Role of surgery in very high-risk PCa

Steven Joniau, MD, PhD

Dept of Urology

University Hospitals Leuven

Belgium

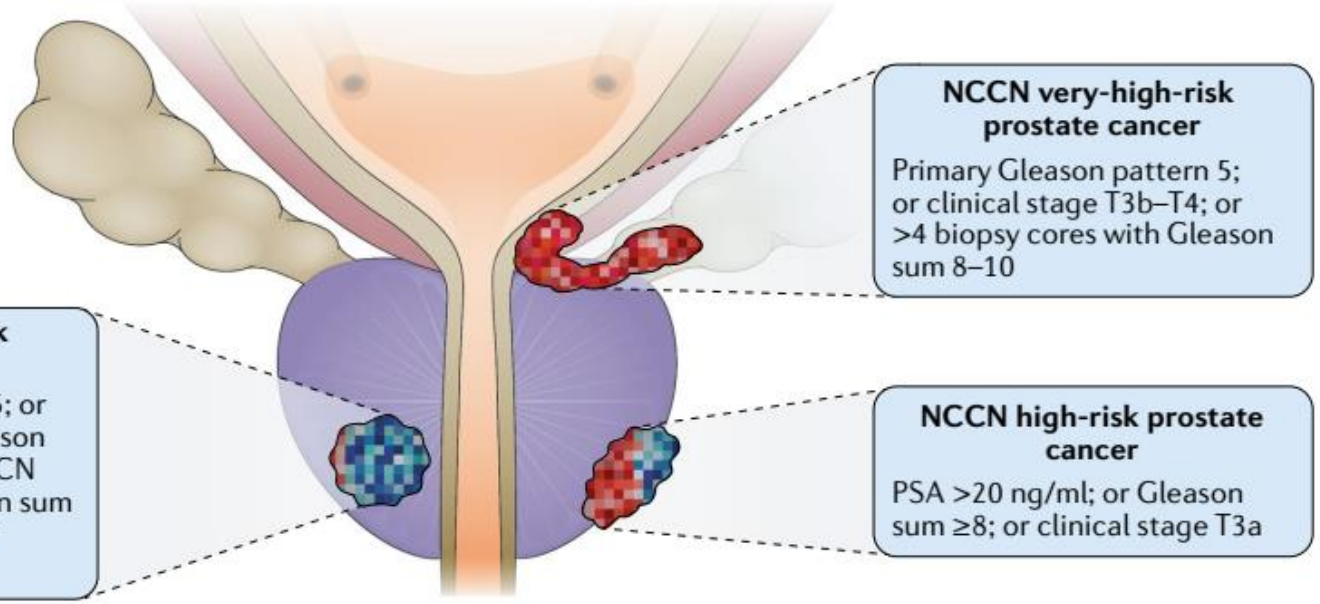
Conflicts of interest

	Research Funding	Speakers Fee	Consultation Fee
Astellas	√	√	√
Astra Zeneca		√	
Bayer	√	√	√
Ferring	√	√	
GSK		√	
Ipsen		√	√
Janssen	√	√	√
MDX Health	√		
Pfizer		√	
Roche	√		√
Sanofi		√	

Very high-risk Prostate Cancer

- Primary Gleason pattern 5
- >4 biopsy cores with Gleason sum 8-10
- Clinical stage T3b-T4
- Multiple NCCN high-risk features

Disease state does **not exist** in EAU PCa Guidelines !



NCCN very-high-risk prostate cancer
Primary Gleason pattern 5; or clinical stage T3b–T4; or >4 biopsy cores with Gleason sum 8–10

Sundi very-high-risk prostate cancer
Primary Gleason pattern 5; or >4 biopsy cores with Gleason sum 8–10; or multiple NCCN high-risk features (Gleason sum 8–10 or PSA >20 ng/ml or clinical stage ≥T3a)

NCCN high-risk prostate cancer
PSA >20 ng/ml; or Gleason sum ≥8; or clinical stage T3a

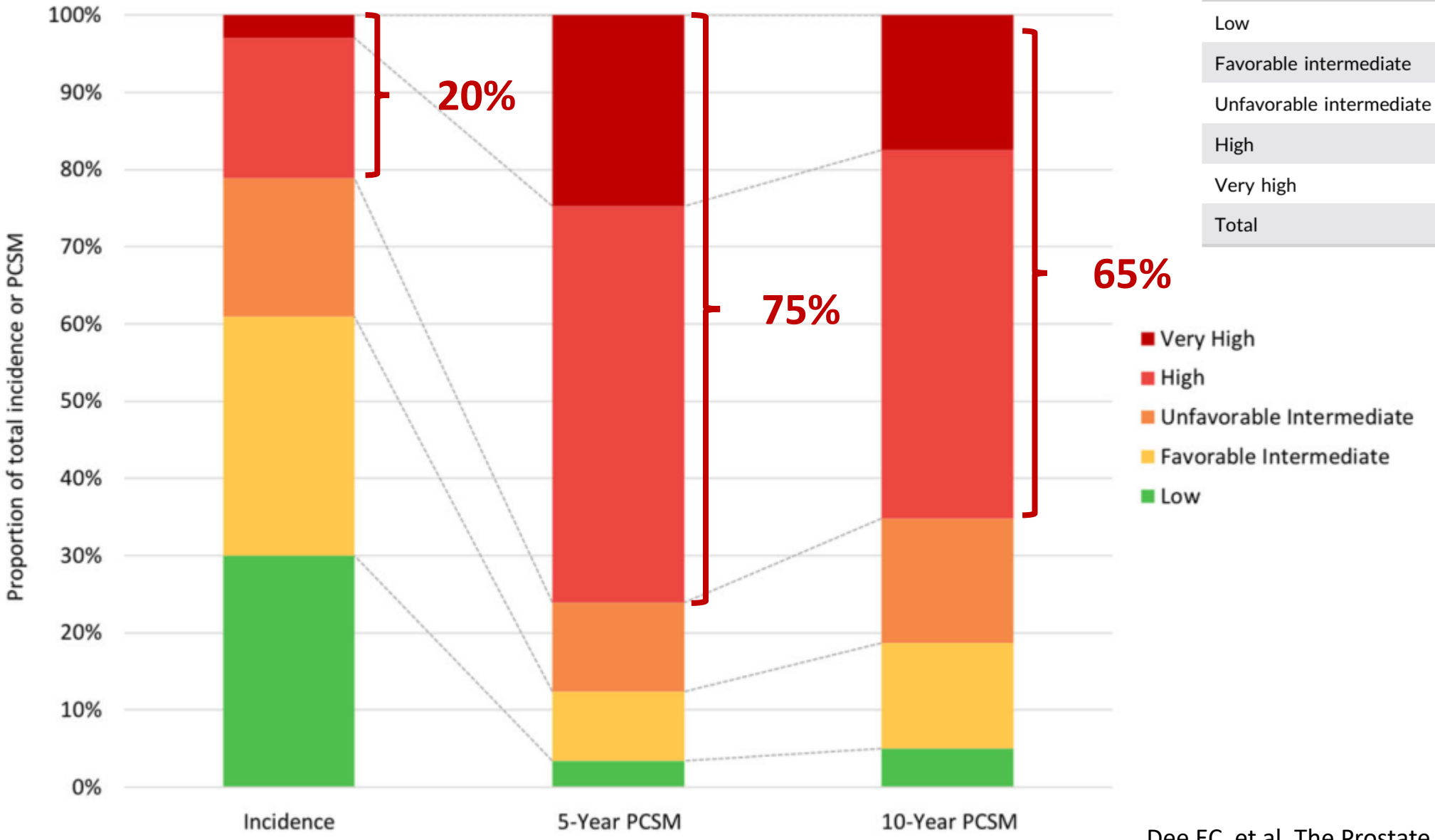
EAU locally advanced high-risk prostate cancer
Any PSA, any Gleason sum and either clinical stage T3–T4; or clinical positive lymph nodes

EAU localized high-risk prostate cancer
PSA >20 ng/ml; or Gleason sum >7; or clinical stage T2c

D'Amico high-risk prostate cancer
PSA >20 ng/ml; or Gleason sum ≥8; or clinical stage ≥T2c

Wilkins LJ, et al. Nat Rev Urol 2020

Background: High-Risk PCa



	2004-2015 SEER cohort	
	% of total diagnoses	% of total 10-y PCSM
Low	29.9	0.7
Favorable intermediate	31.1	2.0
Unfavorable intermediate	17.9	4.0
High	18.1	11.8
Very high	3.0	26.0
Total	100.0	100.0

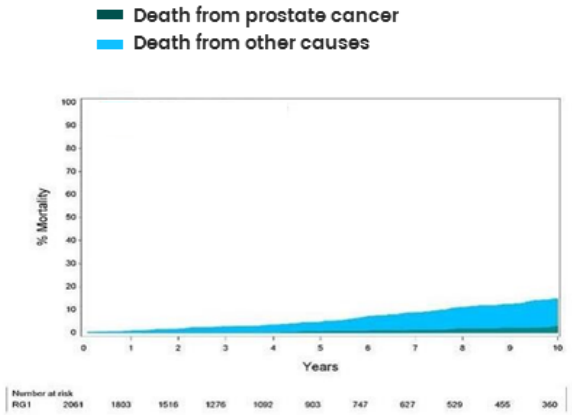
Dee EC, et al. The Prostate 2020

Who is at risk of prostate cancer mortaliy after surgery?

