L’ approccio alle stazioni linfonodali in presentazione di malattia ed all’ eventuale recidiva nodale:

il punto di vista dell’urologo

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PRIMARY LYMPHADENECTOMY IN PC

- WHY?
- HOW?
- FOR WHOM?

CURRENT IMAGING MODALITIES ARE INADEQUATE FOR N STAGING

- CT will detect only 1 out of 10 LNI in contemporary PCs

Briganti A, Eur Urol 2012

- Functional imaging modalities reflecting metabolic changes such us diffusion-weighted MRI or PET-CT have not yet shown to be promising (in a preoperative setting)

Budihardo T, Eur Urol 2011

- Techniques that proved successful (high resolution MRI with nanoparticles) are not yet available

Harisinghani NG, NEJM 2003

Prospective Evaluation of ^{11}C-Choline Positron Emission Tomography/Computed Tomography and Diffusion-Weighted Magnetic Resonance Imaging for the Nodal Staging of Prostate Cancer with a High Risk of Lymph Node Metastases

From February 2008 to August 2009, 36 patients with PCa and no pelvic LN involvement on contrast-enhanced CT with a risk 10- 35% of LN metastasis according to the Partin tables were enrolled in this study.

11C-choline positron emission tomography/computed tomography

	Patient-based analysis	LN region-based analysis
No. of true-positive cases	3	3
No. of true-negative cases	19	294
No. of false-positive cases	1	1
No. of false-negative cases	13	29
Sensitivity	18.8%	9.4%
Specificity	95%	99.7%
PPV	75%	75%
NPV	59.4%	91.0%

Diffusion-weighted imaging

	Patient-based analysis	LN region-based analysis
No. of true-positive cases	6	6
No. of true-negative cases	18	288
No. of false-positive cases	4	7
No. of false-negative cases	8	26
Sensitivity	42.9%	18.8%
Specificity	81.8%	97.6%
PPV	60%	46.2%
NPV	69.2%	91.7%

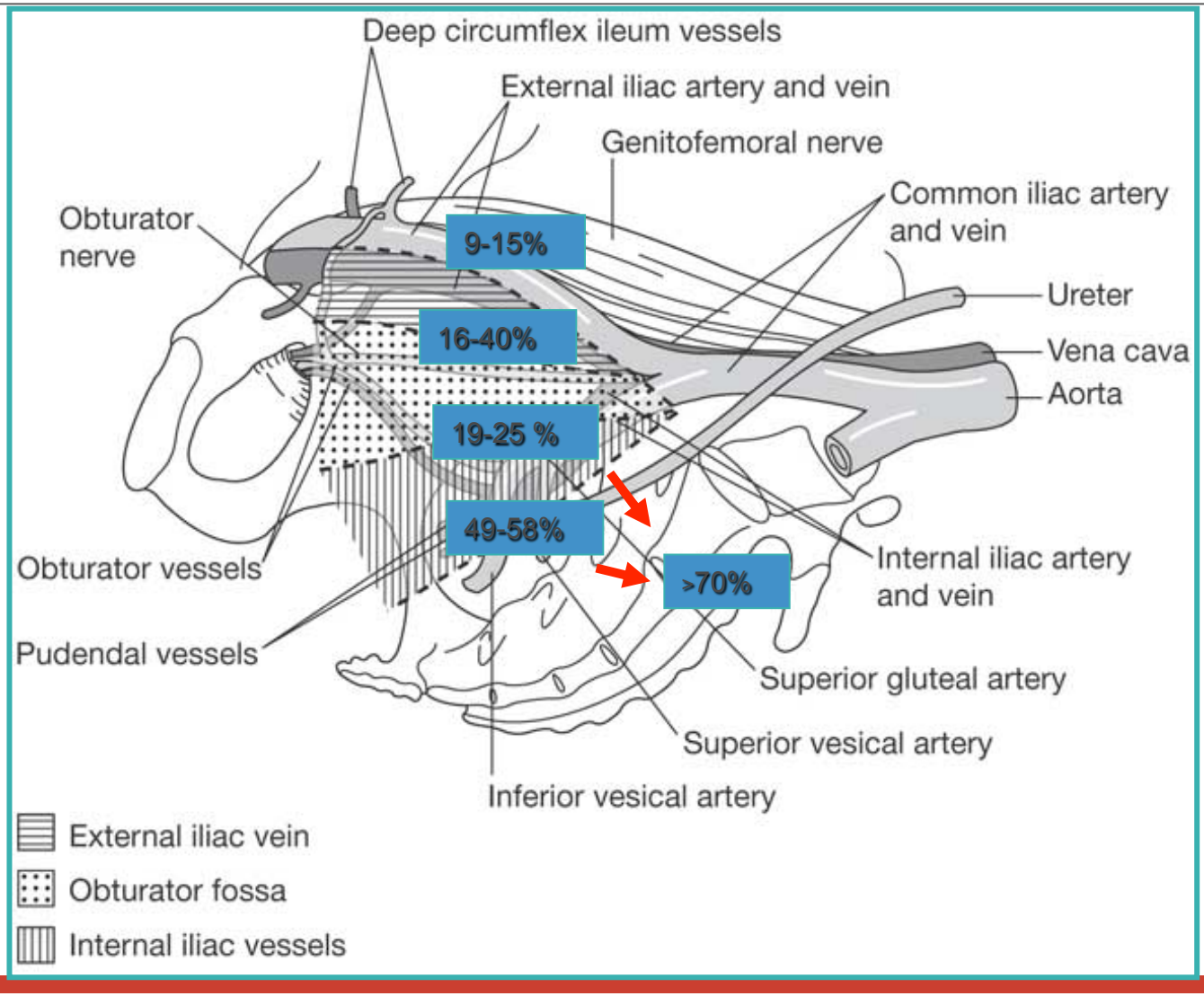
Budiharto et al Eur Urol, 60: 125-130,2011

