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Low Risk Prostate Cancer in Men under Age 65: The Case for Definitive Treatment

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Abstract

The management of low risk prostate cancer, defined as Gleason's sum ≤ 6 , PSA <10 ng/ml, and clinical stage T1c to T2a, remains controversial. There is substantiating evidence to suggest that a subset of early stage, low risk cancers can cause significant patient morbidity and death in the long term. Studies have shown that the natural history of untreated prostate cancer is to progress, particularly after 15 years of followup. The majority of men seeking definitive surgical treatment in contemporary series fall within 55 to 65 years of age and are expected to enjoy an overall life expectancy ranging from about 15 to 30 years, placing these men at long-term risk for disease progression and prostate cancer-specific death if managed expectantly.

During the past two decades, refinements in surgical technique and in the delivery of external beam radiation have resulted in excellent long-term cancer control and favorable quality of life outcomes following treatment. Active surveillance with selective delayed intervention assumes that an individual's cancer will not progress outside the window of curability during the surveillance period, that markers for disease progression are reliable, and that patients are compliant. Until we understand better the long-term natural history of untreated prostate cancer, have more reliable and accurate markers to detect disease progression with certainty, and can risk stratify more precisely the subgroup of men with low risk cancers who will eventually succumb to their disease, early definitive therapy seems prudent.

Keywords

Prostate; Prostate cancer; Curative intervention

Introduction

Prostate cancer is the most common noncutaneous malignancy and the third leading cause of cancer death in men, accounting for an estimated 234,460 new cases and 27,350 deaths annually in the United States (1). Despite these staggering statistics, the optimal management of clinically localized prostate cancer remains controversial. This treatment dilemma stems from the fact that prostate cancer represents a heterogeneous disease that exhibits significant variation in behavior and an uncertain natural history.

Data from autopsy studies have demonstrated the existence of prostate cancer in almost a third of men aged 50 years or older who die of other causes (2). However, the lifetime risk of developing clinically apparent disease is roughly 18% (1) and the chance of death from prostate

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cancer in those diagnosed clinically is estimated to be 20 to 30% (3,4). These findings suggest that although some cancers are invariably lethal, others are latent and will not alter a patient's lifespan. Therefore, available management options for men with localized disease range from conservative approaches (active surveillance with selective delayed intervention or watchful waiting with palliative therapy) to early definitive therapy (radical prostatectomy or radiation therapy) (5).

Prostate-specific antigen (PSA)-based screening, more extensive biopsy regimens, advances in diagnostic techniques, and increased public awareness of the disease have resulted in prostate cancer detection at earlier stages and more favorable prognostic risk categories (6,7). In contemporary series, low risk prostate cancer, defined as Gleason's sum ≤ 6 , PSA <10 ng/ml, and clinical stage T1c to T2a (8), comprises approximately 40% of newly diagnosed cancers. Long-term cancer control in this setting can generally be achieved with adequate local definitive therapy (9,10). However, when managed expectantly, a proportion of purportedly low risk tumors may progress, resulting in the development of metastases and death from disease (11).

In a meta-analysis of 828 men from 6 surveillance series around the world, Chodak and associates (12) showed that the risk of metastasis and cancer-specific mortality 10 years after diagnosis for well-differentiated cancers was 19% and 13%, respectively. Furthermore, 10-year cancer-specific mortality rates were similar in those with well-differentiated and moderately-differentiated tumors, suggesting that a 10-year follow-up interval is insufficient time to allow these tumors to realize their full biologic potential.

In a competing risk analysis of 767 men aged 55 to 74 years who were managed conservatively for localized disease, Albertsen and colleagues (4) found that men with Gleason score 5 or 6 tumors had a modest risk of death from prostate cancer, ranging from 6% to 30%, over 15 years of follow-up.

The natural history of untreated, early-stage prostate cancers (T0-T2 NX MO) beyond 15 years was examined by Johansson et al. in a population-based cohort of 223 consecutive men (11). During the first 10 to 15 years of follow-up, most cancers exhibited an indolent course. However, beyond 15 years, substantial decreases in cumulative progression-free survival (from 45% to 36%), metastasis-free survival (from 77% to 51%), and prostate cancer-specific survival (from 79% to 54%) were noted (11).

Prostate cancers detected at low PSA levels can be highly aggressive. In the placebo group of the Prostate Cancer Prevention Trial (PCPT), prostate cancer was diagnosed in 15.2% of men with an unremarkable digital rectal examination (DRE) and a PSA ≤ 4.0 ng/ml. Of these cancers, 15% had a Gleason score of 7 or higher (13). Moreover, in a recent study of 211 men who died of prostate cancer, Thompson and colleagues (14) reported that a substantial number of these men had features consistent with low risk disease. In their study, 46% (88/192) of men who ultimately died of prostate cancer had tumors consistent with clinical stage T1-T2a at the time of diagnosis, while a third (55/167) had a biopsy Gleason score ≤ 6 .

