High-risk localised prostate cancer: the role of surgery and the development of clinical outcome prediction models

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This PhD thesis is aimed at elucidating some very important issues on high-risk prostate cancer: How can high-risk prostate cancer best be defined? Can we clearly define demarcated prognostic subgroups within the high-risk prostate cancer group which could allow improved patient counselling, comparison of different treatment strategies and proper trial design? What are the outcomes of surgery in high-risk prostate cancer and how can we identify those patients within the heterogeneous group of high-risk prostate cancer who would benefit most from surgery?

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Introduction

Prostate cancer (PCa) constitutes a major health problem and poses specific challenges in the male population. Worldwide, PCa is the second most frequent cancer in men while being the sixth most frequent cause of cancer death. In developed countries, PCa is the most prevalent cancer in men, taking third place in cancer mortality.[1] Studies have demonstrated that patients with high-risk features (cT3, PSA >20 ng/mL, biopsy GS 8-10) have a significantly increased risk of dying from their disease.[2-4] Patients with high-grade PCa who are managed expectantly have a high probability of dying from PCa within ten years of diagnosis. Their estimated risk of dying from PCa is 60-90% at 20 years, depending on the age of the patient. Men with locally advanced PCa (cT3 or cT4 or cT2 with PSA between 50 and 99 ng/mL) who are managed with non-curative intent have a PCa-specific mortality at eight years of 52% (in patients with biopsy GS 8) and 64% (in those with biopsy GS 9-10).[5,6]

Interestingly, there is no definitive consensus regarding the definition of high-risk PCa. For example, D'Amico et al. defined high-risk localised PCa as stage = cT2c, or PSA >20 ng/mL, or GS 8-10, while the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines define high-risk PCa as stage = cT3a or PSA >20 ng/mL or GS 8-10.[1] Furthermore, not all patients diagnosed with high-risk PCa have an invariably poor prognosis. Several reports indicate heterogeneous outcomes for the group of high-risk PCa patients.[2,4] Despite an extensive awareness on PSA screening and early detection of PCa, a fair proportion of patients still present at diagnosis with high-risk PCa. In the recently published European Randomised Study of Screening for Prostate Cancer (ERSPC), 9.8% of the patients had T3/T4 tumours and 8.8% had GS >7 in the screening arm, while in the control arm, these figures were 15.8% and 19.5%, respectively.[7]

Therefore, this thesis about high-risk prostate cancer is aimed at improving the definition, identifying different prognostic groups, revealing which patient might most benefit from surgery and describing the complications and functional results of a surgical approach.

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Keywords: high-risk prostate cancer; locally advanced prostate cancer; risk groups; risk stratification.

