High risk PCa

When surgery is not the best option!!

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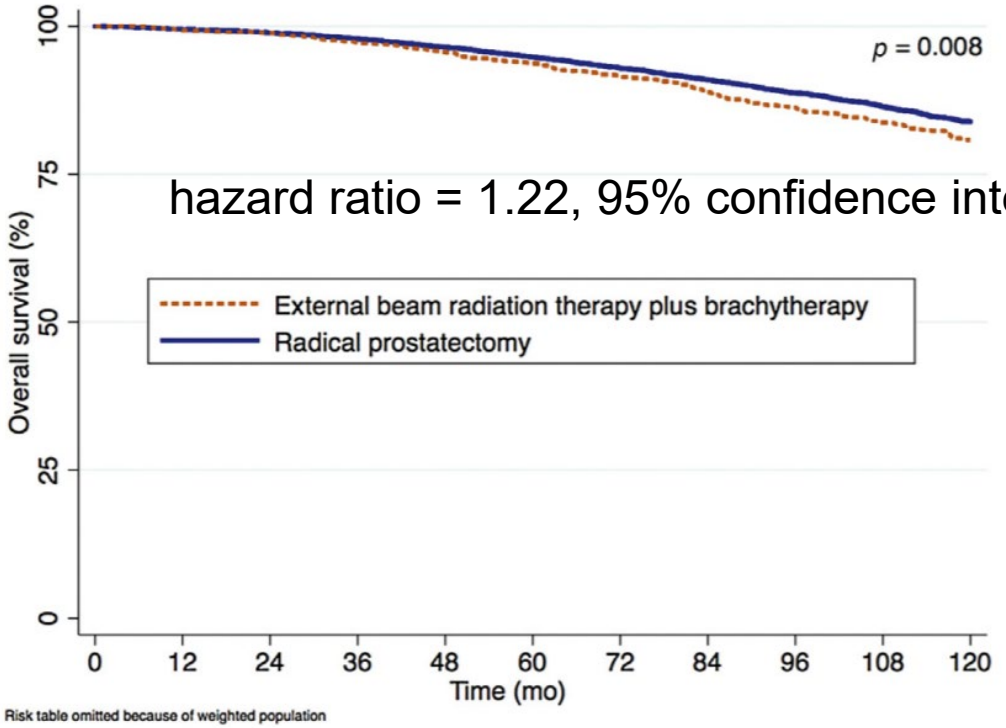
University of São Paulo – School of Medicine

Thank you!!!

Comparative Effectiveness of Radical Prostatectomy Versus External Beam Radiation Therapy Plus Brachytherapy in Patients with High-risk Localized Prostate Cancer



hazard ratio = 1.22, 95% confidence interval 1.05–1.43

In an analysis restricted to young and healthy men presenting with high-risk localized prostate cancer, initial radical prostatectomy is associated with an overall survival benefit compared with external beam radiation therapy plus brachytherapy.

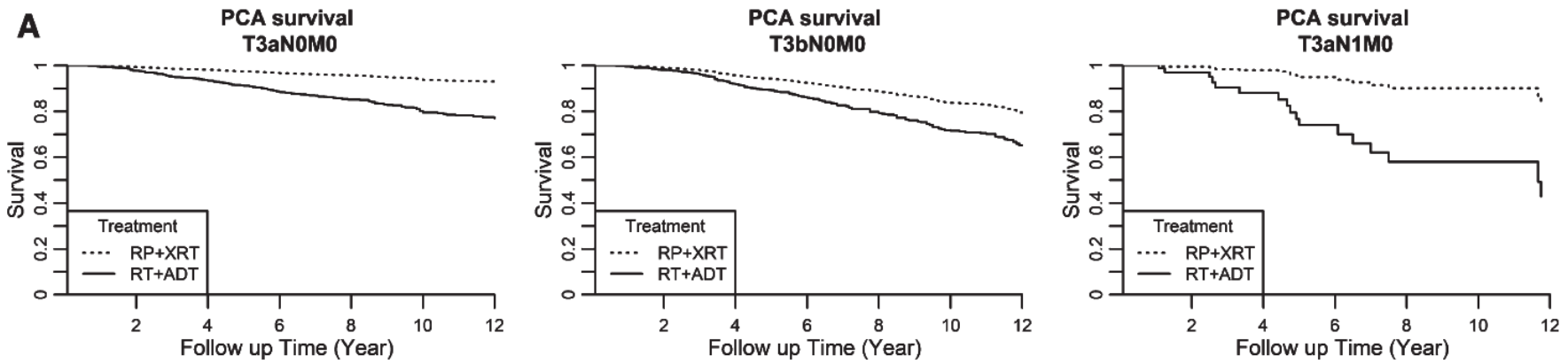
Berg S et al, Eur Urol, 2018

To operate or not to operate?

- Recognizing side effects TMT
- Patients selection – Who benefits the most?
- Life expectancy
- Predicting surgical complications
- Surgery in very high risk/ oligometastatic disease

Side effects of multimodal treatment

Comparative Effectiveness of Radical Prostatectomy With Adjuvant Radiotherapy Versus Radiotherapy Plus Androgen Deprivation Therapy for Men With Advanced Prostate Cancer

