

**CORSO
DI CHIRURGIA
PELVICA
ONCOLOGICA
MININVASIVA:
UP TO DATE**

17 - 18 GENNAIO 2019

POTENZA

Azienda Ospedaliera San Carlo
U.O. UROLOGIA

Palazzo di Vetro, Primo Piano - Sala A
Via Potito Petrone, 85100 Potenza PZ



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

***RUOLO DELLA LINFOADENECTOMIA
IN CHIRURGIA PELVICA ONCOLOGICA***

Prof. Riccardo Schiavina

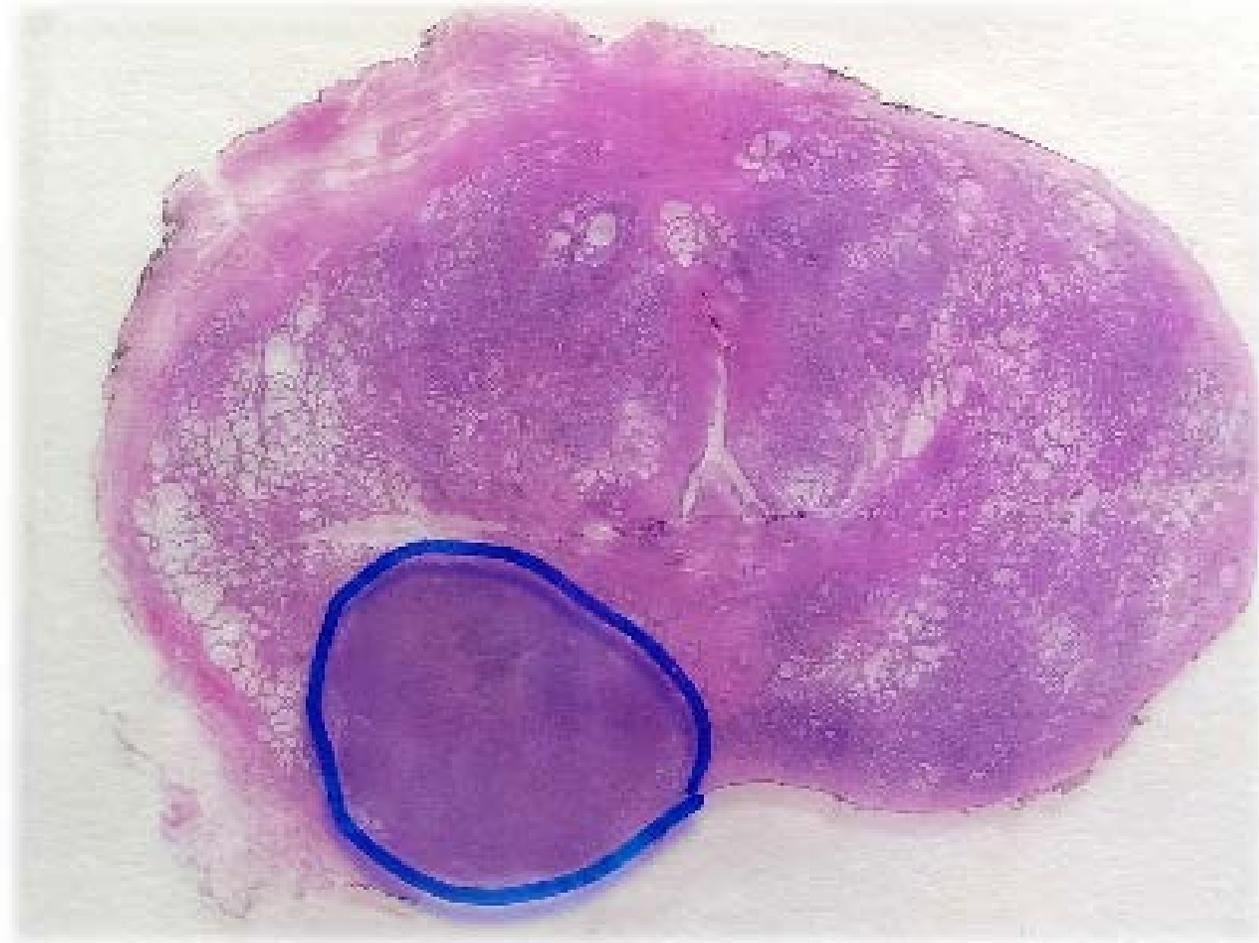
Clinica Urologica

Alma Mater Studiorum- Università di Bologna

Direttore: Prof. E. Brunocilla

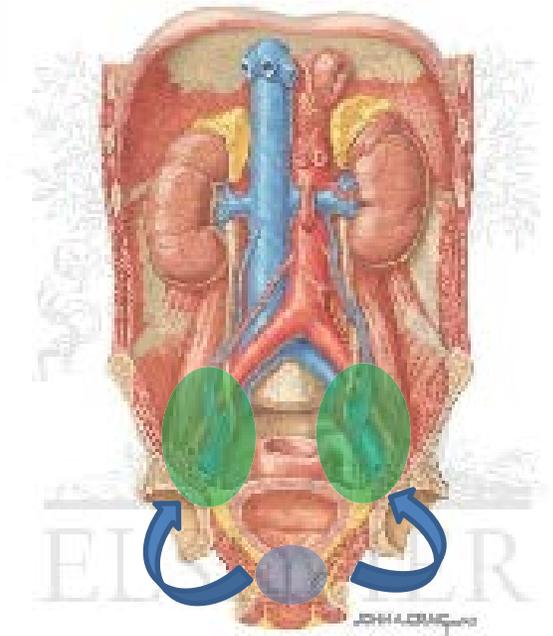


NEOPLASIA PROSTATICA: PLND





- I linfonodi pelvici rappresentano la sede più comune di localizzazione metastatica del tumore prostatico
- 3-24% pN1 al momento della chirurgia a seconda delle casistiche e della classe di rischio



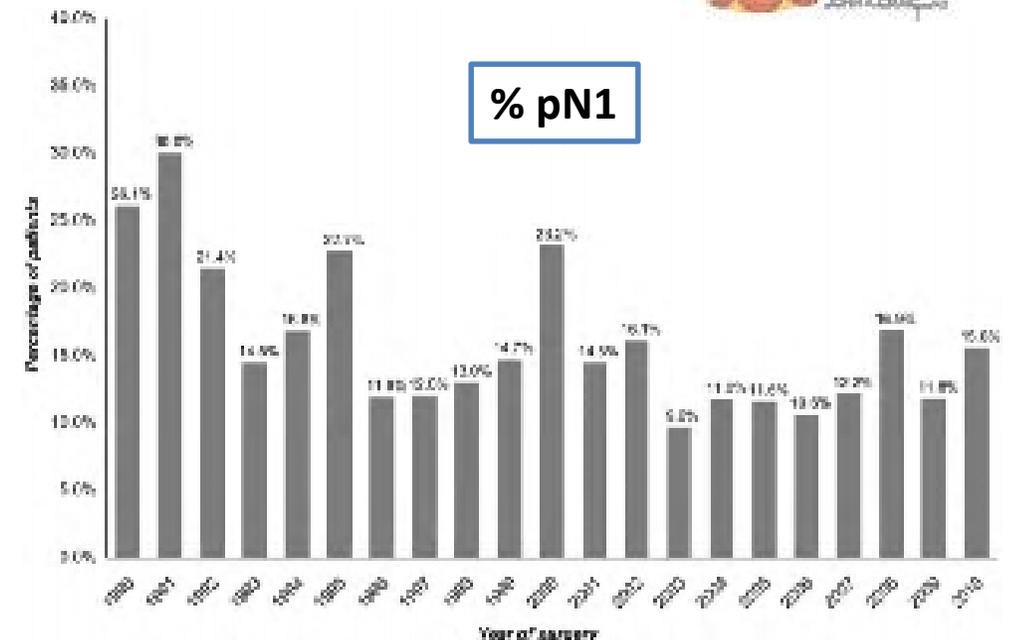
Variation in Pelvic Lymph Node Dissection among Patients Undergoing Radical Prostatectomy by Hospital Characteristics and Surgical Approach: Results from the National Cancer Database

Elyn H. Wang,^{*} James B. Yu,^{*} Cary P. Gross,^{*} Marc C. Smaildone,[†] Nilay D. Shah,[‡] Quoc-Dien Trinh,[§] Paul L. Nguyen,[|] Maxine Sun,[¶] Leona C. Hart[‡] and Simon F. Kim^{*,†,||}



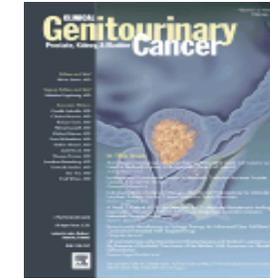
Extended pelvic lymph node dissection in prostate cancer: a 20-year audit in a single center

F. Abdollah¹, N. Suardi¹, A. Bellina¹, M. Bianchi¹, M. Tutolo¹, N. Pizzocci¹, N. Fossati¹, M. Sun², P. del'Oglio¹, A. Salonia¹, P. I. Karaskiewicz², P. Rigatti¹, F. Montorsi¹ & A. Briganti^{1*}





Nodal Occult Metastases in Intermediate- and High-Risk Prostate Cancer Patients Detected Using Serial Section, Immunohistochemistry, and Real-Time Reverse Transcriptase Polymerase Chain Reaction: Prospective Evaluation With Matched-Pair Analysis



54 pazienti affetti da PCa a intermedio e alto rischio

- 20,4% dei pazienti presentavano metastasi linfonodali già alla stadiazione
- L'analisi anatomopatologica del pezzo operatorio (con tecniche SS, IHC e RT-PCR) permesso di individuare un **ulteriore 13%** di pazienti con metastasi linfonodali occulte (OCM)



Outcome oncologico dei pazienti con OCM è **simile** a quello dei soggetti con **metastasi macroscopiche**



Obiettivo dell'imaging

- Escludere una **diffusione polimetastatica** alla diagnosi per evitare un **trattamento locale inutile**
- Identificare pazienti **oligometastatici** alla diagnosi che potrebbero trarre beneficio da un **debulking chirurgico** (???)

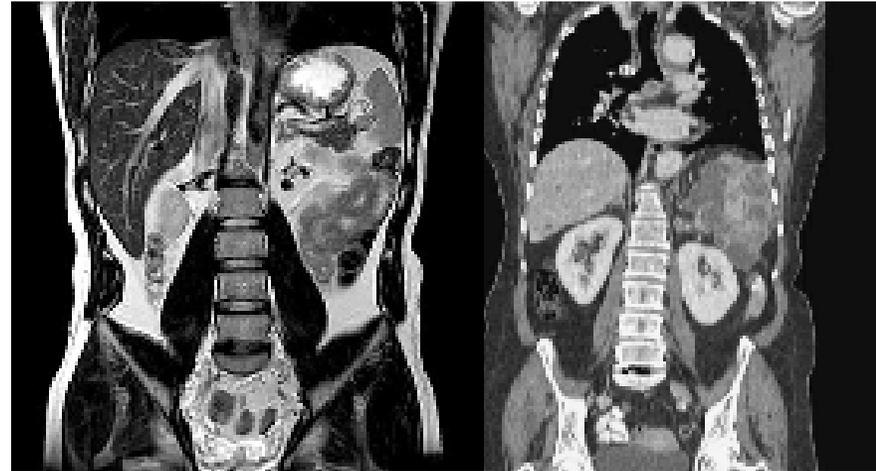




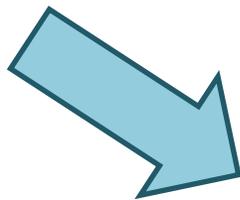
IMAGING CONVENZIONALE

The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis

L' imaging convenzionale (TC, MRI, scintigrafia) si è dimostrato inadeguato per definire e localizzare la sede delle metastasi (linfonodali e sistemiche)



	CT	MRI
Sensibilità	42	39
Specificità	82	82



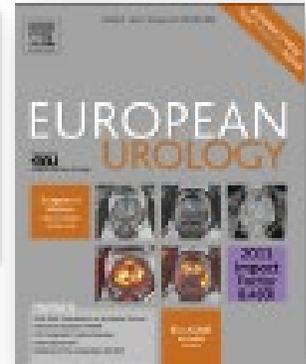
rischio di micrometastasi non visibili all'imaging!!!