LYMPHADENECTOMY (LND) AS THE MOST ACCURATE STAGING PROCEDURE, PROVIDED THAT…

- Obturator fossa restricted LND highly inadequate and no longer acceptable
- LND limited to the **external iliac** and **obturator** location will include only 38% of prostate draining nodes
- To remove 75% of potentually cancer bearing nodes LND should include **internal** and common **iliac vessels**

La Rochelle JC, Urol Clin North Am, 2011

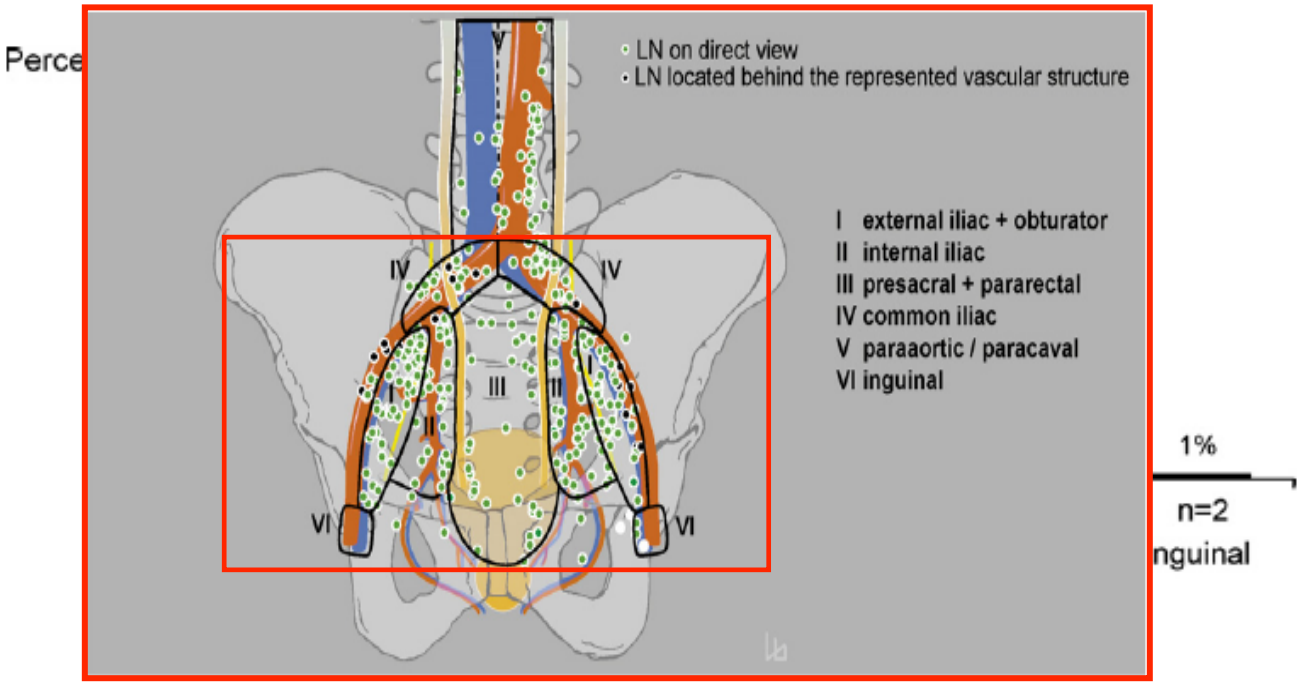
LYMPH NODE METASTASES DISTRIBUTION IN PROSTATE CANCER



Burkhard F, Studer UE World J Urol 26:231-36,2008
Heidenreich A et al J Urol, 167: 1681-86, 2002

SHOULD THE TEMPLATE OF THE PRIMARY LYMPHATIC LANDING SITES OF THE PROSTATE BE REVISITED?

Single-photon emission computed tomography (SPECT)
fused with CT (SPECT/ CT) or MRI (SPECT/MRI)



- *Only 38% of lymph node were found within the area of limited PLND*
- 28% of nodes located in the common iliac /paraaortic/paracaval areas.
- By extending the dissection along common iliac vessels at least up to the ureteric crossing 75% of all nodes potentially harbouring metastasis can be removed

Mattei A et al, Eur Urol, 52:126-32 2008

Lymphatic Spread of Nodal Metastases in High-Risk Prostate Cancer: The Ascending Pathway From the Pelvis to the Retroperitoneum

	Level 2: common iliac and retroperitoneal lymph nodes	
Level 1: pelvic lymph nodes	Positive common and retroperitoneal lymph nodes (n = 14/19; 74%)	Negative common and retroperitoneal lymph nodes (n = 4/19; 21%)
Positive pelvic lymph nodes (n = 18/19; 95%)	14/18 (77.8)	4/18 (22.2)
Negative pelvic lymph nodes (n = 1/19; 5%)	0/19	1/19 (5%)

- **At least 5 lower pelvic positive lymph nodes were found in patients with common iliac positive lymph nodes.**

- **Retroperitoneal involvement was observed only when the common iliac lymph nodes were also involved. Moreover, all patients with positive common iliac lymph nodes also invariably had positive retroperitoneal lymph nodes**

Briganti A et al, Prostate, 2011

PREVALENCE OF NODAL METASTASES IS INCREASED WITH EXTENSIVE LND ACROSS ALL RISK GROUPS

	PLND extent	Mean number of nodes removed	Low risk group (cT1c, PSA<10, Gleason ≤6)	Intermediate risk group (Gleason 7 or PSA 10-20, cT2)	High risk group (cT3 or Gleason 8-10 or PSA>20)
Bhatta-Dar et al, 2004	Limited	NA	0.5%	-	-
Makarov et al, 2006	Limited	5.5	0.5%	-	-
Kawakami et al, 2006	Limited	5.7	0.87%	2%	7%
Yossepowich et al	Limited	NA	4%		12%
Heidenreich et al, 2008	**Extended**	**21**	**5.8%**	**20%**	**55%**
Studer U et al, 2008	**Extended**	**20**	**3%**	**-**	**-**
Briganti A et al, 2009	**Extended**	**17.3**	**1.8%**	**8.2%**	**33.7%**

ARE PREDICTIVE MODELS FOR N+ IN PC RELIABLE?

