The role of surgery as active treatment for high-risk localised prostate cancer seen from an epidemiological perspective

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Abstract

Introduction
Prostate cancer is the most common malignancy in men and represents one of the main causes of cancer-related mortality. This review article concisely clarifies the epidemiology of high-risk localised prostate cancer based on latest evidence concerning its treatment and the role of new prognostic tools.

Discussion
A decrease in high-risk prostate cancer diagnosis has been noted during the last decade, likely resulting from intensified prostate cancer screening. In parallel, prostate cancer mortality has decreased by 40% in the last two decades. Hypothetically, this could be the result of the decreased incidence of high-risk prostate cancer and/or by a better management of the disease.

There is sufficient evidence in the literature demonstrating that active treatment for high-risk localised prostate cancer is associated with an important decrease in prostate cancer mortality when compared to treatment with non-curative intent. Even in node-negative prostate cancer, detected through an extended pelvic lymph node dissection, radical prostatectomy has demonstrated to improve patients’ overall survival compared to patients in whom radical prostatectomy was abandoned. Moreover, recent large retrospective series suggest lower prostate cancer-related mortality rates for radical prostatectomy compared to radiotherapy. However, randomised clinical trials are needed to confirm these results.

Commonly used high-risk prostate cancer definitions, based on pre-operative clinico-pathological findings, are useful but insufficient for stratifying patients’ risk of poor outcome. Therefore, several nomograms have been developed to improve the predictive value of these pre-operative findings. The future for further sub-stratification and personalised medicine, however, lies within the development of biomarkers.

Conclusion
Prostate cancer remains the most frequently diagnosed cancer among men and high-risk prostate cancer represents an important subgroup. When diagnosed with high-risk prostate cancer, mortality rates are high if patients do not undergo treatment with curative intent. The future lies in the development of novel biomarkers, optimising pre-treatment risk stratification and identifying the true ‘high-risk prostate cancer patient’.

Introduction
Prostate cancer (PCa) is a major health care problem because of its high prevalence, health-related costs and mortality; this is even more in case of patients with high-risk disease. At PCa diagnosis, reported incidence rates of high-risk localised PCa vary between 17% (cT3a, PSA > 20 ng/ml, Gleason score (GS) ≥ 8) and 31% (c2cT3a, PSA(prostate-specific antigen) > 20 ng/ml, GS ≥ 8), depending on how this disease was defined. After primary treatment, patients with high-risk localised PCa have a higher risk of disease recurrence and progression (e.g., PSA failure, need for secondary therapy, metastatic progression and PCa-related death) resulting in worse prognosis.

Despite the impact of this high-risk disease, a standardised definition is still lacking. D’Amico initially introduced a risk stratification based on three common available clinical features, by PSA, biopsy GS (bGS), clinical stage (cT) and defined high-risk localised PCa as PSA > 20 ng/ml or bGS ≥ 8 or cT2c. After this, different definitions have been proposed by major scientific associations (e.g., European Association of Urology; American Urological Association; National Comprehensive Cancer Network, Radiation Therapy Oncology Group, Cancer of the Prostate Risk Assessment Score), but a general consensus remains absent.

The importance of recognising this subpopulation in clinical practice cannot be stressed enough, because of their unfavourable prognosis if not treated with curative intent. In 2005, Albertsen et al. showed that patients aged 55–74 years with high-grade disease (bGS 8–10), who were treated conservatively (e.g., observation or immediate or delayed androgen deprivation therapy (ADT)), had a high probability of dying from PCa with estimated 20-year PCa-specific cumulative mortality rates (PCSM) ranging between 60 and 90%.

Recently, Rider et al. published 10- and 15-year estimated PCSM rates of 28.8 and 35.5% (all ages) in patients with high-risk localised PCa (T3 or PSA level 20- < 50 ng/ml or bGS ≥ 8) who were treated without curative intent. These mortality rates were much higher when compared to men diagnosed with low-risk (4.5 and 8.9%) and intermediate-risk (13.0 and 19.6%) PCa.