Risk factors:

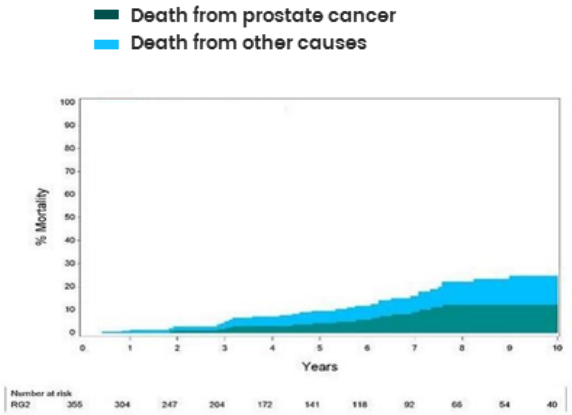
HGLA
- pT≥3b vs <3b
- pGS ≥8 vs <8
- pN1 vs pN0

pN0 + 0–1 RF	pN1 + 0–1 RF	HGLA ± pN1
3%	12%	24%
Good prognosis	Intermediate prognosis	Poor prognosis



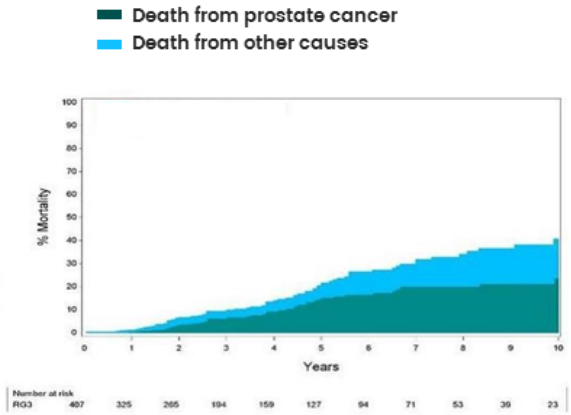
Mortality rates % (95% CI)

Years	PCRD	OCM
5	0.82 (0.28-1.36)	3.89 (2.85-4.93)
10	3.05 (1.71-4.38)	11.83 (9.50-14.16)



Mortality rates % (95% CI)

Years	PCRD	OCM
5	4.35 (1.52-7.18)	4.99 (2.03-7.95)
10	12.28 (6.62-17.93)	12.33 (6.32-18.35)



Mortality rates % (95% CI)

Years	PCRD	OCM
5	15.31 (10.34-20.28)	6.31 (3.06-9.55)
10	23.81 (16.01-31.61)	16.89 (10.04-23.74)

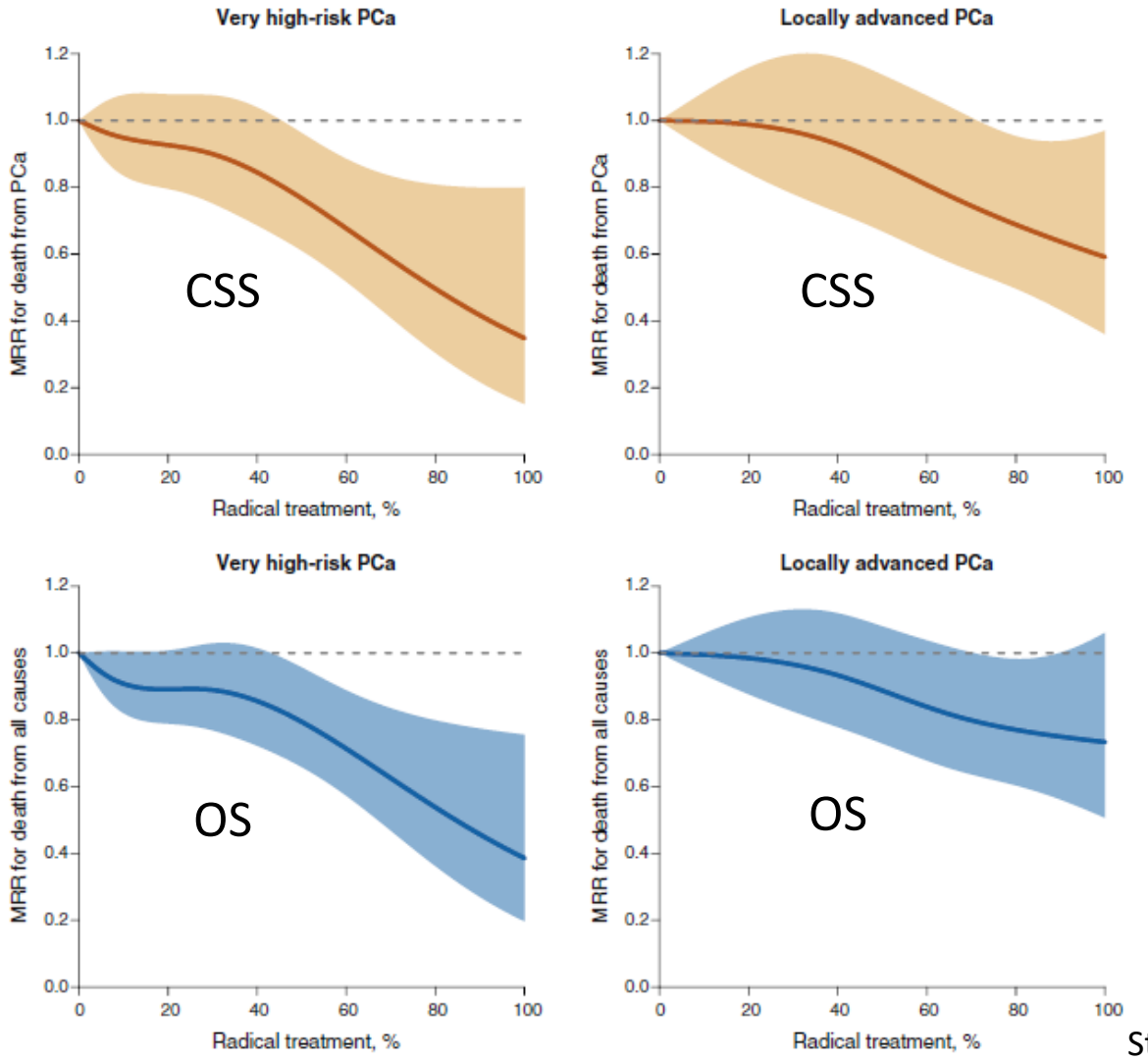
Toscol, et al. The EMPaCT Classifier: A Validated Tool to Predict Postoperative Prostate Cancer-related Death Using Competing-risk Analysis. Eur Urol Focus. 2017 Jan 17. doi: 10.1016/j.euf.2016.12.008.

Adjuvant treatments	Overall n=2823		Good n=2061		Intermediate n=355		Poor n=407	
	n	%	*n*	%	*n*	%	*n*	%
None	1982	70.2	1651	80.1	160	45.1	171	42.0
RT	210	7.4	146	7.1	25	7.0	39	9.6
ADT	454	16.1	208	10.1	121	34.1	125	30.7
RT+ADT	177	6.3	56	2.7	49	13.8	72	17.7

Role of local treatment in very high-risk and locally advanced PCa - PCBaSe

T4 and/or PSA level 50–200 ng/ml, any N, and M0

N=7,500



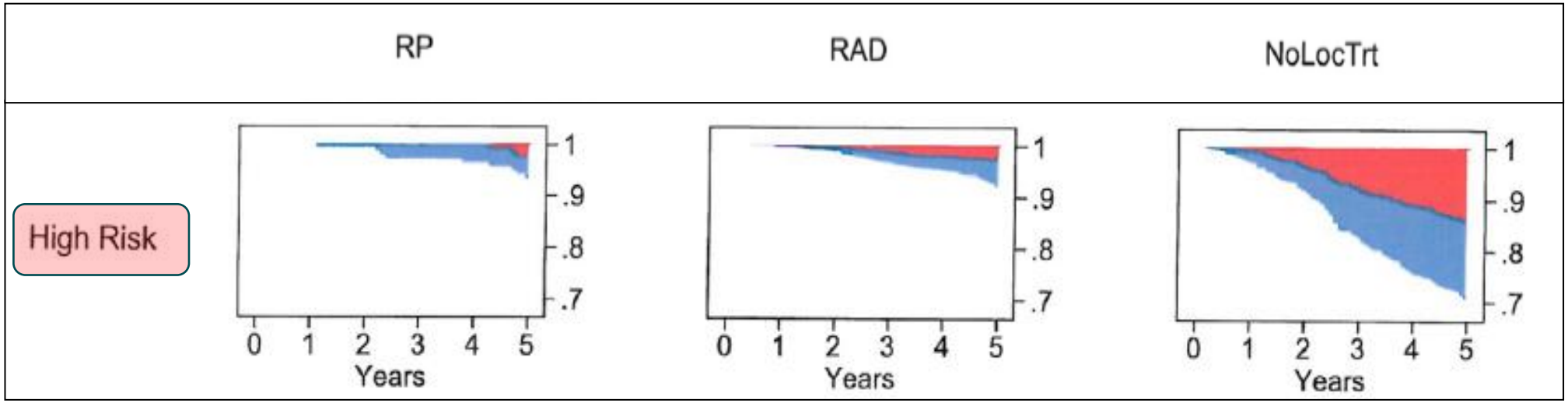
T3 and PSA level <50 ng/ml, any N, and M0

N=10,316

Stattin P, et al. Eur Urol 2017

Treatment and 5-year survival in patients with nonmetastatic PCa: the Norwegian experience

- Retrospective analysis of data from the Norwegian Prostate Cancer Registry, 2004–2005
- 3486 patients, RP (n=895), EBRT +/- ADT (n=1339), or no local treatment (n=1252)
- Clinical stage T1–T3, PSA ≤100 ng/mL, D'Amico risk group stratification



Fossa SD, et al. Urology 2014;83(1):146–152

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to selected patients with high-risk localised PCa as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong

PROSTATE CANCER - LIMITED UPDATE MARCH 2022

What does surgery offer?