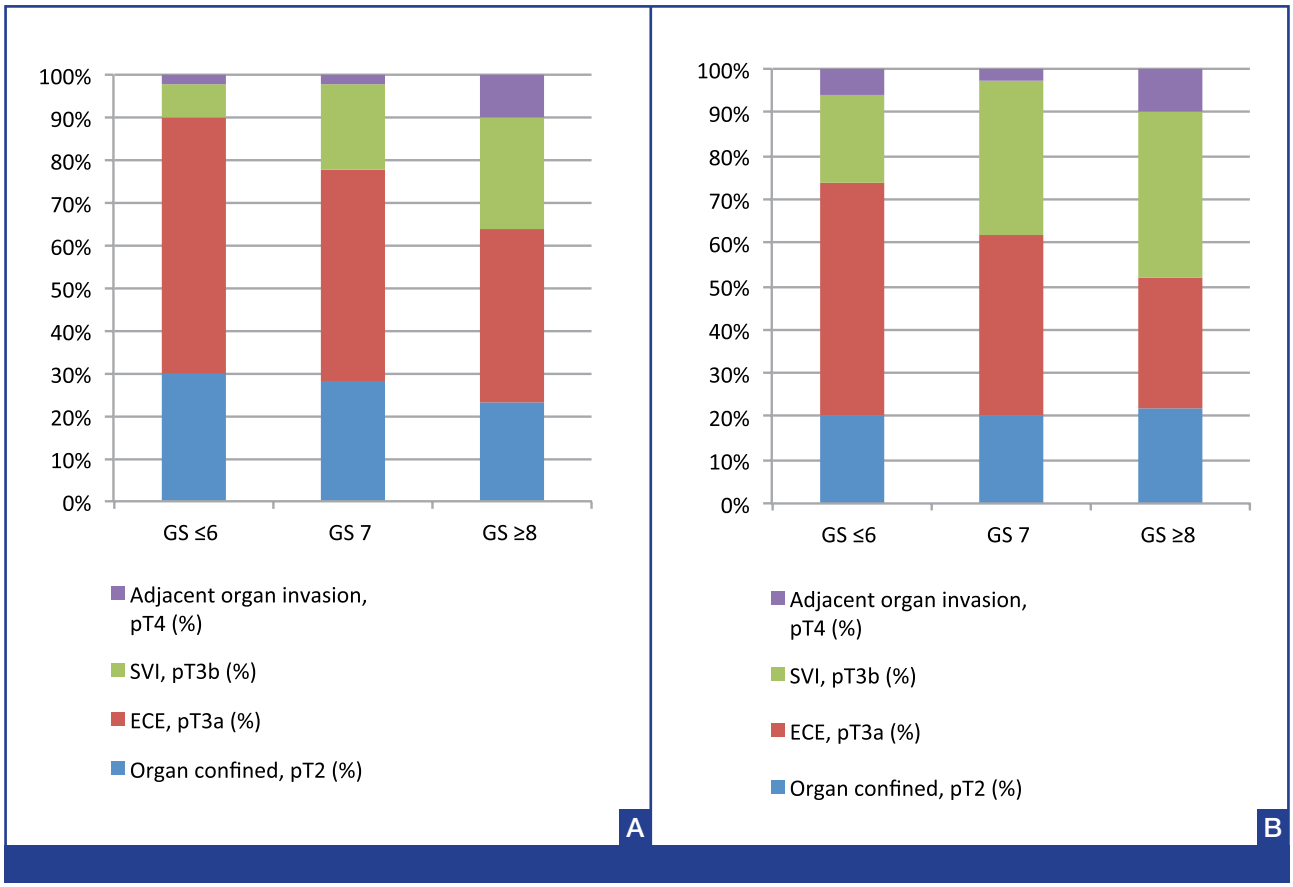

Figure 1. Prediction of pathological stage in cT3a PCa. **1A.** cT3a + PSA ≤ 10 ng/mL. **1B.** cT3a + PSA 10 – 20 ng/mL.

Development of clinical prediction models

The first aim was to better define high-risk PCa within the whole spectrum of the disease. We used data from three tertiary referral centres and assessed generally accepted risk factors which have repeatedly been associated with disease recurrence and PCa-related death: cT3, GS 8-10 or PSA >20 ng/mL.[1-4,8] We also studied the impact of the sum of high-risk factors on pathological and oncological outcomes. Interestingly, all three high-risk factors were confirmed to be able to determine the population at the highest risk of biochemical recurrence (BCR).[8] Moreover, this study clearly demonstrated that the sum of high-risk factors can be used to define a population at an even higher risk of poor oncological outcome. We further assessed whether the use of additional risk factors (cT3-T4 and GS 8-10) could improve outcome predictions in the group of high-risk patients with PSA >20 ng/mL.[9] Unlike clinical stage and GS, PSA is a continuous variable. The value of 20 ng/mL may therefore be considered an arbitrary threshold defining high-risk PCa. The number of high-risk factors was indeed confirmed to be able to further stratify this group into four demarcated subgroups, each with different BPFS, CPFS, CSS and OS. GS was the strongest predictor of progression and mortality.

These observations are important, as they add supportive evidence to the high-risk PCa definitions used by the EAU and NCCN. Furthermore, it is clear that the accumulation of risk factors is associated with an increasingly worse BPFS and even CSS. This observation needed to be confirmed in the total group of high-risk PCa, which brings us to the second aim.

The second aim of this PhD project was to develop a substratification system which can divide high-risk PCa into well-demarcated prognostic subgroups. Various combinations of high-risk factors were tested and finally, an easy-to-use predictive model was designed which allows substratification of high-risk PCa.[10] The model comprises of three prognosis subgroups: a good prognosis subgroup bearing one single risk factor (either PSA >20 ng/mL, stage cT3-T4, or GS 8-10), an intermediate prognosis subgroup encompassing stage cT3-T4 and PSA >20 ng/mL, and a poor prognosis subgroup containing a combination of GS 8-10 with PSA >20 ng/mL and/or cT3-T4. CSS rates were significantly different between the good, intermediate and poor prognosis

