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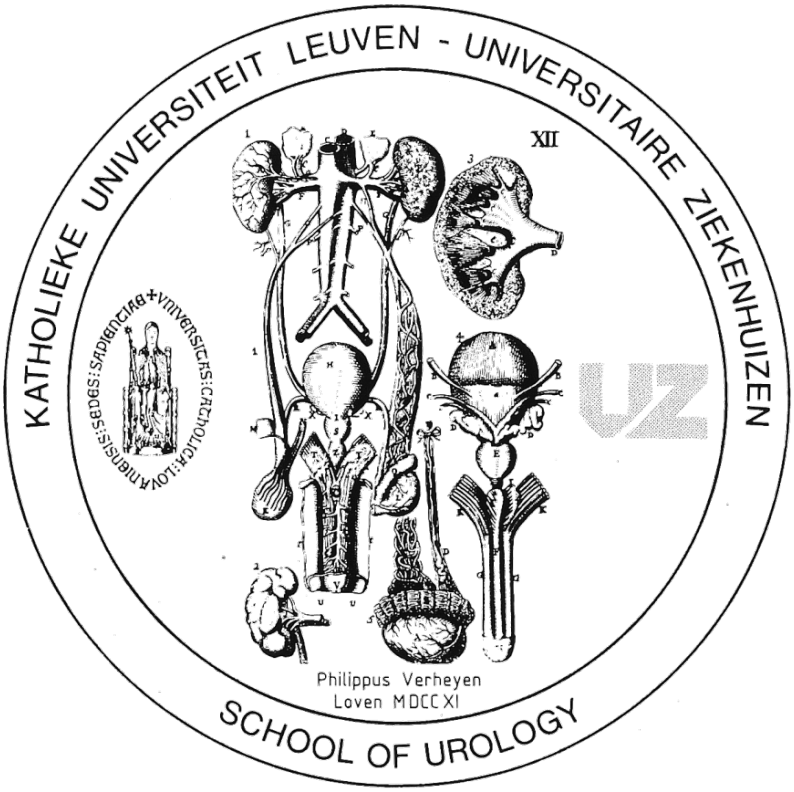
"Preoperative Risk-Stratification of High Risk Prostate Cancer: a Multicenter Analysis"



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preoperative risk-stratification of high risk prostate cancer: a multicenter analysis

Background: Cancer-specific survival within high-risk localised prostate cancer varies dramatically. This puts forward the idea of a subgroup(s) at extraordinary risk, burdened with a very poor prognosis. Establishing the characteristics of these group(s) would have significant clinical implications since high quality preoperative risk stratification remains the cornerstone of therapeutic decision making.

Objective: to stratify high-risk prostate cancer based on preoperative characteristics and evaluating the cancer specific surival after radical prostatectomy.

Method: The EMPaCT multi-center database serves as a retrospective population source for localised high-risk prostate cancer. Preoperative characteristics such as age, biopsy Gleason score, PSA and clinical stage were subcategorised. A multivariate analysis was performed on the predictors showing significant survival heterogeneity after stratification, as observed by a univariate analysis. Based upon the hazard ratios of this multivariate analysis, a proportional score system was created. The most ideal group distribution was evaluated trough Different score cut-off's. The predictive value was tested by the herald C index.

Results:
An overall 5-year cancer specific survival of 94% was noted within the general high-risk cohort (n = 4879). Except for age, all preoperative risk factors showed a significantly differing CSS. Multivariate analysis indicated T4 staging as being the strongest predictor of CSS (HR:3.31), followed by ISUP grade 5 (HR 3,05). A score system was created by doubling the hazard ratios of this multivariate analysis and rounding off to the nearest complete number. Multivariate analysis suggested 0pts - 4pts - 8pts - 12pts as being the most optimal group distribution (p-value: 0.0015). 5-year CSS of these groups were 97%, 93%, 87% an 70% respectively. The calculated Herald C-index of the model was 0.77.