When treating patients with high-risk localised PCa with curative intent, radical prostatectomy (RP) with extended pelvic lymph node dissection (e-PLND) represents one of the possible treatment options.
Yossepowitch et al. showed that when RP is performed in patients with high-risk localised PCa, 10-year PCa mortality rates were excellent. Dependent on the definition used, 10-year PCa mortality rates varied between 3 and 11%\(^2\). These findings indeed suggest that, while current high-risk localised PCa definitions are not sufficient to correctly define this heterogeneous group of patients, the outcomes are far surpassing those of conservative treatments.

Currently, there is a growing interest in the treatment of high-risk localised PCa and in defining the ‘true’ high-risk PCa patient. Therefore, the aim of this review article is to concisely describe the epidemiology of high-risk localised PCa and provide the latest evidence concerning the role of surgery and new prognostic tools in high-risk prostate cancer (HRPCa).

**Discussion**

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

**Diagnosis and incidence**

PCa represents 28% of all cancer diagnoses in men, covering 50% of all diagnosed cancers together with lung/breast and colorectal cancers, which are the most common causes of death from malignant tumours in men\(^1\). Estimations show that in 2008 alone, 899,000 patients were diagnosed with PCa and 258,000 men died because of this disease worldwide. In 72% of cases, PCa was diagnosed in industrialised countries, but the highest mortality rates were reported in South America, the Caribbean and sub-Saharan Africa\(^2\). Recent epidemiological results suggest that in the United States, one in six men will develop PCa during their lifetime with an estimated 238,590 new cases and 29,720 cancer deaths in 2013.

Although incidence rates of PCa are high, they have been decreasing since 2000–2009 with a rate of 1.9%/year, resulting in a 40% reduction in PCa deaths over the last two decades\(^2\). This could be explained by the increased use of PSA as a screening tool and by the improvements in PCa management.

Epidemiological studies from Europe show comparable data with an estimated incidence of 416,700 new PCa cases in 2012 representing 22.8% of cancer diagnoses in men. In total, 92,200 cancer specific deaths are expected, making PCa one of the three cancers men are most likely to die from with a mortality rate of 9.5%\(^4\).

Previous data from the Surveillance, Epidemiology and End Results Program database showed that high-risk localised PCa (≥cT2c or PSA level >20 ng/ml or GS ≥ 8) diagnosis was more common among blacks and increased with age in both whites and blacks. High-grade PCa (GS 8–10) incidence decreased from 47.5/100,000 in 1988–1989 to 38.3/100,000 in 2004–2005 as well as the incidence of cT3/4 PCa, which decreased from 90.9/100,000 in 1988–1989 to 13.3/100,000 in 2004–2005\(^5\).

Cooperberg et al. showed that in a cohort of 10,385 patients diagnosed with localised disease, 31.8% had a high-risk profile (PSA level >20 ng/ml or GS ≥ 8 and/or a cT2c-3a), and a decline in incidence rates was observed from 46.0% in 1990–1994 to 29.9% in 2000–2001 and to 25.1% in 2004–2006\(^6\). This decrease in high-risk localised PCa incidence could hypothetically be explained by an intensified PCa screening during the last decades with earlier diagnosis and treatment. The European Randomised Study of Screening for PCa supports this hypothesis, showing less high grade and stage tumours in the screening group (GS ≥ 8: 8%, cT3/4: 9%) when compared to the control group (GS ≥ 8: 14%, cT3/4: 17%), therefore resulting in lower rates of high-risk disease (cT1-T3 + GS8-10 or cT4) in patients undergoing PCa screening (7.0–7.4 vs. 10.8–12.5%)\(^7\). The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial showed similar data (GS ≥ 8: 8.4 vs. 11.5%, stage III/IV: 3.5 vs. 4.6%)\(^8\).

