Prostate Cancer:

Is There Standard Treatment?

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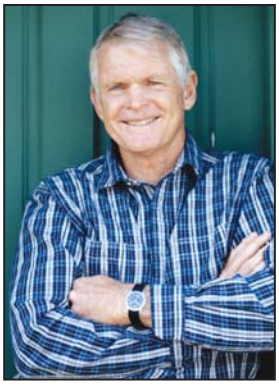
In this article:

According to Canadian Cancer Statistics' estimates for the year 2002, prostate cancer (PCA) represents the most common malignancy in Canadian men and is the second leading cause of death.[1] Its prevalence and mortality rate, make prostate cancer an epidemiologically important disease and a public health priority. Despite its epidemiologic and clinical significance, the importance of early diagnosis of prostate cancer and of its treatment in early, localized stages are still considered controversial. This controversy is attributable to the highly variable natural history of localized prostate cancer, which may range from indolent to highly aggressive. The difference in natural history of prostate cancer precludes a standardized treatment for all men. Instead, treatment recommendation requires a tailored approach, where the natural history of the tumour is considered alongside the patient's life expectancy and his quality-of-life preferences. Herein, we propose to outline the natural history of localized prostate cancer and to address the rationale and modalities for early diagnosis and treatment.

Who has prostate cancer?



Canadian Cancer Statistics suggests that one in nine Canadian men will develop prostate cancer in his lifetime. Of men aged 50 years and older, 3% will die of prostate cancer. However, a significant proportion of men will also die with prostate cancer, with either no or minimal sequelae of the disease. Indeed, autopsy studies demonstrated that microscopic prostate cancer deposits may be found in prostates of as many as 30% of men over fifty. Therefore, prostate cancer is prevalent, and many men may harbor clinically indolent or insignificant tumours.[2] However, in an appreciable proportion of men with histological evidence of prostate cancer, the malignancy represents the most important competitor for life expectancy. The natural history of prostate cancer has been

addressed in two key contributions. Studies identified men with prostate cancer from records of several Connecticut acute care hospitals and Veterans Affairs medical centres. These men were either untreated, or were treated with immediate or delayed hormonal therapy. The survival of these men was compared to that of the general population. The data suggest that in men with localized prostate cancer treated by non-curative intent, survival is compromised by comorbid conditions, in addition to being affected by the grade of cancer.[3]

These data were complemented by a second retrospective observational study, with the objective of providing prostate cancer specific and overall mortality figures, according to prostate cancer grade. The study population consisted of men diagnosed with localized prostate cancer who were either untreated, or were treated with immediate or delayed hormonal therapy. Their age at diagnosis ranged from 55 to 74 years, and all were identified from the Connecticut Tumor Registry. These data demonstrated that men with well and moderately differentiated tumours, corresponding to Gleason grades two to four and five, respectively have a 4% to 7% , and 6% to 11% chance of dying of prostate cancer within 15 years of diagnosis. Men with moderately differentiated tumours of higher grade, that corresponded to a Gleason score of six and seven, respectively had an 18% to 30%, and 42% to 70% chance of dying from prostate cancer within 15 years of diagnosis. Finally, men with poorly differentiated tumours, Gleason eight to 10, had a 60% to 87% chance of dying from prostate cancer within 15 years of diagnosis.[4]

These observational studies suggest that definitive therapy is indicated in most men with Gleason score seven to 10 tumours, as the majority of these men are likely to die of prostate cancer if treated with observation or hormonal treatment. Conversely, most men with Gleason score six or less tumours will die of other causes. In these men, definitive treatment may not be indicated, especially if life expectancy is poor or competing morbidity is significant (Figure 1).

What are the risk factors?

