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Local Progression among Men with Conservatively Treated Localized Prostate Cancer: Results from the Transatlantic Prostate Group

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Abstract

Objectives—Men with clinically detected localized prostate cancer treated without curative intent are at risk of complications from local tumor growth. We investigated rates of local progression and need for local therapy among such men.

Methods—Men diagnosed with prostate cancer during 1990–1996 were identified from cancer registries throughout the United Kingdom. Inclusion criteria were age ≤ 76 yr at diagnosis, PSA level ≤ 100 ng/ml, and, within 6 mo after diagnosis, no radiation therapy, radical prostatectomy, evidence of metastatic disease, or death. Local progression was defined as increase in clinical stage from T1/2 to T3/T4 disease, T3 to T4 disease, and/or need for transurethral resection of the prostate (TURP) to relieve symptoms > 6 mo after cancer diagnosis.

Results—The study included 2333 men with median follow-up of 85 mo (range: 6–174). Diagnosis was by TURP in 1255 men (54%), needle biopsy in 1039 (45%), and unspecified in 39 (2%). Only 29% were treated with hormonal therapy within 6 mo of diagnosis. Local progression occurred in 335 men, including 212 undergoing TURP. Factors most predictive of local progression on multivariable analysis were PSA at diagnosis and Gleason score of the diagnostic tissue (detrimental), and early hormonal therapy (protective). We present a nomogram that predicts the likelihood of local progression within 120 mo after diagnosis.

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Conflicts of interest

None of the authors has any disclosures that would be a potential conflict of interest for this manuscript.

Conclusions—Men with clinically detected localized prostate cancer managed without curative intent have an approximately 15% risk for local progression within 10 yr of diagnosis. Among those with progression, the need for treatment is common, even among men diagnosed by TURP. When counseling men who are candidates for management without curative intent, the likelihood of symptoms from local progression must be considered.

Keywords

Cancer progression; Conservative management; Nomograms; Prostate cancer; Retrospective study; Risk factors; Transurethral resection of the prostate; Treatment outcome; Watchful waiting

1. Introduction

The clinical course of newly diagnosed prostate cancer is difficult to predict because of the lack of firm data about its natural history. While prostate cancer is unequivocally lethal in some patients, most die with, rather than of, their cancer. According to autopsy data, histologically apparent cancer is found in prostates from approximately 42% of men over 50 yr of age who die of other causes [1]. This frequency of histological cancer is about 4-fold higher than the lifetime risk for American men to be diagnosed with prostate cancer (about 11%), while the risk of dying from the disease is only 3.6% [1–3]. Indeed, results from the recently completed Prostate Cancer Prevention Trial suggest that histological prostate cancer is present in 25% of men with a normal digital rectal examination and a serum prostate-specific antigen (PSA) level below 4 ng/ml [4]. While some of these cancers may threaten the health of the patient, many men in this group, particularly those with low-risk cancers, will live out their lives without suffering any sequelae from prostate cancer.

The far greater prevalence of histological than clinically threatening cancers, along with the fact that prostate cancer is often diagnosed in older men with comorbidities, has been cited to support a conservative, nonintervention-based approach to this disease [5–7]. Many clinicians recommend conservative management with observation until disease progression, followed by hormonal therapy. Miller et al [8] identified 24,405 men with lower-risk prostate cancers using data from 13 Surveillance, Epidemiology, and End Results registries. Within this lower-risk group, the likelihood of curative therapy versus expectant management varied significantly among subgroups defined by age and tumor grade. Overall, 13,537 of these men (55%) underwent initial curative therapy, 2564 (10%) with radical prostatectomy and 10,973 (45%) with radiation therapy. If one assumes that initial expectant management is appropriate for all lower-risk cancers, then all 55% were potentially overtreated.

Men with prostate cancer are at risk not only of metastases and death, but also morbidity because of local cancer progression. Local progression can result in obstruction, hematuria, pain, and the need for additional local therapy. Aus et al [9] examined prostate cancer patients who were treated without curative intent to determine their need for hospital care and palliative treatment. Of 514 men who died from their disease, 41% required one or more transurethral prostatic resections, and 17% required an upper urinary tract procedure to alleviate symptoms from local progression. Similarly, Brasso et al [10] examined 4790 men with clinically localized prostate cancer identified from the Danish Cancer Registry. Nearly 90% of patients underwent transurethral resection of the prostate (TURP) within a year of diagnosis and 30% required repeat resection. One third of the patients underwent orchiectomy to treat disease progression, with a median time from diagnosis to orchiectomy of 23 mo. Lastly, Steineck et al [11] studied men with localized prostate cancer who participated in a randomized comparison between radical prostatectomy and watchful waiting. Men in the watchful waiting group completed a self-assessment questionnaire at a median of 48 mo after diagnosis. Despite this

relatively short follow-up, 44% reported obstructive voiding and 45% reported low or moderate quality of life.