Choline PET/CT

Review - Prostate Cancer

Utility of Choline Positron Emission Tomography/Computed Tomography for Lymph Node Involvement Identification in Intermediate- to High-risk Prostate Cancer: A Systematic Literature Review and Meta-analysis



Evangelista L, et al, 2013

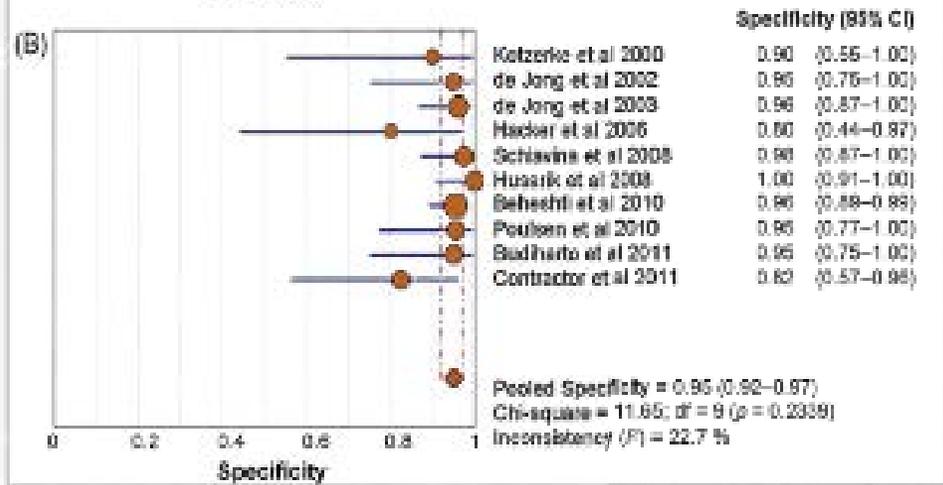
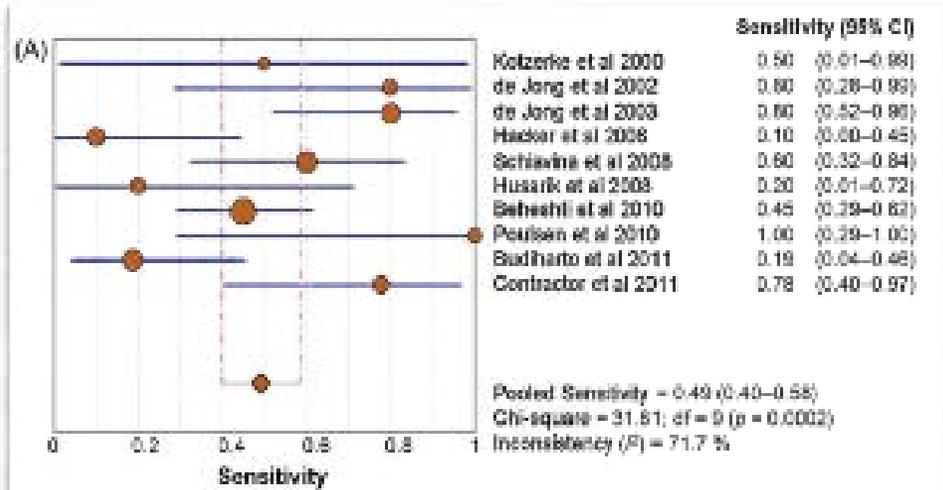


Table 3 - Pooled diagnostic accuracies for choline positron emission tomography/computed tomography

	Pooled value	95% confidence interval
Sensitivity	49.2	39.9-58.4
Specificity	95	92-97.1
Positive likelihood ratio	8.346	4.499-15.482
Negative likelihood ratio	0.549	0.365-0.824
Diagnostic odds ratio	18.999	7.109-50.773



5.3.2.2 Choline PET/CT

^{11}C - or ^{18}F -choline positron emission tomography (PET)/CT have good specificity for LN metastases, but their reported sensitivity falls in a wide range of 10-73% [265, 266].

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51-66%) and 92% (95% CI: 89-94%), respectively [267]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10-35%), the sensitivity was only 8.2% in a region based and 18.9% at a patient-based analysis, which is too low to be of clinical value [268].

In intermediate/high-risk patients, comparisons between choline PET/CT and diffusion-weighted MRI yielded contradictory results, with PET/CT sensitivity found to be superior [269], similar [270, 271] or inferior [268] than that of diffusion-weighted MRI.

Due of its low sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases, or to rule out a nodal dissection based on risk factors or nomograms (see Section 6.1.2.1.1).

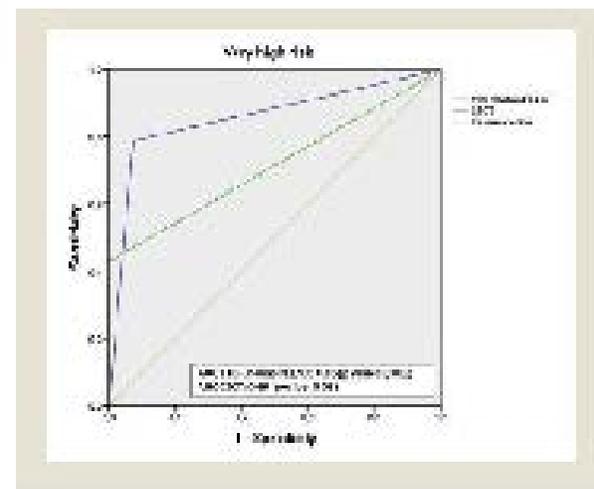
**EAU - ESTRO - ESUR -
SIOG Guidelines on
Prostate Cancer
2018**

Ancora oggi la PET non è raccomandata nella stadiazione preoperatoria del tumore prostatico per la bassa sensibilità



Preoperative Staging With ¹¹C-Choline PET/CT Is Adequately Accurate in Patients With Very High-Risk Prostate Cancer

Riccardo Schiavina,^{1,5} Lorenzo Bianchi,¹ Federico Mineo Bianchi,¹
Mauro Borghesi,^{1,5} Cristian Vincenzo Pultrone,¹ Hussam Dababneh,¹
Paolo Castellucci,² Francesco Ceci,² Cristina Nanni,² Caterina Gaudiano,³
Michelangelo Fiorentino,¹ Angelo Porreca,⁶ Francesco Chesca,¹ Andrea Minervini,⁷
Stefano Fanti,¹ Eugenio Brunocilla^{1,5}



PET colina è significativamente più accurata (86%) della TC (69%) nella stadiazione linfonodale preoperatoria dei pazienti «Very high risk»

VHR

- cT≥T2c or
- >5 positive cores Gs 8-10 or
- primary biopsy Gs= 5 or
- PSA >30 ng/ml or
- 3 high-risk features

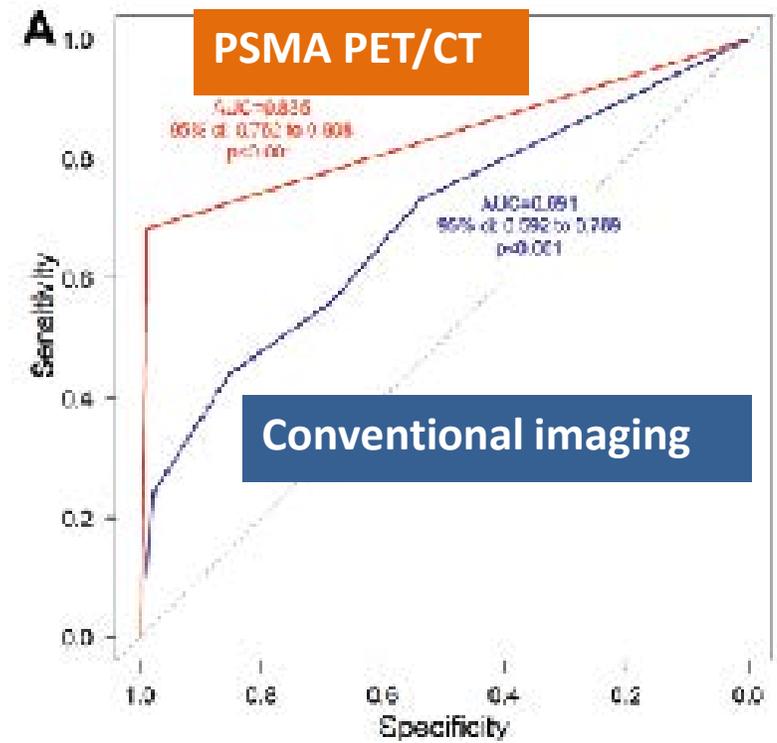
Characteristic	Very High Risk	
	¹¹ C-Choline PET/CT	CECT
Sensitivity	71.4%	25%
Specificity	92.9%	79.3%
PPV	90.9%	25%
NPV	76.4%	79.3%
AUC	0.86	0.69
95% CI	0.71-1	0.52-0.86
P	.001	.05



PSMA PET/CT

Diagnostic Efficacy of ⁶⁸Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer

	68Ga-PSMA PET/CT	Conventional imaging
Sensibilità	65.9	43.9
Specificità	98.9	85.4
Accuratezza	88.5	72.3



PSMA PET/CT: accuratezza migliore dell'imaging convenzionale e della Choline PET/CT ma ancora *grossi limiti di sensibilità!!!*



EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2018

Intermediate-risk PCa	LE	Strength rating
In predominantly Gleason pattern 4 (\geq ISUP 3), use prostate multiparametric magnetic resonance imaging (mpMRI) for local staging.	2b	Weak
In predominantly Gleason pattern 4, include at least a cross-sectional abdominopelvic imaging and bone-scan for metastatic screening.	2a	Weak

High-risk localised PCa/locally advanced PCa	LE	Strength rating
Use prostate mpMRI for local staging.	2b	Strong
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	Strong

«Medicina difensiva»?



Ad oggi nessuna metodica di imaging può sostituire la **PLND** che rimane il **gold standard** per la **stadiazione linfonodale**



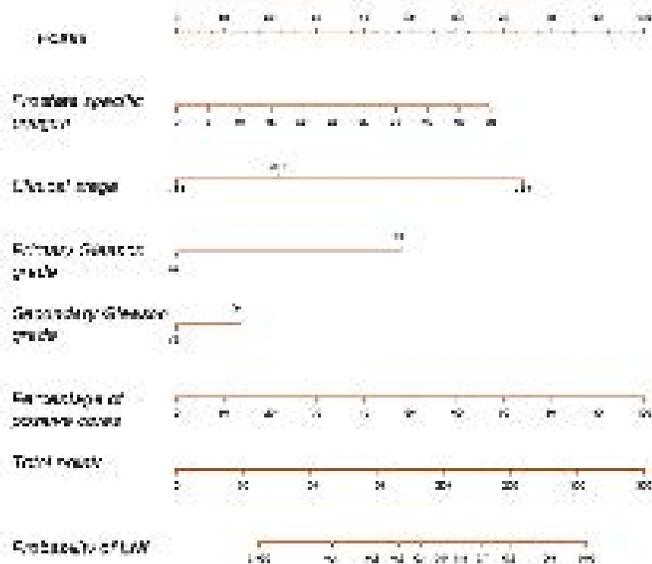


La comune pratica clinica prevede l'utilizzo di **nomogrammi clinico-patologici** per predire il rischio di interessamento linfonodale e guidare la linfoadenectomia pelvica...