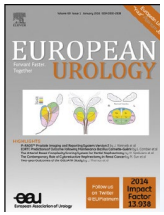


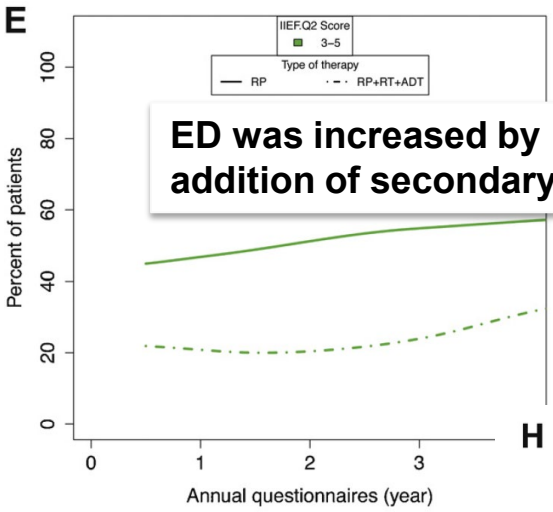
	Treatment		
Adverse Outcome	RP + Adjuvant XRT (n = 451), %	XRT + ADT (n = 2590), %	*P*
Urinary incontinence			
Diagnosis	49.1	19.4	<.0001
Procedures	12.4	1.6	.0007
Erectile dysfunction			
Diagnosis	28.3	20.4	.0212
Procedures	8.4	3.7	.0186

Primary RP+RT had a lower risk of death from prostate cancer and had improved overall survival in comparison with RT + ADT. Men who received RP + RT had higher rates of ED and UI.

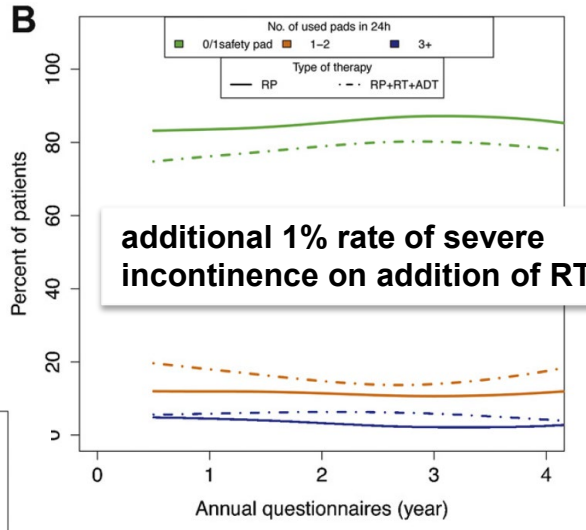
Jang et al, Cancer, 2018

Functional Outcomes and Quality of Life After Radical Prostatectomy Only Versus a Combination of Prostatectomy with Radiation and Hormonal Therapy

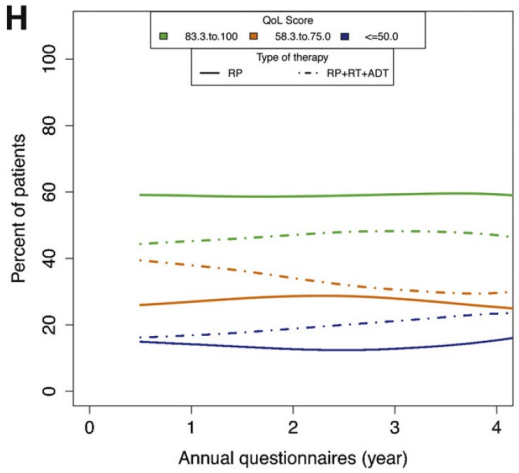




ED was increased by 18% on addition of secondary RT



additional 1% rate of severe incontinence on addition of RT



QoL was reduced by 11% by RT plus an additional 13% by ADT

Secondary RT and ADT after RP have an additive negative influence on urinary function, potency, and QoL. Patients with high-risk disease should be counseled on the potential impairment of functional outcomes due to multimodal tx.

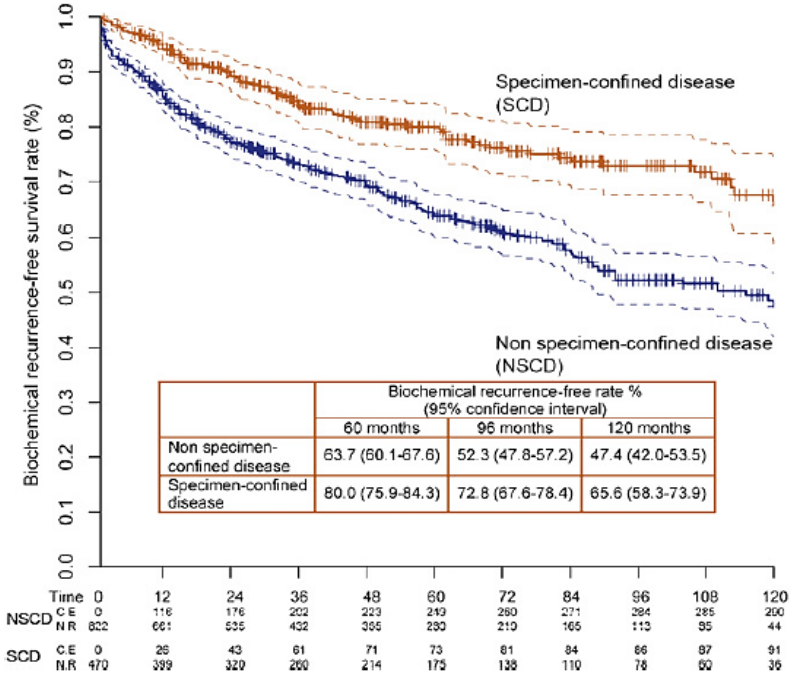
Adam M et al, Eur Urol, 2017.

Who are the best candidates for surgery??