These studies provide strong evidence that men with prostate cancer can experience significant symptoms from and require treatment for local progression. While watchful waiting may be a reasonable option for some men, evaluation of this approach should not be based solely on rates of metastases and death from prostate cancer. This study summarizes outcomes from a well-characterized group of men with clinically localized prostate cancer managed conservatively. The risk of local progression and factors associated with progression are reported.

2. Methods

2.1. Study population and data collection

This was a population-based study in which databases from six cancer registries in England, Wales, and Scotland were queried to identify men histologically diagnosed with prostate cancer between January 1990 and December 1996, and aged 30–76 yr (inclusive) at date of diagnosis. After obtaining appropriate hospital approvals to comply with the Data Protection Act of 1994, tumor registrars and medical students conducted on-site medical record reviews at each of 51 hospital trusts.

Men were included only if they had clinically localized prostate cancer diagnosed by TURP or needle biopsy, a baseline serum PSA level available within 6 mo of their diagnosis that was ≤ 100 ng/ml, no radical prostatectomy or radiation therapy within 6 mo after diagnosis, no evidence of metastatic disease (by bone scan, radiograph, computed tomography [CT] scan, magnetic resonance imaging, bone biopsy, lymph node biopsy, or pelvic lymph node dissection) at the time of diagnosis, no other clinical sign of metastasis within 6 mo of diagnosis (including pathologic fracture, soft tissue metastasis, spinal compression, or bone pain), and were alive for at least 6 mo after their diagnosis. Patients with an unknown diagnostic procedure ($N = 39$) were omitted from modeling. Clinical staging was centrally reviewed and, when missing, was assigned by a urologist on the basis of documentation of the digital rectal examination. Cases that could not be staged were designated as clinical stage Tx and omitted from modeling.

Original histology materials from the diagnostic procedure (prostate biopsy or TURP) were requested, collected, and centrally reviewed by referee pathologists to confirm the diagnosis and to determine grade with the use of the Gleason grading system. Only slides were requested for patients diagnosed by needle biopsy, and only blocks were requested for patients diagnosed by TURP. The requested histology materials for approximately 12% of cases were missing or unidentifiable in hospital pathology databases. Patients with missing histological material were excluded from the statistical analyses.

Early hormonal therapy was defined as either orchiectomy or luteinizing hormone-regulatory hormone agonist therapy initiated within 6 mo of the diagnosis of prostate cancer. Local progression was defined as an increase in clinical stage from T1/2 to T3/T4 disease and/or the need for TURP >6 mo after the diagnosis of cancer to relieve local symptoms. Our review did not include an assessment of the need for upper urinary tract diversion (ureteral stent or nephrostomy tube). Outcomes were determined through medical records and cancer registry data.

2.2. Statistics

The rate of local progression was estimated by means of the cumulative incidence method. Cox proportional hazards regression was used for multivariable analysis. Continuous variables

were initially fitted by using restricted cubic splines to relax linearity assumptions. No variable selection was performed. This Cox model was the basis for a nomogram.

Nomogram validation comprised two activities. First, discrimination was quantified with the concordance index, which is similar to the area under the receiver operating characteristic curve, but appropriate for censored data. The concordance index provided the probability that, in a randomly selected pair of patients in which one patient experienced local progression before the other, the patient who progressed first had the worse predicted outcome from the nomogram. We used bootstrapping to obtain a relatively unbiased estimate of the concordance index.

Second, calibration was assessed. Assessment was done by grouping patients with respect to their nomogram-predicted probabilities and then comparing the mean of the group with the observed Kaplan-Meier estimate of local progression. Again, bootstrap correction was used for this activity. All analyses were performed with S-Plus 2000 Professional software (Statistical Sciences, Seattle, WA, USA) with the Design and Hmisc libraries added.