**Natural history and surgical therapy**

The natural course of high-risk localised or locally advanced PCa can be associated with very high mortality rates, as shown by the results of the Prostate Cancer Data Base Sweden study in which a cohort of 12,184 patients with localised and locally advanced PCa at T3/4 or cT2 with PSA=50-99ng/ml were treated with non-curative intent. The 8-year PCSM was 52% for GS 8 and 64% for GS 9–10 disease irrespective of age; PCSM rates in patients aged >85 years were still 42%. In every age group, GS was the strongest predictor of PCSM (GS ≥ 9 delete vs. GS 8: HR: 2.32 (95% CI: 2.07–2.61)\(^9\). More recently, a large study from the National Prostate Cancer Register of Sweden, analysing a cohort of 30,159 patients with HRPCa (cT3 or PSA: 20–<50 ng/ml or GS ≥ 8), found 15-year cumulative PCSM rates of 21.7 and 35.5% when treated with (EBRT (+ADT), RP + e-PLND) or without (ADT) curative intent, respectively. Mortality rates were highest in regionally (49.1%) and distant metastatic (69.5%) disease. These data emphasise the deadliness of this disease, which is greatly reduced when treated with curative intent, irrespective of age\(^10\).

Even though it is clear that treatment with curative intent is of utmost importance in high-risk localised PCa, it is still heavily debated which is the optimal treatment option. The two major approaches are EBRT + ADT or RP + e-PLND; in many cases,
a multi-modal approach needs to be considered. In clinical practice, however, hormonal treatment is still largely used. When evaluating trends of different therapeutic approaches for high-risk localised PCa (cT2c-T3a, PSA > 20 ng/ml, GS ≥ 8), Cooperberg et al. showed that during 1990–2007, there was an increase in hormonal treatment (20 to 29%), a decrease in EBRT (22 to 11%) and comparable rates of surgery being performed (45 to 42%)1.

The aims of surgery as primary treatment for high-risk localised PCa are local tumour control, staging and grading optimisation. This optimal staging has two purposes: firstly, it permits a more individualised approach and secondly prostate specimens may be used for research purposes. Surgery is not only interesting for its staging purposes, since there are also convincing data showing the efficiency of RP. Engel et al. analysed a cohort of 1,413 patients with node-positive disease and compared patients who did vs. those who did not undergo RP. They concluded that patients with node-positive disease in whom RP was abandoned, had a two times higher risk of overall mortality when compared to patients in whom RP was completed (HR: 2.04; 95% CI: 1.59–2.63; p < 0.0001)17. Supporting these results, a post-hoc analysis from the SPCG-4 trial, randomising patients with localised PCa to watchful waiting or RP, showed 10-year cumulative PCSM rates of 14.1 and 9.5% respectively; younger patients with more aggressive disease features had most benefit from surgery18. More recently, a large retrospective series on high-risk localised PCa patients treated by RP + e-PLND confirmed the excellent outcomes following surgery and showed that even senior adults with two to three high-risk factors without major co-morbidities had low CSM rates, comparable to younger patients. As expected, other cause mortality was the leading cause of death in this group, however without having an impact on CSM rates19. The PIVOT trial, randomising patients with localised PCa for RP vs. observation, showed significantly lower PCSM rates after performing surgery for patients with PSA > 10 ng/ml (5.6 vs. 12.8%; p = 0.02) and high-risk PCa (cT2c-T3a, PSA ≥ 20 ng/ml, GS ≥ 8; 9.1 vs. 17.5%; p = 0.04) when compared to observation20.

Although there is sufficient evidence showing the efficacy of RP in patients with high-risk PCa, there is a paucity of evidence comparing different treatment options. In a retrospective analysis from the Memorial Sloan Kettering Cancer Centre (MSKCC), Zelefsky et al. suggested that RP + e-PLND had a better outcome when compared to intensity-modulated radiotherapy (IMRT; dose ≥81Gy), especially in high-risk localised PCa patients (8-year PCSM: RP 3.8 vs. IMRT 9.5%)21. Another large retrospective series by Boorjian et al. showed that HRPCa patients treated with EBRT alone (median dose 72Gy) had a higher risk of systemic progression (HR: 1.53; 95% CI: 1.05–2.23; p = 0.03) and PCSM (HR: 2.14; 95% CI 1.35–3.39; p = 0.001) when compared to patients undergoing RP22. To clearly define the optimal treatment option for localised high-risk PCa patients, there is an urgent need for a randomised clinical trial comparing radiotherapy and surgery. While interesting and highly needed, such study still might not provide all the answers to optimally guide treatment in each individual because of the heterogeneity of the disease. With the purpose of handling this major problem, many interesting biomarkers are being studied and implemented in order to help predict disease aggressiveness.