These studies collectively demonstrate that early stage, low risk cancers can cause significant patient morbidity and death in the long term. While the combination of clinical stage, biopsy cancer grade, and PSA levels can provide risk-stratification for cancers at low risk of progression following definitive treatment, their utility as predictors of outcome remains limited when considering expectant management for these tumors. Until better methods are available to accurately identify men for whom expectant management may be safely offered, early definitive treatment should be considered for patients with an estimated life expectancy exceeding 15 years.

Further evidence supporting the rationale for early intervention comes from a randomized trial conducted by the Scandinavian Prostate Cancer Group that compared radical prostatectomy with watchful waiting for early stage prostate cancer (15). Though it is uncertain how applicable these data are to patients with PSA-detected cancers, this randomized trial provided evidence that surgical therapy, when compared to watchful waiting, reduced the risk of overall mortality (relative risk of 0.74 in surgery group), prostate-cancer specific mortality (relative risk of 0.56 in surgery group), distant metastasis (relative risk of 0.60 in surgery group), and local progression (relative risk of 0.33 in surgery group). Though the absolute reduction in the risk of death after 10 years was relatively small, reductions in the risks of metastasis and local tumor progression were substantial and differences in prostate cancer-specific mortality were already apparent at 5 years, implying that the difference in mortality will be even greater with longer follow-up.

In the era of PSA screening, tumors are generally being detected approximately 10 years earlier in their natural history when compared to those detected by digital rectal examination alone (16). The median age of men seeking definitive surgical treatment in contemporary radical prostatectomy series ranges from 58 to 64 years old (6,7,9). These men are expected to enjoy an overall life expectancy ranging from 17 to 29 years (17) and may therefore be at long-term risk for disease progression and prostate cancer-specific death if managed expectantly (11).

Results of early definitive therapy

Radical prostatectomy

Prior to studies that characterized the anatomy of the dorsal vein complex, the striated urethral sphincter, and the neurovascular bundles of the pelvic nerves, radical prostatectomy was not widely adopted because of significant morbidities. The majority of men were rendered impotent, many suffered urinary incontinence, and considerable bleeding was common following the retropubic approach (18). Subsequent to these improvements in surgical techniques, radical prostatectomy has evolved into a procedure that affords excellent long-term cancer control and acceptable rates of continence and potency (9).

From 1983 to 2003, 4,400 men with clinically localized prostate cancer (clinical stage T1 to T2) underwent radical prostatectomy at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York or at Baylor College of Medicine, Houston, Texas. Of these men, 1,723 (39%) were categorized as having low risk disease [Table 1]. Long-term cancer control following radical prostatectomy was excellent for men with low risk disease. Notably, a small proportion of these men developed disease progression despite treatment, suggesting that some tumors in this favorable risk group may not exhibit “low risk” behavior [Figure 1]. Furthermore, 30% of tumors clinically considered low risk were upgraded pathologically to a Gleason sum of 7 or greater and 16% were proven non-organ confined when the radical prostatectomy specimen was evaluated, implying again, that certain clinically low risk cancers may harbor features consistent with intermediate to high risk disease [Table 2]. The concordance between biopsy and radical prostatectomy Gleason score was 56% at best in the later years, with biopsy Gleason score underestimating the grade of the tumor 33% to 55% of the time [Figure 2].

In men with low risk cancers 55 years old or younger, continence and potency rates following radical prostatectomy with bilateral nerve preservation were excellent. Roughly 80% were potent, continent, and cancer free two years after surgery [Figure 3].

Radiotherapy

While radiation therapy is widely used for men with low risk cancers, conclusive evidence from prospective randomized studies comparing outcomes by treatment modality are lacking.

Available data from retrospective comparisons suggest that rates of biochemical recurrence and survival are similar for radical prostatectomy, interstitial radiation therapy, or external beam radiotherapy in the intermediate-term (8). With the introduction of intensity modulated radiation therapy (IMRT), precise delivery to the tumor target is achieved while reducing the exposure of the rectum and bladder to high doses of radiotherapy, thereby minimizing treatment toxicity.

Between 1996 and 2000, 561 men with clinically localized prostate cancer were treated with IMRT at MSKCC. Of these men, 203 (36%) were categorized as having low risk disease. Using ASTRO and Houston definitions for biochemical relapse, the 8-year actuarial PSA relapse-free survival outcomes for men with low risk disease were 85% and 89%, respectively. Before treatment, 403 (72%) men were potent. In this group of patients, erectile dysfunction developed in 49%. Long term toxicities were minimal, as the 8-year actuarial estimates of late grade 2 or greater rectal and urinary toxicity were 1.6% and 15%, respectively (10).