Conclusion:
An accessible pre-operative model for risk stratification of newly diagnosed high-risk prostate cancer is presented. The heterogeneous cancer specific survival of high-risk localised prostate cancer after radical prostatectomy is illustrated. The model is clinically accessible through an easy-to-use online calculator, presenting cancer specific survival based on individualised high-risk prostate cancer patient characteristics.

1. Introduction:

Prostate cancer (PCa) is the second most common cancer among men. It represents the 5th most frequent cause of cancer related death (1). According to the WHO cancer report (2014), 1.1 million men received a new diagnosis of prostate cancer in 2012 causing 0.3 million disease related deaths (2). Since the introduction of PSA screening in the beginning of the 80's an impressive incidence rise has been observed. fortunately, this trend was counterbalanced by a reduction in mortality since the 90's due to earlier detection and improved curative treatments. although, mortality attributed to PCa is expected to rise in the following decades implying an expanding burden to society (3).

Localised PCa is prognostically stratified as low, intermediate or high-risk as suggested by D'Amico in 1998 (4,5). Currently, management of prostate cancer embraces active surveillance, racial prostatectomy (RP) with or without pelvic node dissection and radiotherapy (RT). As illustrated by the PROTECT-Trial, no significant difference in prostate cancer specific mortality was observed between RP and RT over a 10-year period (6). However, observed prostate cancer specific mortality was low, probably due to the absence of risk stratification. whereas low risk prostate cancer is most prevalent and known to have a good prognosis, high risk prostate cancer is rarer but contributes most to cancer specific death (6).

Depending on fitness, low risk prostate cancer (LRPCa) is manageable trough active surveillance or radical prostatectomy (RP) without lymph node dissection (LAD). RP has shown to significantly reduce the overall mortality of Intermediate-risk prostate cancer (IRPCa) (7). If probability of lymph node invasion exceeds 5%, an additional extended LAD is recommended (4). Although general consensus concerning treatment of high-risk prostate cancer (HRPCa) is lacking, a multimodal strategy including RP with extended LAD is advised in localised disease (4). Favourable results have grown new interest in surgical management of locally advanced Pca (8). If life expectancy is unfavourable, watchful waiting (WW) is applicable to all stages (4).

HRPCa, according to the national comprehensive cancer network (NCCN), is defined as Gleason score ≥8, PSA >20ng/ml or clinical stage ≥T3a (9). Interestingly the EAU differs from this as it defines HRPCA from a clinical stage exceeding T2c (4). An overall established definition of high-risk disease is thus lacking. Remarkably, metastasis free survival (MFS) varies form 70% - 95% and 10-year biochemical recurrence (BCR) shows a variability of 50% (5,10). Efforts to dissect this heterogeneity have been undertaken, as illustrated by Joniau et al (11) .

High quality risk stratification remains the cornerstone of therapeutic decision making. This retrospective study aims to stratify localised high-risk prostate cancer into subgroups showing a significantly differing CSS. Through this stratification we aim to identify and correlate patient and tumour related characteristics so individual patients can be profiled within the heterogeneous prognosis of high-risk PCa.

2. Patients and methods:

i. Patient population

The European Multicenter Prostate Cancer Clinical and Translational (EMPaCT) research database served as the source for our patient cohort. This International research database contained 9167 men from 14 institutions who underwent radical prostatectomy for locally advance prostate cancer between 1986 and 2016. Each institution acted in accordance of their own standards, indications and treatment protocols. Since only patients with complete datasets could be included, the criteria for exclusion were defined as: lacking a preoperative PSA (n:121), absent Gleason biopsy score (n:1070), incomplete staging (n:1966) and lost to follow up (n:1014). Staging evaluation was in accordance with the 2002 TNM system. All biopsies were guided by rectal ultrasound (RUS) and evaluated by an experienced pathologist in the respective center. Follow up was defined as an annual symptom evaluation and serum PSA measurement. Cancer related deaths were judged by the treating urologist or oncologist. No distinction was made concerning adjuvant or salvage therapies which were admitted on individual bases and institutional preferences. From this eligible cohort, all high-risk (PSA ≥ 20 ng/ml and/or GS ≥8 and/or cT ≥ T2c) patients were identified and included (figure 1).