Maleness, age, and family history of prostate cancer represent the foremost risk factors of prostate cancer. Prostate cancer is testosterone dependent, thus maleness is the most important risk factor. Prostate cancer is virtually unknown in eunuchs and in men with castrate levels of testosterone. When present in family history, the risk of prostate cancer has been shown to be on average threefold higher than in population controls. Based on this consideration, surveillance with prostate-specific antigen (PSA) is indicated as of the age of 40 in men with a positive family history, which is defined as the presence of at least one affected first-degree relative. Race represents an additional risk factor. African Americans are at higher risk. Vasectomy is not considered to represent a risk factor for prostate cancer. The link between diet and several malignancies has been investigated in animal experiments, where prostate cancer was also addressed. They suggested that low-calorie and low-fat diets may be protective. Population-based nutrition studies also suggest that selenium, vitamin E, lycopene and soy supplements may also have a protective effect.

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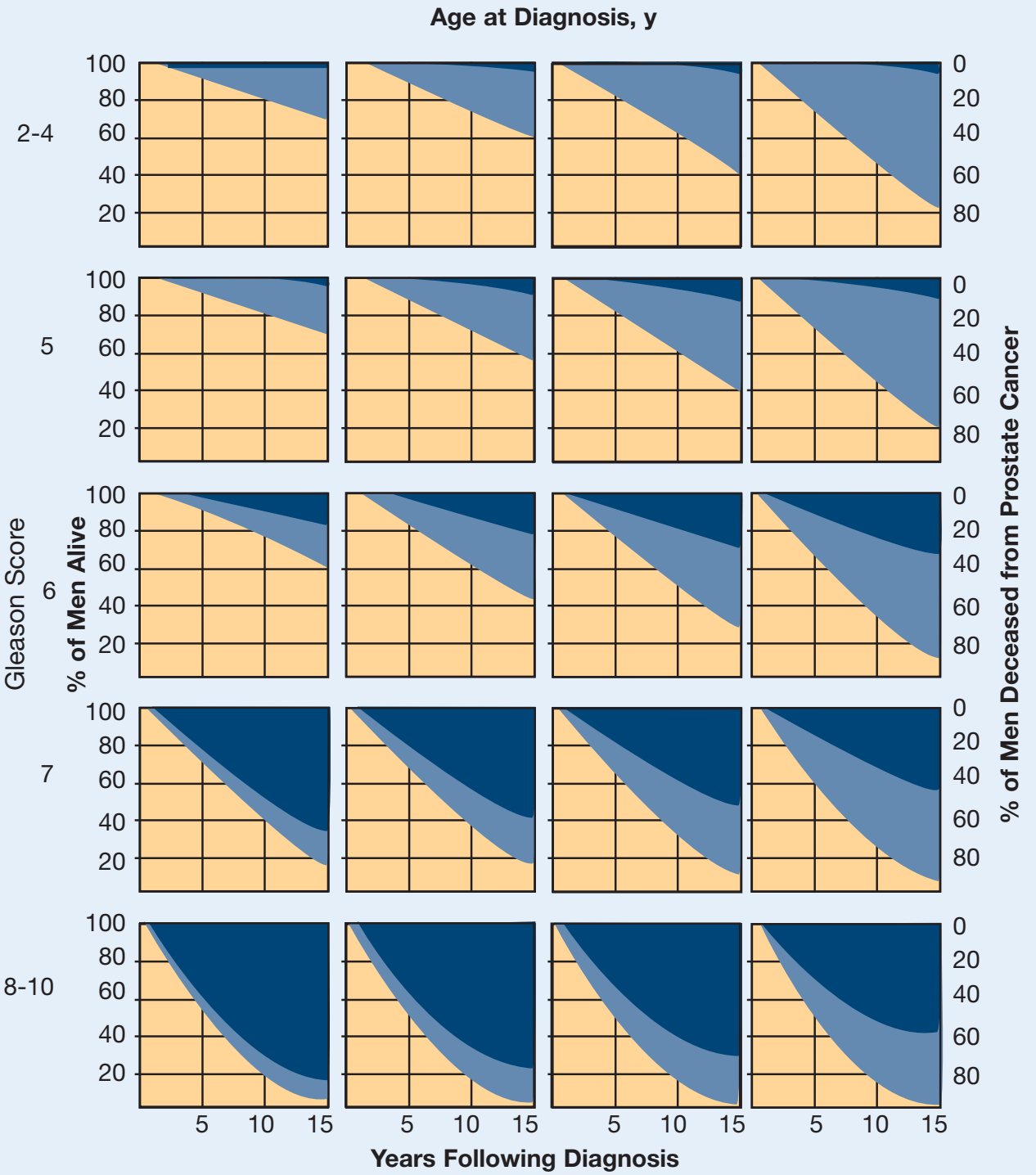


Survival (white lower band) and cumulative mortality from prostate cancer (dark grey upper band) and other causes (light grey middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. Percentage of men alive can be read from the left-hand scale, and percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale.