The role of pre-operative predictive models

As discussed above, when evaluating outcomes of high-risk localised PCa after RP authors have used different definitions. Yossepowitch et al. assessed how accurately these definitions could identify patients likely to receive secondary cancer therapy, develop metastatic progression or die of PCa. They analysed these outcomes using different risk definitions in a cohort of 5,960 patients from MSKCC who were surgically treated. Each of the studied high-risk definitions was associated with an increased risk of secondary cancer therapy and metastatic progression. Depending on the definition used, 35–76% of patients did not require additional therapy and 72–91% of patients did not develop metastasis 10 years after RP23. Comparing different treatment options is difficult because different classification systems are being used and because of the inter-observer variability of pre-treatment clinico-pathological features.

Moreover, GS is down-graded (from biopsy to post-operative specimen) in up to 45% of cases and staging errors (higher pathological stage after surgery in 68% or down-staging from cT3 to pT2 tumours in 26%) are common23–25. For the diagnosis of extra-capsular disease and seminal vesicle invasion, magnetic resonance imaging performs better compared to digital rectal examination, which only has an accuracy of 60%26.

Since pre-operative clinico-pathological features in isolation are no optimal tools to predict tumour characteristics and disease outcomes, new predictive models have recently been proposed to predict specimen confined disease and lymph node invasion (LNI). Recently, Briganti et al. proposed a nomogram incorporating age, iPSA, clinical stage and biopsy GS, which had a 72% accuracy in predicting specimen confined PCa. This information helps identifying patients at high risk of post-operative local failure (positive surgical margins or locally advanced disease (pT3b/4, pN1))27. Briganti et al. proposed another nomogram based on PSA, clinical stage, biopsy GS and the percentage of positive biopsy cores to predict LNI with an accuracy of 87.6%28.
The clinico-pathological features used in these nomograms are still affected by the inter-observer variability. Even though current nomograms are useful at guiding decision making, the future lies within pre-operative biomarkers which have already shown to improve the accuracy of predictive models. Therefore, these data should stimulate continuing efforts in biomarker research, which could and will open new perspectives to a better and clinically useful risk stratification for PCa and identifying the ‘true’ high-risk patient.

Conclusion

PCa remains the most frequently diagnosed cancer among men with high-risk localised PCa representing an important subgroup. During the last decades, the incidence rates of high-risk localised and locally advanced PCa have decreased likely as a result of intensified PCa screening which has led to earlier diagnosis and treatment. However, when diagnosed with high-risk localised PCa, mortality is high if patients do not undergo treatment with curative intent. Currently, patients still too often receive hormonal treatment as monotherapy, a practice which is based on the historical belief that HRPCa cannot be cured. Recent evidence however shows excellent cancer-specific survival following RP, even in very high-risk patients with regional LNI. However, reported outcomes after RP vary significantly depending on the high-risk definition used and as a result of the inter-observer variability of pre-treatment clinico-pathological features. Because of this heterogeneity, there is still no optimal treatment for the high-risk localised PCa patient, which does not only impact clinical practice but also has its effect on designing randomised trials comparing treatment options. Recently, several useful nomograms have been proposed in order to optimise the prognostic value of current clinico-pathological features. Nevertheless, while being useful and more accurate than clinical features in isolation, pre-treatment nomograms are still lacking sufficient accuracy. The future lies in the development of novel biomarkers and their introduction into nomograms, optimising pre-treatment risk stratification and identifying the ‘true’ high-risk PCa patient.

References

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