3. Results

The men included in this study have been described in detail elsewhere [12]. Briefly, 2333 men had clinically localized prostate cancer not treated definitively within 6 mo of diagnosis and were eligible for evaluation. Diagnosis was by TURP in 1255 men (54%) and needle biopsy in 1039 (45%) men, and was unspecified in 39 (1%) men. More than half of the men (54%) had a serum PSA level ≤ 10 ng/ml at the time of diagnosis. Men with a serum PSA level ≥ 50 ng/ml accounted for 13% of the study population. Of the 2333 men in our study population, 1347 (58%) had a bone and/or CT scan (1307 bone scans, 201 CT scans, 161 both), either before diagnosis or within 6 mo after their diagnosis date. Those having a bone scan and/or CT scan had to have a negative study to be included. Because screening for prostate cancer was not commonly practiced in the United Kingdom during the time frame of this study, only 2% were assigned clinical stage T1c. Most men had well to moderately differentiated prostate cancer. The majority of men were managed expectantly, with only 29% treated with hormonal therapy within 6 mo of their diagnosis. Most men (79%) were diagnosed after age 65 yr. Median follow-up was 85 mo (range: 6–174). After 10-yr of follow-up, 24% of patients had died from prostate cancer and 31% had died from other causes. Patients' clinical characteristics are summarized in Table 1.

Local progression was defined as an increase in clinical stage from T1/2 to T3/T4 disease, T3 to T4 disease, and/or the need for TURP to relieve local symptoms >6 mo after the diagnosis of cancer. Local progression was found in 335 men. Despite 54% of men having been diagnosed with prostate cancer by TURP, 212 men required a TURP to control local symptoms during follow-up. The likelihood of local progression from the time of diagnosis is shown in Fig. 1.

In multivariable analysis, the factors associated with local progression were the serum PSA at the time of diagnosis, the Gleason score of the diagnostic tissue (biopsy or TURP), and the timing of hormonal therapy (Table 2). Early hormonal therapy (initiated within 6 mo of diagnosis) was protective ($p < 0.001$; hazard ratio = 0.41), while increasing serum PSA level at diagnosis and increasing Gleason score were detrimental.

A nomogram predicting the freedom from local progression for 120 mo appears in Fig. 2. Upon bootstrapping, the nomogram was found to have a concordance index of 0.672. The calibration of the nomogram appears in Fig. 3. In general, the nomogram is reasonably well calibrated.

4. Discussion

Most studies addressing expectant management of prostate cancer have primarily focused on progression to metastatic disease and prostate cancer death [5,6,13–16]. These studies suggest that selected men with prostate cancer managed expectantly will have a very low risk of dying from prostate cancer. These studies do not, however, address issues of local cancer progression, its impact on patient quality of life, and the need for local therapy.

The impact of local progression on a patient's quality of life can be significant. For example, in the Scandinavian Prostate Cancer Group's randomized study comparing radical prostatectomy to watchful waiting [11], although erectile dysfunction and incontinence were higher in men treated with radical prostatectomy, men on watchful waiting experienced significantly more obstructive voiding complaints and bowel problems. As a result, the groups had similar levels of treatment-related distress. In a recent follow-up to this study, local progression in the watchful waiting group, defined as progression to clinical stage T3/4 cancer or obstructive symptoms requiring intervention, occurred in 27% at 5 yr and increased to 44% at 10 yr [17].

Our retrospective study found more modest rates of local progression and need for treatment than those reported in the Scandinavian study and several other studies [9,10]. During the time frame of this study, approximately 15% of men developed symptomatic local progression requiring a change in treatment. TURP during follow-up was required in 9%, despite the fact that 54% of men had a TURP to make their diagnosis of prostate cancer. This rate of local progression over a median of 7 yr is approximately half that seen in over 5 yr in the Scandinavian study (15% vs. 27%). This finding may be related to the fact that the diagnosis was made by TURP in only 14% of patients in the Scandinavian study compared with 54% of our patient population. In addition, 29% of patients in our study underwent early hormonal therapy (<6 mo from diagnosis), while this practice was uncommon in the watchful waiting arm of the trial from the Scandinavian Prostate Cancer Group. Our analysis certainly underestimated the impact of local cancer progression because our population included a majority of men diagnosed by TURP and it did not include patients' need for ureteral stenting or nephrostomy tube placement.