Figure 1. The impact of tumour grade and comorbidity on survival in men with localized prostate cancer treated with non-curative intent.

Table 1

1992 UICC Clinical TNM Stage

T1a	Incidentally diagnosed prostate cancer during transurethral prostatic resection for benign prostatic hypertrophy. Cancer is present in less then 5% of tissue resected. These cancers require a needle guided biopsy of the prostate to determine their true T stage and Gleason pattern.
T1b	Incidentally diagnosed prostate cancer during transurethral prostatic resection for benign prostatic hypertrophy. Cancer is present in more then 5% of tissue resected. These cancers require a needle guided biopsy of the prostate to determine their true T stage and Gleason pattern.
T1c	Needle biopsy detected prostate cancer (non-palpable and not visible on ultrasound)
T2a	Palpable tumour that involves less than half a lobe.
T2b	Palpable tumour that involves more than half a lobe, but not both lobes.
T2c	Palpable tumour that involves both lobes.
T3a	Unilateral extracapsular extension
T3b	Bilateral extracapsular extension
T3c	Invasion of seminal vesicles
T4	Fixation or invasion of adjacent structures.
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes. Regional lymph nodes are situated within the true pelvis.
M0	Absence of distant metastasis
M1a	Distant metastases to non-regional lymph nodes
M1b	Distant metastases to bone
M1c	Distant metastases to other sites.

D Stages

D0	Clinically localized despite persistently elevated enzymatic serum acid phosphatase titers.
D1	Regional lymph nodes only
D2	Distant lymph nodes, metastases to bone or visceral organs
D3	D2 patients who relapsed after adequate hormonal therapy

What are the diagnostic tools?

PSA elevation represents the most common indication for urologic referral to rule out the presence of prostate cancer. Its usefulness in suggesting the presence of cancer is based on a higher rate of secretion into the serum in the presence of malignant prostatic cells. The contribution to circulating serum PSA has been shown to be tenfold higher when a gram of prostate cancer is compared to a gram of benign prostatic tissue.

Age-specific PSA ranges have been proposed. These increase the sensitivity of PSA in younger men and increase its specificity in older men. The ranges are as follows: 40 to 49 years old: 0 ng/ml to 2.5 ng/ml, 50 to 59: 0 ng/ml to 3.5 ng/ml, 60 to 69: 0 ng/ml to 4.9 ng/ml and 70 to 79: 0 ng/ml to 5.9 ng/ml. A further attempt at improving the performance of PSA consisted of the rate of PSA change over time, termed PSA velocity. Rate of change exceeding 0.75 ng/ml per year has been shown to be 72% specific and 95% sensitive in predicting presence of prostate cancer on needle biopsy. However, at least three measurements need to be obtained within a two-year period, therefore the usefulness of PSA velocity is limited to men with adequate followup. Furthermore, assay-related differences in individual PSA values, as well as individual physiologic variation in PSA levels may confound the calculation of PSA velocity. A molecular isoform of PSA, termed free PSA, has been shown to improve the specificity of the traditional PSA cut-off. Presence of cancer is associated with low free PSA levels. The most useful clinical applica-

tion of free PSA is to detect cancer in men with normal (0 ng/ml to 4 ng/ml) PSA levels and in men with borderline (4.1 ng/ml to 10 ng/ml) PSA elevations. In men with normal PSA levels, free PSA values between 0 and 25% have been shown to be 90% sensitive and 24% specific. In men with PSA values between 4.1 ng/ml and 10 ng/ml, a cut-off of 20% has been suggested and this practice was shown to result in sensitivity of 95% and specificity of 29%.

