken as worth 0.85 years as a continent man. The study concluded that treatment offered only marginal benefit, and in some cases was even harmful, especially in grade I cancers and in older (>65) men (29).

This study has attracted considerable criticsm (30, 46, 52). The most important determinant of the benefits of therapy in the model is the rate at which a localized prostate cancer will progress to metastases in the absence of active therapy. Despite their detailed literature review, the PORT investigators were able to provide only broad estimates of this rate. Subsequently Chodak and colleagues published a pooled analysis of a large series of men managed expectantly (33). They reported a metastatic rate that was 3-8 times *greater* than in the port analysis. When we inserted these new rates into the original PORT decision-analysis model, leaving all other factors unchanged, the benefits of treatment appeared considerably greater. A 65 years old man with a grade II cancer gained 2.41 quality-adjusted life years (compared to 0.33 in the PORT analysis) and was 50% more likely to be alive 15 years later if he were treated with radical prostatectomy than with watchful waiting (Figure 4) (30).

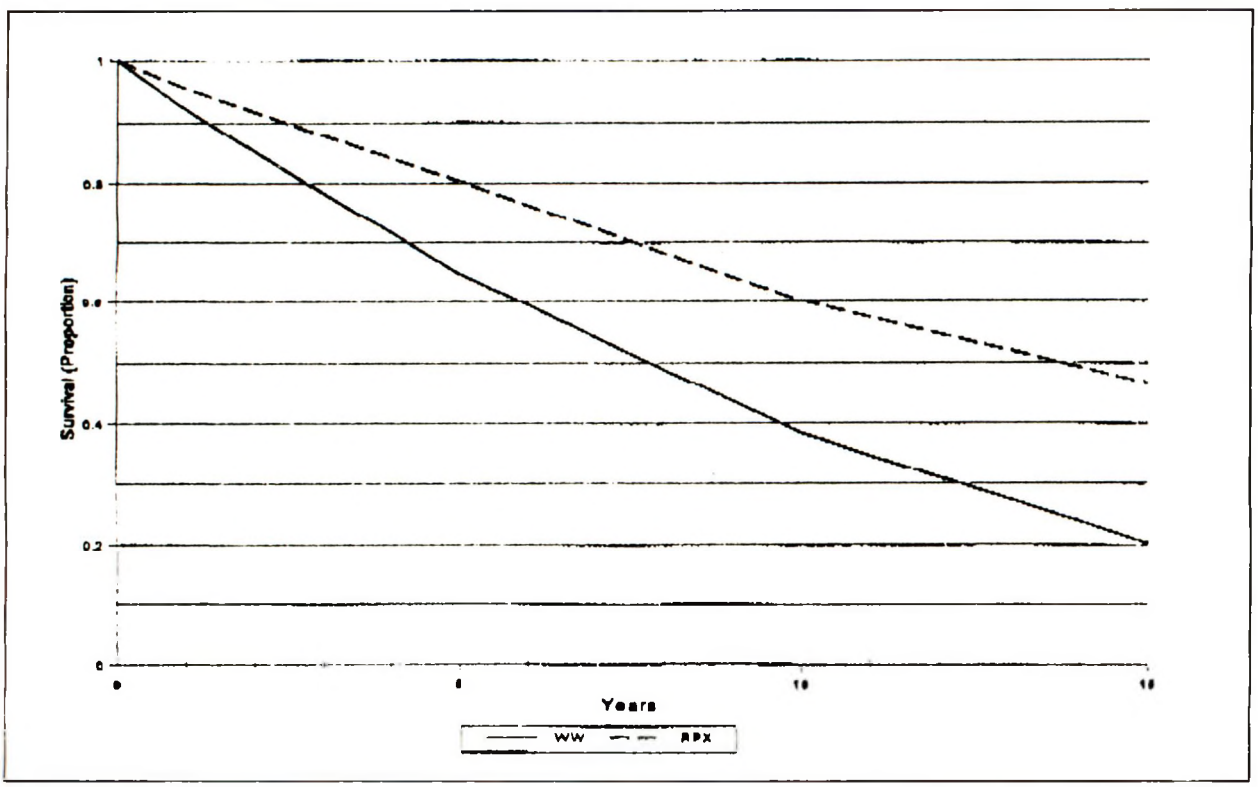

Fig 4. Metastasis free survival curves for grade 2 patients using Chodak metaanalysis rates of metastasis (From, Beck, J. B. et. al. J. Urol., 152:1894, 1994).

The PORT decision-analysis model is sound and could prove to be a useful tool to analyze the risks and benefits of therapy in this complex disease, but the model is only as good as the quality of information available. A model is just a model. For definitive proof of the benefits of early treatment of clinically localized prostate cancer, long-term randomized controlled prospective trials are essential (53).

Age Issue. In choosing therapy for an individual patient with a clinically localized prostate cancer, the age and general health of the patients remain critically important factors because of the well established protracted course of the disease (50, 54). The beneficial effect of treatment is minimal at 5 years and only becomes substantial 8-10 years after therapy (Figure 4) (30). In 1989 males at age 70 on the average have a life expectancy of 12.1 years and males at age 75 less than 10 years (Table VII). Thus, the potential benefits of treatment decrease rapidly as men grow old (13, 54).