Identifying the Best Candidate for Radical Prostatectomy Among Patients with High-Risk Prostate Cancer

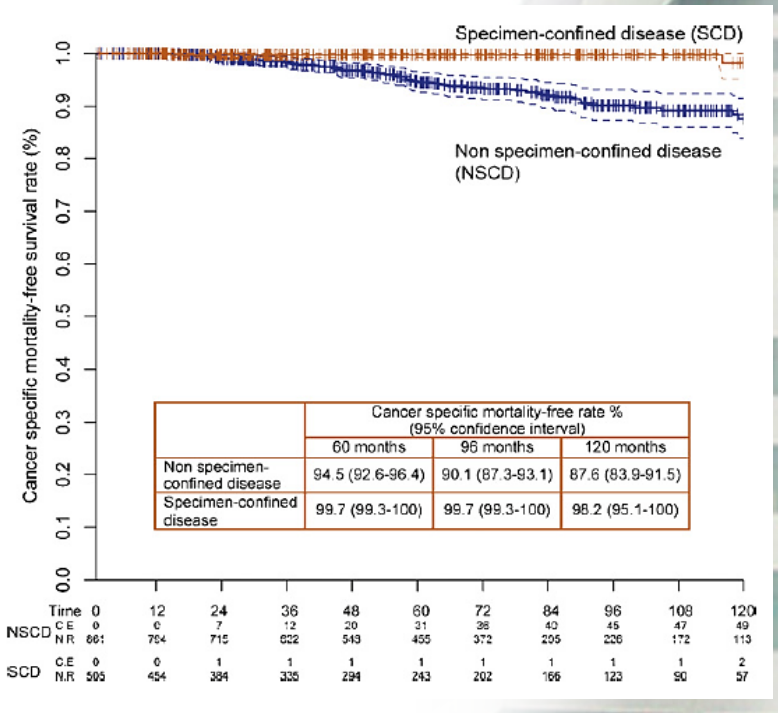
Alberto Briganti [a,,1], Steven Joniau [b,1], Paolo Gontero [c], Firas Abdollah [a], Niccolò M. Passoni [a], Bertrand Tombal [d], Giansilvio Marchioro [e], Burkhard Kneitz [f], Jochen Walz [g], Detlef Frohneberg [h], Chris H. Bangma [i], Markus Graefen [j], Alessandro Tizzani [c], Bruno Frea [k], R. Jeffrey Karnes [l], Francesco Montorsi [a], Hein Van Poppel [b], Martin Spahn [f]*

BCR-free survival



	Biochemical recurrence-free rate % (95% confidence interval)		
	60 months	96 months	120 months
Non specimen-confined disease	63.7 (60.1-67.6)	52.3 (47.8-57.2)	47.4 (42.0-53.5)
Specimen-confined disease	80.0 (75.9-84.3)	72.8 (67.6-78.4)	65.6 (58.3-73.9)

CSS survival



	Cancer specific mortality-free rate % (95% confidence interval)		
	60 months	96 months	120 months
Non specimen-confined disease	94.5 (92.6-96.4)	90.1 (87.3-93.1)	87.6 (83.9-91.5)
Specimen-confined disease	99.7 (99.3-100)	99.7 (99.3-100)	98.2 (95.1-100)

Roughly 40-50% of patients with high-risk PCa have SC disease (pT2–pT3a, node -, margins -) at final pathology and have excellent long-term outcomes with RP alone

Briganti et al, Eur Urol, 2012.

WHO ARE THE BEST CANDIDATES FOR SURGERY?

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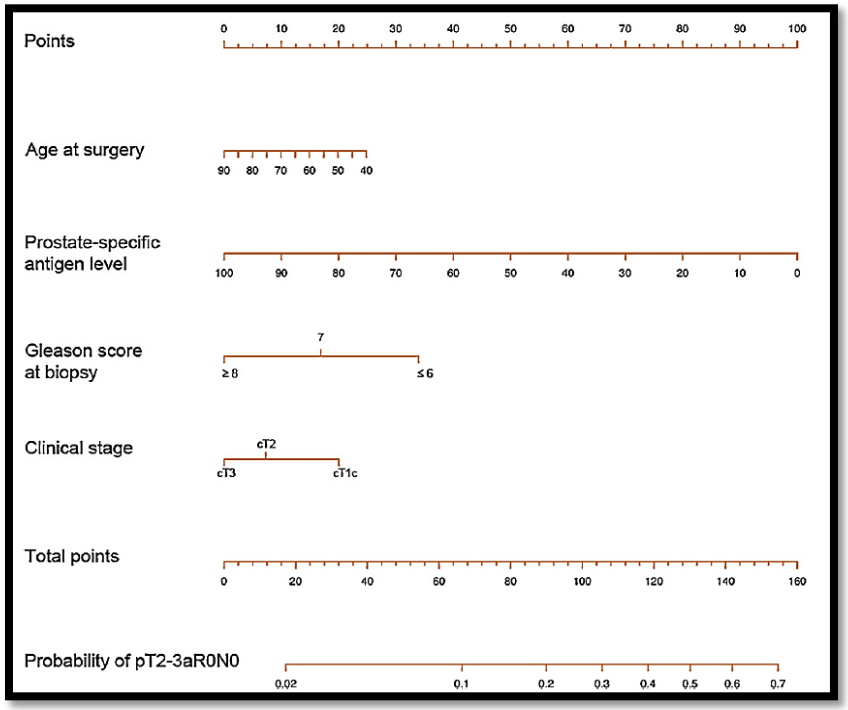

SC disease showed excellent cancer control rates at long-term follow-up achieved by RP alone in the vast majority of the cases

Briganti et al, Eur Urol, 2012.

Which Patients with Clinically Node-positive Prostate Cancer Should Be Considered for Radical Prostatectomy as Part of Multimodal Treatment? The Impact of Nodal Burden on Long-term Outcomes

	HR (95% CI)	*p* value
Prostate-specific antigen at diagnosis	1.01 (1.00–1.01)	0.001
Clinical stage		
T1	Reference	
T2	0.94 (0.48–1.85)	0.9
T3	0.72 (0.36–1.42)	0.7
Biopsy Gleason grade group		
1–3	Reference	
4–5	2.35 (1.26–4.36)	0.01
Number of suspicious nodes at preoperative imaging	1.56 (1.15–2.01)	0.01
Maximum diameter of suspicious nodes at preoperative imaging	1.02 (0.99–1.04)	0.2
Site of suspicious nodes at preoperative imaging		
Pelvis	Reference	
Retroperitoneum	2.54 (1.37–4.72)	0.01

Surgery in a multimodal setting might play a role in PCa patients with biopsy grade group 1–3 and/or enlarged nodes in the pelvis. GG 4–5 PCa and lymphadenopathies in the retroperitoneum had worse oncologic outcomes.