BRIGANTI

KATTAN

PARTIN



Pre-Radical Prostatectomy



Prostate Cancer

Become Our Patient | Already Our Patient

Harvard

PARTIN TABLES



Linee guida e indicazioni

Pelvic Lymph Node Dissection in Prostate Cancer

Briganti A et al, 2009



- La PLND può essere **evitata** nei casi di **PCa low-risk**, per la bassa probabilità (<8%) di riscontrare un quadro N+.
- Un rischio >5% (Briganti nomogram, MSKCC, or Roach nomogram) è un' **indicazione ad eseguire PLND con template esteso**

EAU	>5% rischio sec. Briganti's, non eseguire nei low risk
AUA	Non si esprime sul cut-off, non indicata nei low-risk
NCCN	Cut-off >2%, non indicata nei low risk

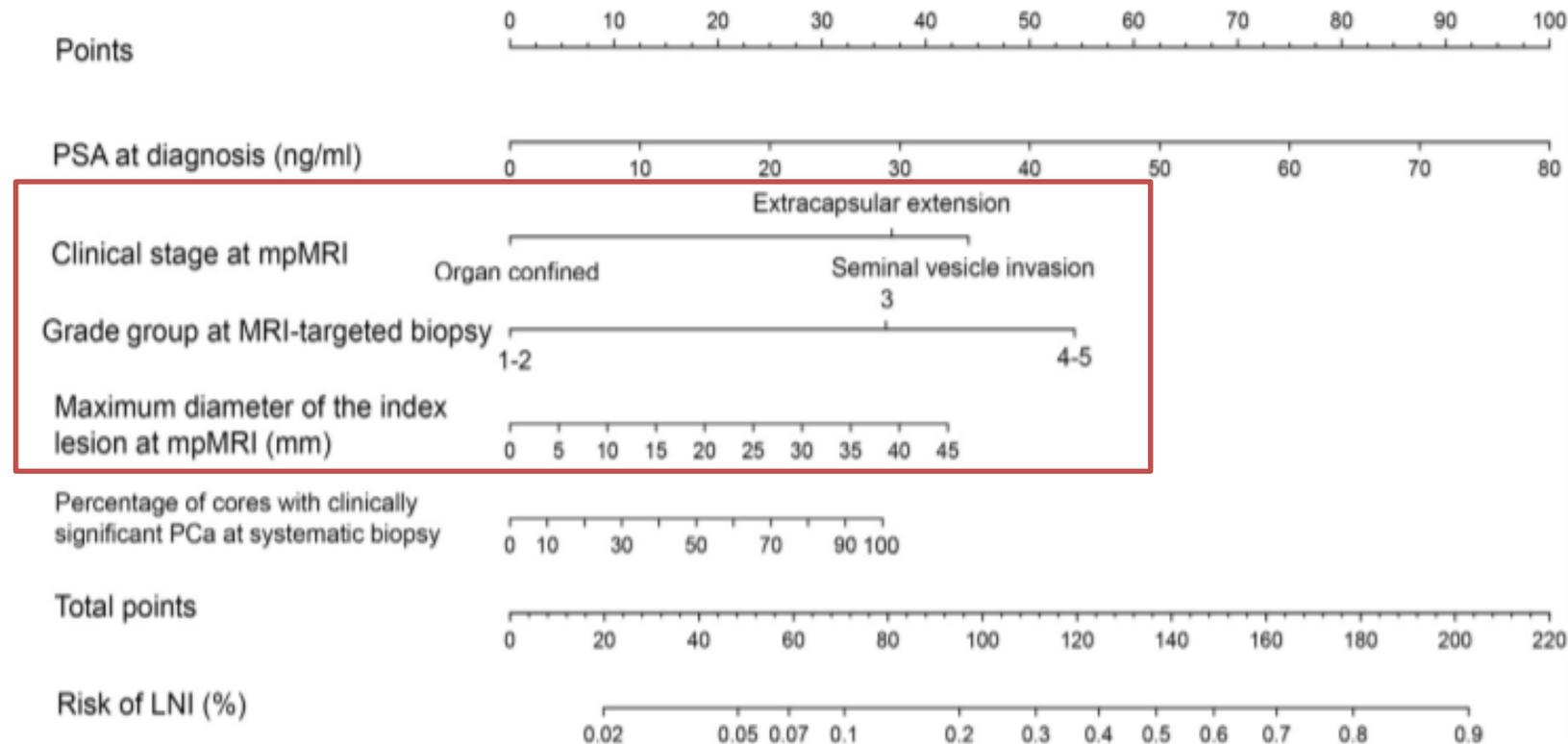
mpMRI: update del nomogramma di Briganti



2018

A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies

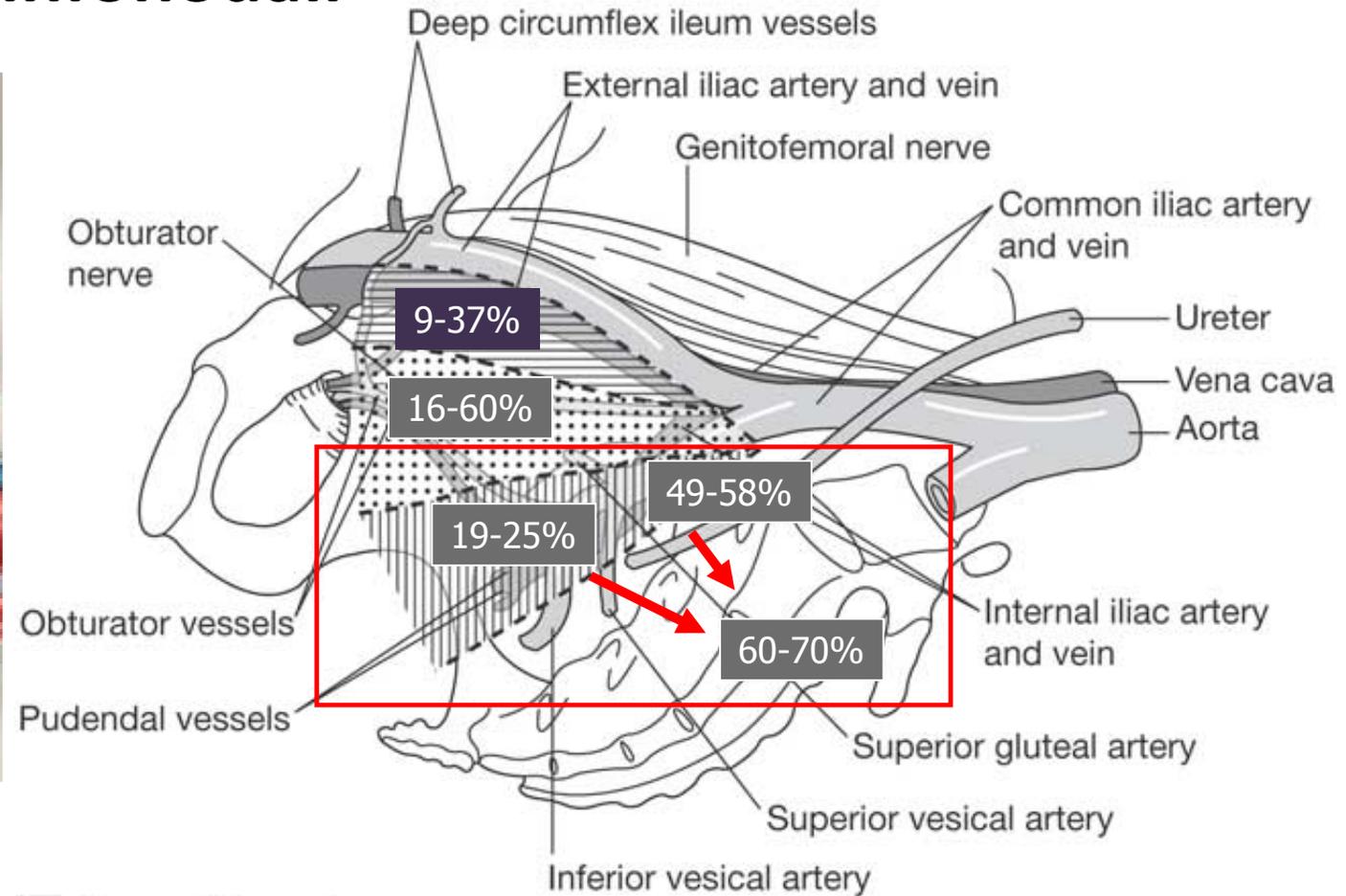
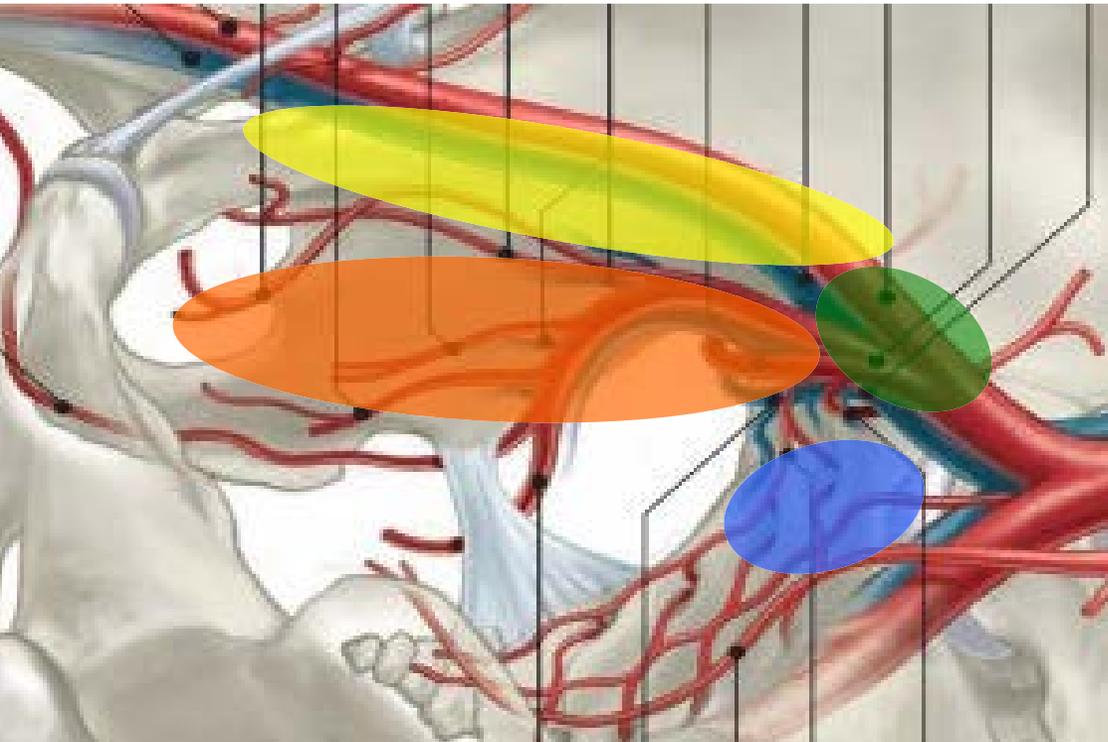
Giorgio Gandaglia¹, Guillaume Ploussard¹, Massimo Valerio¹, Agostino Mattel², Cristian Flori³, Nicola Fossati⁴, Armando Stabile⁵, Jean-Baptiste Beauval⁶, Bernard Mulvaud⁷, Mathieu Roumiguié⁸, Daniele Robesti⁹, Paolo Dell'Oglio¹⁰, Marco Moschini¹¹, Stefania Zamboni¹², Arnas Rakauskas¹³, Francesco De Cobelli¹⁴, Francesco Porpiglia¹⁵, Francesco Montorsi¹⁶, Alberto Briganti¹⁷