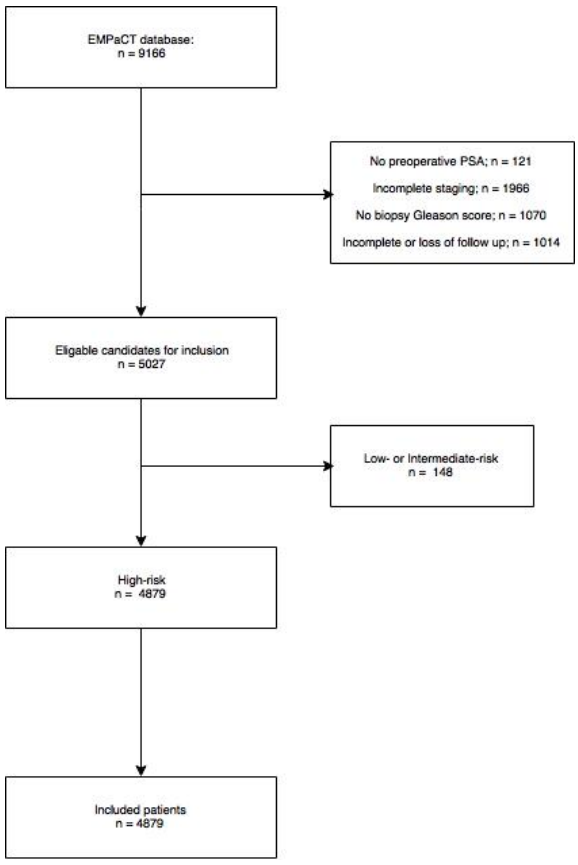

figure 1: patient selection EMPaCT database

ii. Statistical analysis

Possible preoperative prognostic variables were identified and stratified into subcategories evaluating cancer specific survival. PSA was further subcategorised into a <20ng/ml, a 20 ng/ml – 50 ng/ml and a > 50 ng/ml subgroup. Clinical stage was divided into T1, T2, T3a+b and T4 categories. Biopsies were categorised by the international Society of Urological Pathology (ISUP) grading. Finally, a Gleason core 5 subcategory was created and age was stratified into <60 years old, 60 – 69 years old and ≥70 years old. A univariate analysis of these preoperative variables was performed to evaluate their impact on CSS. A multivariate cox regression analysis was performed on the significant variables. Based on these hazard ratio's (HR) a proportional score system was created. Multiple cut-off values were tried and the different possibilities were compared by multivariate cox regression analysis. The most appropriate model was selected and its prognostic value was calculated using the concordance index (C-index). All univariate and multivariate analyses were performed using MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium)**.** The C-index was calculated using SAS-software version 9.4 (SAS Institute Inc., Cary, NC, USA). P-values <0.05 were considered to be significant.

3. Results:

i. Study population

4879 men met criteria for final inclusion. A mean follow-up of 60,5 months was noted with an interquartile range of 65 months (21mo – 84mo). The average PSA amounted to 22,7 ng/ml (0 ng/ml – 1710 ng/ml). A biopsy Gleason Score of <7 was most prominent within HRPC. Clinical stage cT3 showed most prevalent, constituting 37,5% of all high-risk cases. An overview of the characteristic of the population is given in table 1. The mean 5, 10 and 15-year survival were 94%, 89.5% and 84,6% respectively.