Gandaglia G et al, Eur Urol, 2018.

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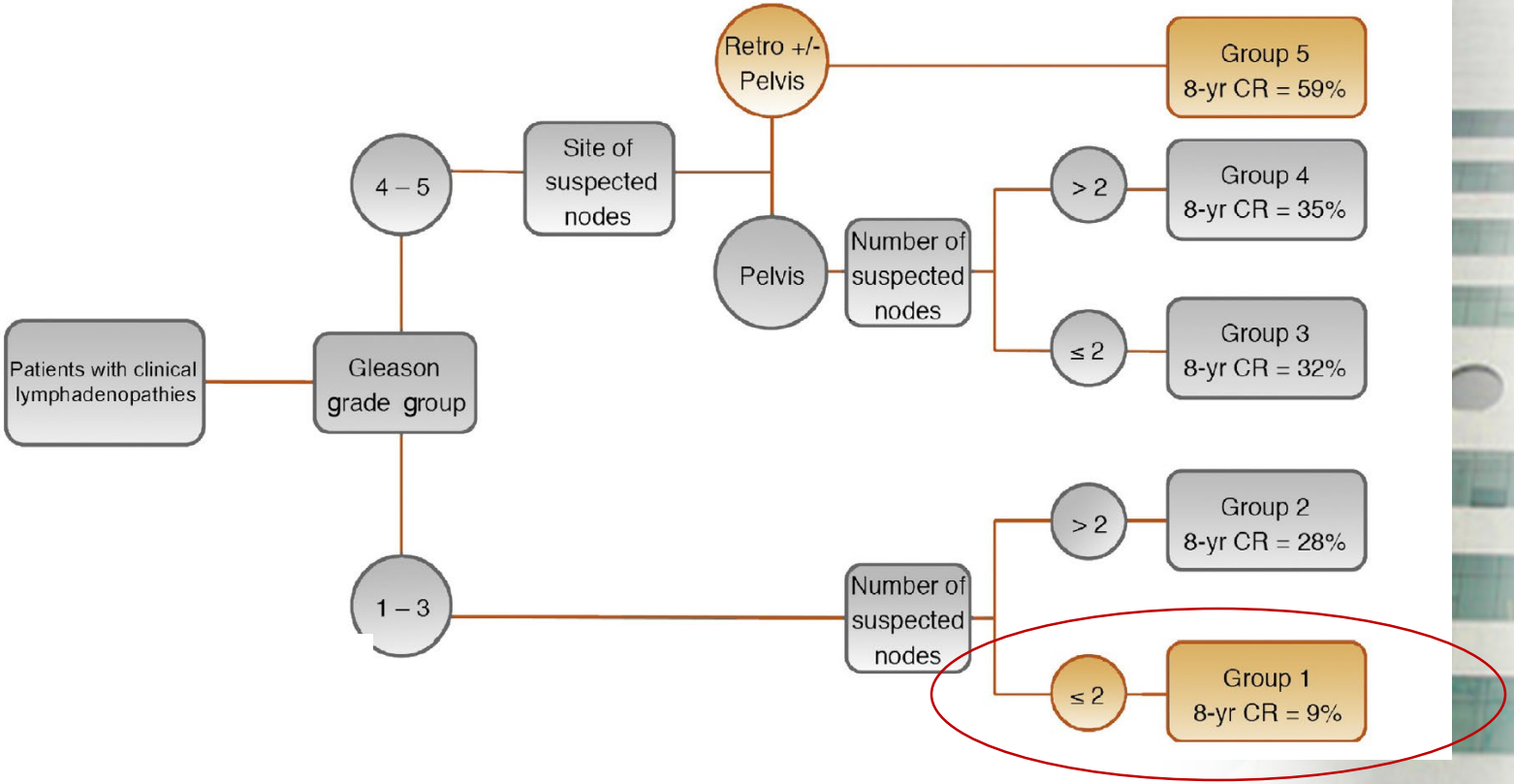

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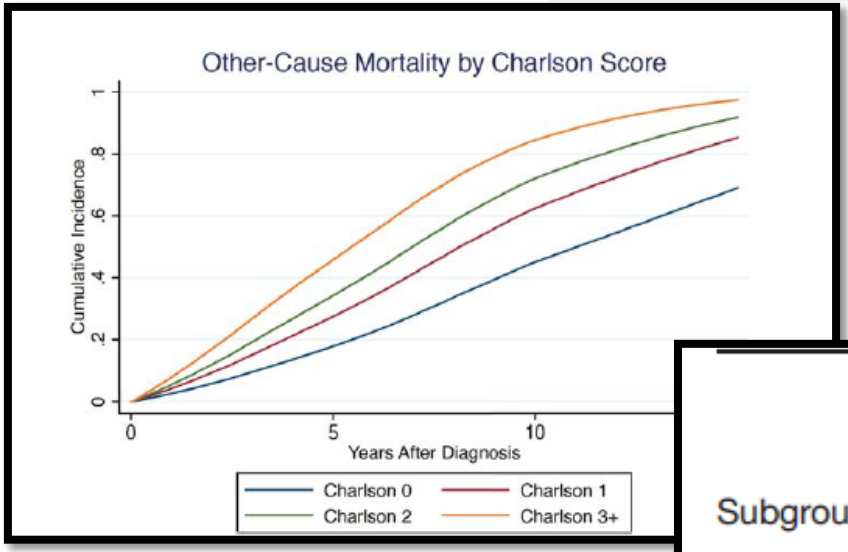
Life expectancy