AUC: 86% vs. 82%



Distribuzione delle metastasi linfonodali



-  External iliac vein
-  Obturator fossa
-  Internal iliac vessels

Burkhard F, Studer UE *World J Urol* 26:231-36,2008

Heidenreich A et al *J Urol*, 167: 1681-86, 2002

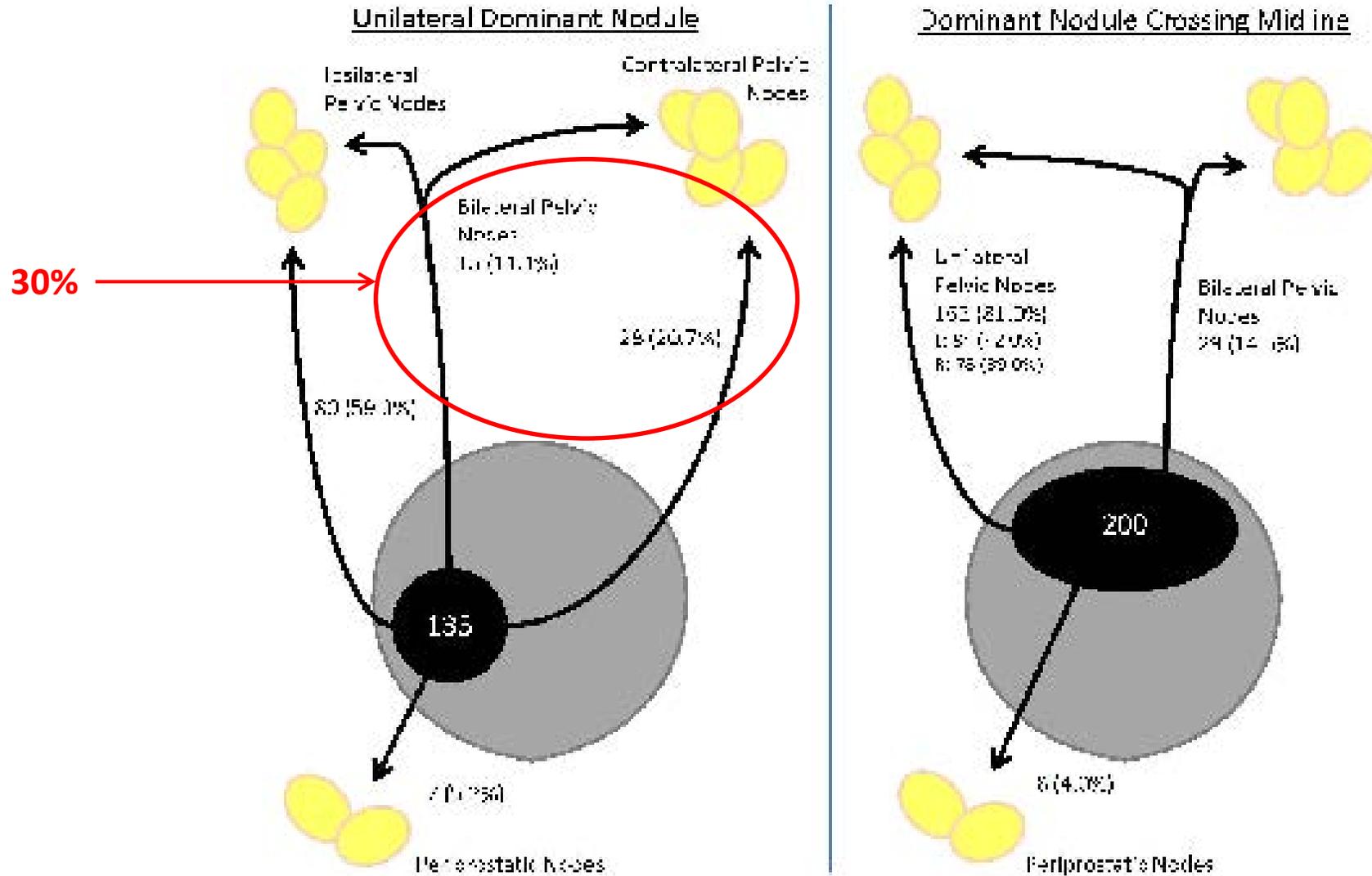
Godoy et al, *J Urol*, 2012;187:2082-6

Pathological and Oncologic Outcomes For Men With Positive Lymph Nodes at Radical Prostatectomy: The Johns Hopkins Hospital 30-Year Experience

Template

Phillip M. Pisansky, Michael A. Cardin, Ashley E. Ross, Zhongyong Peng, Bruce J. Denek, Edwain M. Schaeffer, Victor P. Fan, Jonathan I. Epstein, Alan W. Partin, Patrick C. Walsh, and Trinita L. Blalock

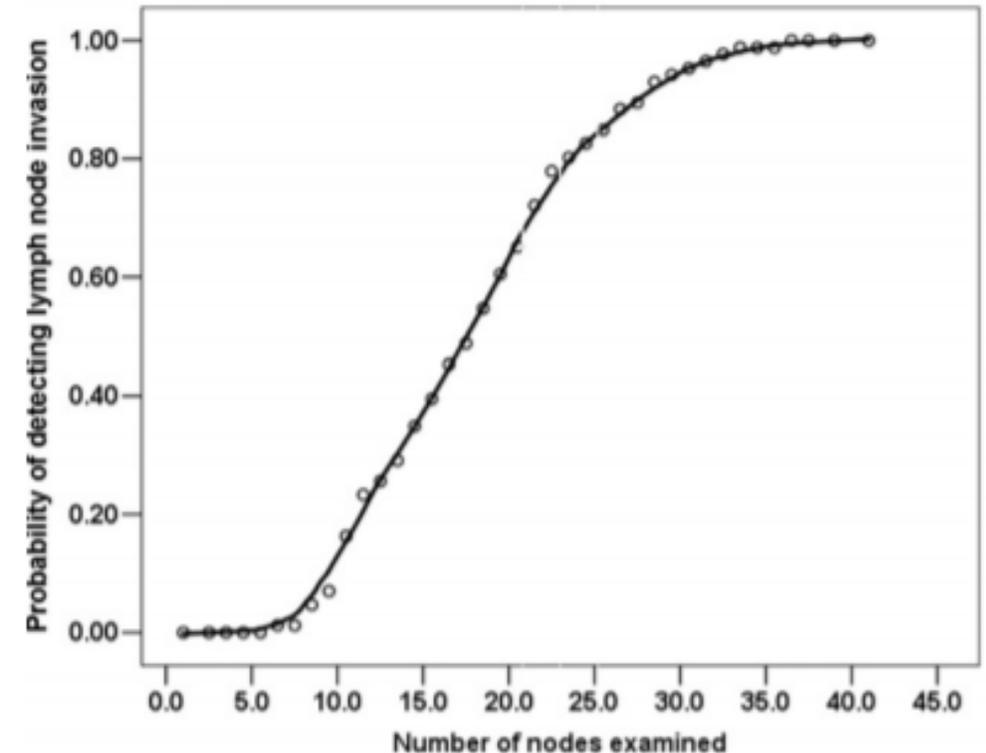
The Prostate 73:1673-1680 (2013)





PLND template

- La **PLND estesa (con o senza i linfonodi presacrali)** migliora significativamente la possibilità di individuare delle metastasi linfonodali
- Stadiazione corretta fino al **75-97%**



Critical Assessment of Ideal Nodal Yield at Pelvic Lymphadenectomy to Accurately Diagnose Prostate Cancer Nodal Metastasis In Patients Undergoing Radical Retropubic Prostatectomy



RARP vs RRP

Pelvic Lymph Node Dissection During Robot-assisted Radical Prostatectomy: Efficacy, Limitations, and Complications— A Systematic Review of the Literature

Guillaume Pignatelli^{1,2,3,4}, Alberto Briganti¹, Alexandre de la Taille^{5,6}, Alexander Hesse¹, Axel Heidenreich⁷, Mani Menon⁸, Jukka Salski⁹, Anandesh K. Tewari¹, James A. Eastham¹⁰

2014

Pelvic Lymph Node Dissection in Prostate Cancer

Briganti A et al, 2009

	Patients	Approach	Median/mean number of lymph nodes removed	Prevalence of LNI	Average LNI rate
Yuh et al.	143	RARP	20 (9-65)	13%	≈12%
Van der Poel et al.	440	RARP	14 (11-19)	8.2%	
Mattei et al.	60	RARP	12 (9-17)	12%	
Silberstein et al.	120	RARP	16 (11-21)	13%	
Yee et al.	32	RARP	18 (12-28)	13%	
Feicke et al.	99	RARP	19	16%	
Heidenreich et al	103	RRP	28	26.2%	≈15%
Briganti A et al	1,020	RRP	19.1	11.8%	
Bader A et al	365	RRP	21	24%	
Toujier et al	471	RRP	13.1	11.4%	
Godoy et al	427	RRP	16	8.2%	
Abdollah et al	5,274	RRP	17.4	13.8%	



PLND estesa vs. limitata

Complication	Limited PLND (n=64)	Extended PLND (n=108)
Linfocele	6 (9%)	19 (18%)
TVP	1 (1.5%)	1 (1%)
TEP	1 (1.5%) ^a	5 (4.5%) ^a
Ematoma	0 (0%)	2 (3%)
Infezione di ferita	0 (0%)	4 (6%)
Sepsi	0 (0%)	2 (3%)
Totale	8 (12.5)	33 (31%)

Extended pelvic lymphadenectomy for prostate cancer: will the previously reported benefits be reproduced in hospitals with lower surgical volumes?

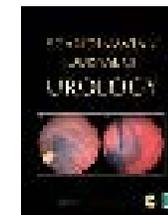
Lindberg C et al, 2009

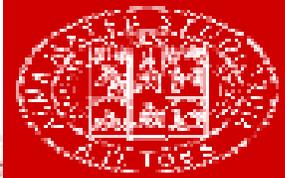
Pelvic Lymph Node Dissection in Prostate Cancer

Briganti A et al, 2009

Pelvic lymph node dissection in prostate cancer: indications, extent and tailored approaches

Bianchi L et al, 2015

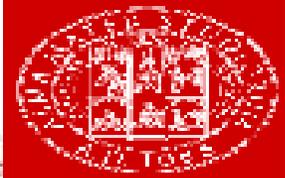




231 CASI PROSPETTICI SINGOLO CENTRO, COMPLICANZE LEGATE ALLA LINFECTOMIA A 30 GG

Complicanze post-operatorie, n (%)	Popolazione Globale (n=231)	Open (n=142)	Robotica (n=89)	p
Linfocele	56 (24,2%)	44 (31%)	12 (14%)	0,002
Linfocele sintomatico	20 (8,6%)	15 (10,6%)	5 (5,6%)	0,19
Edema	17 (7,4%)	16 (11,3%)	1 (1,1%)	0,004
Infezioni	4 (1,7%)	2 (1,4%)	2 (2,2%)	0,50
Febbre >38°C	16 (6,9%)	11 (7,7%)	5 (5,6%)	0,37
Drenaggio percutaneo del linfocele	17 (7,4%)	12 (8,5%)	5 (5,6%)	0,30
Trombosi Venosa Profonda (TVP)	6 (2,6%)	3 (2,1%)	3 (3,4%)	0,56
Embolia Polmonare (EP)	1 (0,4%)	0 (0%)	1 (1,1%)	0,38
Almeno 1 complicanza	72 (31,2%)	57 (40,1%)	15 (16,9%)	<0,001

Unpublished data (2015)



Analisi multivariata

Parametro	Linfocele		Linfocele sintomatico		Edema post-operatorio		Volume linforrea	
	OR	p	OR	p	OR	p	β	p
Procedura Open Robotica	Ref 0,96 (0,92-1)	0,049			Ref 0,88 (0,79-0,99)	0,04	-0.25	<0,001
Estensione PLND Limitata/Standard Estesa/Super-Estesa	Ref 1,09 (1,01-1,18)	0,03	Ref 1,16 (1,05-1,28)	0,002	Ref 1,22 (1,08-1,37)	0,001		
Stato linfonodale, pN pN0 pN1	Ref 1,16 (0,42-3,21)	0,77					0.31	<0,001
Numero di linfonodi positivi							-0.1	0,21
Giornate di eparina	1,11 (1,02-1,20)	0,01	1,1 (1,03-1,2)	0,004	1,14 (1,05-1,23)	0,002	0.19	0,003

PLND: ruolo terapeutico?