1. Highly efficient locoregional disease debulking
2. Single-modality treatment in selected patients, thus opportunity for treatment de-escalation
3. Minimally invasive approach: robotics
4. Satisfactory functional and quality of life outcomes

Backside of the coin…

1. More extensive surgery compared with low/intermediate risk PCa
   - Higher risk of incontinence/erectile dysfunction
   - Higher complication rates: lymphedema/lymfocele/…
2. Often first step in a multimodal approach
3. No Level 1 evidence (yet…)

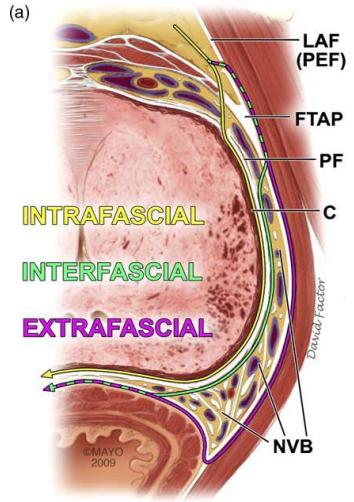
More extensive surgery

SCALE OF AGGRESSIVENESS

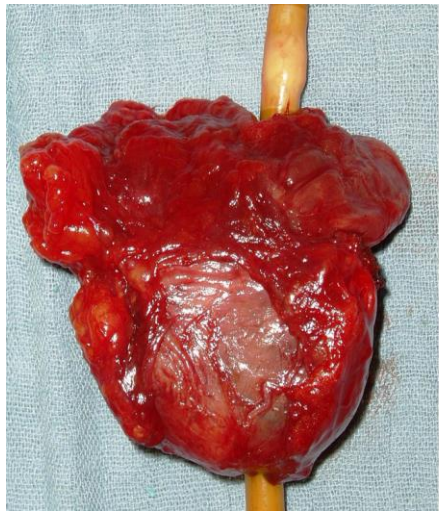
LOW-RISK → **INTERMEDIATE RISK** → **HIGH-RISK**

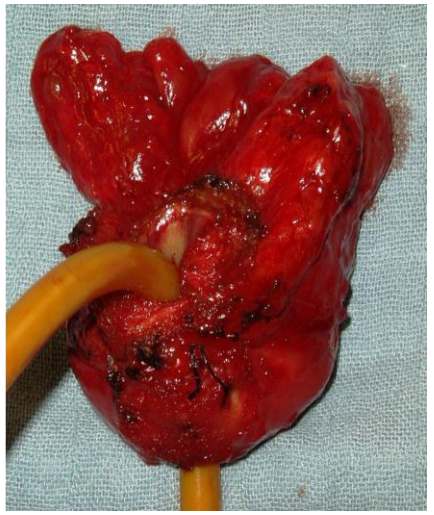
Nerve sparing, intrafascial
'Pealing-out' of seminal vesicles
No PLND

'Tailored' nerve-sparing
Extended PLND if risk >7%

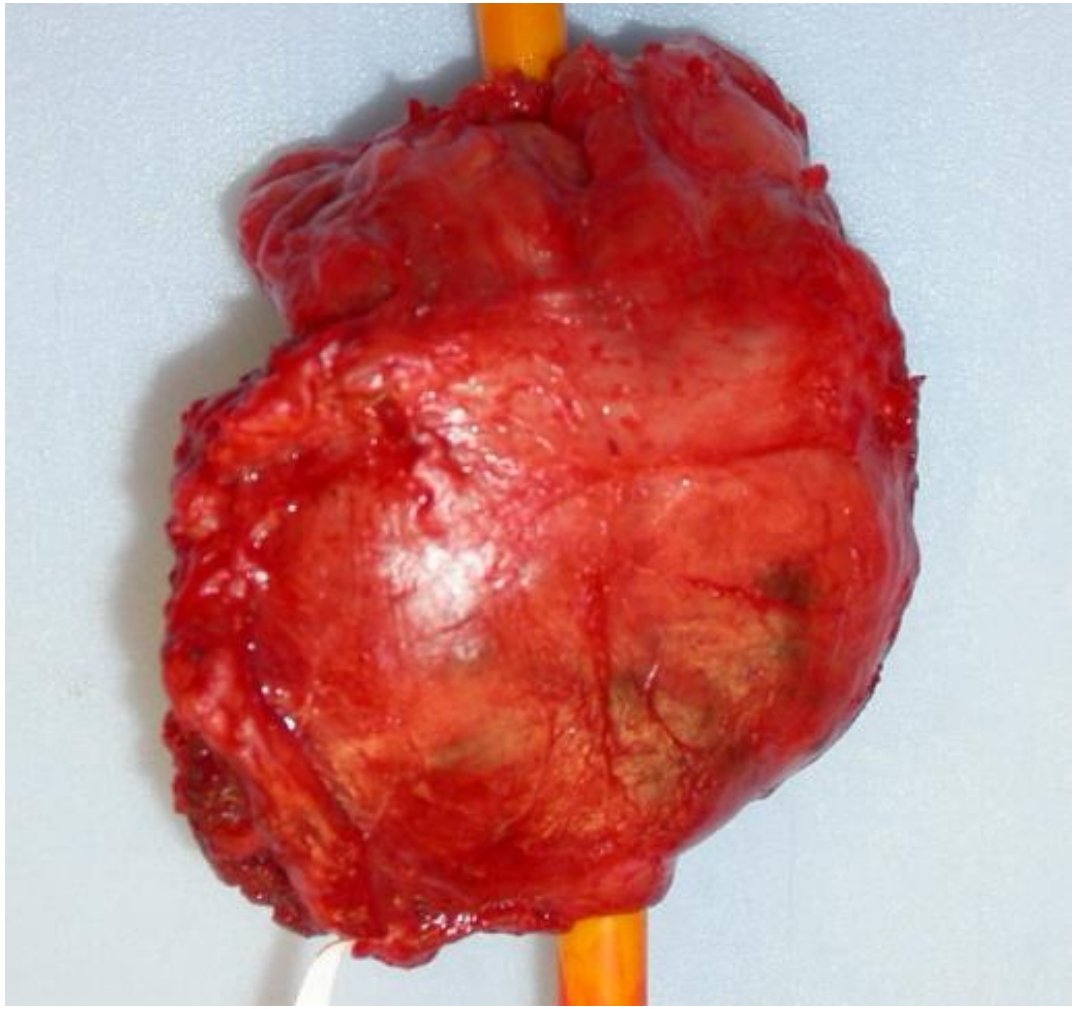


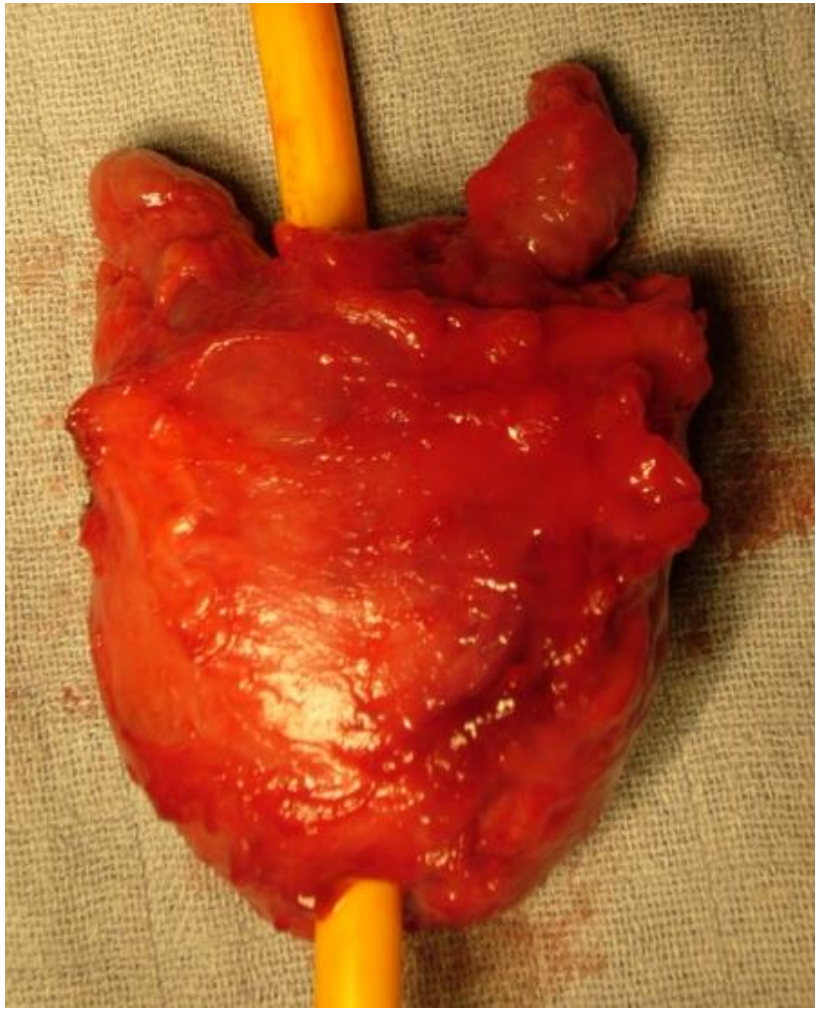
More often non-nerve sparing, extra-fascial
Wide resection of seminal vesicles
Extended PLND