CCI and PCSM



Subgroup	Subhazard Ratio (95% Confidence Interval)[b] Entire Cohort	Well and Moderately Differentiated Tumors
Full cohort	**0.50 (0.48-0.53)**	**0.56 (0.52-.60)**
Charlson 0	**0.50 (0.47-0.53)**	**0.56 (0.52-0.61)**
Charlson 1	**0.52 (0.46-0.60)**	**0.55 (0.45-0.66)**
Charlson 2	**0.55 (0.44-0.70)**	**0.67 (0.46-0.96)**
Charlson ≥3	0.85 (0.62-1.18)	1.14 (0.70-1.89)

The cancer-specific survival benefit from aggressive treatment for early-stage prostate cancer diminishes with increasing comorbidity at diagnosis. Men with Charlson scores ≥ 3 garner no survival benefit from aggressive treatment

Daskivich et al, Cancer 2014, Dec 1;120(23):3642

Can we reliable estimate life expectancy??

Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer

BJUI
BJU International

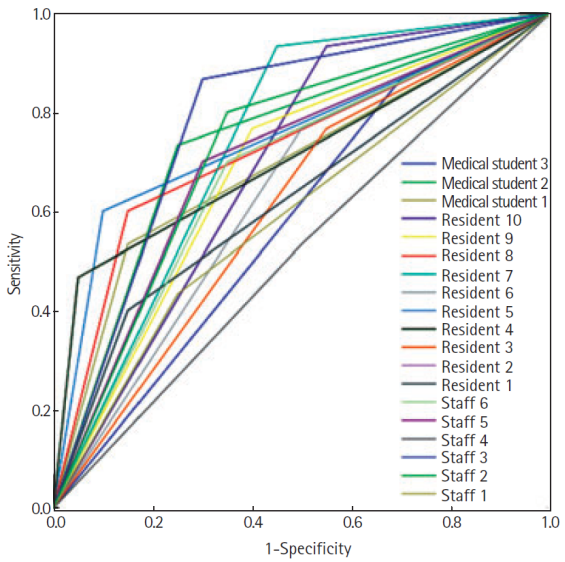


FIG. 2.
ROC curves of the 19 clinicians participating in the study.

The mean overall predictive accuracy was 0.68 (0.64–0.71). Individual accuracy ranged from 0.52 (staff) to 0.78 (staff).

Clinicians are relatively poor at predicting LE; tools to predict LE might be able to improve clinicians' performance in this important part of decision-making about prostate cancer treatment.

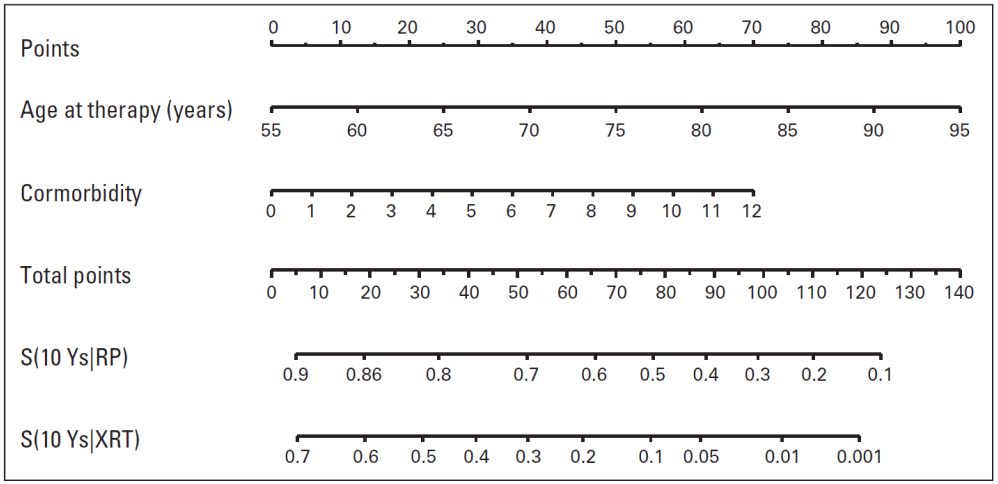
Waltz et al, BJU international 2017

A Nomogram Predicting 10-Year Life Expectancy in Candidates for Radical Prostatectomy or Radiotherapy for Prostate Cancer

JOURNAL OF CLINICAL ONCOLOGY

Table 2. Univariable and Multivariable Cox Regression Analyses of the Effect of Age, CCI, and Treatment Type on Overall Mortality in Men Who Did Not Receive Secondary Therapy After RP or EBRT (N = 9,131)

Variable	Univariable			Multivariable		
	Rate ratio	95% CI	*P*	Rate ratio	95% CI	*P*
Age at treatment						
Continuously coded	1.13	1.12 to 1.14	< .001	1.07	1.06 to 1.07	< .001
CCI						
Continuously coded	1.35	1.33 to 1.38	< .001	1.16	1.13 to 1.20	< .001
Treatment type						
EBRT *v* RP	6.56	6.06 to 7.11	< .001	3.80	3.47 to 4.12	< .001



In conclusion, our nomogram represents an accurate, user friendly, contemporary, and highly generalizable model for predicting 10-year LE in candidates for definitive PCa therapy

Waltz et al, JCO 2009,

A Nomogram Predicting 10-Year Life Expectancy in Candidates for Radical Prostatectomy or Radiotherapy for Prostate Cancer

JOURNAL OF CLINICAL ONCOLOGY

Table 3. Nomogram-Derived Probability Cutoffs for 10-Year LE After Radical Prostatectomy or External-Beam Radiation Therapy in Men With 10-Year or Longer Follow-Up or Who Died During the Study Period (n = 4,422)