The choice of treatment for early-stage prostate cancer is complex, requiring a consideration of the risk posed by a given cancer, the likelihood that treatment will improve outcomes, and the impact of treating (or not treating) on quality of life. An additional consideration is that, while not curative, TURP as a treatment is less morbid and carries fewer side effects than either radical prostatectomy or radiation therapy delivered for curative intent. The nomogram developed for predicting local progression (Fig. 2) can be used when counseling men about the risks and benefits of watchful waiting.

Results from our multivariable analysis suggest that the serum PSA level at diagnosis, the Gleason sum in the diagnostic tissue specimen, and the use of early hormonal therapy influence the likelihood of local progression. Collectively, these findings suggest that there is a subgroup of men with prostate cancer in whom conservative management might be the preferred treatment option, especially if age or comorbidities limit life expectancy to 10 yr or less. Men with more worrisome clinical features, however, are at risk for disease progression and death from prostate cancer. In Chodak et al's series [7], 66% of men with poorly differentiated cancer were dead of prostate cancer by 10 yr. Albertsen et al [5,6] reported the results of a population-based study in Connecticut of 451 men between the ages of 65 and 75 yr with clinically localized prostate cancer treated conservatively. The cancer-specific mortality rate at 10 yr was 9% for well-differentiated cancers (Gleason sum 2–4), 24% for moderately differentiated cancers (Gleason 5–7), and 46% for poorly differentiated cancers. Compared with age-matched

controls, men with localized prostate cancer (mean age: 70.9 yr) lost an estimated 3.8–5.2 yr of life. While the authors emphasized that men with well-differentiated tumors survived as long as age-matched controls, this favorable group included only 9% of the patient population. The remaining 91% experienced markedly shortened survival with conservative treatment. Our results also demonstrate that the histological features at the time of diagnosis influence local cancer progression. Men with Gleason score ≥ 7 were at significant risk for cancer progression.

In addition to Gleason scoring, the serum PSA level at diagnosis and the timing of hormonal therapy were also predictors of local progression. Interestingly, an intermediate level of PSA put the patient at highest risk for local progression. Note that the nomogram indicates maximal risk for a PSA around 30 ng/ml, while a PSA level of 90 ng/ml carries approximately the same risk as a PSA of 4 ng/ml. This is probably because patients with a low PSA level tend not to progress rapidly, and patients with a very high PSA likely progress to distant disease and death before experiencing local progression.

Men receiving early hormonal therapy were far less likely to develop local progression than men treated later in the course of their disease. This finding supports prior studies that demonstrate an advantage associated with hormonal therapy given early, as opposed to being delayed until symptomatic progression, for men with locally advanced or early metastatic prostate cancer [18,19]. In one of these studies, conducted by the Medical Research Council, progression from locally advanced but nonmetastatic (M0) prostate cancer to metastatic disease (M1) was significantly more rapid in men receiving deferred hormonal therapy compared with men receiving early therapy [18]. Similar to our results, local progression was also more common, with twice as many men in the deferred treatment group undergoing a TURP. In addition, more men developed ureteric obstruction if hormonal therapy was delayed. However, hormonal therapy certainly carries its own side effects including hot flashes, muscle wasting, osteoporosis, and perhaps premature cardiac death. Certainly not all men managed with watchful waiting should be treated with immediate or even early hormonal therapy. Only those at risk for progression should be considered for such therapy.

There are several potential limitations to our study. The first is our definition of localized prostate cancer, which includes men with a PSA ≤ 100 ng/ml. While this is a fairly broad PSA selection criterion and certainly some of our patients had micrometastatic disease at diagnosis, none had radiographic evidence of metastasis at diagnosis and/or within 6 mo of diagnosis. Of the 2333 men in our study population, 1347 (58%) had a bone and/or CT scan (1307 bone scans, 201 CT scans, 161 both), either before diagnosis or within 6 mo after their diagnosis date. Those having a bone scan and/or CT scan had to have a negative study to be included. Only 13% had a PSA level ≥ 50 ng/ml and more than half had a PSA level < 10 ng/ml. In addition, our nomogram accounts for these baseline differences in serum PSA levels and is generally applicable to men with a clinical diagnosis of prostate cancer. The second potential limitation is the use of TURP as a definition of progression. TURP can be for either BPH or cancer progression. While beyond the scope of this manuscript, men undergoing a TURP in our series had extensive cancer in their pathology specimens. None of the men undergoing TURP for progression had minimal cancer in their resected tissues. There are no published or readily searchable data to know the likelihood that, during the time frame of this study, men of a similar age would require a TURP within 7 yr in the United Kingdom. However, if we make some assumptions the likelihood can be roughly estimated. We must assume that a man having a TURP would first have tried medical therapy with either an alpha-blocker and/or a 5-alpha-reductase inhibitor. If this assumption is acceptable, then data regarding the incidence of TURP in the treatment arm of medical therapies for benign prostatic hyperplasia (BPH) can be used. In the large phase 3 study of finasteride, the TURP rate in the treatment arm within 4 yr was 5% [20]. Similar findings were published in the Medical Therapy of Prostatic Symptoms study [21]. While not discussed in these manuscripts, the incidence of prostate cancer in these men