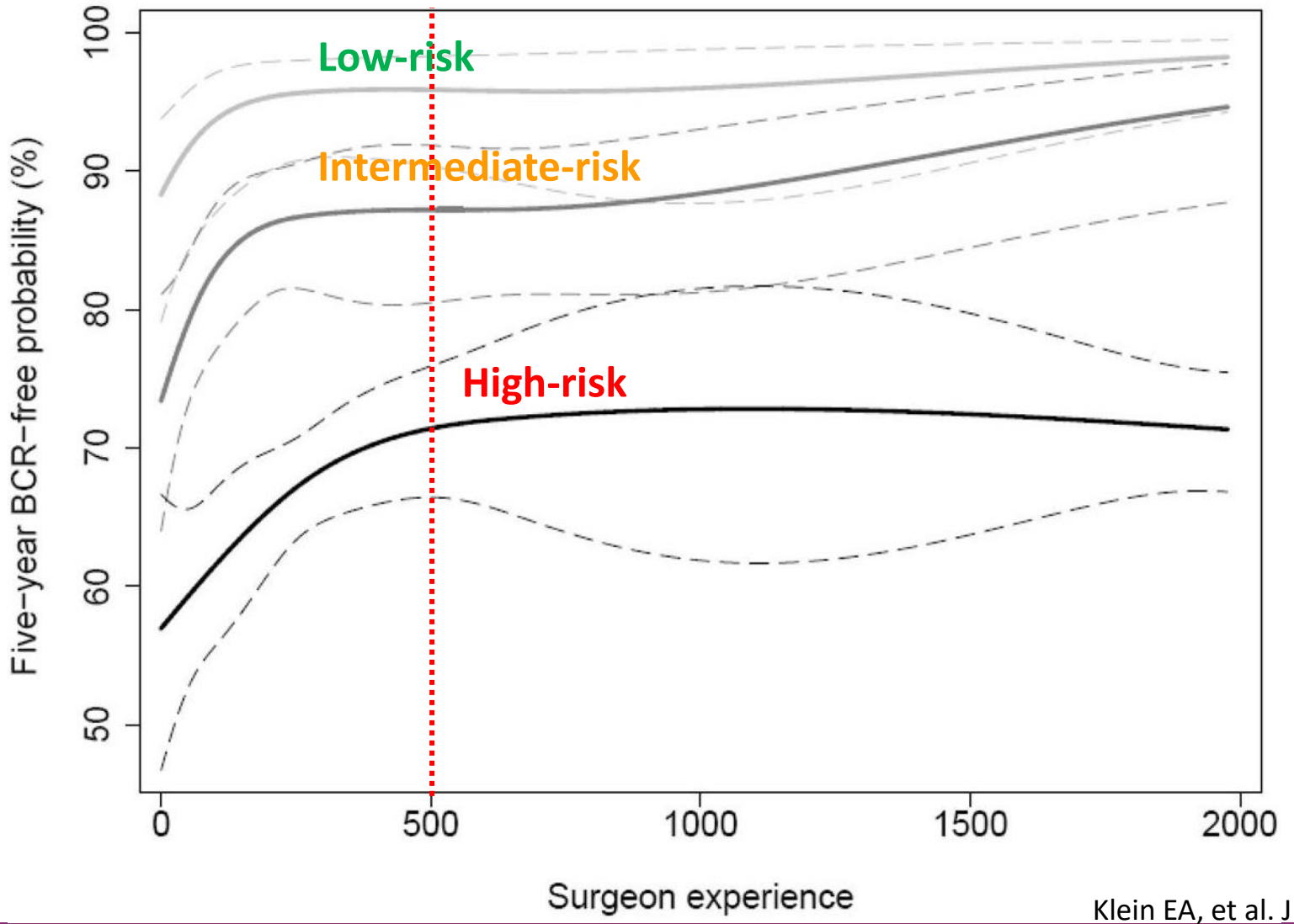


However, NVB preservation is possible in >50% of cases





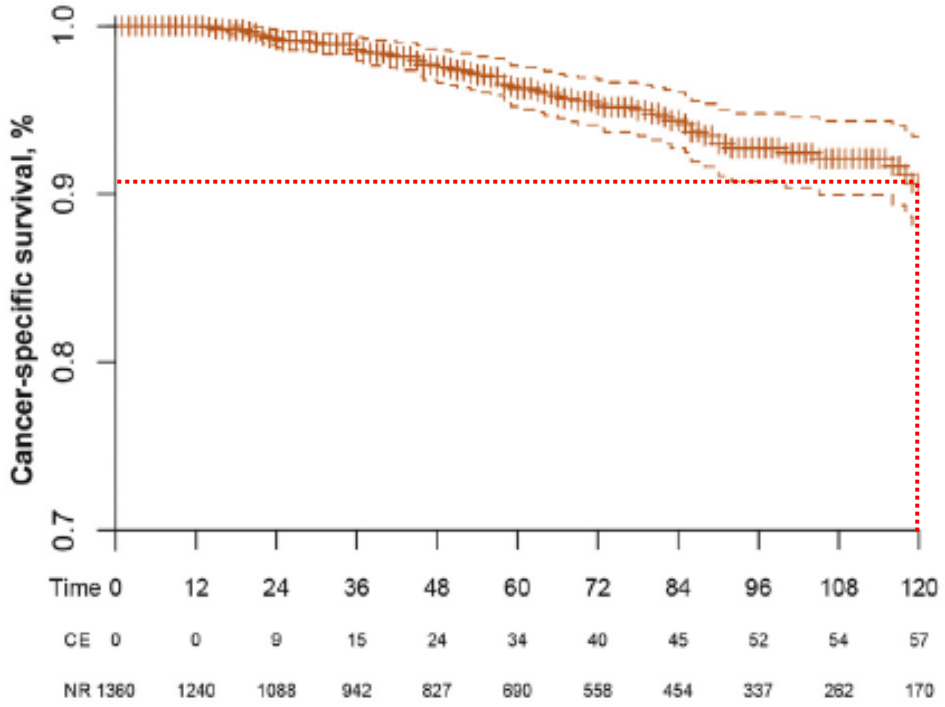
The importance of surgeon experience

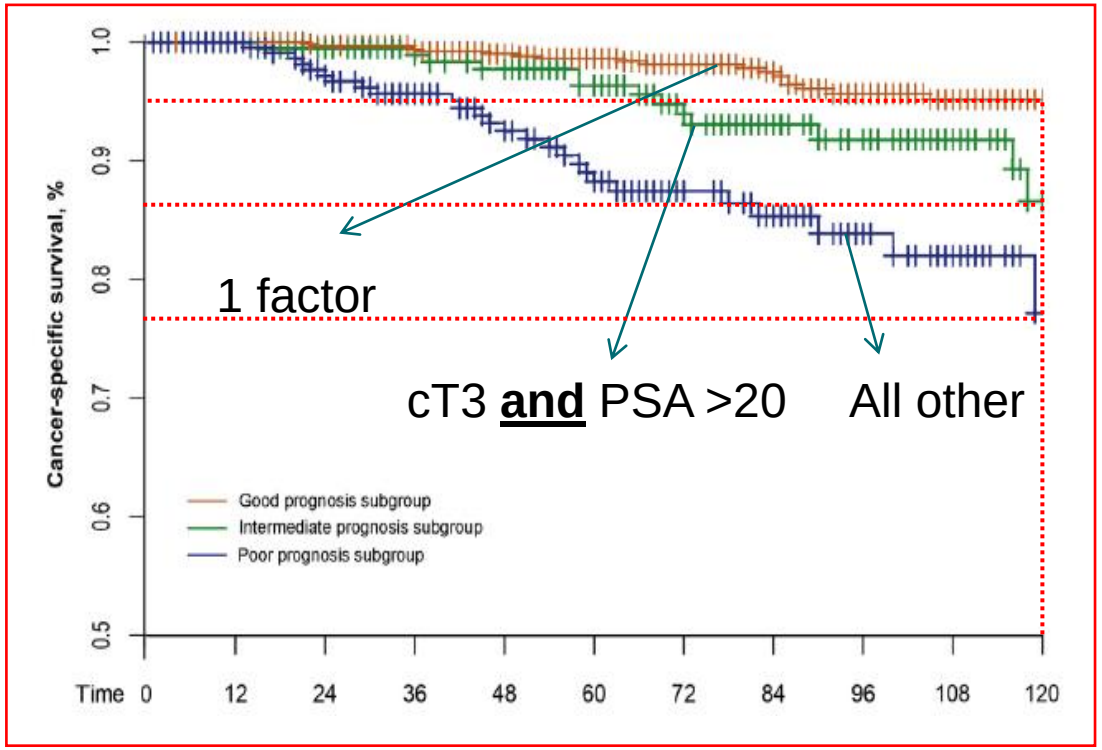


Klein EA, et al. J Urol 2008

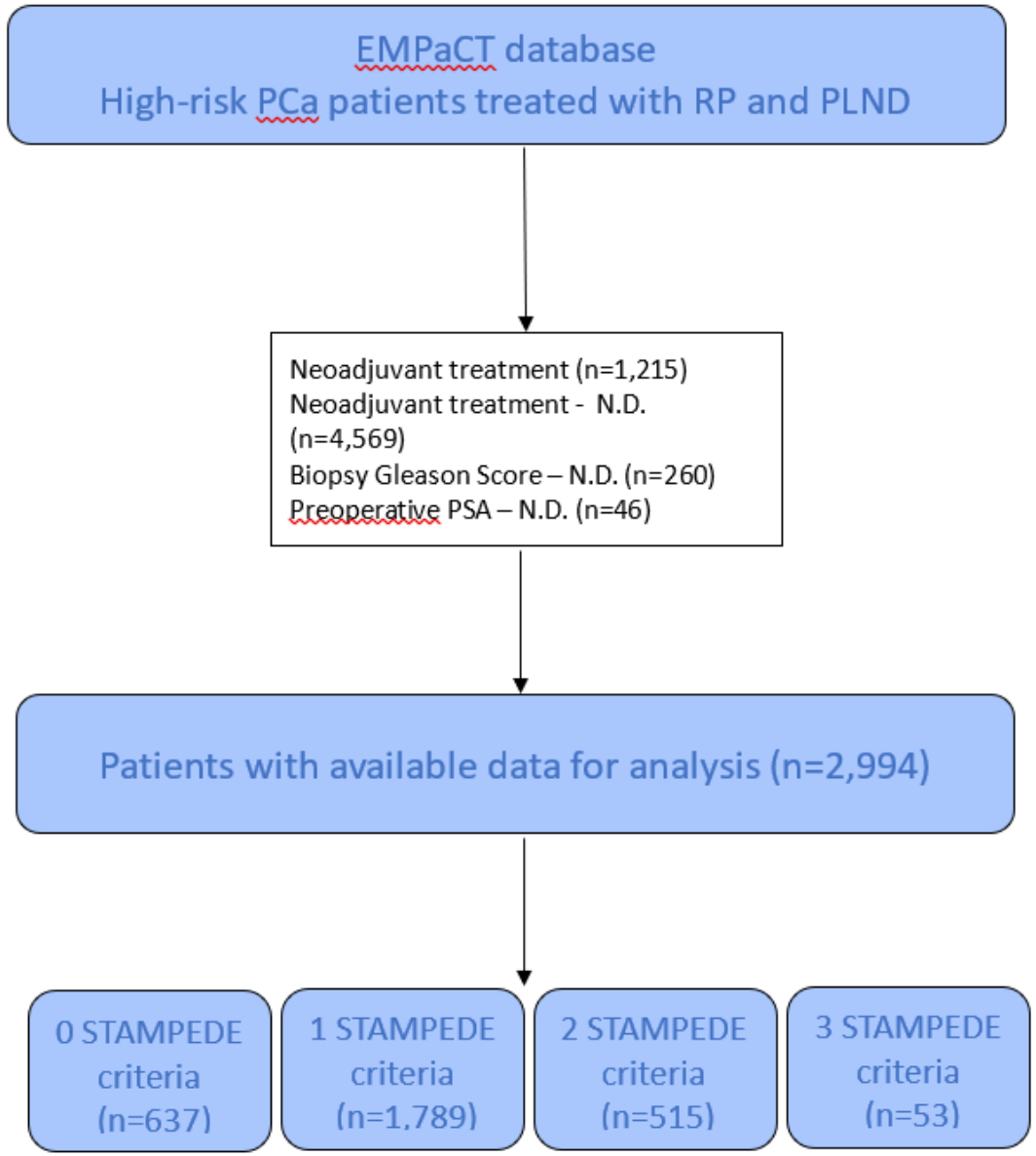
Stratification of High-risk Prostate Cancer into Prognostic Categories: A European Multi-institutional Study

Steven Joniau [a,,†], Alberto Briganti [b,†], Paolo Gontero [c], Giorgio Gandaglia [b], Lorenzo Tosco [a], Steffen Fieuws [d], Bertrand Tombal [e], Giansilvio Marchioro [f], Jochen Walz [g], Burkhard Kneitz [h], Pia Bader [i], Detlef Frohneberg [i], Alessandro Tizzani [c], Markus Graefen [g], Paul van Cangh [d], R. Jeffrey Karnes [j], Francesco Montorsi [b], Hein Van Poppel [a], Martin Spahn [k], European Multicenter Prostate Cancer Clinical and Translational Research Group (EMPaCT)*





Joniau S and Briganti A, et al. Eur Urol 2015



Joniau S, et al. *Unpublished data*

Patient characteristics

Clinical and pathological characteristics	EAU High-risk n=2994	STAMPEDE factors 0-1 (non-high-risk) n=2426	STAMPEDE factors 2-3 (high-risk) n=568
Age (year), median (IQR)	65 (60-70)	65 (60-70)	66 (61-70)
PSA (ng/ml), median (IQR)	13 (7-25)	12 (7-24)	19 (9-50)