included patient cohort characteristics n = 4879				
Age	Mean (SD)		64,892 (6.8)	
	Median (IQR)		65 (60-70)	
PSA (ng/ml)	Mean (SD)		22,7 (41,6)	
	Median (IQR)		13 (7-27)	
	<20 µg/l		2859 (58,6)	
	20 – 50 µg/l		1415 (29)	
	> 50 µg/l		373 (7,6)	
Clinical stage, n (%)	cT1		1755 (36)	
	cT2		1245 (25,5)	
	cT3	N.O.S.	1830 (37,5)	745 (15,3)
		cT3a		948 (19,4)
		cT3b		137 (2,8)
	cT4		49 (1,0)	
biopsy Gleason score, n (%)	≤ 7		2457 (50,4)	
	8	N.O.S	1466 (30,0)	143 (2,9)
		3+5		156 (3,2)
		4+4		1116 (22,9)
		5+3		51 (1.0)
	9	N.O.S.	855 (17,5)	60 (1,2)
		4+5		608 (12,5)
		5+4		187 (3,8)
	10		101 (2,1)	
Follow up (months)	Mean		60,5 (53,8)	
	Median		48 (21-84)	
	min		0	
	max		293	

Table 1: Characteristics of study population. N.O.S: not otherwise specified

ii. Univariate analysis

PSA, clinical stage, Gleason biopsy score, age and the presence of a Gleason grade 5 underwent categorization and univariate analysis for cancer specific survival as primary outcome (figure 2). PSA was divided into three groups: less than 20 ng/ml, 20 ng/ml – 50 ng/ml and more than 50ng/ml. Gleason score was categorised by the ISUP groups. Clinical stage was divided into four groups: T1, T2, T3a+b and T4. Three age groups were identified by cut-off values of 60 and 70 years old. Finally, the presence of a primary Gleason grade 5 was dichotomised as present or absent. Except for age, all subdivisions of these preoperative risk factors showed significantly differing CSS.