L'effetto terapeutico-oncologico rimane dibattuto

- In **pN0** per possibile **rimozione di micrometastasi non visualizzate all'esame patologico**
- In **pN1** per **rimozione dei foci metastatici**

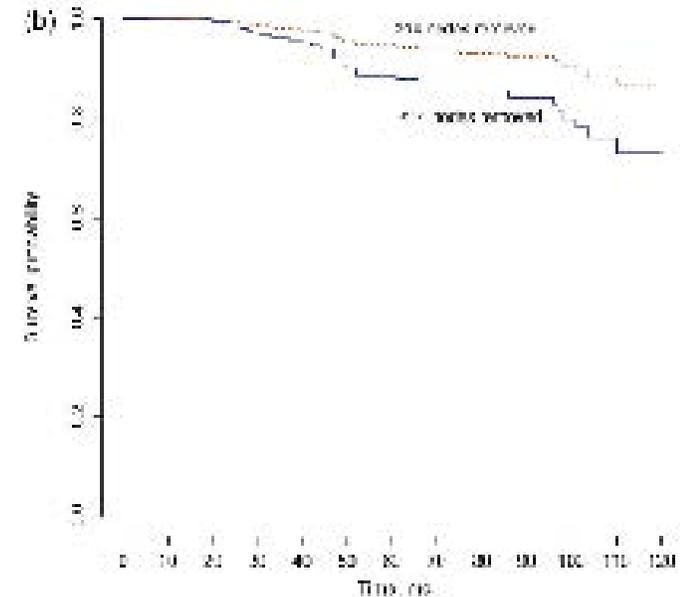
More Extensive Pelvic Lymph Node Dissection Improves Survival in Patients with Node-positive Prostate Cancer

Abdollah F. et al, 2015



—↑CSS 15-20% Heidenreich et al. 2007 Eur Urol

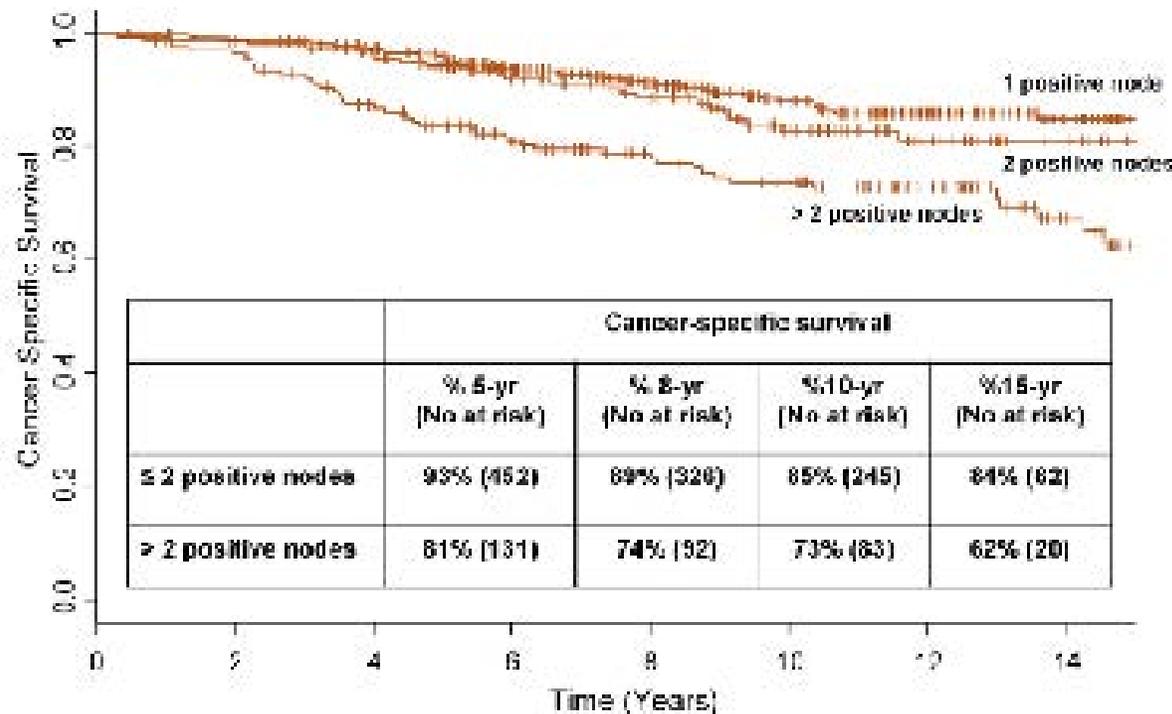
—**1 RCT**: extended vs limited: ↑BCR-free surv (12%
rischio intermedio, 20% alto rischio; $p < 0.04$) Ji J. J Surg Res 2012





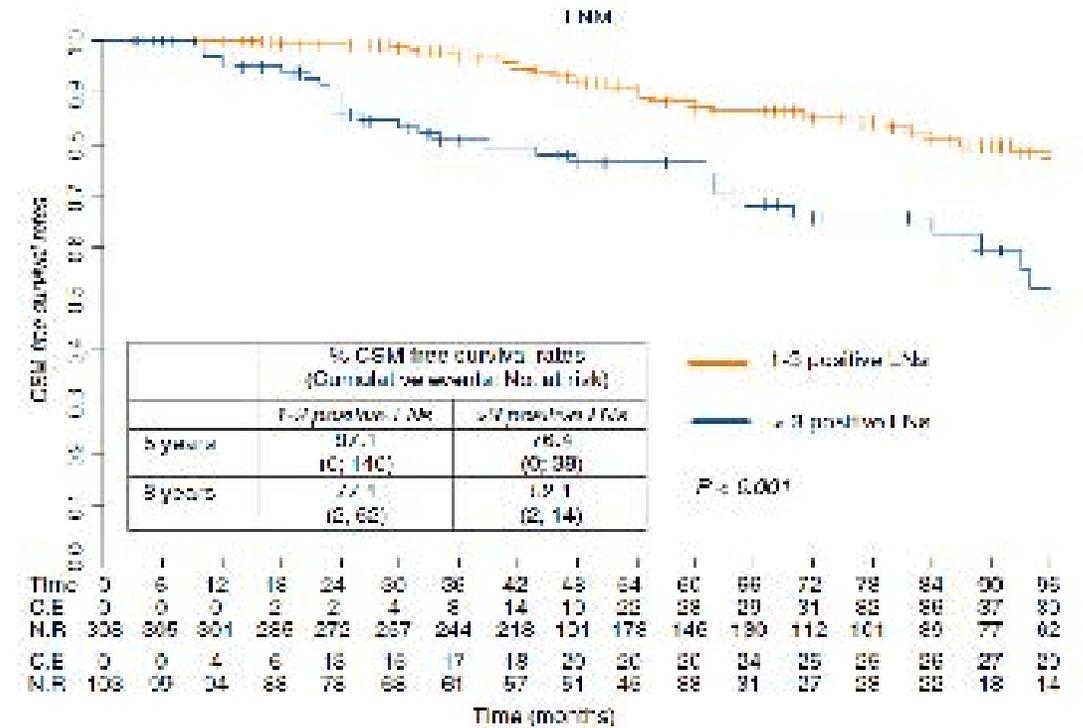
pN1 non sono tutti uguali!!

Two Positive Nodes Represent a Significant Cut-off Value for Cancer Specific Survival in Patients with Node Positive Prostate Cancer. A New Proposal Based on a Two-Institution Experience on 703 Consecutive N+ Patients Treated with Radical Prostatectomy, Extended Pelvic Lymph Node Dissection and Adjuvant Therapy
Briganti et al., 2008



Predicting survival in node-positive prostate cancer after open, laparoscopic or robotic radical prostatectomy: A competing risk analysis of a multi-institutional database

Schiavina et al., 2016





pN1: PLND è curativa?

The Role of Prostate-specific Antigen Persistence After Radical Prostatectomy for the Prediction of Clinical Progression and Cancer-specific Mortality in Node-positive Prostate Cancer Patients

Lorenzo Binetti^{1,2,3}, Alessandro Nini^{1,2}, Marco Bianchi^{1,2}, Giorgio Gandaglia¹, Nicola Fossati¹, Nazareno Suardi¹, Marco Moschini¹, Paolo Dell'Oglio¹, Riccardo Schiavina¹, Francesco Montorsi¹, Alberto Briganti^{1,2,3}

2016

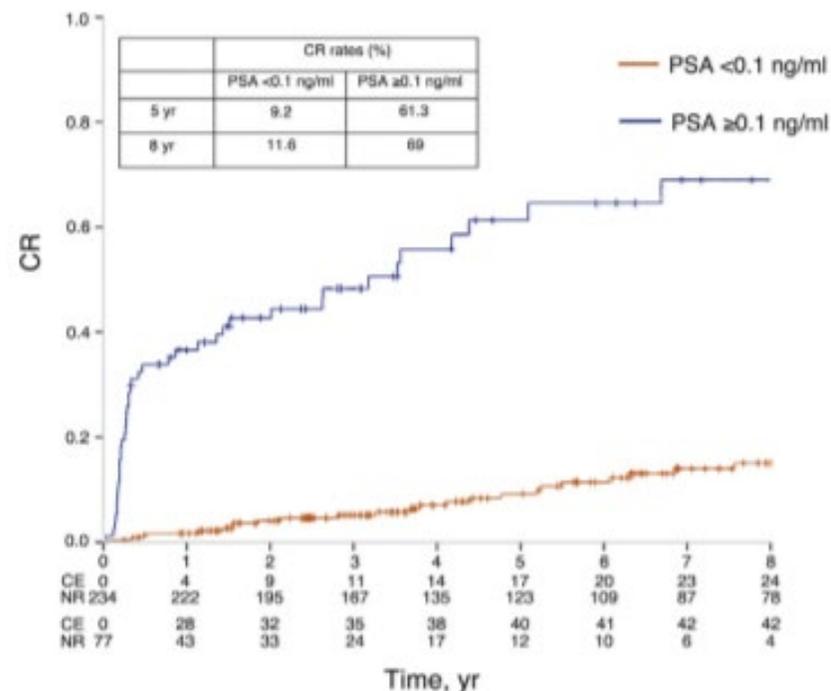


319 pN1 → RP + PLND

FU: 4,5 anni

83 pazienti (26%) hanno una **persistenza di PSA** (PSA > 0,1 ng/ml) a 6 settimane dopo chirurgia

