

## PROSTATE CANCER: A PERSPECTIVE

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Interest in adenocarcinoma of the prostate (CAP) and specifically the efforts toward early detection of this common neoplasm have achieved astounding levels. This is not surprising, considering that prostate cancer is the most prevalent malignancy in American males with an annual incidence approaching 240,000. Even more threatening, however is the mortality rate of this malignancy which is approaching 40,000 per year, making CAP the second highest cause of cancer related deaths in American males. The lifetime risk for a male developing a clinically significant CAP is one out of ten with 30% of these men dying of their cancer. The recent popular press reports of prostate cancer deaths in prominent Americans has placed the disease at the public forefront. Recent modifications of recommendations for the early detection of prostate cancer by the American Cancer Society and the American Urologic Association have furthered interest in the disease. However, the staggering economic implications of prostate cancer have captured the attention of health care managers seeking to modify the national approach to health care delivery with particular attention being paid to CAP. Unfortunately much confusion remains concerning this ubiquitous neoplasm. Much of the controversy arises from necropsy studies which reveal that 40-50% of men over the age of 50 harbor evidence of CAP, while only 10% develop clinically significant disease. In addition, there was a widely circulated Swedish study inferring that there was no need to treat most prostate cancers, because the cohort of elderly patients in that highly selected study, had similar 10 year survival rates whether the cases of CAP were treated with aggressive or non-aggressive therapy. Another contemporary difficulty with our current efforts to cure CAP are limited by an inability to accurately stage patients which thus leads to over treating patients with metastatic disease. Currently, questions which arise concerning the care of the patient with prostate cancer include: First, of those men with clinically significant CAP, whom should we give strong consideration for aggressive treatment with attempt to cure and who can be treated nonaggressively? Second, can one predict which prostate malignancies will pursue an aggressive course and can one detect those patients with clinically significant cancers at

an early stage? Finally can we identify those patients, with incurable subclinical micrometastatic disease and exclude these patients from the morbidity of ineffective radical treatment?

Concerning the initial query, prior to embarking upon a discussion of which prostate cancer patients should be treated for their disease, one must first have an understanding of the actuarial survival statistics of men in their 50's through eighties. Since CAP is predominantly a disease of mature men with mean and median presentation in the mid sixties, co-morbidity clearly can negatively impact survival in the cohorts of patients expected to harbor CAP. Life expectancy data culled from life insurance actuarials reveal:

<u>AGE</u>	<u>LIFE EXPECTANCY</u>
60	17.5 year s
70	11 years
80	6.2 years

The median 10 year survival statistics reveal:

<u>AGE</u>	<u>Median 10 year survival</u>
60	77.6%
70	52.2 %
80	19.7%

Next one must factor the mortality rates of prostate cancer. Unfortunately one finds that there exist no well performed randomized prospective studies evaluating CAP survival statistics and therefore a firm epidemiological perspective of prostate cancer does not exist. There are, however, several retrospective outcome studies that do shed light on CAP progression and mortality.

First, Hanash, et. al. at the Mayo clinic (J.Urol. 107:450,1972 and personal communication) reported on 179 patients followed for a mean of 15 years following, a diagnosis of prostate cancer and

found a 45% 15 year disease specific mortality and an overall mortality of 55%. This study also revealed the great magnitude of the morbidity caused by CAP as 41% of patients required palliative surgery for bladder outlet obstruction, 37% required palliative XRT for bone metastasis and 27% required urinary diversion for ureteral obstruction. He concluded that there was a significant cancer specific morbidity and mortality at 15 years for prostate cancer.

A more contemporary study (J.Urol. 153:506A,1995) by Aus from Sweden found that of 536 patients who were registered with a diagnosis of CAP and died between 1988 and 1990, 62% died directly or indirectly from the malignancy. For those patients who survived more than 10 years following the diagnosis of CAP, 63% died of causes directly attributable to the CAP. Concerning morbidity, 61% of all patients required palliative surgical or radiotherapy treatment for complications of CAP

AUTHOR	CAP Mortality	PALLIATIVE PROCEDURES
Hanash (1972)	45%	41% TURP 37% XRT 27% Urinary diversion
Aus (1995)	62%	41% TURP 31% XRT 17% Urinary diversion

Both studies comment that mortality and morbidity from prostate cancer increases significantly 10 years following initial diagnosis.