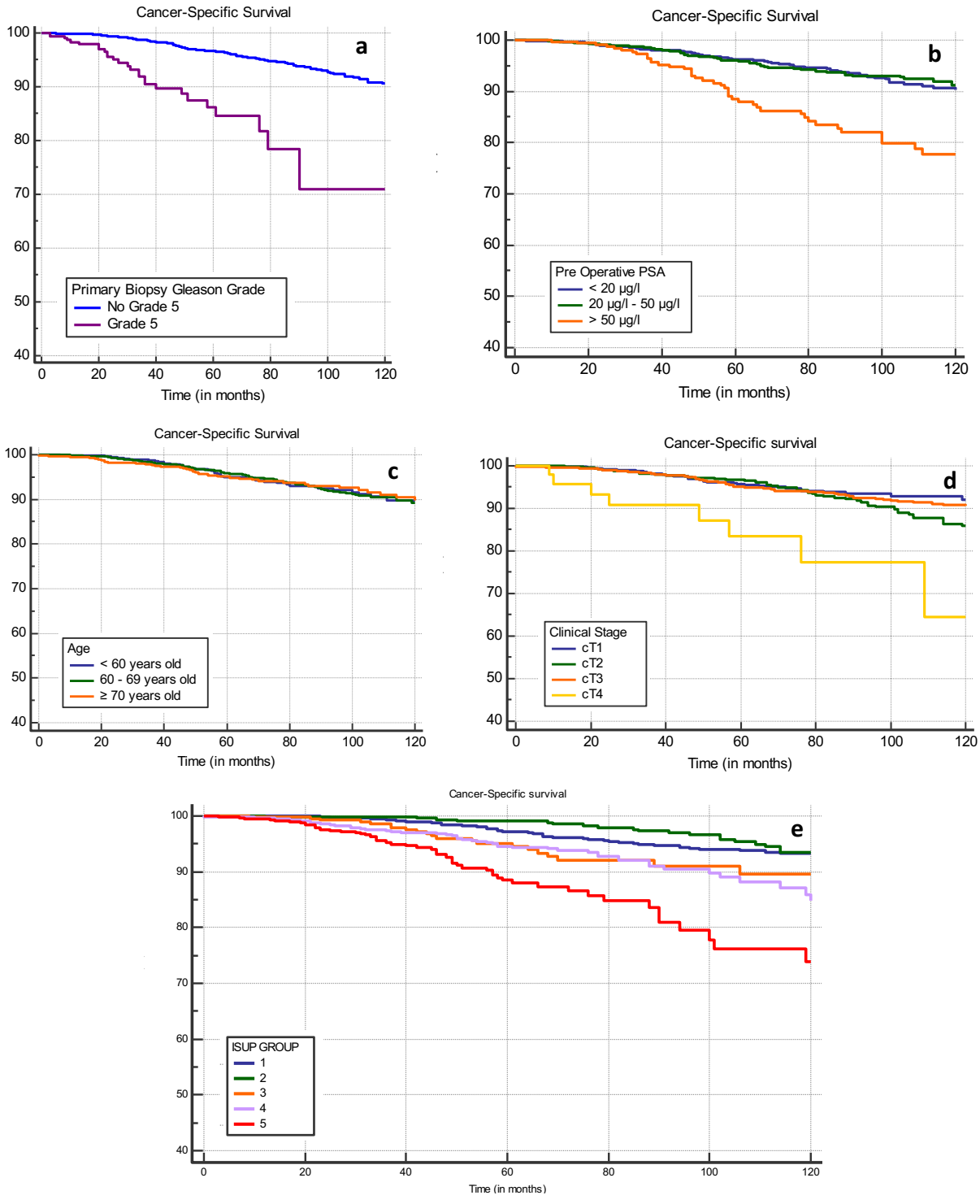

Figure 2: Univariate analysis of stratified preoperative risk factors: presence of a biopsy Gleoson grade 5 (a), PSA (b), age (c), clinical stage (d) and ISUP group (e)

iii. Multivariate analysis

The preoperative risk factor groups which showed a significantly differing CSS were included in a multivariate cox regression analysis. The strongest CSS predictor was T4 clinical stage (HR: 3,31), followed by ISUP grade group 5 (HR: 3,05). Based upon the hazard ratios from the multivariate analysis, a proportional score was determined for each subgroup. This score system was then applied to all patients. Score-based groups were identified who showed significant differing CSS. Different cut-offs were evaluated. After multivariate analysis the 0-4pts, 4-8pts, 8-12pts and > 12pts was selected as being the most optimal distribution due to strongly differing CSS between all groups (p-value: <0.0001) (fig 3). 5-year CSS of these groups were 97%, 93%, 87% and 70% respectively.

		P-value	Exp(b)	Points
PSA	*< 20 ng/ml*	reference		0
	20-50 ng/ml	**0,03**	1,48	3
	> 50 ng/ml	**< 0,0001**	2,97	6
Clinical Stage	*≤T2b*	reference		0
	T2c	**0,0145**	1,82	4
	T3a+b	0,4	1,14	0
	T4	**0,01**	3,31	7
ISUP	*≤3*	reference		0
	4	**0,0001**	2,21	4
	5	**< 0,0001**	3,05	6
Primary Gleason grade 5	*no*	reference		0
	yes	**0,0002**	2,57	5