Presence of suspicious rectal examination findings and/or elevation of serum PSA or of its enhanced forms indicates the need for prostate biopsy. Multi-core biopsies of the prostate are performed under ultrasound guidance. Suspicious (hypoechoic) appearance of the gland on ultrasound may suggest additional biopsies. In its absence, a minimum of six biopsies are routinely obtained from the peripheral zone of the gland, where most cancers originate. Transrectal ultrasound allows to determine the volume of the prostate, which in turn allows to determine the expected benign contribution to circulating serum PSA. Since prostate cancer releases more PSA per unit of volume than does BPH, a PSA to volume ratio allows to grade the risk of cancer on biopsy. A higher risk based on this calculation may prompt additional biopsies.

What are the stages?

Effective treatment relies on accurate stage definition (Table 1). Prostate cancer staging relies on the TNM system (T refers to primary tumour, N describes the extent of lymph node involvement, and M refers to the presence or absence of metastases). In prostate cancer, additional variables have been shown to complement the TNM system and aid in providing accurate cancer control predictions. These include serum PSA at presentation, Gleason score on needle biopsy, and the number of biopsy cores involved with cancer. These are available prior to definitive treatment and may be used to predict recurrence-free survival, according to selected treatment modality. For men contemplating external beam radiotherapy, treatment dose in Gy and use of neoadjuvant hormonal therapy represent predictors of outcome. After definitive therapy, such as radical prostatectomy, the TNM staging is complemented by variables that define presence of pathologically confirmed lymph node invasion, extracapsular extension and surgical margin status. Therefore, staging of surgical patients tends to be less biased than that of men treated with alternative treatment modalities, such as external beam radiotherapy or brachytherapy.

Practice Pointer

Cancer-control outcomes associated with surgery and external beam radiotherapy are comparable for low- and intermediate-grade tumours. Long-term surgical outcomes, however, appear superior in higher risk patients.

Several cancer control predictive tools have been devised to help stratify men according to their cancer control potential. Of several stratification schemes, three have been widely adopted in the urologic oncology community. These include the Partin Tables that predict the pathologic stage of the tumour (organ confinement, prostatic capsule invasion, lymph node invasion, and seminal vesicle invasion). Partin Tables rely on preoperative serum PSA, digital rectal examination findings (clinical T stage), and needle biopsy Gleason score. However, men tend to be more interested in what is their individual chance of being cured with a given treatment modality. Kattan recurrence-free predictions at five years after treatment are now available (www.nomograms.org).[5,13] These are very helpful in the process of treatment selection. Variables derived from pathologic tumour assessment after radical prostatectomy may be used in the post-operative Kattan nomogram which predicts seven year recurrence-free probability. These predictions are helpful in deciding whether adjuvant treatment is necessary. The predictive accuracy of the post-operative nomogram is superior to the pre-operative version, as pathologic staging is more accurate than clinical staging.