PSA >40 ng/ml, n (%)	324 (11)	129 (5)	**195 (34)**
Clinical stage (cT), n (%)			
cT1	478 (16)	465 (19)	13 (2)
cT2	892 (30)	862 (36)	30 (5)
cT3-4	1624 (54)	1099 (45)	**525 (93)**
Biopsy Gleason Score (GS), n (%)			
GS 6	984 (33)	954 (39)	30 (5)
GS7	980 (33)	911 (38)	69 (12)
GS8-10	1030 (34)	561 (23)	**469 (83)**
Number of STAMPEDE criteria, n (%)			
0	637 (21)	637 (26)	-
1	1789 (60)	1789 (74)	-
2	515 (17)	-	515 (91)
3	53 (2)	-	53 (9)

Joniau S, et al. *Unpublished data*

Tumor characteristics

Clinical and pathological characteristics	EAU High-risk n=2994	STAMPEDE factors 0-1 (non-high-risk) n=2426	STAMPEDE factors 2-3 (high-risk) n=568
Pathological stage (pT), n (%)			
pT2	1178 (39)	1073 (44)	**105 (19)**
pT3a	1068 (36)	863 (36)	205 (36)
pT3b-4	742 (25)	484 (20)	258 (45)
NA	6 (0)	6 (0)	-
Pathological Gleason Score (GS), n (%)			
GS 6	600 (20)	567 (23)	**33 (6)**
GS 7	1364 (46)	1229 (51)	**135 (24)**
GS 8-10	1019 (34)	620 (26)	399 (70)
NA	11 (0)	10 (0)	1 (0)
Pathological lymph nodes stage (pN), n (%)			
pN0	2257 (75)	1947 (80)	**310 (55)**
pN1	710 (24)	455 (19)	255 (45)
pNx	27 (1)	24 (1)	3 (0)
Number of nodes removed, median (IQR)	12 (7-19)	11 (7-18)	13 (8-22)
Surgical margins status, n (%)			
Negative	1804 (60)	1535 (63)	**269 (47)**
Positive	1159 (39)	867 (36)	292 (52)
NA	31 (1)	24 (1)	7 (1)