- Most of these tools are derived from routinely available variables (PSA, Gleson score, T staging)

- Partin tables and most nomograms were derived using a limited LND, so are likely to underestimate LNI

  Makarov DV, Urology 2007

- Curiosuly, the Roach formula, criticized to overestimate LNI, was found to be 80% accurate when validated with a large series of extended LND

  Abdollah F, Int J Rad Oncol 2012

IS LND THERAPEUTIC? EVIDENCE PRO

- Significant inverse association between the number of nodes removed and BCR in N- patients: removal of micrometastatic disease?

  Masterson TA, J Urol 2006

- Survival advantage for patients with > 4 nodes removed (for both N+ and N-) as compared to < 4 nodes

  Joslin SA, Urology 2006

- A significant proportion of men with LNI have BCR free survival without adjuvant therapy

  Schumacher MA, Eur Urol 2008

IS LND THERAPEUTIC? EVIDENCE AGAINST

- Whatever we say, given the absence of randomised trials, this question cannot simply be answered with an acceptable level of evidence

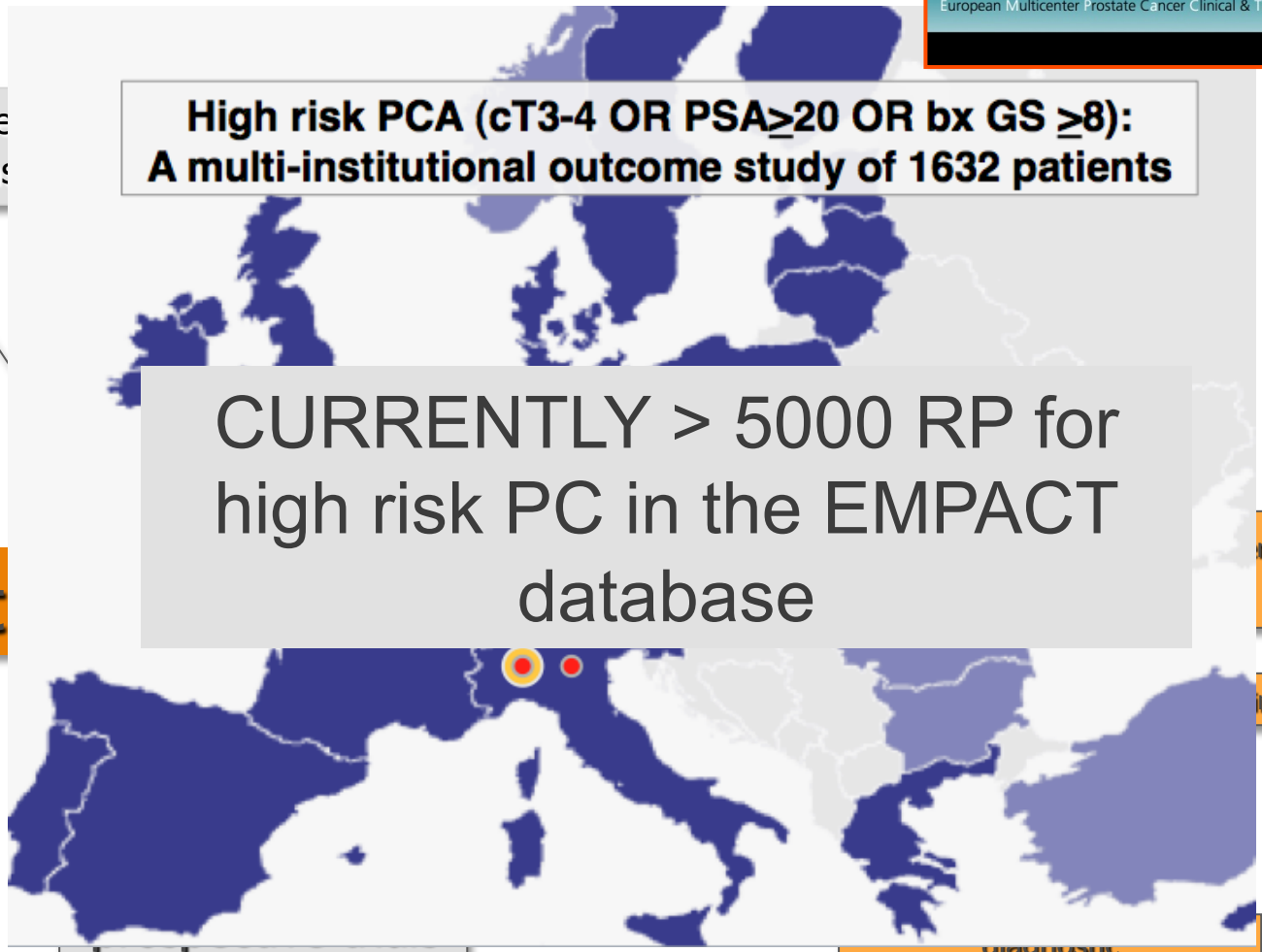
- The *Will Rogers phenomenon (bias)* is likely to explain:
  - why N0 patients with eLND are falsely attributed a better prognosis than N0 patient with limited LND (more N+ are detected with eLND and removed
  - why N+ with eLND have better prognosis than N+ with limited LND (N+ with eLND are likely to have lower disease volume)

Albertsen PC, J Natl Cancer Inst 2005

EMPaCT-Study Group

European multice
clinical databas

High risk PCA (cT3-4 OR PSA≥20 OR bx GS ≥8):
A multi-institutional outcome study of 1632 patients