PSA value at 6 weeks after surgery



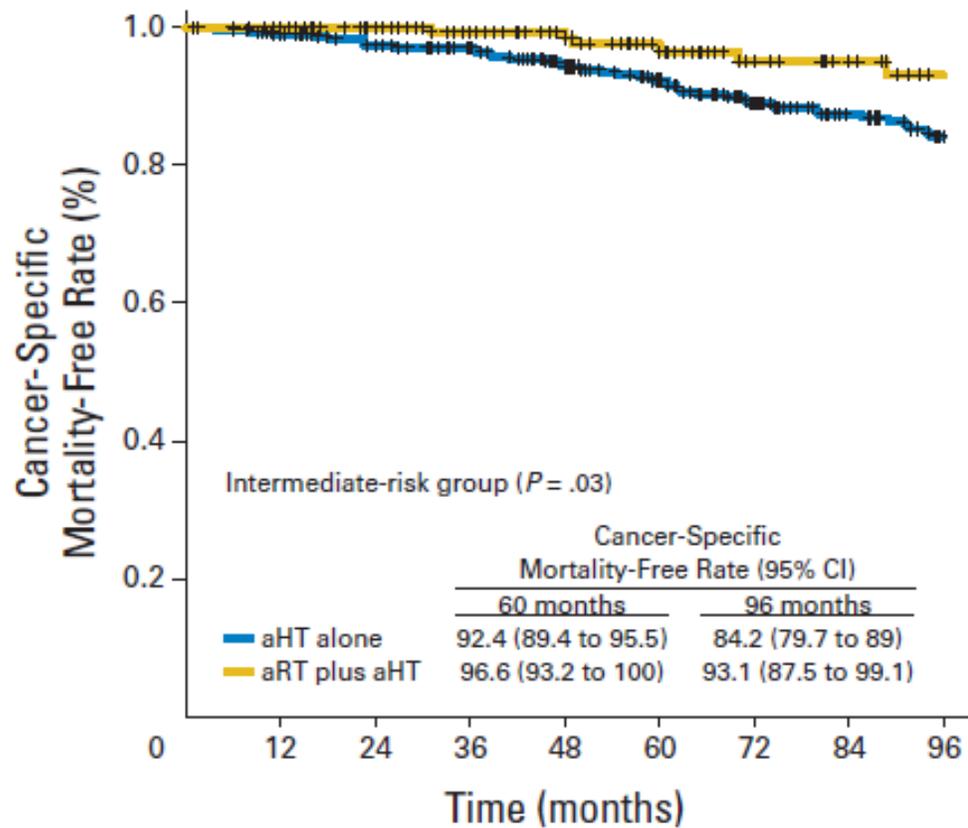


pN1: PLND è curativa?

Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer

JOURNAL OF CLINICAL ONCOLOGY

Abdollah F. et al, 2014

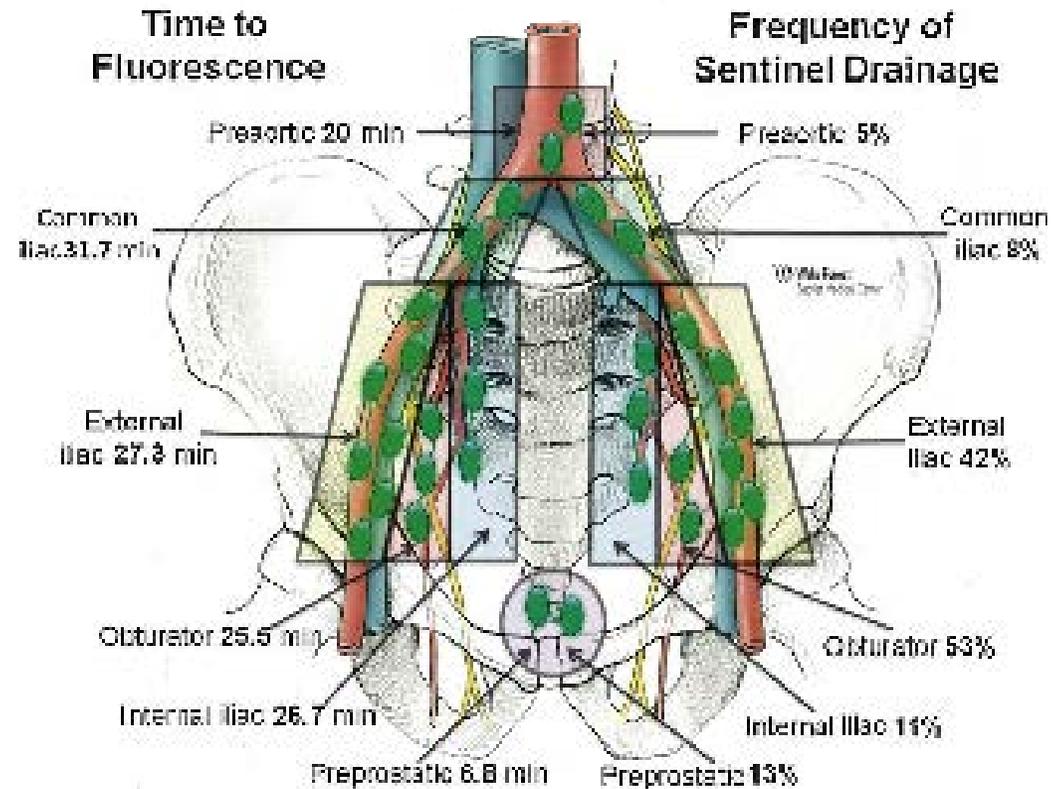
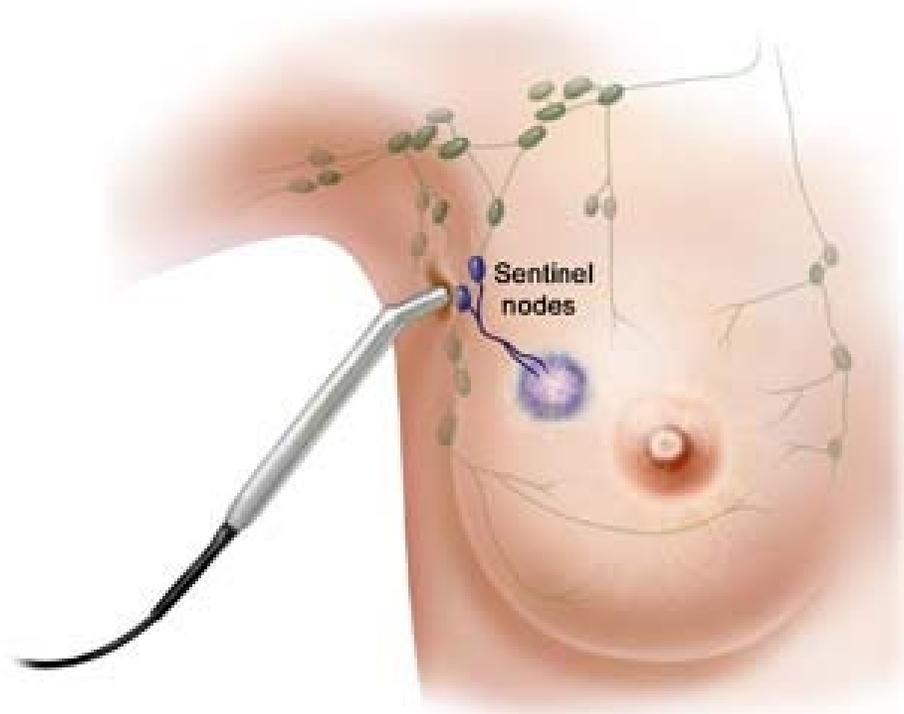


1107 pN+

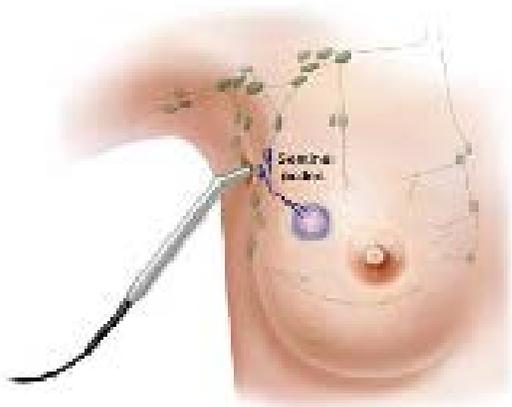
Tuttavia, nella maggior parte dei pazienti pN1 è necessario un **approccio multimodale (RT+ADT)** per migliorare la sopravvivenza cancro specifica!!



LND *sentinella*?



Sentinel LND



Il razionale di linfonodo sentinella (ormai standardizzato per la neoplasia della mammella e per il melanoma) prevede una **linfadenectomia mirata alla regione di drenaggio tumorale (99Tc con gamma probe)**, risparmiando regioni in cui è improbabile trovare metastasi linfonodali, riducendo le complicanze della PLND

Validation of sentinel lymph node dissection in prostate cancer: experience in more than 2,000 patients

G. Hell - B. Dorn - H. Wengenmair - D. Weckermann - J. Seuk

2009

Iniezione di (99m)Tc-nanocolloid intraprostatica 2 ore prima della RP in **2000 pz**

Detection rate: 98%

Falsi positivi: 6%

Tutti hanno fatto sentinel LND + standard/extended PLND!!!

Reliability of sentinel node procedure for lymph node staging in prostate cancer patients at high risk for lymph node involvement

LAURA VAN DEN BERGH^{1*}, STEVEN JONIAUX^{2*}, KAREN HAUSTERMANS¹, CHRISTOPHE M. DEBOOSE², SOFIE ISEBART¹, RAYMOND OYEN¹, FELIX M. MOTTAGHY^{3*}, FILIP AMEVE², JOOST BERKERS^{4*}, HENDRIK VAN POPPEL² & EVELYNR LEBRET^{5*}

2015

74 pazienti ad alto rischio: sentinel LND + super-extended

Sensibilità: 76%

Sentinel LND ha **correttamente identificato 75% pazienti pN1** e **18% dei pazienti ha LNM** identificati da sentinel LND **fuori dal template della PLND estesa**

Ma in meno del 50% dei pazienti è possibile risparmiare una PLND estesa

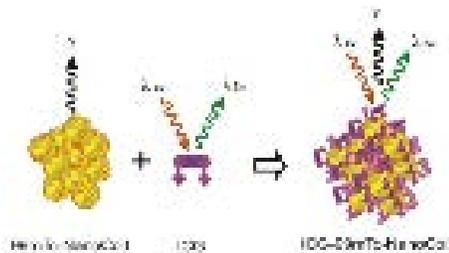
Sentinel LND robotica e ICG

Tecnologia con fluorescenza a infrarossi consente di superare i limiti della sentinel LND con Tecnezio: **miglior risoluzione spaziale e detection real time**

Intraoperative Laparoscopic Fluorescence Guidance to the Sentinel Lymph Node in Prostate Cancer Patients: Clinical Proof of Concept of an Integrated Functional Imaging Approach Using a Multimodal Tracer

Henk G. van der Poel^{1,2}, Tessa Buckle^{1,2}, Oscar R. Brouwer^{1,2}, Renato A. Valdés Olmos³, Fijis W.B. van Leeuwen^{1,2} 2011

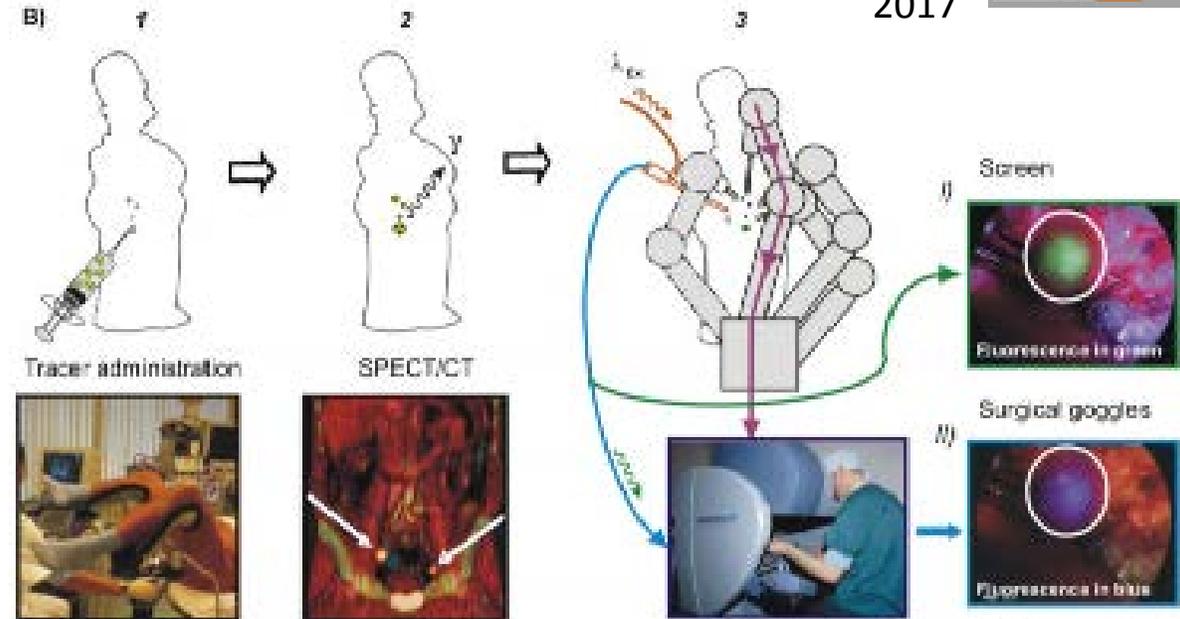
- Iniezione intraprostatica di una **molecola noncolloid** combinata sia con **99m Tc** che con **ICG**