Nomogram-Derived Probability of 10-year LE (%)	Patients Below Cutoff (of total)		TN*		FN†		TP‡		Negative Predictive Value (%)
	No.	%	No.	%	No.	%	No.	%	
10	371	8.4	364	13.4	7	0.4	1,705	99.6	98.1
20	738	16.7	712	26.3	26	1.5	1,686	98.5	96.5
30	1,159	26.2	1,089	40.2	70	4.1	1,642	95.9	94.0
40	1,623	36.7	1,490	55.0	133	7.8	1,579	92.2	91.8
50	1,940	43.9	1,739	64.2	201	11.7	1,511	88.3	89.6
60	2,177	49.2	1,916	70.7	261	15.2	1,451	84.8	88.0
70	**2,493**	**56.4**	**2,100**	**77.5**	**393**	**23.0**	**1,319**	**77.0**	**84.2**
80	3,287	74.3	2,449	90.4	838	48.9	874	51.1	74.5
90	4,367	98.8	2,701	99.7	1,666	97.3	46	2.7	61.9

In conclusion, our nomogram represents an accurate, user friendly, contemporary, and highly generalizable model for predicting 10-year LE in candidates for definitive PCa therapy

Waltz et al, JCO 2009,

Predicting Surgical Complications

ORIGINAL ARTICLE

Vol. 44 (x): 2018 August 8.[Ahead of print]
doi: 10.1590/S1677-5538.IBJU.2017.0339

Predictive factors for prolonged hospital stay after retropubic radical prostatectomy in a high-volume teaching center

Rafael F. Coelho [1], Mauricio D. Cordeiro [1], Guilherme P. Padovani [1], Rafael Localli [1], Limirio Fonseca [1], José Pontes Junior [1], Giuliano B. Guglielmetti [1], Miguel Srougi [1], William Carlos Nahas [1]

[1] *Divisão de Urologia, Instituto do Câncer de Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil*

Resultados

Multivariada – Preditores dentre fatores pré-operatórios (Idade como variável individual)

Idade	Variável contínua	1,050	1,023 – 1,078	<0,001
ICC				
	Variável contínua	1,401	1,118 – 1,756	0,003
ICC (Binário)				
	0	Referência	-	-
	≥1	1,818	1,272 – 2,600	0,001
Escore ASA				
	1	Referência	-	-
	3	3,192	1,616 – 6,308	<0,001
Raça				
	Branco	Referência	-	-
	Negro	1,910	1,103 – 3,307	0,021
Volume prostático (USGTR) - (ml)				
	Variável contínua	1,006	1,001 – 1,011	0,033

Early Complication Rates in a Single-Surgeon Series of 2500 Robotic-Assisted Radical Prostatectomies: Report Applying a Standardized Grading System

Rafael F. Coelho [a,b,c], *Kenneth J. Palmer* [a,b], *Bernardo Rocco* [a,b,d], *Ravendra R. Moniz* [e], *Sanket Chauhan* [a,b], *Marcelo A. Orvieto* [a,b], *Geoff Coughlin* [a,b], *Vipul R. Patel* [a,b,*]

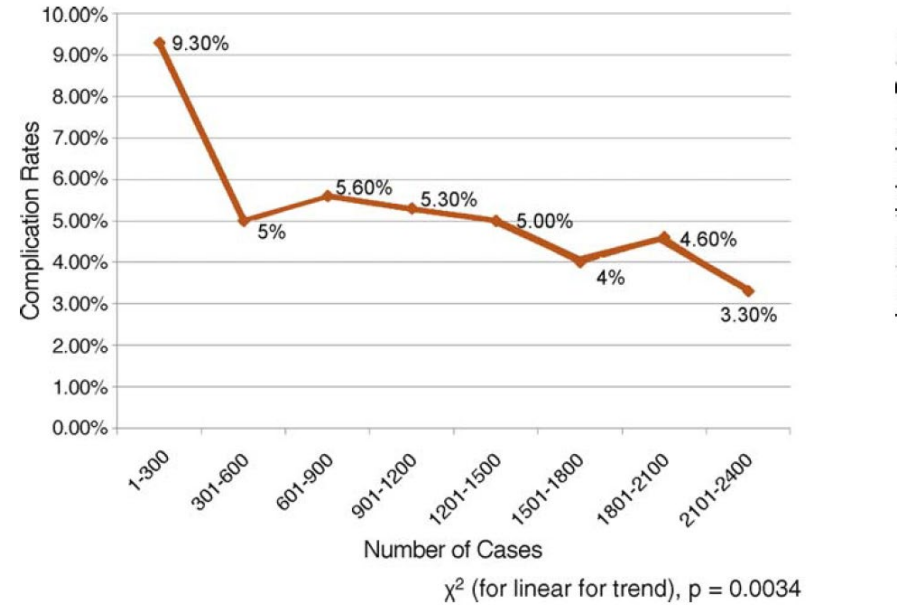


Fig. 1 – Complication rates versus surgeon's experience.

RARP is safe for high risk Pca. Complication rates demonstrated a tendency to decrease as the surgeon's experience increased.