CURRENTLY > 5000 RP for high risk PC in the EMPACT database

Let

netic/epigenetic regulation

n vivo models

diagnostic

(CCC-SU, ECTU-Wü, EORTC-GU group)

preclinical therapeutic tests

EXTENT OF PLND IN HIGH RISK PROSTATE CANCER

LND extension (n patients)	5-year projected CSS	10-year projected CSS	p-value
Limited LND (obt fossa +/- ext iliac) (n=396)	96.2%	90.3%	0.485
Extended LND (obt fossa + ext iliac + hypogastric) (n=180)	96.8%	96.8%	
<8 nodes removed (n=279)	96.6%	92.3%	0.901
≥8 nodes removed (n=491)	97.4%	92.7%	
<10 nodes removed (n=398)	97.5%	93.9%	0.232
≥10 nodes removed (n=371)	96.5%	90.7%	
<12 nodes removed (n=485)	97.1%	93.4%	0.340
≥12 nodes removed (n=288)	96.2%	89.5%	
<14 nodes removed (n=572)	96.8%	92.4%	0.736
≥14 nodes removed (n=201)	96.5%	92.7%	
<18 nodes removed (n=664)	96.5%	91.7%	0.168
≥18 nodes removed (n=109)	100%	100%	
<20 nodes removed (n=696)	96.6%	92.0%	0.321
≥20 nodes removed (n=77)	100%	100%	

Joniau S et al, AUA 2010

ARE PATIENTS LN+ AT SURGERY CANDIDATE FOR ADJUVANT/SALVAGE RADIOTHERAPY?

- If radiotherapy does not cure N+ disease, eLND may represent the best tool to select the ideal candidate for radiotherapy

- Based on retrospective evidence:

  - Patients with LNI (with a median of 2.5 + nodes) seem to benefit from adjuvant RT combined with ADT as compared to ADT alone

    Da Pozzo L, Eur Urol 2009

  - Limited N+ disease have a dramatic high BCR free survival (39% in the study of Bader with 1 + node) and exceptionally high long term survival without adjuvant therapy (94% 10 y CSS with 1+N, similar to N0!)

    Bader P, J urol 2003
    Cheng L, Cancer 2001

WHICH PC SHOULD RECEIVE LND AT SURGERY?

GUIDELINE	INDICATION FOR PLND	EXTENT OF PLND
European Association of Urology^	Men with **intermediate** (cT2a, PSA 10-20 ng/ml, biopsy Gleason score=7) or **high risk** (>cT2b, PSA>20 ng/ml, Gleason score≥8) prostate cancer **Controversial in low risk**	Extended
American Urological Association §	PLND generally reserved for patients with higher risk of nodal involvement	Not indicated
National Comprehensive Cancer Network*	PLND can be excluded in patients with <7% predicted probability of lymph node metastases by nomograms, although some patients with nodal metastases will be missed. An extended PLND is preferred when PLND is performed.	Extended

^EAU 2013 prostate cancer guidelines, available at www.uroweb.org
§ Thompson I et al J Urol, 177:2106-31, 2007
* www.ncnn.org

CONCLUSION

PRIMARY LYMPHADENECTOMY IN PC

- WHY: **STAGING**
- HOW: **EXTENDED**
- FOR WHOM: **INTERMEDIATE/HIGH RISK**

Conclusion primary LND

- Lymphadenectomy is at present the best and the only reliable LN staging procedure as long it is extended at least to the internal iliac nodes

- While no definitive curative role for LND in primary PC has been defined yet, a proportion of patients with minimal nodal disease at eLND (≤ 1-2 nodes) appear to be cured without AT

SALVAGE LYMPHADENECTOMY IN PC (sLND)

For whom?

- Hormone naive PCs
- NM-CRPC

INTRODUCTION

- Up to 40% PC will eventually undergo BCR after surgery
- Traditionally, salvage radiotherapy is offered when local pelvic recurrence is suspected while HT is offered for systemic recurrence
- Current advances in imaging have identified a peculiar type of recurrence: **systemic disease progression limited to the regional or retroperitoneal lymph node**
- The beneficial effect of extensive LND in primary PC without hormones could provide a rationale approach to salvage LND

DIAGNOSTIC AND TECHNICAL ISSUES

- Performance of Coline PET/CT scan in detecting LN relapse is poor
  - A specificity of 80-90% means that in 10-20% we will not find positive nodes at surgery
  - A sensitivity of 30-60% implies that positive nodes will be detected outside the region indicated by PET/CT

Passoni N et al, Urol Oncol in press
Scattoni V, Eur Urol 2007

- The anatomical landmarks of sLND have not been defined yet
  - When relapse is confined to the pelvis, should we procede to removal of retroperitoneal nodes?
  - In retroperitoneal relapse, should disection be carried down to the whole pelvis? It may be extremely tricky to re-do a lymphadenectomy in the site of a previous one