table 2: multivariate analysis of preoperative risk factors

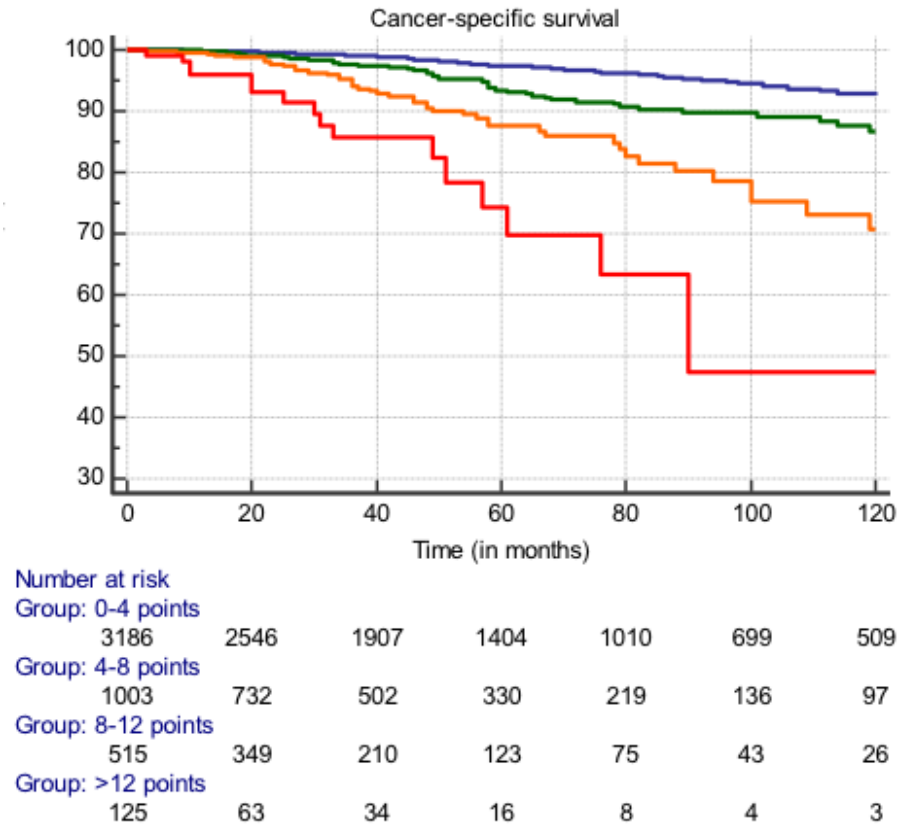

figure 3: Ten-year CSS, blue line: 0-4pts, green line: 4-8pts, orange line 8-12pts, red line: >12pts

iv. Score Validation

In order to assess the predictive value of this score system, the concordance index (c-index) was determined. A value of 0.77 was noted, implying a good correlation between the model determined subgroups and the CSS. The model is accessible online trough as an easy-to-use clinical tool.
(https://app.calculoid.com/?#/calculator/41236).

4. Discussion

When confronted with a new diagnosis of localised prostate cancer, it is common to divide patients into low-, intermediate- and high-risk subgroups (4). These groups are known to harbour a significantly differing prognosis. To date, this risk stratification remains the cornerstone of therapeutic decision making. Although there is no discussion concerning the need for surgical treatment in the high risk group, CSS is known to vary strongly thus suggesting this group to be quite heterogeneous (5). This can easily be illustrated by observing CSS after categorisation by the number of high risk factors. Intuitively a poorer prognosis is observed in patients showing multiple high-risk factors (fig 4).