- Confronto tra **SPECT/CT preoperatoria (Tc 99)** e **NIF in corso di chirurgia (ICG)**: alta correlazione tra le due tecniche (radioattiva e fluorescenza) → **85%**

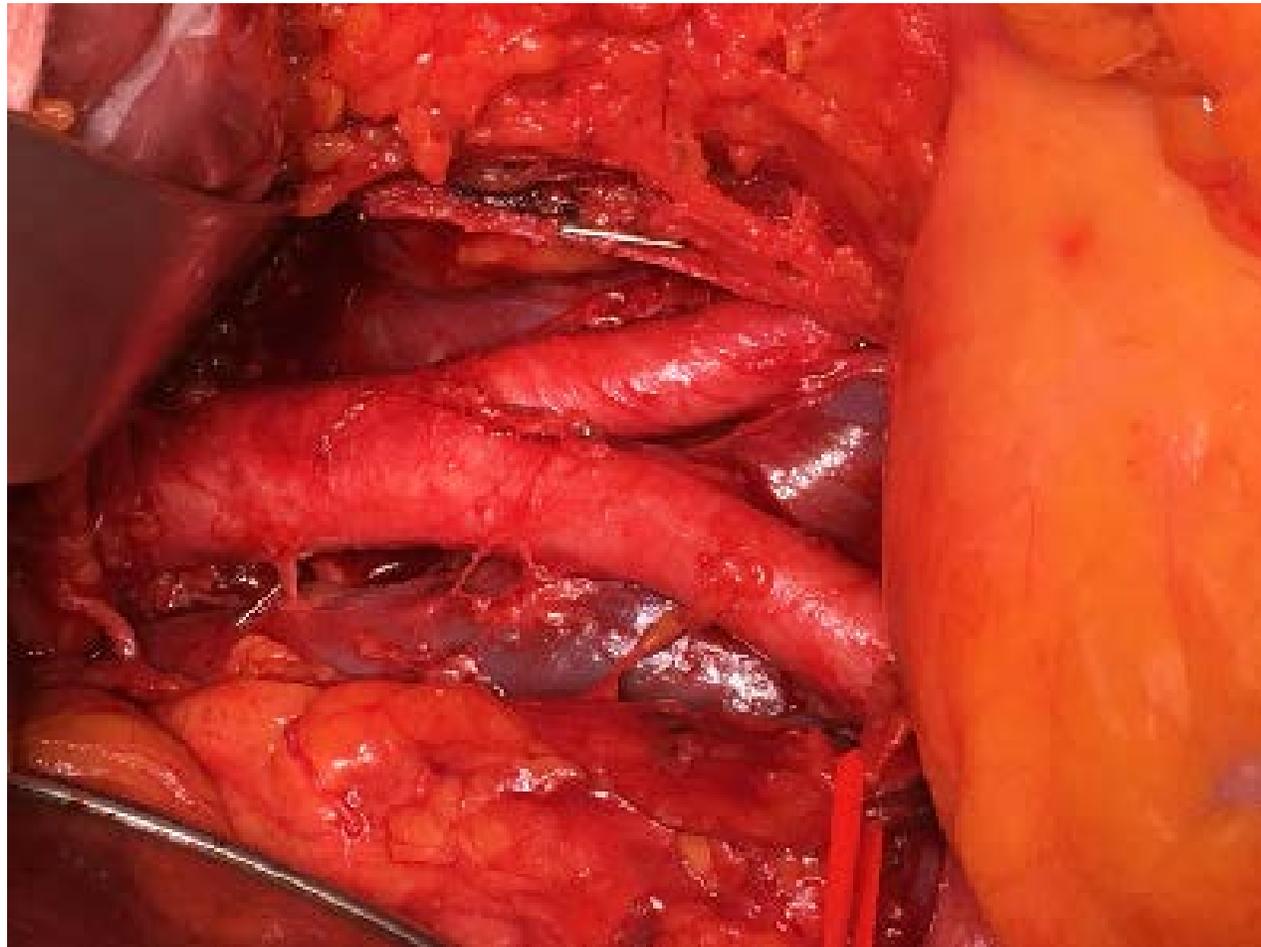
Multispectral Fluorescence Imaging During Robot-assisted Laparoscopic Sentinel Node Biopsy: A First Step Towards a Fluorescence-based Anatomic Roadmap

Nyuke S. van den Berg^{1,2}, Tessa Buckle³, Gijs H. Kleijjan^{4,5}, Henk G. van der Poel¹, Fijis W.B. van Leeuwen^{1,2,6} 2017





NEOPLASIA PROSTATICA: salvage LND



has given rise to a new...METS-directed therapies

Detection of Lymph-Node Metastases with Integrated [¹¹C]Choline PET/CT in Patients with PSA Failure after Radical Retropubic Prostatectomy: Results Confirmed by Open Pelvic-Retroperitoneal Lymphadenectomy

Scattoni, *Eur Urol* 2007

Histological verification of ¹¹C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer

Schilling, *BJU Int* 2008

Pelvic/Retroperitoneal Salvage Lymph Node Dissection for Patients Treated With Radical Prostatectomy With Biochemical Recurrence and Nodal Recurrence Detected by [11C]Choline Positron Emission Tomography/Computed Tomography

Rigatti, *Eur Urol* 2011

Complete PSA Remission without Adjuvant Therapy after Secondary Lymph Node Surgery in Selected Patients with Biochemical Relapse after Radical Prostatectomy and Pelvic Lymph Node Dissection

Winter, *Adv Urol* 2012

Long-term Outcomes of Salvage Lymph Node Dissection for Clinically Recurrent Prostate Cancer: Results of a Single-institution Series with a Minimum Follow-up of 5 Years

Suardi, *Eur Urol* 2013

Salvage Lymph Node Dissection with Adjuvant Radiotherapy for Nodal Recurrence of Prostate Cancer

Jilg *JUrol* 2012

Pelvic Lymph Node Dissection for Nodal Oligometastatic Prostate Cancer Detected by ⁶⁸Ga-PSMA-Positron Emission Tomography/Computerized Tomography

Hijazi *The Prostate* 2015

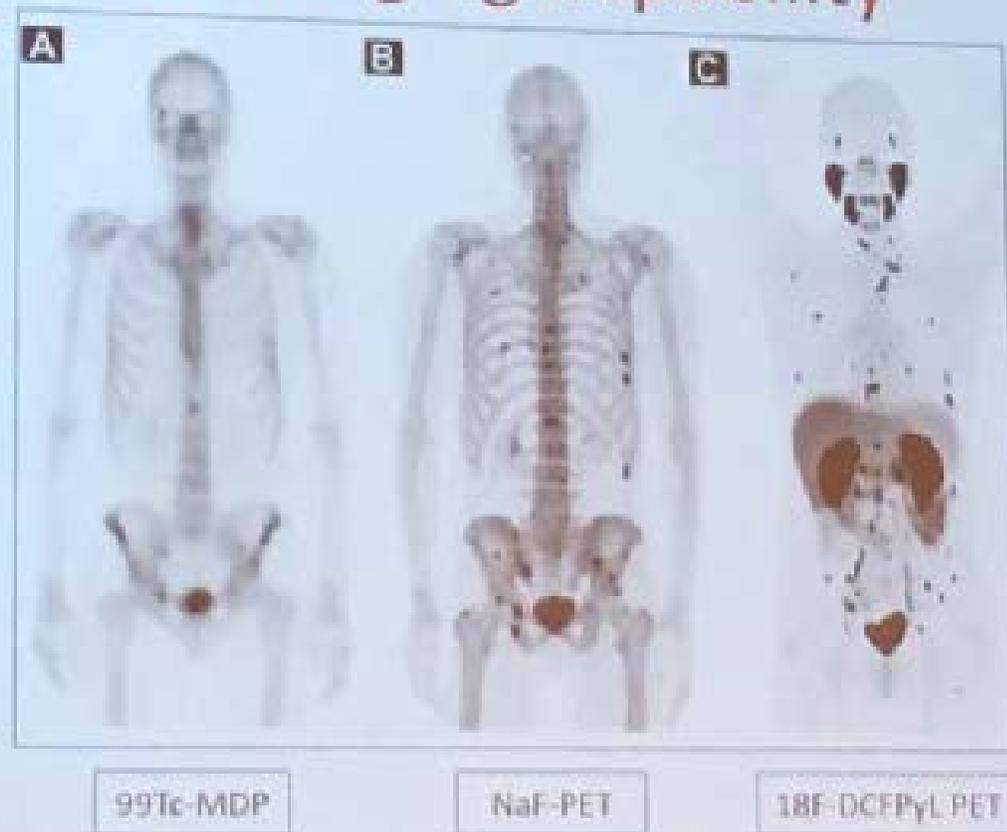


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sLND: possiamo contare veramente sull'imaging?



“Oligometastatic” May Be Merely a Reflection of Imaging Capability





The main limits of PET/CT:

5 mm of resolution of scanners

When Choline-PET/CT finds

a suspected lesion, **nearly twice as many metastases are present**

Diameter of metastatic deposit (mm) (No. of LNs)	Detection rate of PET/CT
0.1–1.9 (n = 6)	0 (0%)
2–4.9 (n = 10)	3 (30%)
5–9.9 (n = 16)	7 (43%)
> 10 (n = 9)	7 (77%)
Total (n = 41)	17 (41%)

How can the performance of choline-PET/CT be improved in clinical practice?



a che valore del PSA possiamo vedere qualcosa?



