Global update on defining and treating high-risk localized prostate cancer with leuprolelin: a USA perspective – identifying men at diagnosis who are at high risk of prostate cancer death after surgery or radiation therapy

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Prostate-specific antigen doubling time (PSA-DT) after surgery or radiotherapy (RT) is known to be a predictive factor for death from prostate cancer (prostate cancer-specific mortality, PCSM). An analysis of two multi-institutional databases, including 8669 men with prostate cancer treated with surgery or RT, found that a PSA-DT of <3 months, and the specific value of the PSA-DT when ≥3 months, appeared to be surrogate endpoints for PCSM after surgery or RT. While many PSA failures occur after local therapy for localized prostate cancer, few of these patients go on to die from their disease, so it is important to identify other factors associated with PCSM, so that the subgroup of high-risk patients can be identified. An analysis was undertaken to determine whether patients at risk of PCSM could be identified using information available at diagnosis. The results showed that risk factors for PCSM were a PSA velocity of >2.0 ng/mL/year, a Gleason score of 8–10 and an increasing PSA level. However, the most important risk factor that had an impact on both PCSM and all-cause mortality was a PSA velocity of ≥2.0 ng/mL/year. PSA kinetics are being increasingly used in the setting of rising PSA levels after radical prostatectomy or RT, and several studies showed that the rate of increase in PSA level at the time of recurrence is closely associated with time to cancer death. A PSA-DT of <3 months is associated with a poor prognosis, and represents 15–20% of PSA failures in the general population and 6–7% of PSA failures in a screened population, such as those included in clinical trials. Better risk-assessment models are needed to help to identify at an early stage men who are at high risk of prostate cancer death and those who are at low risk, so that each subgroup can receive the most appropriate therapy for their disease.

KEYWORDS
prostate cancer, high-risk, hormone therapy, USA

INTRODUCTION
This review assesses the USA perspective on the treatment of men with high-risk localized prostate cancer, focusing on identifying men at diagnosis who have a high-risk of prostate cancer death after surgery or radiation therapy (RT).

PSA KINETICS
PSA doubling time (PSA-DT) after surgery or RT is known to be a predictive factor for death from prostate cancer [1]. The hypothesis that a short PSA-DT after treatment is a surrogate endpoint for prostate cancer-specific mortality (PCSM) was investigated by analysing two multi-institutional databases including 8669 men with prostate cancer treated with surgery (5918) or RT (2751) for localized or locally advanced, non-metastatic disease. The PSA-DT was significantly associated with time to PCSM and with time to all-cause mortality (ACM) (P < 0.001). After a PSA-defined recurrence, a PSA-DT of <3 months was significantly associated with time to PCSM (median time 6 years; hazard ratio, HR, 19.6). It was concluded that a PSA-DT after treatment of <3 months and the specific value of the PSA-DT when ≥3 months appear to be surrogate endpoints for PCSM after surgery or RT. The investigators recommended that consideration be given to initiating androgen suppression therapy at the time of a PSA-defined recurrence when the PSA-DT is <3 months, to delay the imminent onset of metastatic bone disease.

Despite the many PSA failures that occur after local therapy for localized prostate cancer, only a few of these patients have PCSM. In fact, many PSA failures do not result in metastatic disease or death from prostate cancer. In the USA, the probable reason is that the average age at diagnosis is 60–65 years, and at that stage there are other competing causes of death. In addition, the clinical course from PSA failure to death from prostate cancer can be protracted in some forms of prostate cancer, and often might not be reached before death from other causes.