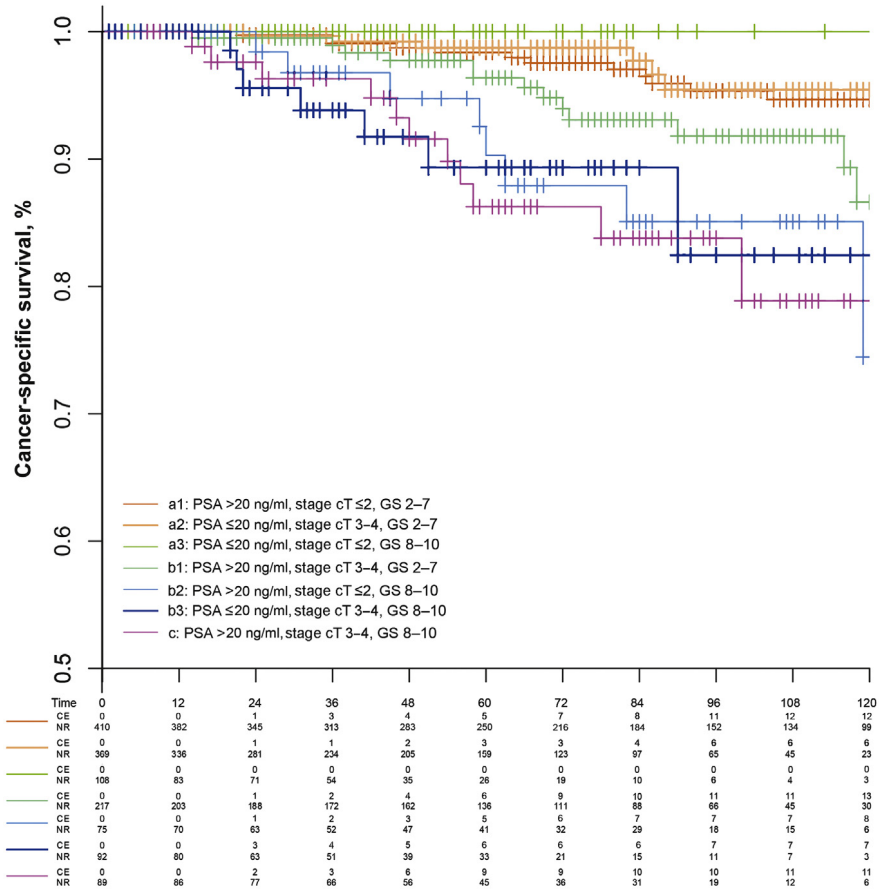

Figure 4: Prostate cancer–specific survival for the extended model with seven subgroups of high-risk prostate cancer patients. 1. Joniau S, Briganti A, Gontero P, et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol. 2015;67(1):157-164. doi:10.1016/j.eururo.2014.01.020.

Historically, tumours with unfavourable characteristics (PSA >100ng/ml, Gleason Score 9 – 10, T4 or cN1) were not considered ideal candidates for surgery (9). This is largely due to fear for occult metastasis, which is not yet detectable by conventional staging technology at a given time. However, favourable results have been achieved in surgical treatment for non-metastatic, hormonal sensitive locally advanced prostate cancer (8).

Previous efforts have been undertaken to stratify high-risk PCa (10,11). The capability to distinguish good from poor surgical candidates remains critical in clinical practice.

Sundi et al. illustrated that the presence of a primary grade 5 on biopsy, or ≥5 cores showing a Gleason score 8-10 were predictive for a significantly increased risk of metastasis and cancer specific mortality (5). Unfortunately, no data concerning number of positive biopsy cores is available in the EMPaCT database. However, univariate analysis of ISUP grading and presence of a primary Gleason grade 5 clearly shows its independent prognostic significance. Thus, our findings are in concord with Sundi et al.'s observation.

It has been suggested that PSA is a less valuable predictor (11,12). Gontero et al. illustrated that, although prognosis diminishes with rising PSA, no absolute upper limit for radical prostatectomy exists (12). This biomarker is susceptible to a couple of difficulties. Firstly, it is a continuous variable. A clear cut-off is lacking. Secondly, our results suggest that PSA harbours the weakest CSS prognostic predictive value (HR 1.48). Only very high PSA values (>50 ng/ml) are good predictors for poor CSS (HR 2.97). These findings thus align with general belief that this biochemical marker should not be decisive in therapeutic decision making, except if extremely elevated.

Although age showed no independent value in the univariate analysis of CSS, it is very important in therapeutic decision making since age is mostly inversely proportional to general fitness. unfortunately, our data and model has no eye for comorbidity such as a Charlson score since this information was only available for a minority of patients.

Further evaluation shows that patients with a higher score were more likely to need adjuvant therapy such as androgen deprivation therapy, radiotherapy or both. Furthermore, we were able to illustrate that scores proportionately correlate to higher risks for biochemical recurrence, positive surgical margins and lymph node invasion (table 3).

	n	Adjuvant therapy +		Biochemical recurrence		surgical margins: R1 +		Positive lymph nodes: N+	
0-4pts	2998	582	20,4%	215	7,2%	926	30,9%	587	19,6%
4-8pts	831	275	33,0%	147	17,7%	439	52,8%	346	41,6%
8-12pts	471	208	44,2%	116	24,6%	307	65,2%	264	56,1%
>12pts	108	54	50,0%	31	28,7%	86	79,6%	72	66,7%

Table 3: need for adjuvant therapy and rates of (average) biochemical recurrence, positive surgical margins and lymph node invasion. Stratified by model subgroups.