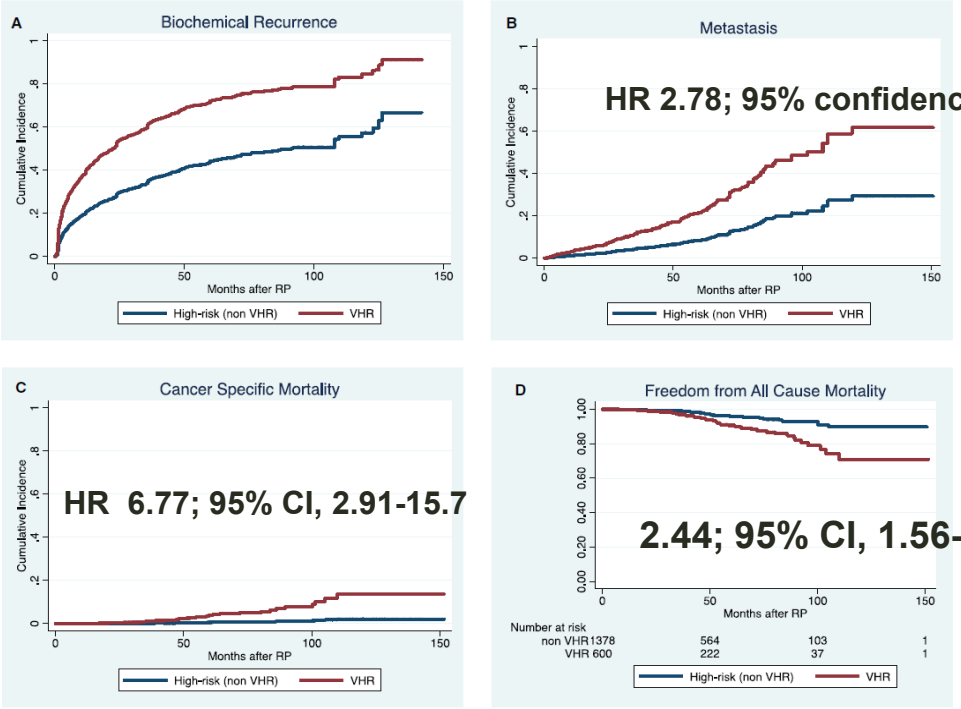
Coelho RF et al, Eur Urol 2010

Surgery in very high risk/ oligometastatic disease

Original Article

Outcomes of Very High-Risk Prostate Cancer After Radical Prostatectomy: Validation Study From 3 Centers

VHR PCa Hopkins criteria: primary Gleason pattern 5 on biopsy, >4 biopsy cores with a Gleason sum of 8 to 10, or multiple individual NCCN high-risk features.



a validation study of patients who underwent RP for high-risk PCa, VHR criteria were strongly associated with adverse pathologic and oncologic outcomes.

Chapin et al, Cancer 2018

Randomized, Phase III Trial of Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery) of the Primary Tumor in Metastatic ([illegible]) Prostate Cancer (PC)

SWOG

Planned follow-up up to 8 years

- Histologically or cytologically proven prostate carcinoma
- Documented evidence of M1 disease
- Androgen dependent disease measured by declining PSA.
- Treatment initiation with BST no longer than 6 months prior to randomization
- ECOG PS 0 or 1
- Life-expectancy >2 years
- Must be a candidate for surgery and/or radiation therapy

RANDOMIZED

1:1

N = 1273

TREATMENT

Best Systemic Therapy (BST) + Surgery or Radiation Therapy

Best Systemic Therapy (BST)

Primary efficacy endpoint: Overall Survival

NCT03678025

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Martini-Klinik

Prostatakrebszentrum

Universitätsklinikum Hamburg-Eppendorf

Impact of Radical Prostatectomy as Primary Treatment in Patients With Prostate Cancer With Limited Bone Metastases (g-RAMPP)

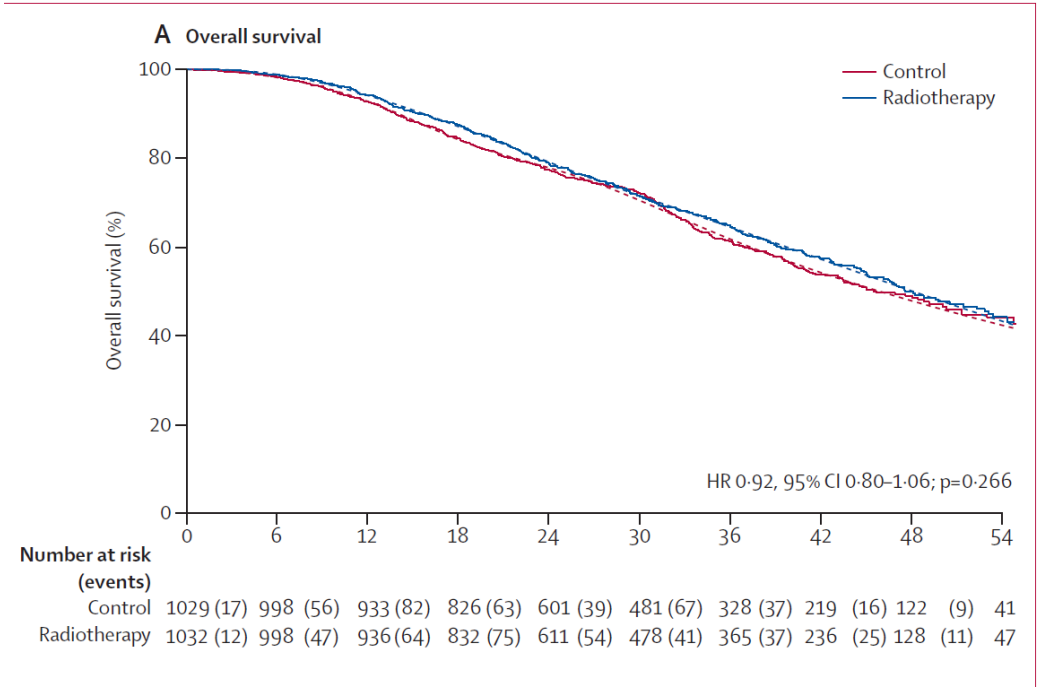
- Martini-Klinik (2015)
- 452 patients (Fase III)
- BST X BST + RP
- endpoint – 5 year CSS