IDENTIFYING HIGH-RISK PATIENTS
Identifying high-risk patients should be based on factors associated with PCSM. Candidates at diagnosis include Gleason score, PSA level, PSA velocity, clinical T category, and in the future are also likely to include genetic factors. While such risk groupings are undoubtedly valuable and a good starting point, they are less useful for assessing the individual patient. Currently, no scheme captures all of the information needed to assess whether a particular individual is at low or high risk, whereas for a population it is possible to group patients by risk. For example, a patient with T1c disease, a Gleason score of 6 and a PSA level of 6 ng/mL would be categorized as ‘low risk’ using these factors alone. However, if all 12 cores at biopsy have a Gleason score of 6, if there is a minor component of Gleason 5, if he has a rapid increase in his PSA level in the year before diagnosis, or if he is hypogonadal and the PSA level of 6 ng/mL does not in fact represent his true PSA value, then this indicates that this patient should be considered in a higher risk
category. These individual variations could account for some of the PSA failures in so-called ‘low-risk’ patients.

To investigate this, an analysis was undertaken to determine whether patients at risk of PCSM could be identified using information available at diagnosis, such as PSA velocity in the year before diagnosis, PSA level at diagnosis, biopsy Gleason score, and clinical T category.

Two studies of the following cohorts of patients were undertaken between 1998 and 2002: (i) 1095 men undergoing radical prostatectomy (RP) for clinical category T1c and T2 prostate cancer at the Barnes Jewish Hospital (St. Louis, MO, USA) [2]; their mean age was 65.4 years, and they were followed for a median of 5.1 years. (ii) 358 patients aged 65.4 years, and they were followed for a median of 4.0 years.

Endpoints were time to PCSM and ACM after treatment. The predictors evaluated were PSA velocity (>2 vs ≤2 ng/mL/year), PSA level at diagnosis (a continuous variable), biopsy Gleason score (≥8 vs 7 vs ≤6), clinical T category (T2 vs T1c), and age at diagnosis (a continuous variable) for the ACM endpoint.

The results for PCSM showed that, of the factors investigated, PSA velocity, PSA level and high Gleason score were all significantly predictive of PCSM (Table 1). The T category was only predictive of PCSM in the surgically managed patients, but not the RT-treated patients. The results for ACM show which of these factors cause an increase in ACM in this population of men with prostate cancer. The change in PSA velocity was the most important factor and caused a significant increase in ACM for both RP- and RT-treated patients. Other than age, no other factors investigated had a significant influence on both treatment methods. Thus, the factor most strongly linked to cancer death, to such an extent that it also increased ACM, is PSA velocity before diagnosis. Based on these findings it is recommended that PSA velocity should be determined in otherwise low-risk patients.

An analysis of a subgroup of low-risk patients from this study who had RP showed that the number of deaths from prostate cancer was higher in men with a PSA velocity of >2 ng/mL/year than in men with lower velocities (P < 0.001) [Fig. 1] [2]. There were similar results in both low-risk and high-risk patients who had RT; men with lower PSA velocities had fewer cancer deaths [3]. Thus a PSA velocity >2 ng/mL/year in the year before diagnosis essentially turns an otherwise low-risk patient into a high-risk patient. The threshold of 2 ng/mL/year for PSA velocity was selected as this was the value of upper quartile for men undergoing surgery. The absolute value of this threshold is less clinically relevant than the amount of the increase over a given time.

As more screening is undertaken, PSA levels seen at presentation are decreasing. Of men with PSA levels of <3 ng/mL, 5% have Gleason scores of 8–10 [4]. Thus, over time, the utility of the PSA level will decrease and it is likely that the value of PSA velocity analyses will increase. The detection of impalpable disease is also increasing, so the utility of the T category is becoming less. Gleason score remains important, but there has also been a stage migration towards lower Gleason scores.

To summarize, men categorized as having low-risk disease (based on PSA level, Gleason score and T category) whose PSA has risen >2 ng/mL in the year before diagnosis are likely to follow the clinical course of high-risk disease. For those considering RT, the combination of RT and hormonal therapy (HT) has survival benefits in this setting, and the addition of chemotherapy could also be considered. For those considering RP a clinical trial is currently underway to evaluate chemotherapy plus RP vs RP alone.