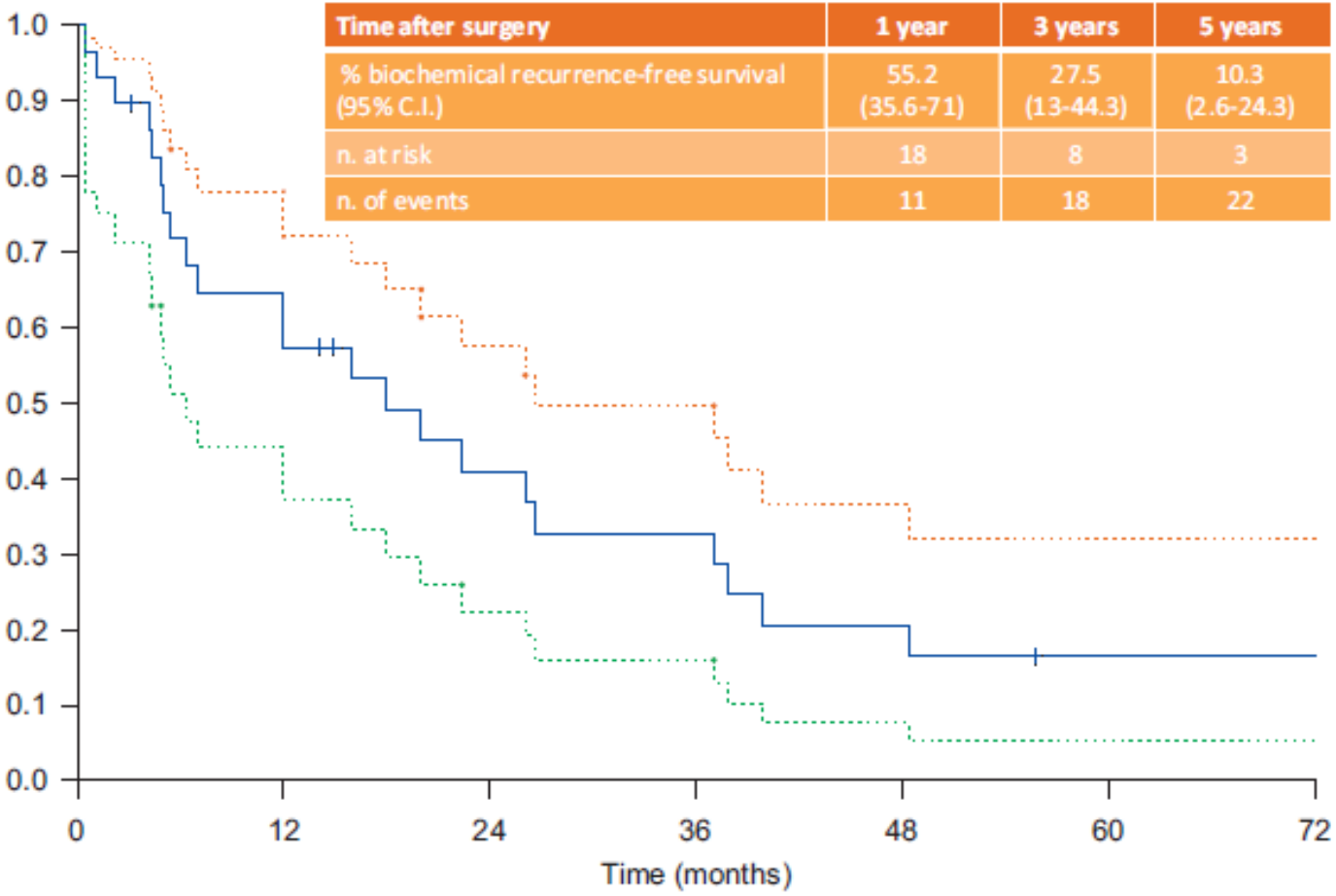
ONCOLOGICAL OUTCOMES

Cohort type	Single-institution *	Single-institution #	Multi-institutions §
N. of patients	72	52	162
Pre-operative PSA (ng/ml) Mean Median	 3.7 1.5	 3.9 1.1	 3.6 1.9
N. of lymph nodes removed at SLND Mean Median	 30.6 29.0	 23.3 17.0	 24.6 20.0
N. of positive nodes removed at SLND Mean Median	 9.8 2.0	 9.7 4.0	 6.1 2.0
Initial PSA response (<0.2 ng/ml)	57% (32% had HRT)	46% (52% had adjuvant sRT)	41%
5-year BCR-free survival	19%	9%	---
5-year progression-free survival	34%	26%	---
5-year cancer-specific survival	75%	78%	---

*Rigatti P, Eur Urol 2011
#Jilg CA, J Urol 2012, § Suardi N, AUA 2013

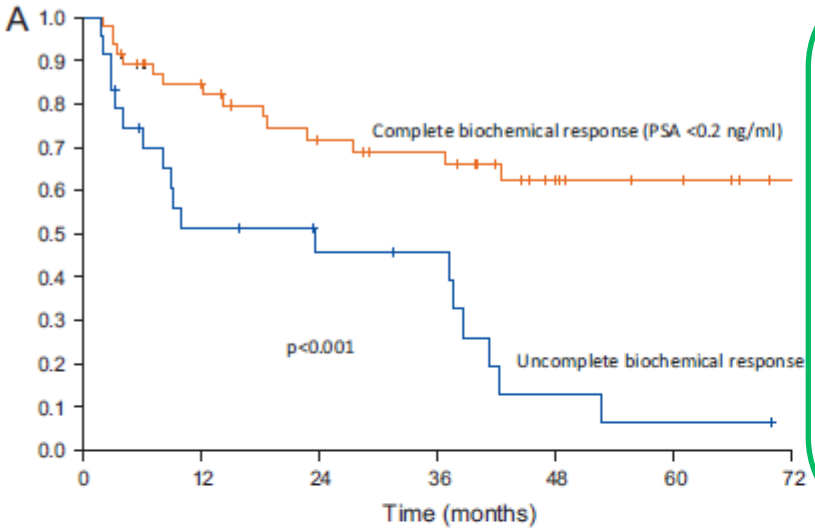
Salvage LND in hormone-naive Pca
Time to BCR