Locally Advanced (T3) Cancer

The results of definitive treatment, whether radical prostatectomy or radiotherapy, for clinical stage T3 prostate cancer are poor because many already have occult metastases. When a cancer extends palpably beyond the prostate into the lateral sulci or seminal vesicles, lymph node metastases will be found in 30-50% (55). Even in carefully selected patients with small T3 cancers, seminal vesicle invasion will be present in 67% and positive lymph nodes 20% (9). Technically, the prostate can be removed with no greater morbidity for T3 cancers than for T1-2, with the exception of higher risk of impotence. While there may be some palliative benefit of removing the primary tumor, the chances for long-term cure are poor. Despite the local therapy employed, the survival rates for these patients is determined by the final common treatment, hormonal therapy, and will be about 25-50% less than age-matched men in the general population (56). The 15 year survival rates with radiotherapy for stage T3 tumors are about half of the normal expected survival, and nearly 90% of patients have rising PSA levels within 10 years (46).

Adjuvant hormonal therapy may improve the results of radical prostatectomy or radiotherapy for stage T3 disease, but equivalent results might be achieved with hormonal therapy alone (57).

We recommend hormonal therapy for older men and those with serious co-morbid conditions. Most T3 cancers are treated with definitive external beam irradiation therapy, often preceeded by 2-4 months of (temporary) androgen ablation. Young healthy men are sometime treated with radical prostatectomy, to control the primary tumor and to provide definitive staging. In about 20% of men with a clinical stage T3 cancer and with negative pelvic lymph nodes, the cancer may have been overstaged and can be confined to the prostate pathologically (58).

Cryotherapy have recently been introduced to ablate the local lesion while avoiding some of the complications of radical surgery, but there is not sufficient experience to evaluate the efficacy or safety of this new modality which should be considered experimental at this time (59). Cryotherapy may prove most useful to treat local recurrence after radical prostatectomy or radiotherapy. Salvage radical prostatectomy has been used successfully to eradicate the local tumor when it recurs after radiotherapy. The complication rate is considerably higher than in non-irradiated patients. In our series about 30% of patients have no evidence of recurrent cancer 8 years after salvage prostatectomy (undetectable serum PSA level) (42). Most patients with recurrent cancer are treated with hormonal therapy, which provides excellent local control and delays metastases with little morbidity (46, 60).

Metastatic Prostate Cancer (N+, M+)

The prospects of cure with any treatment in patients with lymph node metastases are less than 15%. There is no evidence that radiotherapy benefits men with nodal metastases (56, 61, 62). In a retrospective study comparing radical surgery, radiotherapy and expectant management those treated with prostatectomy fared best, but they also had less advanced disease (63).

Table VII- Life expectancy of males in the U.S.A. by age in 5 year increments.

AGE	LIFE EXPECTANCY (Years)
50	26.4
55	22.3
60	18.6
65	15.2
70	12.1
75	9.4
80	7.1
85	5.3

From Vital Statistics of the United States, 1989.

Hormonal therapy is the mainstay of treatment for men with disseminated prostate cancer and requires the removal of circulating androgens which act to stimulate the growth of prostate cancer cells (64). About 85% of men with metastatic prostate cancer respond to androgen ablation, although objective partial responses occur in only 20% and complete responses are rare. There is no definitive evidence that early hormonal therapy provides any survival advantage over therapy delayed until the patients become symptomatic, though most physicians prefer to begin therapy when there is evidence of disease progression in order to avert symptoms. Androgen ablation is usually achieved with medical (LHRH agonists) or surgical castration, which appear to be equivalent (46).

The value of combination hormonal therapy (medical or surgical castration plus antiandrogen) has been evaluated extensively (65). The large intergroup study was designed to compare leuprolide + flutamide with leuprolide + placebo in a prospective randomized controlled trial of 605 patients. Both median progression free survival (16.5 mo. vs. 13.9 mo.), and overall survival (35.6 mo. vs. 28.3 mo.) were greater in the group that received leuprolide + flutamide. A similar benefit to "maximal androgen blockade" was also reported by EORTC (66).

In hormone refractory patients, the results of secondary hormonal manipulations have been poor. Because these cancers are still responsive to androgens, lifelong androgen suppression should be maintained. Objective tumor responses have been reported following discontinuation of flutamide in patients with hormone refractory disease (so called flutamide dependent subgroup of patients) (67). Cytotoxic chemotherapy has been largely ineffective in treating prostate cancer. The combination of estramustine and vinblastine is the most promising current regimen. Trials combining these two agents in hormone refractory patients showed a 50% response rate using PSA as a criterion (68). Suramin achived objective responses in about a third of the hormone refractory patients, and several of them have responded for more than one year (69). Ketoconazole, primarily an antifungal agent, impairs the production of androgens by inhibiting corticosteroid synthesis. Castrate levels of antiandrogens rapidly occur within 4 to 8 hours of a 400 mg oral dose. It is especially helpful when there is a need for rapid androgen response, such as occurs in impending spinal cord compression (70).

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