An analysis of PSA kinetics is also being increasingly used in the setting of a rising PSA level after RP or RT. Several studies have shown that the rate of rise of PSA at the time of recurrence is closely associated with the time to cancer death.

The Radiation Therapy Oncology Group 9202 trial is a study of men with T2c–T4 prostate cancer treated with RT plus either short-term (an LHRH agonist plus flutamide for 2 months before and during RT) or long-term (as short-term therapy but then LHRH monotherapy continued for 2 years after RT) HT. The results show that men with a PSA-DT of ≥12 months have a significantly better prostate cancer survival rate than men with a PSA-DT of <12 months [Fig. 2] [5,6].

Another study including data from the Cancer of the Prostate Strategic Urological Research
Endeavor showed a marked difference in cancer-specific survival and deaths in men with a PSA-DT <3 months compared to men with a PSA-DT ≥3 months, whether they had undergone RT or RP before salvage HT (Fig. 3) [7]. The ability of the PSA response to predict time to PCSM after salvage HT was assessed using data from a single-institution and two pooled multi-institution databases containing baseline, treatment, and follow-up information on men who had salvage HT for PSA failure after RP or RT. The PSA response was defined as the absolute value of the ratio of the rate of PSA change after salvage HT to the rate of PSA change before salvage HT. The PSA response was significantly associated with time to PCSM after salvage HT in both the study (199 men; \( P = 0.001 \)) and validation (1255; \( P < 0.001 \)) cohorts. Men with a PSA response of ≤1 had a significantly shorter time to PCSM than men with a PSA response of >1 in both the study (HR, 3.6; \( P = 0.01 \)) and validation (HR 12.8; \( P < 0.001 \)) cohorts.

A third study from Johns Hopkins Hospital also showed that, as PSA-DT decreased, there was a corresponding increase in PCSM in men with PSA recurrence after RP [Fig. 4] [8]. The investigators analysed a retrospective cohort of 379 men who had had RP and a biochemical recurrence. The PSA-DT (<3.0 vs 3.0–8.9 vs 9.0–14.9 vs ≥15.0 months), Gleason score ≤7 vs 8–10, and time from RP to biochemical recurrence (≤3 vs >3 years) were all significant risk factors for time to PCSM.

Results from these studies indicate that, in the general population, 15–20% of men with PSA failure fall into the ‘short PSA-DT’ group (<3 months) associated with a very poor prognosis, whereas in a screened population within a clinical trial 6–7% of men with PSA failure fall into this group. This does not suggest a decrease in mortality due to PSA screening but rather a stage migration phenomenon.

Therefore older men with prostate cancer with long PSA-DTs, where the risk of prostate cancer death is relatively low, might need no further therapy. The potential adverse effects of HT (not only hot flashes, bone changes and anaemia, but also evidence of insulin resistance, arterial stiffness, unfavourable lipid profiles, and cardiovascular effects) might outweigh the benefits in this population of patients. Better risk-assessment models are required to help to identify at an early stage men who are at high risk of prostate cancer death and who might benefit from aggressive therapies, and similarly to identify men who are at low risk for prostate cancer death and who can be safely observed.

CONCLUSIONS

Risk factors for PCSM are a PSA velocity of >2.0 ng/mL/year, a Gleason score of 8–10 and an increasing PSA level. The most important risk factor that has an impact on both PCSM and ACM is a PSA velocity of >2.0 ng/mL/year. The PSA-DT is significantly associated with PCSM in men treated with RP, RT, or RT plus both short- and long-term HT. A PSA-DT of <3 months is associated with a poor prognosis and represents 15–20% of PSA failures in the general population and 6–7% of PSA failures in a screened population, such as those included in clinical trials.

CONFLICT OF INTEREST

None declared.

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Abbreviations: RP, radical prostatectomy; RT, radiation therapy; PCSM, prostate cancer-specific mortality; ACM, all-cause mortality; PSA–DT, PSA doubling time; HT, hormone therapy.