was essentially zero. Our patient population was not a group of men with BPH; they were treated because of their clinical findings suspicious for prostate cancer. Hence, if a 5% TURP rate occurs in those men at highest risk for requiring a TURP for BPH, the rate in our series far exceeds that figure and is unlikely to reflect BPH in our patient population.

By combining a variety of clinical and histological variables into a predictive model (nomogram), the individual patient can be counseled regarding his risk of local progression if his clinically diagnosed prostate cancer is managed without curative intent.

5. Conclusions

Men with clinically diagnosed localized prostate cancer managed without curative intent have at least a 15% risk of developing local progression within 10 yr of diagnosis. While many patients may not develop symptoms from metastatic disease or die from prostate cancer, local progression is common, even among men who were diagnosed by TURP. Our data suggest that earlier initiation of androgen-deprivation therapy is protective. When counseling men with clinically diagnosed localized prostate cancer about treatment options, the likelihood of symptoms from local progression must be considered by those men who are candidates for management without curative intent.

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Fig. 1.
Cumulative probability of local progression over time. Numbers at top indicate patients at risk.

Fig. 2.
Nomogram for probability of remaining free from local progression for 120 mo.

Fig. 3. Calibration of local progression nomogram. Horizontal axis is the nomogram prediction of probability of freedom from local progression. Vertical axis is actual freedom from local progression estimated at 120 mo with the Kaplan-Meier method. Vertical bars represent 95% confidence intervals.

Table 1
Descriptive statistics for the 2333 men in this study

Variable	N	%
Clinical stage		
T1	506	22
T2	612	26
T3	269	12
Not available, Tx	946	41
Gleason score		
≤ 5	61	3
6	681	29
7	500	21
8	250	11
9 or 10	164	7
Not available	677	29
Method of diagnosis		
Needle biopsy	1039	45
TURP	1255	54
Unspecified	39	2
Year of diagnosis		
1990	54	2
1991	109	5
1992	225	10
1993	346	15
1994	471	20
1995	551	24
1996	577	25
Serum PSA (ng/ml)		
Minimum	0.0	
First quartile	4.5	
Median	12.0	
Mean	20.9	
Third quartile	29.0	
Maximum	100.0	
Age at diagnosis (yr)		
Minimum	44.3	
First quartile	66.1	
Median	70.1	
Mean	69.0	
Third quartile	73.1	
Maximum	76.0	

PSA, prostate-specific antigen; TURP, transurethral resection of the prostate.

Table 2
Multivariable analysis of risk factors for local cancer progression

Variable	<i>p</i> value	Hazard ratio (95% CI)
Clinical stage	0.23	
T2 vs. T1		1.33 (0.90–1.97)
T3 vs. T1		1.49 (0.93–2.37)
Gleason grade	<0.001	
3 + 4 vs. <4 + <4		1.23 (0.78–1.94)
4 + 3 vs. <4 + <4		1.53 (0.90–2.59)
4 + 4 vs. <4 + <4		2.37 (1.49–3.77)
> 4 or >4 vs. <4 + <4		4.38 (2.73–7.03)
Serum PSA level	0.003	
10 vs. 4		1.31 (1.12–1.53)
20 vs. 4		0.56 (0.40–0.78)
Age at diagnosis (60 vs. 50 yr)	0.85	0.97 (0.71–1.33)
Method of diagnosis (needle vs. TURP)	0.697	1.06 (0.78–1.46)
Early hormones	<0.001	0.41 (0.28–0.60)

95% CI, 95% confidence interval; PSA, prostate-specific antigen; TURP, transurethral resection of the prostate.