Discussion

Active surveillance with selective delayed intervention assumes that an individual's cancer will not progress outside the window of curability during the surveillance period, that markers for disease progression are reliable, and that patients are compliant. Furthermore, patient anxiety about living with untreated cancer in those on active surveillance can be substantial and cannot be ignored. El-Geneidy et al. (19) found that 17 of 38 (45%) men sought therapy without evidence of disease progression while on active surveillance.

It is thus far impossible to determine with certainty which tumors will ultimately progress and lead to death. Serial PSA levels, PSA velocity, PSA doubling time (PSA DT), changes in digital rectal examination findings over time, and prostate needle biopsy findings have been evaluated as markers for disease progression. Results have been variable, imperfect, and oftentimes, unreliable (20-23).

For example, numerous studies have shown an association between PSA DT and progression in surveillance studies (19,24,25) while others have not (21). In an active surveillance program beginning in 1995, Klotz and associates evaluated 299 men considered to have low risk prostate cancer (25). Criteria for intervention included a PSA DT <2 years or histologic progression of tumor to Gleason sum of 8 or higher on rebiopsy. About a third of patients came off surveillance, 15% because of a rapid PSA DT, 4% for histologic progression, 3% for clinical progression, and 12% due to patient preference. Of 24 men with a rapid PSA DT who underwent radical prostatectomy, 14 patients (58%) were found to have non-organ confined cancers (pT3a to pT3c) and 2 patients (8%) had lymph node involvement. In this study, PSA DT was associated with progression and more aggressive tumors. Conversely, in a study of 88 men on expectant management, Patel et al. failed to demonstrate a significant association between shorter PSA DT and disease progression (21). In fact, nearly half of the patients in the study had a negative PSA doubling time, reflecting the limited impact these cancers had on serum PSA. Of the 31 patients ultimately treated in this series, 17 underwent radical prostatectomy, 13 received radiotherapy, and 1 received androgen ablation therapy. Gleason scores were greater in the prostatectomy specimen in 15 of 17 cases. Seven cases (41%) were upgraded to Gleason sum 7 at the time of prostatectomy. One patient (6%) had seminal vesicle involvement and positive surgical margins while 2 (12%) had extracapsular extension with negative surgical margins. None of the 17 men undergoing radical prostatectomy had thus far demonstrated clinical or biochemical evidence of progression at a median followup time of 41 months.

Clearly, novel biomarkers and more accurate radiographic and local staging techniques will be required to better risk stratify and monitor low risk patients on surveillance. On the contrary,

early definitive intervention has been shown to offer excellent long-term cancer control with low morbidity. It may obviate the need for multimodal therapies and more extensive treatments (extended surgery, androgen deprivation therapy, high dose radiation) that may be required once disease has progressed. In addition, salvage therapy is rarely necessary in the setting of low risk prostate cancer following definitive treatment.

Conclusion

Given the opportunity to detect prostate cancer at an earlier stage when cure is possible, it remains uncertain whether we can safely delay treatment in these men, knowing that some low risk patients have tumors with the capacity to metastasize and cause death. Early definitive treatment with radical prostatectomy or radiotherapy offers these men a chance for excellent long-term cancer control within the window of curability. Furthermore, continued refinements in surgical technique and in the delivery of external beam radiation have resulted in favorable quality of life outcomes following treatment.

Until we understand better the long-term natural history of untreated prostate cancer, have more reliable and accurate markers to detect disease progression with certainty, and can risk stratify more precisely the subgroup of men with low risk disease who will eventually succumb to their disease, early definitive therapy seems prudent.

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Figure 1.

Progression-free survival following radical prostatectomy according to risk group for 4,400 men with clinically localized prostate cancer undergoing radical prostatectomy at Memorial Sloan-Kettering Cancer Center or Baylor College of Medicine from 1983-2003

Figure 2. Concordance of Gleason's score between biopsy and radical prostatectomy specimens

Figure 3. Trifecta outcomes in men under 55 years old after undergoing bilateral nerve sparing radical prostatectomy

Table 1

Risk Groups for 4,400 men presenting to Memorial Sloan-Kettering Cancer Center or Baylor College of Medicine for radical prostatectomy between 1983-2003

Risk Group	PSA	Gleason Score	Clinical Stage	Number of men (%)
Low	<10	2-6	T1c to T2a	1723 39
Intermediate	10-20	7	T2b	1371 31
High	>20	8-10	T2c	1306 30

Table 2

Pathological features of low risk prostate cancer in 1,723 radical prostatectomy specimens

Radical prostatectomy Gleason's score	Number of men	%
≤6	1206	70
3+4	448	26
4+3	52	3
8-10	17	1
Extracapsular extension		
Focal	121	7
Established	121	7
Seminal vesicle involvement	24	1.4
Lymph node involvement	14	0.8
Positive surgical margins	241	14