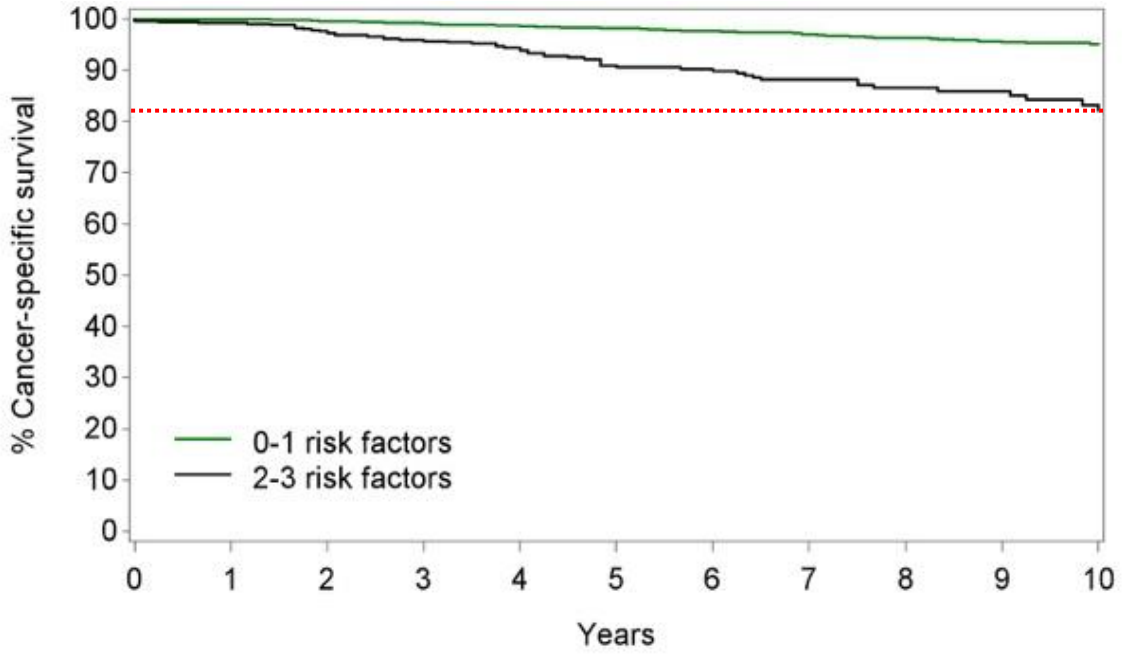
Joniau S, et al. *Unpublished data*

Adjuvant treatments

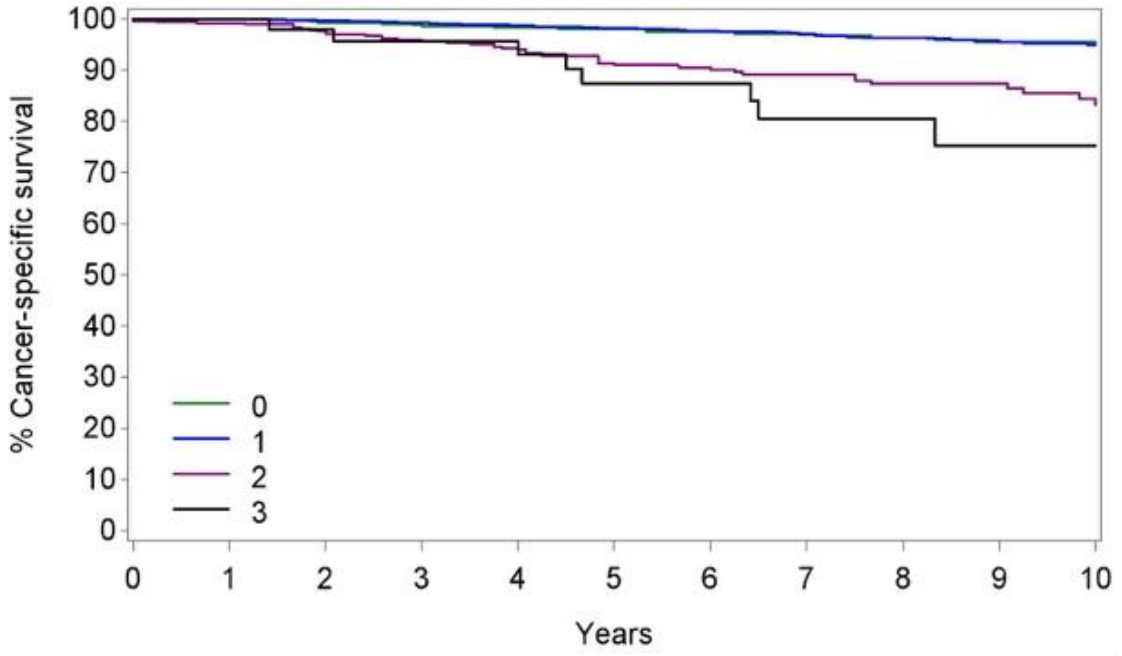
Clinical and pathological characteristics	EAU High-risk n=2994	STAMPEDE factors 0-1 (non-high-risk) n=2426	STAMPEDE factors 2-3 (high-risk) n=568
Adjuvant Radio Therapy, n (%)			
No	2213 (74)	1859 (77)	**354 (62)**
Yes	441 (15)	305 (13)	136 (24)
NA	340 (11)	262 (10)	78 (14)
Adjuvant Hormonal Therapy, n (%)			
No	2081 (70)	1803 (74)	**278 (49)**
Yes	605 (20)	390 (16)	215 (38)
NA	308 (10)	233 (10)	75 (13)
Follow-up (months), median (IQR)	60 (28-100)	60 (28-102)	56 (29-89)
Cancer related death, n (%)	124 (4)	71 (3)	**53 (9)**
Death by any cause	400 (13)	285 (12)	115 (20)
Year of surgery, n (%)			
≤2005	1501 (50)	1230 (51)	271 (48)
≥2006	1493 (50)	1196 (49)	297 (52)

Joniau S, et al. *Unpublished data*

Cancer-specific survival



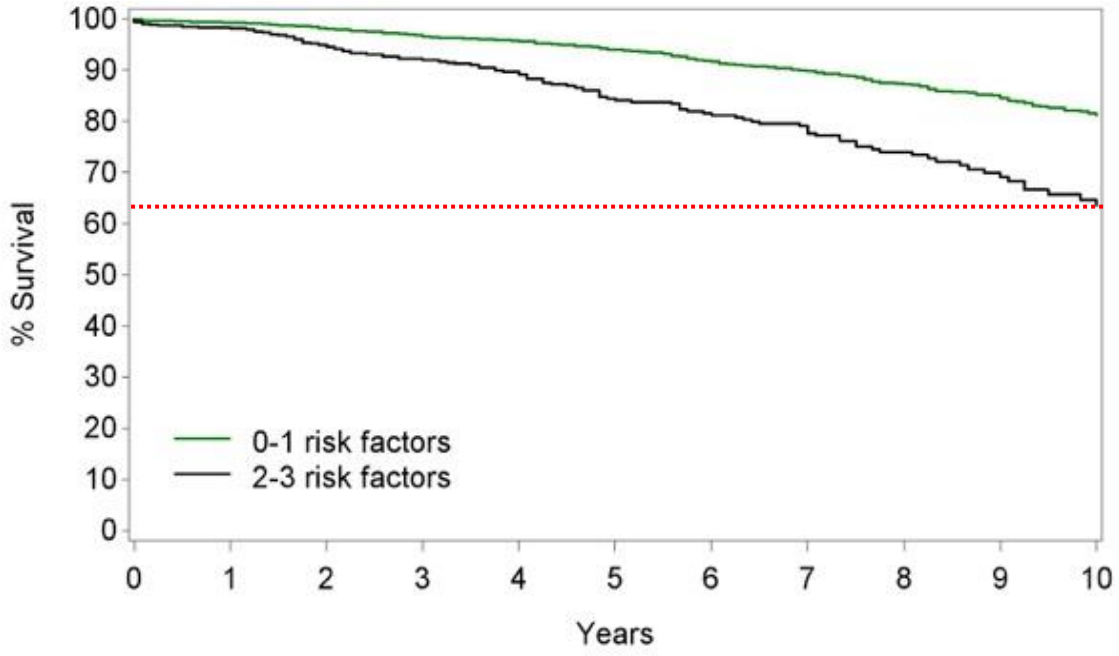
Number at risk											
0-1 risk factors	2426	2143	1906	1678	1486	1240	1014	846	685	557	414
2-3 risk factors	568	525	459	392	332	261	209	171	123	91	60



Number at risk											
0	637	517	445	400	371	329	275	246	209	175	140
1	1789	1626	1461	1278	1115	911	739	600	476	382	274
2	515	474	415	352	295	234	187	152	110	81	56
3	53	51	44	40	37	27	22	19	13	10	4

Joniau S, et al. *Unpublished data*

Overall survival



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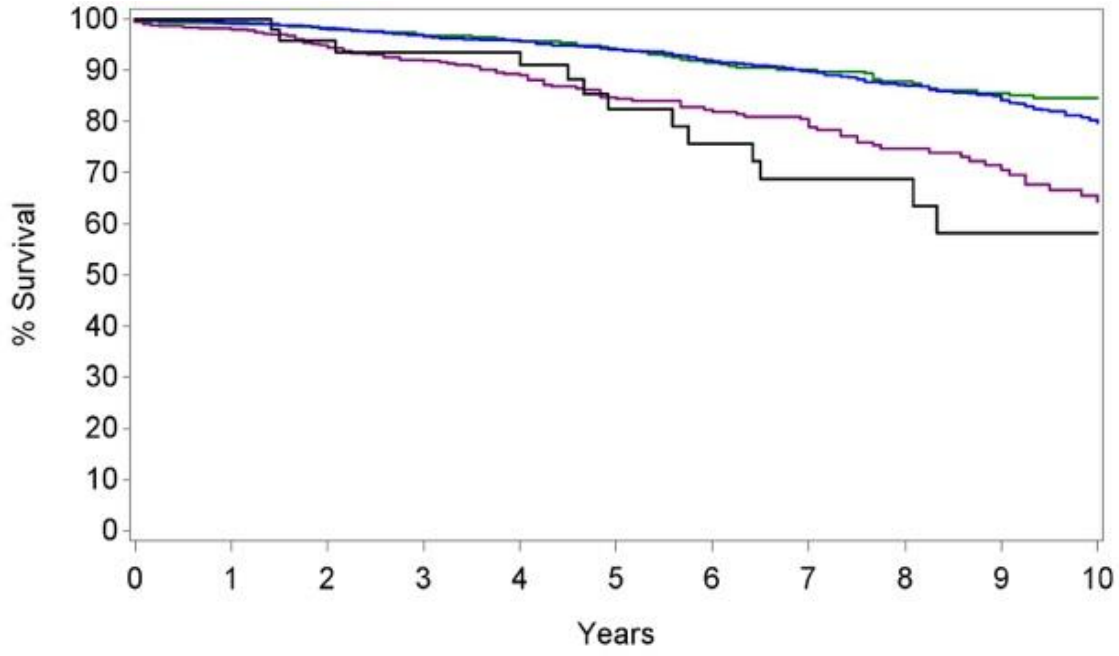