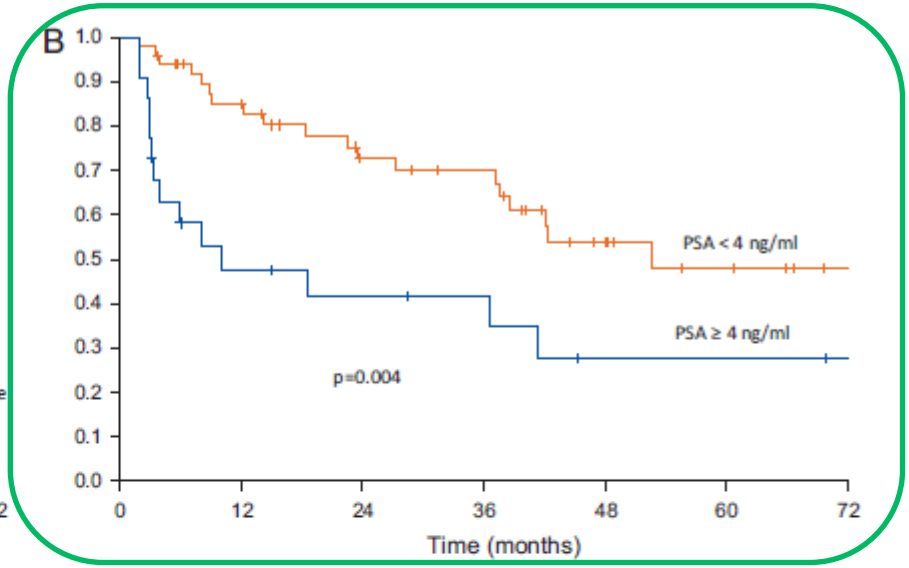
Time after surgery	1 year	3 years	5 years
% biochemical recurrence-free survival (95% C.I.)	55.2 (35.6-71)	27.5 (13-44.3)	10.3 (2.6-24.3)
n. at risk	18	8	3
n. of events	11	18	22

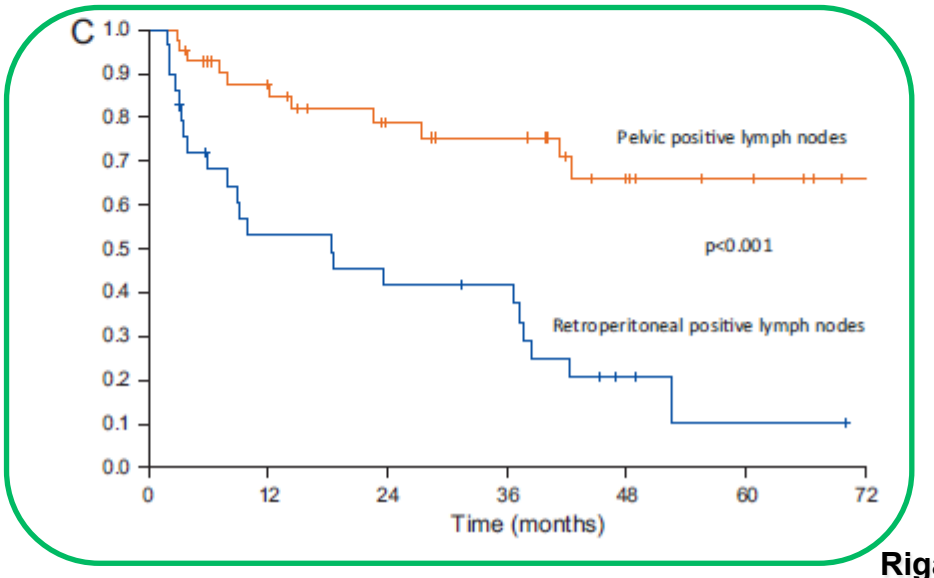


Rigatti P, et al., Eur Urol 2011

Salvage LND in hormone-naive Pca
CAN WE PREDICT THE RESPONDER?