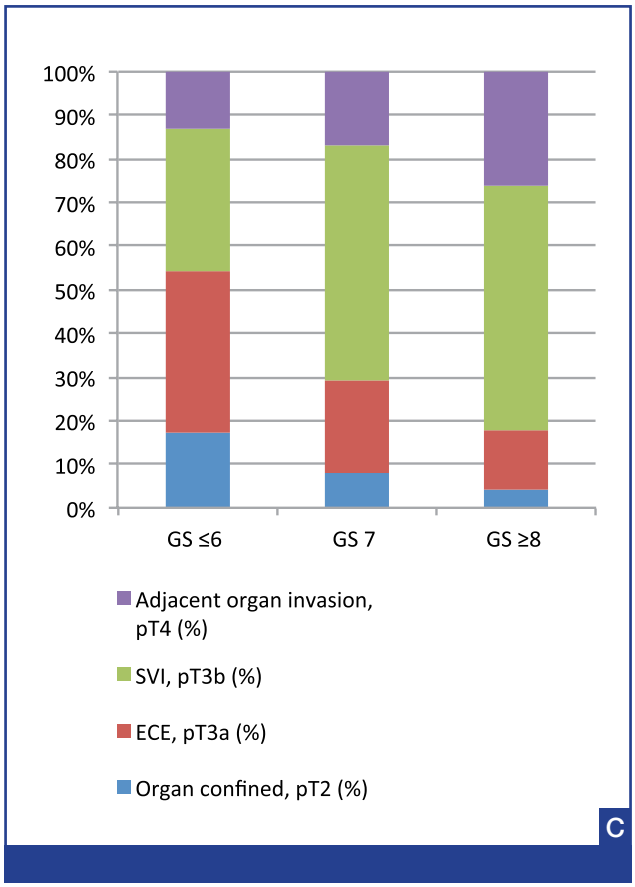

Figure 1C. cT3a + PSA > 20 ng/mL.

subgroups. In addition, the substratification provided a clear distinction in OS and CPFS rates between the three subgroups, with survival rates being the lowest in the poor prognosis subgroup. The predictive accuracy of this model was high, i.e. the 5-year AUC was 0.70 and this was not different from the model including all seven possible combinations of dichotomised high-risk factors. As such, this study is the first to propose a new substratification of high-risk PCa including number and combinations of risk factors and based on survival and histopathological outcomes after radical prostatectomy (RP).

A specific subgroup of high-risk PCa patients is those with locally advanced disease. The optimal management in such patients continues to be debated. Although surgical treatment has traditionally been discouraged because of an increased risk of positive surgical margins, LN metastases and/or distant relapse, recent guidelines indicate that surgery may have a place in the management of cT3a PCa.[1] The third aim of this PhD project was to develop pre-treatment models which can help to identify patients with locally advanced PCa who might benefit most from RP. We present graphs predicting pathological outcomes after RP for patients with cT3a PCa based on pre-treatment PSA levels and biopsy GS (*Figures 1A-C*).[11] The risk of positive LN also increases with preoperative PSA levels and biopsy GS. These graphs may be used widely when counselling patients preoperatively. Moreover, they may equally be used by radiation oncologists and medical oncologists in treatment planning for high-risk PCa patients. In a second study, also fitting within the third aim of the project, a preoperative nomogram predicting specimen-confined PCa was constructed.[12] Roughly 40% of the patients were confirmed to have specimen-confined PCa after surgery. First, specimen-confined PCa was confirmed to be associated with exceptionally good BPFS (66%) and CSS (98%), compared with non-specimen-confined PCa (BPFS 47% and CSS 88%, both $p<0.001$). Second, a nomogram was constructed using all available preoperative clinical variables (age at surgery, PSA, biopsy GS and clinical stage). The nomogram demonstrated a 72% accuracy in predicting specimen-confined PCa.

The fourth aim was to analyse the role of surgery in very high-risk PCa. We performed a detailed analysis of patients with cT3b-T4 PCa from our centre.[13] Intriguingly, over-staging in this very high-risk PCa group was still substantial, with roughly one third of the patients having organ-confined disease or capsular perforation only. Those patients were often cured by surgery alone, as 35.3% of the whole group did not receive any form of (neo)adjuvant treatment and 21.6% remained free of additional therapies at a median follow-up of 108 months. CPFS at ten years was 72.5% and CSS was 91.9%. This paper is one of the very few reports of the possible role of surgery in very high-risk PCa. The study adds evidence to the ability of surgery in obtaining local disease control and -more intriguingly- to the importance of local disease control in achieving extremely good CSS and OS at long term follow-up.

The final aim of the project was to explore complications and functional results of RP in locally advanced PCa. We analysed the records of 139 consecutive patients with cT3 PCa, treated at the Department of Urology, University Hospitals Leuven.[14] Even though a more extensive, non-nerve-sparing surgery was performed in most of the patients (as would be expected in locally advanced disease), continence rates and perioperative complications were not different compared with published series on RP in organ confined PCa. In many aspects, this PhD project has clarified some of the lingering uncertainties regarding the definition and prognostic substratification of high-risk PCa and the role of

Key messages for clinical practice

1. High-risk prostate cancer constitutes a very heterogeneous group of conditions depending on the number of high-risk factors.
2. A good, intermediate and poor prognosis high-risk prostate cancer category can be distinguished on the basis of the clinical stage, the PSA level and the Gleason Score.
3. Locally advanced, high-risk localised and even very high-risk prostate cancer can be treated by initial surgery in the frame of a multimodal approach, considering the possible need of adjuvant or salvage radiotherapy or hormonal treatment.

surgery in high-risk PCa. Already, the EAU PCa guidelines have adopted and implemented the results of three of the seven published papers included in this project.[1]

Conclusion

Better identification of those patients who harbour a potentially lethal form of PCa has a far-reaching impact on global healthcare. Undoubtedly, further development of risk stratification models and tumour markers are crucial in this process and will change the face of PCa management forever. Truly individualised PCa care is on the horizon.

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