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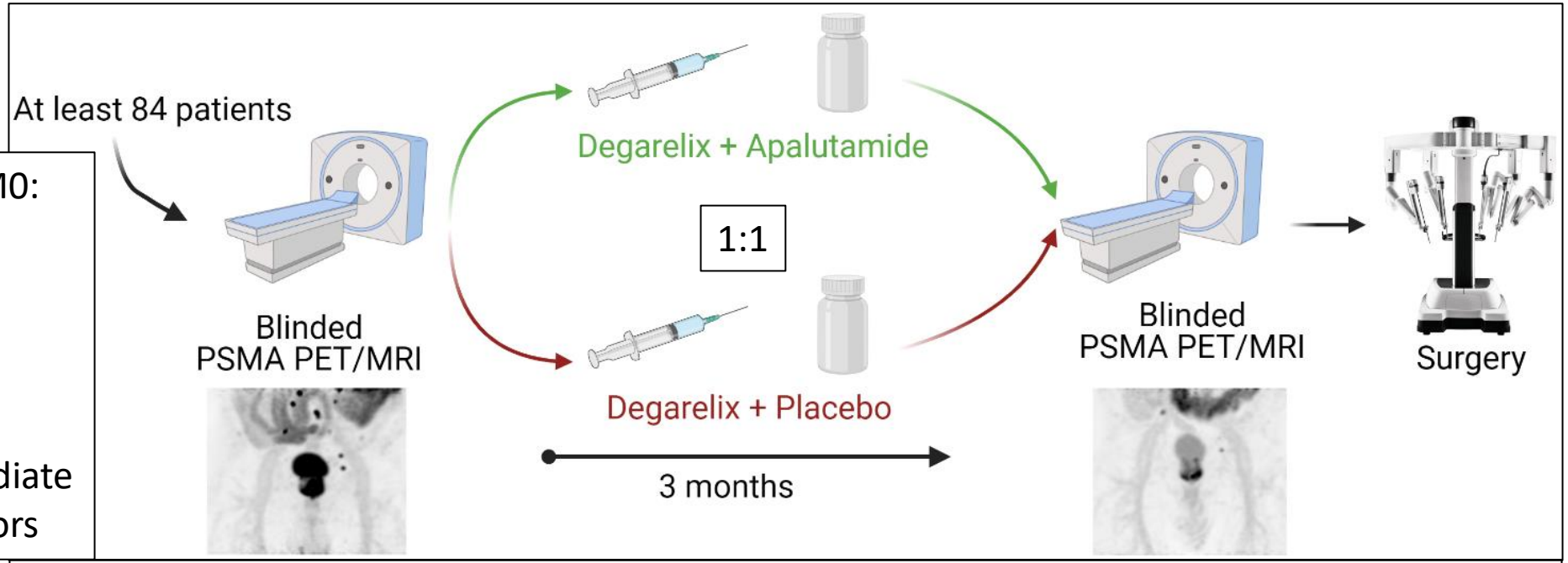
2	515	474	415	352	295	234	187	152	110	81	56
3	53	51	44	40	37	27	22	19	13	10	4

Joniau S, et al. *Unpublished data*

	Cancer Specific Survival		Overall Survival	
STAMPEDE factors	**5-year (95%CI)**	**10-year (95%CI)**	**5-year (95%CI)**	**10-year (95%CI)**
All patients	96.7 (95.9-97.4)	92.8 (91.2-94.1)	92.1 (90.9-93.2)	78.0 (75.4-80.3)
0	98.1 (96.4-99.1)	95.5 (92.7-97.4)	94.0 (91.3-95.9)	84.6 (79.9-88.2)
1	98.2 (97.3-98.8)	95.0 (93.2-96.5)	94.0 (92.6-95.2)	79.7 (76.2-92.7)
0+1 (non-high-risk)	**98.2 (97.4-98.7)**	**95.2 (93.7-96.4)**	**94.0 (92.8-95.0)**	**81.2 (78.6-83.6)**
2	91.0 (87.8-93.7)	83.2 (77.4-88.2)	84.4 (80.3-87.7)	64.4 (56.5-71.2)
3	87.4 (75.1-95.5)	75.3 (58.6-89.1)	82.4 (66.3-91.3)	58.2 (37.2-74.4)
2+3 (high-risk)	**90.6 (87.5-93.3)**	**82.2 (76.7-87.1)**	**84.2 (80.2-87.4)**	**63.6 (56.3-70.1)**

ARNEO: Study design & Endpoints

High-risk, M0:
- cT3-4
- PSA>20
- GS 8-10
- cN1
- 2-3 intermediate risk factors



Primary endpoint:

Difference in % Minimal Residual Disease (<0.25ml)

Secondary endpoints:

- PSA kinetics
- Toxicity, QoL,
- Biomakers for pathological response: PSMA PET/MRI and immunohistochemistry (ERG, PTEN, PSMA, Ki67, p53, GR) on diagnostic biopsies

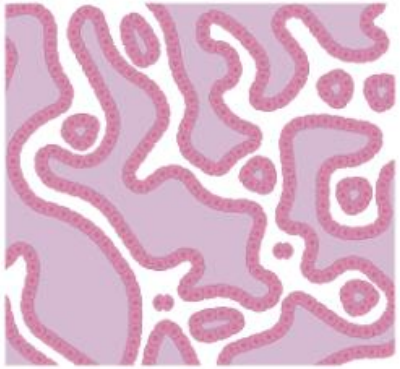
Results: Baseline patient characteristics

Baseline characteristics: Degarelix + Placebo (n=44)

Median 11.2 ng/ml

PSA <10	20 (45%)
PSA 10-20	14 (32%)
PSA >20	10 (23%)

≤cT2	12 (27%)
cT3a	20 (46%)
cT3b	7 (16%)
cT4	5 (11%)
cN1	5 (11%)



ISUP ≤ 3	13 (29%)
ISUP 4	17 (39%)
ISUP 5	14 (32%)

Baseline characteristics: Degarelix + Apalutamide (n=45)

Median 12.6 ng/ml

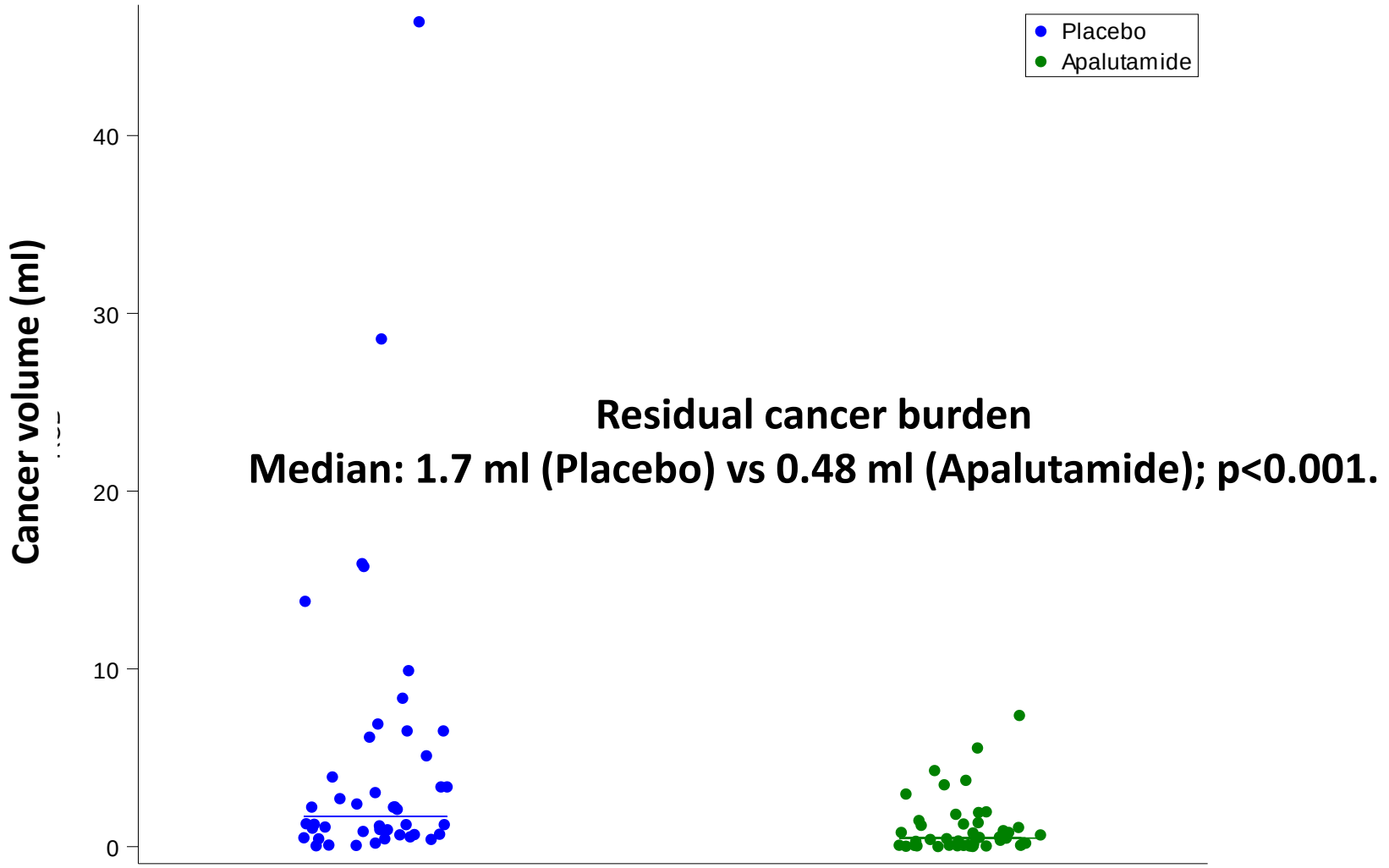
PSA <10	20 (44%)
PSA 10-20	14 (31%)
PSA >20	11 (25%)

≤cT2	12 (26%)
cT3a	18 (40%)
cT3b	12 (27%)
cT4	3 (7%)
cN1	7 (16%)

ISUP ≤ 3	16 (35%)
ISUP 4	10 (22%)
ISUP 5	19 (43%)