Preoperative Independent Predictors

End point: Time to progression

Rigatti P, et al., Eur Urol 2011

Salvage LND in hormone-naive Pca
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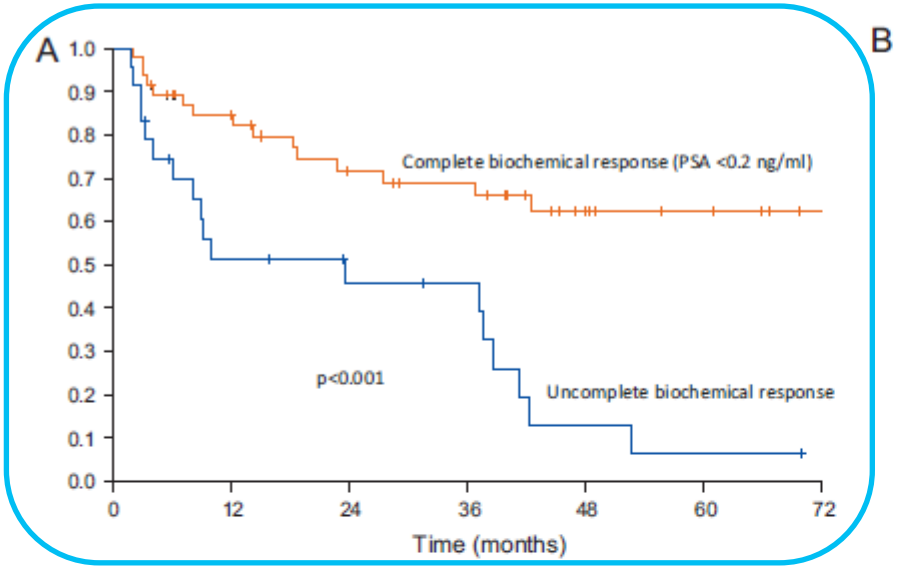
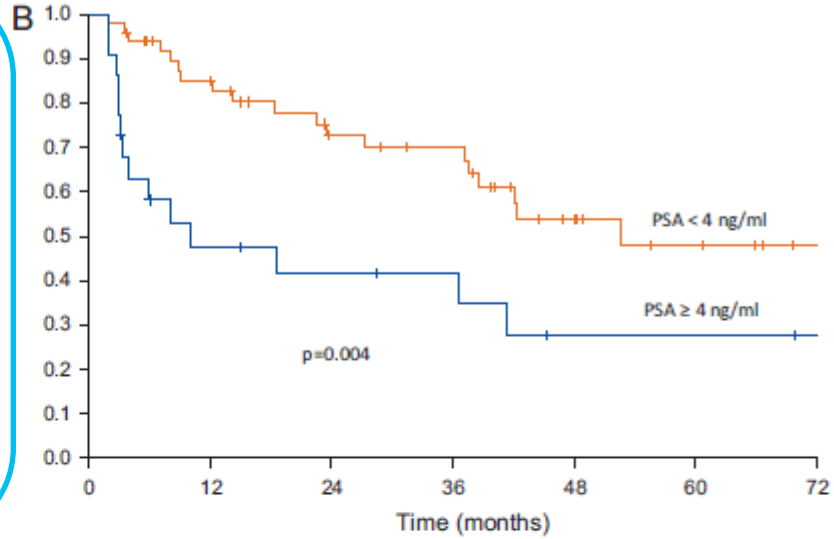
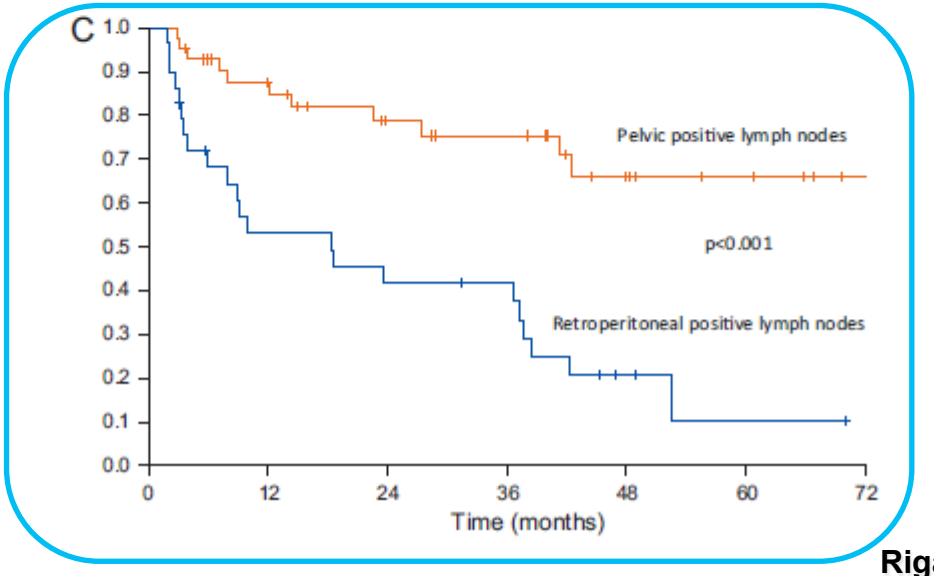






Postoperative Independent Predictors

End point: Time to progression

Rigatti P, et al., Eur Urol 2011

Salvage LND in NM-CRPC

- Multicenter, retrospective cohort study (Leuven, Milan, Mayo Clinic)
- N=40
- All patients underwent primary RP for localized/locally advanced Pca, all developed disease recurrence for which they received ADT
  - RP Gleason score
    - 2-6 in 11.1%
    - **7 in 41.7%**
    - **8-9 in 47.2%**
  - Positive LN at RP: **25%**
- Patients were followed until they reached NM-CRPC status, but detectable LN+ at Abdominal CT or 11-C choline PET-CT

Suardi N, Briganti A, Karnes RJ, Joniau S, et al. Submitted, EAU 2013

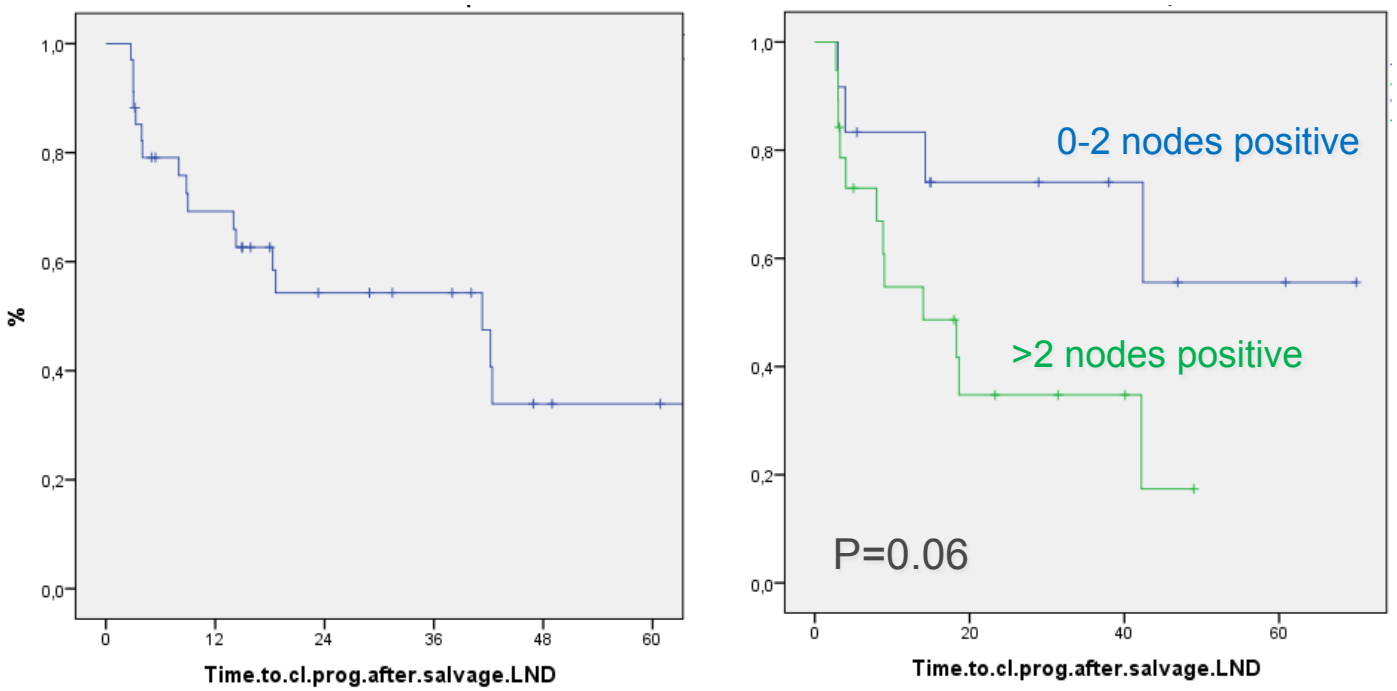
Salvage LND in NM-CRPC

- Patient and tumor characteristics at sLND:

N=40	Mean / N (%)	Median, range
Age (yrs)	66.1	66, 50-79
PSA (ng/ml)	4.2	2.3, 0.18-23.1
PLND RPLND	39 (97.5%) 33 (82.5%)	
N of nodes removed	28.9	25, 4-85
N of positive nodes	10.4	4, 0-43
N of patients with LN+	36 (92.3%)	
PSA post sLND	1.2	0.19, 0-13.9
PSA-drop	3.1	1.9, -2.9-23.1
N of patients with PSA <0.2 ng/ml	17 (43.6%)	

Suardi N, Briganti A, Karnes RJ, Joniau S, et al. EAU 2013

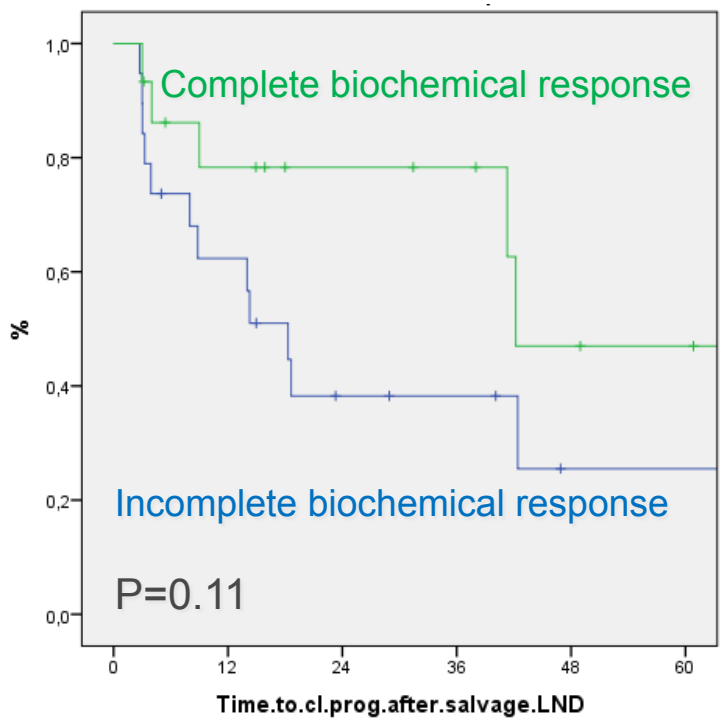
Time to clinical recurrence following sLND in NM-CRPC



- Number of positive nodes predicts time to clinical recurrence. Cut-off >2 positive nodes.

Suardi N, Briganti A, Karnes RJ, Joniau S, et al. Submitted, EAU 2013

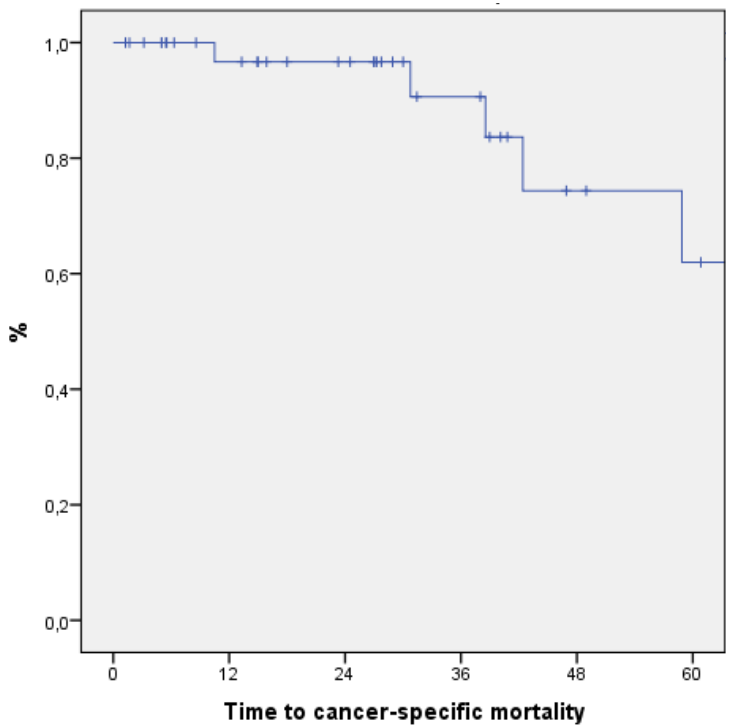
Time to clinical recurrence following sLND in NM-CRPC



- Undetectable PSA after sLND is associated with longer time to clinical recurrence

Suardi N, Briganti A, Karnes RJ, Joniau S, et al. Submitted, EAU 2013

Cancer-specific survival following sLND in NM-CRPC



- At 5 years follow-up, CSS was 63%

Suardi N, Briganti A, Karnes RJ, Joniau S, EAU 2013

Conclusions sLND

- Salvage LND in selected cases with cN+ hormone naif or NM-CRPC may render PSA undetectable in roughly 45% of patients and prolong time to clinical recurrence

- This novel surgical approach is currently not standardized as a technique, nor have selection criteria been defined yet

- It remains experimental, yet worhty to be further explored with acceptable morbidity