Finally, a well publicized Swedish study by Johansson (J.Urol., 152: 1753, 1994) revealed that the 10 year disease specific mortality of men diagnosed with prostate cancer at a mean age of 72 was only 10%. Further, this study found that within the first 10 years following the diagnosis of prostate cancer in this cohort of patients, there was no survival difference between patients treated by radical prostatectomy and hormonal ablation therapy. It was this study which received a great deal of coverage

in the lay press, being cited as a strong reason to pursue a non-aggressive course of treatment for localized prostate cancer. However, the study was skewed in that it evaluated predominately well differentiated tumors in older patients (mean age 72 years at the time of diagnosis) whose overall mortality was 66%. In fact, in those patients with moderate or poorly differentiated cancer the disease specific mortality was 15-56% at 10 years.

Based on these studies, therefore, it would appear that prostate cancer does result in significant morbidity and mortality, usually 10 years or more following diagnosis. Therefore, patients with a diagnosis of CAP who have an actuarial life expectancy of greater than 10 years deserve consideration of treatment for disease cure. Conversely, one may wish to pursue a more conservative approach in those patients with interceding comorbidity and a diagnosis of CAP whose life expectancy is less than 10 years.

The second question to be answered is: can one discern clinically insignificant tumors that will likely remain quiescent from those that will act aggressively and likely progress? A study to define more completely the variables that can be used to predict those patients with a low biological potential of CAP requiring limited treatment from those needing more extensive therapy, (J. Urol., 140:1340, 1988) retrospectively reviewed 232 patients with incidentally discovered malignancy. Progression intervals were related consistently and directly to the initial volume extent and grade differentiation of the tumor. That is, larger more aggressive tumors progressed in a constant and in fact linear fashion.

GRADE	PERCNT PROGRESSION AT 10 YEARS	
	Volume of tumor < 1%	Volume of tumor > 5%
Low	6%	22%
Moderate	41%	86%
High	61%	97%

Interestingly this study corroborates the Johansson study in that low volume well differentiated tumors tended not to progress, while high grade, larger volume tumors did progress.

Following up on this study Stamey et. al. (Cancer, 71: 933, 1993) utilizing a statistical model found that significant prostate cancers, that is those with the propensity to progress or metastasize, were those with a volume equal to or greater than 0.5 cc's. Conversely, tumors with a volume less than 0.5 cc's are considered unlikely to progress or cause significant morbidity or mortality. Interestingly, when one reviews the necropsy data which historically have yielded a 40-50% prevalence of CAP in men over age 50, the majority of these pathologic identified cancers were only microfoci with volumes less than 0.2cc's.

These studies, therefore, argue that one can predict the probability of progression of prostate cancer based on tumor volume and grade. That is, patients with larger volume, moderate or high grade tumors likely will progress and are potential candidates for treatment, whereas low grade low volume disease portends a low likelihood of progression.

Regarding the third query concerning the ability to detect patients with clinically significant cancers at an early stage, currently it appears that the technology to identify these patients does exist. Tumors which are organ confined and potentially treatable, are identifiable through early detection with a combination of the digital rectal examination (DRE) and serum prostate specific antigen (PSA) evaluations. Prior to the use of PSA for early detection, 65% of all newly diagnosed prostate cancers were metastatic and incurable. Following the introduction of the serum prostate specific antigen assay for prostate cancer screening the vast majority of cancers now identified are organ confined and potentially curable (70-74%). Multiple pathological studies reveal that over 90% of prostate cancers found by PSA screening are significant. That is, they are moderate to high grade malignancies and have a volume greater than 0.5cc's. (Ohori et.al., J. Urol: 152, 1714, 1994; Smith and Catalona J.Urol: 152, 1732, 1994). Thus it appears that we currently have the ability to identify patients with early potentially curable disease through early detection by PSA.