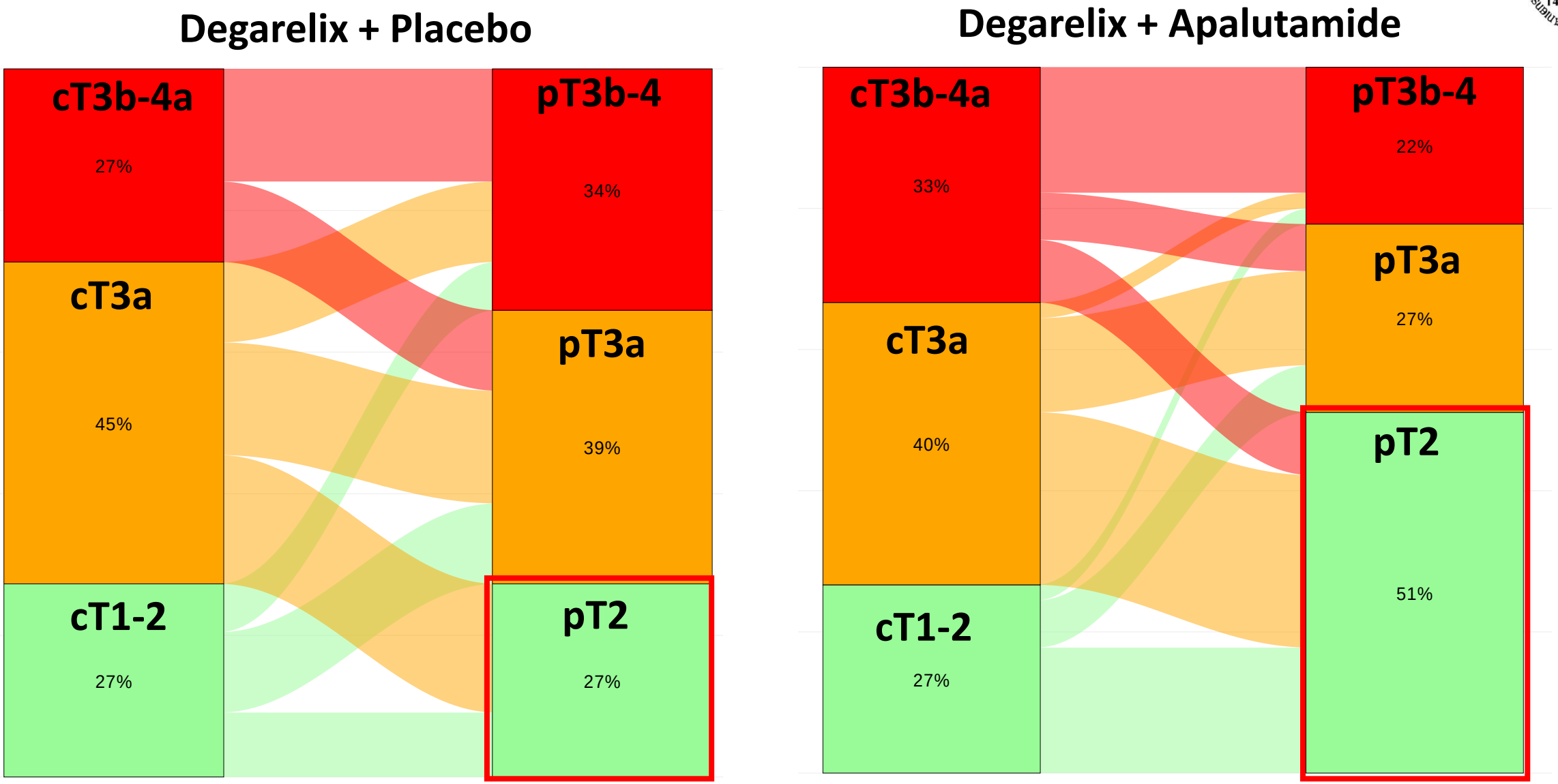
± 25% PSA >20 **± 75% ≥ cT3a** **10-15% cN1** **± 65% ≥ ISUP 4**

Results: primary endpoint



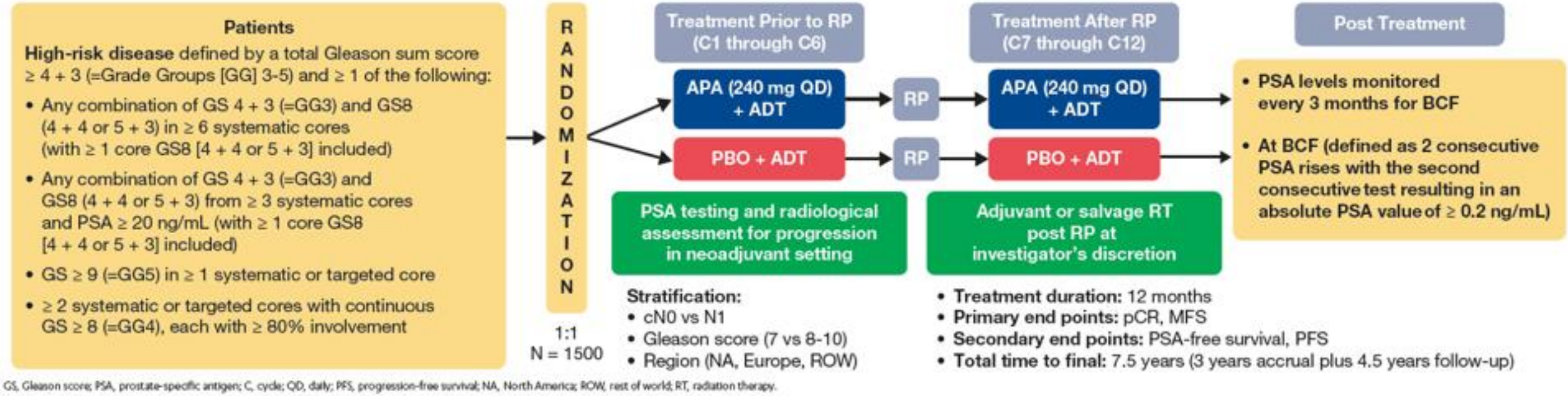
Minimal residual disease (<0.25ml) was 38% in the apalutamide arm vs. 9% in the placebo arm. P=0.002, RR 4.2

Results: downstaging



Downstaging to pT2-disease was significantly more frequent in the apalutamide arm (**51% vs. 27%, p=0.03**).

Phase III PROTEUS trial



GS, Gleason score; PSA, prostate-specific antigen; C, cycle; QD, daily; PFS, progression-free survival; NA, North America; ROW, rest of world; RT, radiation therapy.

Oncologic and Functional Outcomes after Radical Prostatectomy for High or Very High Risk Prostate Cancer: European Validation of the Current NCCN Guideline

Raisa S. Pompe, Pierre I. Karakiewicz, Zhe Tian, Philipp Mandel, Thomas Steuber, Thorsten Schlomm, Georg Salomon, Markus Graefen, Hartwig Huland and Derya Tilki*

From the Martini-Klinik Prostate Cancer Center (RSP, PM, TS, TS, GS, MG, HH, DT) and Department of Urology (PM, TS, DT), University Hospital Hamburg-Eppendorf, Hamburg, Germany, and Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Quebec, Canada (RSP, PIK, ZT)

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- **2,672 high-risk and 1,369 very-high-risk** PCa patients who underwent RP
- Longitudinal assessment of **Erectile Function**: score of 3 or more on question 2 of IIEF-5: "…how often were your erections stiff enough for penetration?"
- Longitudinal assessment of **Continence**: 0 or maximum 1 safety pad per day
- **69%** of patients underwent unilateral (36%) or bilateral (33%) NVB preservation

Oncologic and Functional Outcomes after Radical Prostatectomy for High or Very High Risk Prostate Cancer: European Validation of the Current NCCN Guideline

Raisa S. Pompe, Pierre I. Karakiewicz, Zhe Tian, Philipp Mandel, Thomas Steuber, Thorsten Schlomm, Georg Salomon, Markus Graefen, Hartwig Huland and Derya Tilki*

From the Martini-Klinik Prostate Cancer Center (RSP, PM, TS, TS, GS, MG, HH, DT) and Department of Urology (PM, TS, DT), University Hospital Hamburg-Eppendorf, Hamburg, Germany, and Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Quebec, Canada (RSP, PIK, ZT)

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- Overall, **return of EF** was seen in **30%** of high-risk and **27%** of very-high-risk PCa patients at 1 year
- In preop potent patients with bilateral NS surgery, these figures were **45%** and **44%**, respectively
- Overall, **return of continence** was seen in **82%** of high-risk and **81%** of very-high-risk PCa patients at 1 year
- Age was a predictor of erectile function recovery
- Age ≤60 and bilateral NVB preservation were predictors of regaining continence

Summary of surgery for very high-risk PCa

1. When performed by an experienced surgeon, surgery is a highly effective treatment for (very) high-risk PCa in men with a sufficient life expectancy.
2. OS and CSS are convincing and in line with RT based treatment.
3. Surgery is often the first step of a multimodal treatment strategy, but offers an opportunity for treatment de-escalation in a significant proportion of patients.
4. Regaining erectile function is achieved in 1/3 (total) and 1/2 (preop. potent) patients. Surgeons should perform NS surgery whenever possible.
5. Return of continence is in the range of 81% at 1 year after surgery.
6. Further efforts to improve CSS and OS are needed. (Neo-)adjuvant systemic treatment may be the optimal strategy to achieve this. RCT's are ongoing.