1.Patients with newly diagnosed prostate
2.At least one and at most 5 bone metastases in imaging tests (bone scintigraphy, CT, MRT or PET) at diagnosis with no evidence of visceral metastasis. Patients with evidence of lymph node metastasis (N1) are allowed
3.PSA ≤ 200 ng/ml at diagnosis (without ADT)
4.Asymptomatic or mild symptomatic disease
5.Locally resectable tumour stage
6.ECOG Performance Score 0-1
7.Submission of the patient's written declaration of informed consent following explanation
8.Age ≥ 18 - ≤ 75 years

NCT02454543

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

THE LANCET



Radiotherapy to the prostate did not improve survival for unselected patients with newly diagnosed metastatic prostate cancer

Parker C. et al, The Lancet, 2018

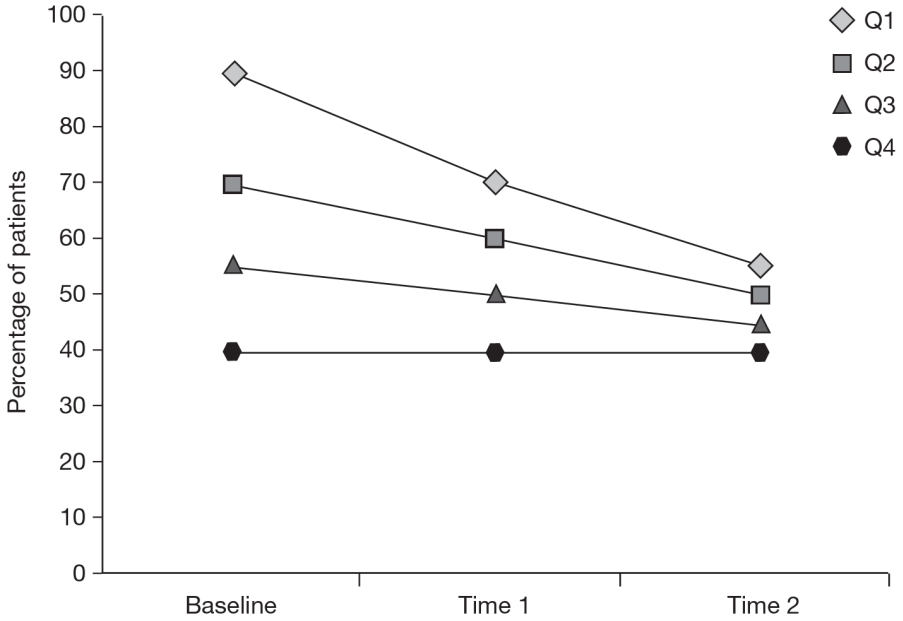
Caution!!!!!

REVIEW

www.nature.com/clinicalpractice/rheum

Primer: the fallacy of subgroup analysis

Francis Guillemin



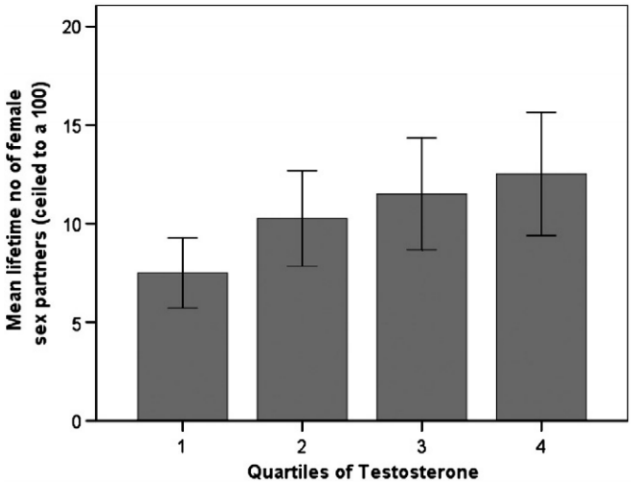
Subgroup analyses can lead to conclusions that do more harm than good (FN or FP conclusion)and generally considered hypothesis generating rather than practice changing

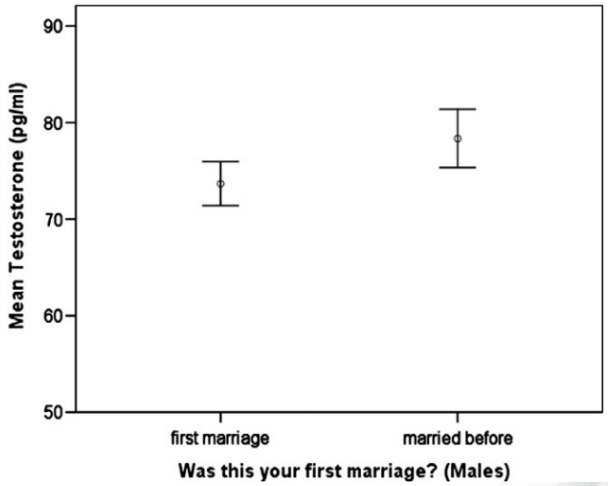
CONCLUSIONS

- ✓ **RP is a safe and feasible option** for the treatment of locally advanced prostate cancer with CSS rates at least similar to RDT+HT
- ✓ Patients with **high-risk prostate cancer benefit the most** from radical prostatectomy.
- ✓ Patients selection is key in order to maximize oncologic outcomes while minimizing toxicity
- ✓ The most important factors implied in the patient's selections are **Age**, **Life expectancy**, **C Comorbidity Index**, **PSA, biopsy Gleason and Clinical stage**

Testosterone levels and their associations with lifetime number of opposite sex partners and remarriage in a large sample of American elderly men and women

Thomas V. Pollet [a,*], Leander van der Meij [a,b], Kelly D. Cobey [a], Abraham P. Buunk [c]





Married men tended to have lower T than single, divorced or separated men (r(637)=−0.069, p= 0.08)

MARRIAGE = CASTRATION

Pollet TV et al, Homrones and Behavior , 2