Table 2

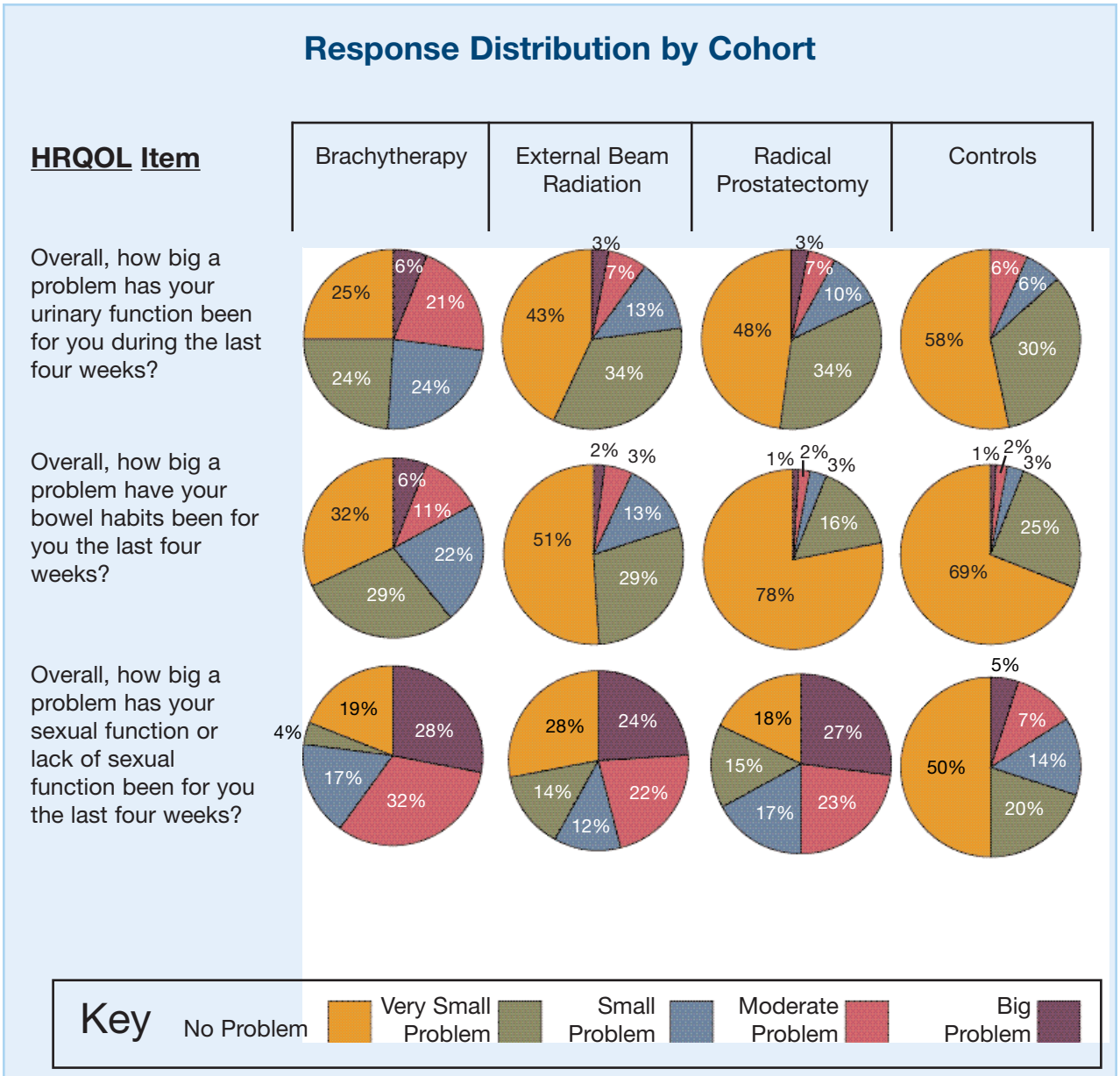
Treatment Options According to the 1992 UICC Clinical TNM Stage

T1a T1b	Transurethral resection of the prostate diagnosed prostate cancer. For proper staging, transrectal biopsies and formal reassessment of clinical T-stage, according to digital rectal examination findings, are required prior to treatment selection.
T1c T2a	Standards of care: surgery and external beam radiotherapy. Option: brachytherapy if PSA less then 10 ng/ml and Gleason score of six or less.
T2b T2c	Surgery or External beam radiotherapy (usually in combination with hormone therapy).
T3a T3b	External beam radiotherapy combined with hormone-therapy or Surgery in selected cases.
T3c T4	External beam radiotherapy and/or Hormone therapy.
N1 M0 M1a M1b M1c	Hormone therapy is standard of care. If patient becomes resistant to hormone therapy (stage D3), palliation is standard of M1a care. Research is ongoing to improve life expectancy. New treatment options include biphosphonates (zoledronic acid) and chemotherapy M1c (mitoxantrone/prednisone or taxotere based).

What is the treatment?