This model was created as a tool to aid the clinician in estimating the CSS of his patients within the heterogeneous high-risk PCa group. It is able to distinguish those who will fare well from those who will benefit poorly from RP, irrespective of future need for adjuvant therapy. It can thus help tilt the scale towards more or less intense treatment based upon more detailed high-risk patient and tumour characteristics.

Remarkably, the lowest score category (0pts-4pts) makes up a very significant part of the entire cohort (n = 3186; 65,3%). This implicates that practitioners are already intuitively

capable of selecting the best from the worst within the high-risk Pca group. This selection bias is a major explanation for the favourable 5- and 10-year CSS of the general HRPCa cohort.

The magnitude of this international multi-center patient cohort is undoubtable the major strength of this study. Compromising more than 20 years of interinstitutional data collection, each center treated patients according to their own protocol and standards. This presents a more realistic reflection of general population and practice. Secondly, this subcategorization of established preoperative high-risk factors enables a more accurate prediction of CSS after RP, thus helping to identify those with good prospects after surgery. Thirdly, by using ISUP grading we follow the new pathological classification. Finally, the model is made clinically accessible through an easy-to-use online calculator.

This study Is however not without weaknesses. Firstly, a retrospective study has inherent limitations due to variable data quality. Secondly, the EMPaCT database consists only of men treated by RP, thus a selection bias of fit men is inevitable. thirdly, no data was available concerning the number of positive cores in biopsy samples, as suggested by Sundi et al. Finally, interinstitutional variability impedes standardisation.

5. Conclusion

By subdividing the established preoperative high-risk factors for prostate cancer, a new model is presented. The extended stratification provides a more accurate prediction of CSS after radical prostatectomy for localised high-risk prostate cancer. A free online calculator is offered to simplify clinical use.

Ethical approval:

This study was approved by the ethical committee of the University Hospitals Leuven

Conflict of interest:

The authors declare to agree with the content of the manuscript and that they have no conflict of interest.

References:

1. Ehrlich PF. Wilms tumor: Progress and considerations for the surgeon. Surg Oncol. 2007;16(3):157–71.

2. Boyle P, Severi G, Giles GG. The epidemiology of prostate cancer. Urol Clin North Am. 2003;30(2):209–17.

3. Wong MCS, Goggins WB, Wang HHX, Fung FDH, Leung C, Wong SYS, et al. Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries. Eur Urol. 2016 Nov 1;70(5):862–74.

4. Santis D, Henry A, Joniau S, Lam T, Matveev V, van der Poel H, et al. Prostate Cancer EAU -ESTRO -SIOG Guidelines on.

5. Sundi D, Wang V, Pierorazio P, Han M, Bivalacqua T, Ball M, et al. Very-high-risk localized prostate cancer: definition and outcomes. Prostate Cancer Prostatic Dis. 2013;17(10):57–63.

6. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415–24.

7. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical Prostatectomy versus Observation for Localized Prostate Cancer. n engl j med . 2012;3673.

8. Oderda M, Joniau S, Spahn M, Gontero P. Debulking surgery in the setting of very high-risk prostate cancer scenarios. BJU Int. 2012;110(6B).

9. NCCN. National Comprehensive Cancer Network: Guidelines Prostate Cancer Version 2.2017. 2017.

10. Gnanapragasam VJ, Lophatananon A, Wright KA, Muir KR, Gavin A, Greenberg DC. Improving Clinical Risk Stratification at Diagnosis in Primary Prostate Cancer: A Prognostic Modelling Study. Beck AH, editor. PLOS Med. 2016 Aug 2;13(8):e1002063.

11. Joniau S, Briganti A, Gontero P, Gandaglia G, Tosco L, Fieuws S, et al. Stratification of

high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol. 2015 Jan 1;67(1):157–64.

12. Gontero P, Spahn M, Tombal B, Bader P, Hsu C-YY, Marchioro G, et al. Is there a prostate-specific antigen upper limit for radical prostatectomy? BJU Int. 2011;108(7):1093–100.