The accepted treatment modalities for localized prostate cancer consist of either definitive treatment or watchful waiting. Externally delivered radiotherapy and radical surgery represent the standards of care for localized prostate cancer of all grades and stages. Brachytherapy, or interstitial radiation represents an alternative to external delivery. Men treated with brachytherapy are subjected to permanent insertion of radioactive iodine or palladium seeds through the perineum into the prostatic stroma. This form of treatment is appropriate for men with palpably unremarkable glands (stage T1c) or with small palpable nodules (stage T2a), with serum PSA elevations less than 10 ng/ml and with Gleason scores of six or less. The restriction of brachytherapy to men with very favourable tumour characteristics is related to less effective and less durable cancer control outcomes, if given to men as monotherapy, with more aggressive tumours. Cancer control outcomes associated with surgery and external beam radiotherapy are comparable for low- and intermediate-grade tumours. However, long-term surgical outcomes appear superior in higher risk patients.[6,12] The efficacy of radiation regimens is directly related to the dose of radiation and to the mode of delivery. In higher risk tumours, cytoreductive hormonal ablation is administered in a temporary fashion before, during, and for varying amounts of time after radiotherapy. It is associated with increased cancer control rates. Reports suggest that this increase in cancer control rates also translates into superior survival in men treated with adjuvant hormonal cytoreduction. Table 2 provides an overview of treatment options, according to disease stage.

Cancer control rates are widely available and are based on large scale multi-institutional cohorts of men treated with one of the three primary treatment modalities. However, it is only recently that one of the index treatments, radical prostatectomy, has been addressed in a formal, randomised comparison with watchful waiting. The study addressed 695 Swedish men who were diagnosed with localized prostate cancer between 1989 and 1999. Of these, 348 were randomized to watchful waiting and 347 to radical prostatectomy. At a median followup of 6.2 years,



Severity of overall urinary, bowel, and sexual bother reported by subjects after localized prostate cancer therapy and by age-matched controls. The distribution of participant responses to each of three specific survey questions, representing the three highest loading EPIC bother items, are shown.

Figure 2. Treatment modality specific detriments related to urinary, sexual and bowel function. These three domains represent the key disease-specific health-related quality-of-life areas in men treated for localized prostate cancer.

men treated with radical prostatectomy were 50% less likely to die of prostate cancer (16 versus 31 prostate cancer specific deaths), 37% less likely to develop distant metastases (35 versus 54 patients with distant metastases), and 69% less likely to develop local tumour progression (40 versus 108 men with local tumour progression).[5]

Due to short followup, the data are not mature enough to make valid conclusions about the effect of definitive treatment on overall survival. However, the data strongly suggest a benefit related to treatment versus no treatment, when intermediate endpoints, such as local progression and metastasis are considered. Despite these limitations, the study reinforces the findings of Albertsen and colleagues, which suggest that a subset of prostate cancers, those of higher grade and possibly stage, represents an important competitor for life expectancy.[12]

What are the outcomes?

The importance of health-related quality-of-life (HRQOL) outcomes relates to several singularities of prostate cancer which distinguish it from other cancers. Prostate cancer is unlike other more aggressive cancers, where survival determines the type and course of treatment. In prostate cancer, a tenuous balance exists between quantity and quality-of-life. Therefore, combined and simultaneous consideration of cancer control and HRQOL outcomes is necessary in prostate cancer.[6-11]

The tenuous balance between quantity and quality-of-life represents one of the rationales for assessment of HRQOL in localized prostate cancer. Therefore, careful consideration of HRQOL is imperative when treatment is discussed. Modality specific detriment profiles should be discussed, as shown in (Figure 2).

Prostate cancer represents a highly prevalent disease. Studies are ongoing to determine the benefits of screening for prostate cancer. However, early detection and wide use of serum PSA appears to translate into measurable cancer control benefits. In men with good life expectancy, treatment of Gleason grade six or higher localized prostate cancer appears to be warranted. A randomised trial addressing men with localized prostate cancer suggests that radical prostatectomy results in superior cancer control outcomes relative to watchful waiting. Selection of treatment alternatives should be based on individual cancer control and health-related quality-of-life considerations. CME

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