¹¹C-Choline PET/CT for restaging prostate cancer. Results from 4,426 scans in a single-centre patient series

Choline PET/CT

Tiziano Graziani¹ · Francesco Ceci¹ · Paolo Castellucci^{1,5} · Giulia Polverari¹ ·
Giuseppe Maria Lima¹ · Filippo Lodi¹ · Alessio Giuseppe Morganti² ·
Andrea Artizzoni² · Riccardo Schiarina⁴ · Stefano Fanti¹

Esperienza di Bologna con 4426 pazienti

	Overall positivity (%)
PSA range (ng/mL)	
1 – 2 (995 scans)	44.7
<1.16 (1,426 scans)	26.8
>1.16 (3,000 scans)	65.1
Ongoing ADT PSA mean (1,766 scans)	66.1
Overall population (4,426 scans)	52.8

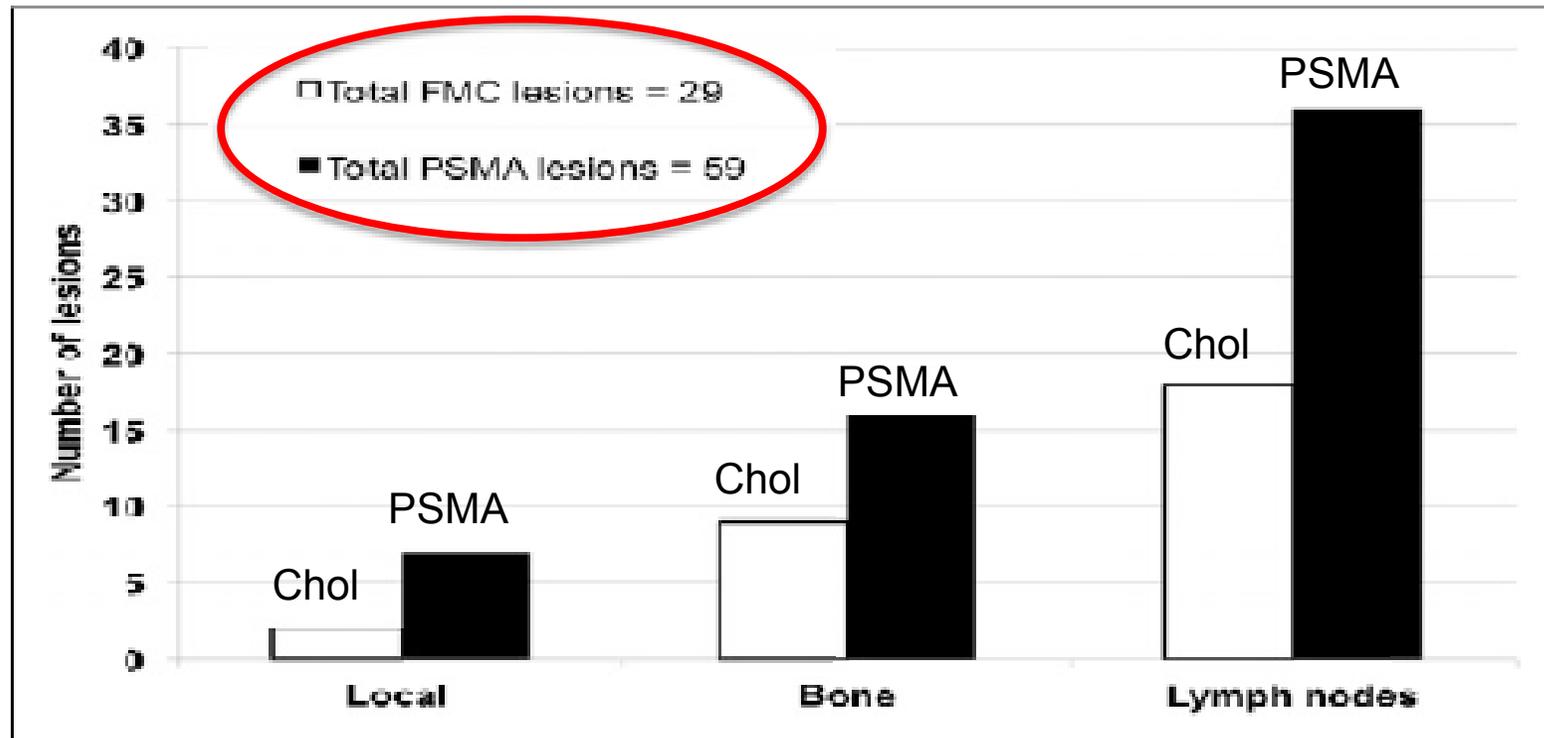
Grossi limiti di detection rate e accuratezza!!



Detecting the Site of the Disease Relapse: **PSMA**-PET/CT

Prospective Comparison of ^{18}F -Fluoromethylcholine Versus ^{68}Ga -PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy

J Nucl Med 2015; 56:1185–1190



**Morigi JJ et al
2015.**

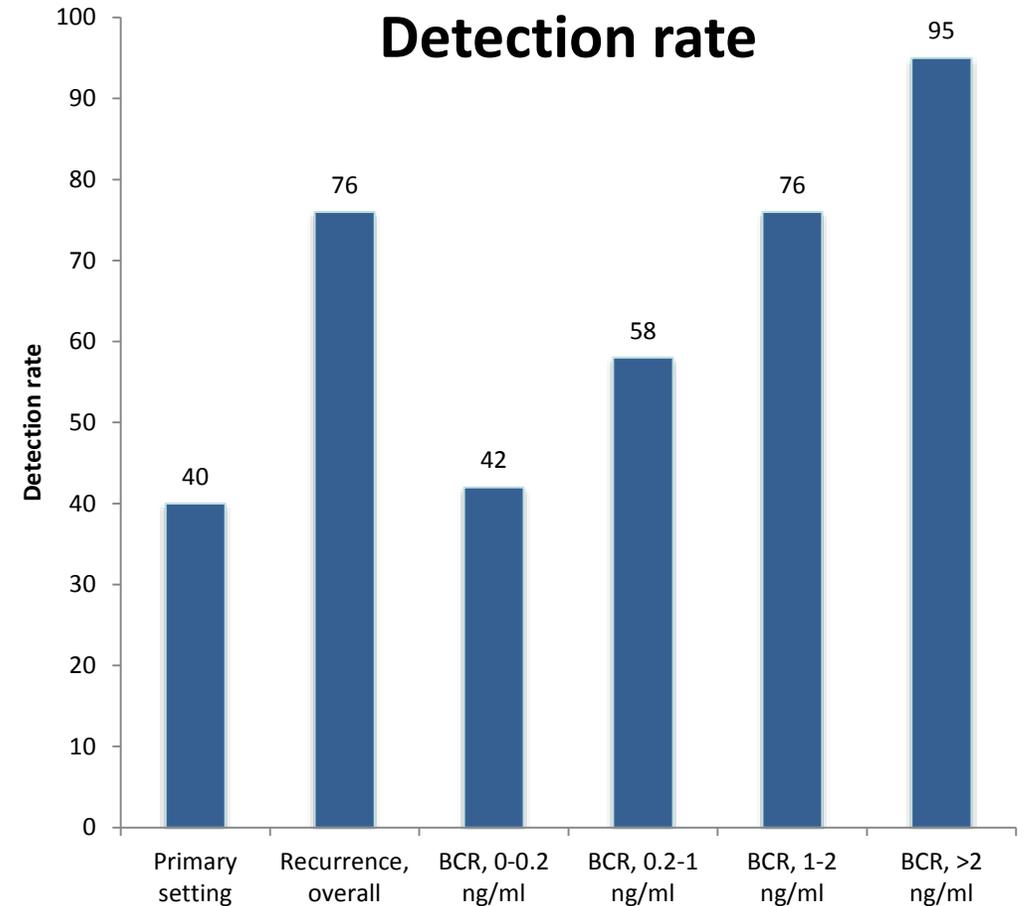


PSMA-PET/CT

Sensitivity, Specificity, and Predictors of Positive ^{68}Ga -Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis

Perera et al. *Eur Urol* 2016;70:926-37
Joice et al. *Curr Opin Urol* 2017;27:533-41

La PET/CT con ^{68}Ga -PSMA è, ad oggi la metodica di imaging **più sensibile** per identificare la sede di recidiva, **già con PSA < 1 ng/mL**





Chirurgia di salvataggio:

***Esiste un reale vantaggio per la s-PLND
rispetto al trattamento standard?***



Linfoadenectomia di salvataggio

6.6.7 *Metastasis-directed therapy*

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. A recent systematic review clearly highlighted that at this time this approach must, as yet, be considered as experimental [577].

La s-LND : numerosi studi retrospettivi



Contemporary Role of Salvage Lymphadenectomy in Patients with Recurrence Following Radical Prostatectomy

2017

Firas Abdollah ^{1,2}, Alberto Briganti ³, Francesco Montorsi ⁴, Arnulf Stenzl ⁵, Christian Stief ⁶,
Bertrand Tombal ⁷, Heir Van Poppel ⁸, Karim Touijer ⁹

sLND: outcomes oncologici, studi monocentrici di casistica

Table 2 – Studies including patients with lymph node-recurrent prostate cancer treated with salvage lymph node dissection

Study	Patients, no.	PSA at SLND, ng/ml, mean	Nodes removed, no., mean	Positive nodes, no., mean	Gleason score	Complete response, %	Follow-up period, mo, mean	5-yr BCR-free survival, %	5-yr progression-free survival, %	5-yr cancer-specific survival, %
Bianchi et al. [18]	15	1.7	13.0	NA	NA	NA	13.7	NA	NA	NA
Winter et al. [32]	0	2.0	NA	NA	NA	NA	24 ^{††}	NA	NA	NA
Martini et al. [33]	8	1.6	11.6	1.0	2-6: 25% 7: 37% 8-10: 38%	NA	NA	NA	NA	NA
Schilling et al. [28]	10	10.0	7.1	2.8	2-6: 20% 7: 60% 8-10: 20%	NA	NA	NA	NA	NA
Riganti et al. [8]	72	3.7	30.6	9.8	2-6: 18% 7: 44.3% 8-10: 37.6%	56.9	39.4	19	34	75
Jig et al. [7]	52	3.0	23.3	9.7	2-6: 23% 7: 40% 8-10: 37%	46	35.5 [†]	0	25	78
Suardi et al. [59]	162	3.6	24.6	6.1	NA	40.7	29.7	41	47	86
Suardi et al. [62]	59	3.9	29.5	8.9	2-6: 20.3% 7: 44.1% 8-10: 35.6%	59.3	81.1	79.4	52.0	89.1

LIMITI:

1. Studi retrospettivi monocentrici
2. Breve follow-up
3. Scarso numero di pazienti
4. Guidati dalla PET-colina

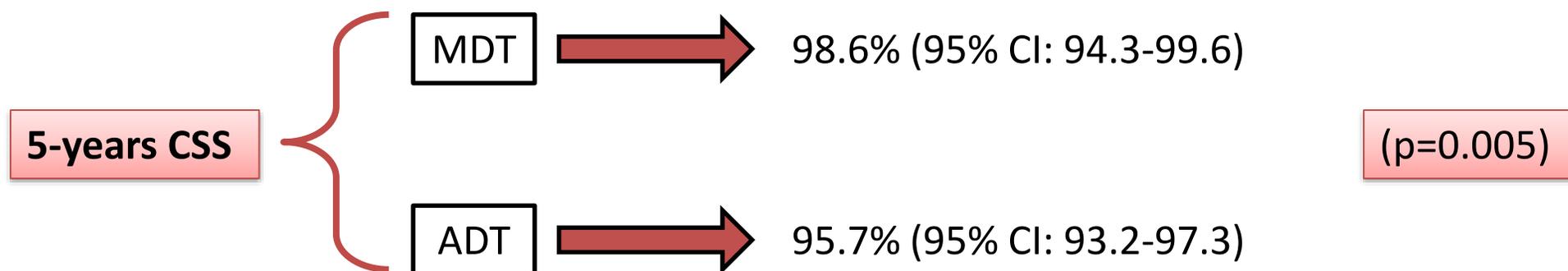


Standard of Care Versus Metastases-directed Therapy for PET-detected Nodal Oligorecurrent Prostate Cancer Following Multimodality Treatment: A Multi-institutional Case-control Study

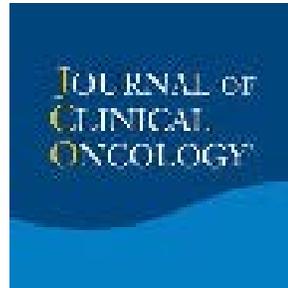
Steubert T et al; 2018

- 1816 pazienti sottoposti a sola **ADT** dopo BCR
- 263 pazienti **metastasis directed treatment**:
 1. 166 linfadenectomia di salvataggio
 2. 97 radioterapia stereotassica
- **Follow up** mediano di 5,8 anni

MDT vs. approccio standard: primo studio controllato



MDT per CaP nodale oligorecidivo sembra migliorare la CSS



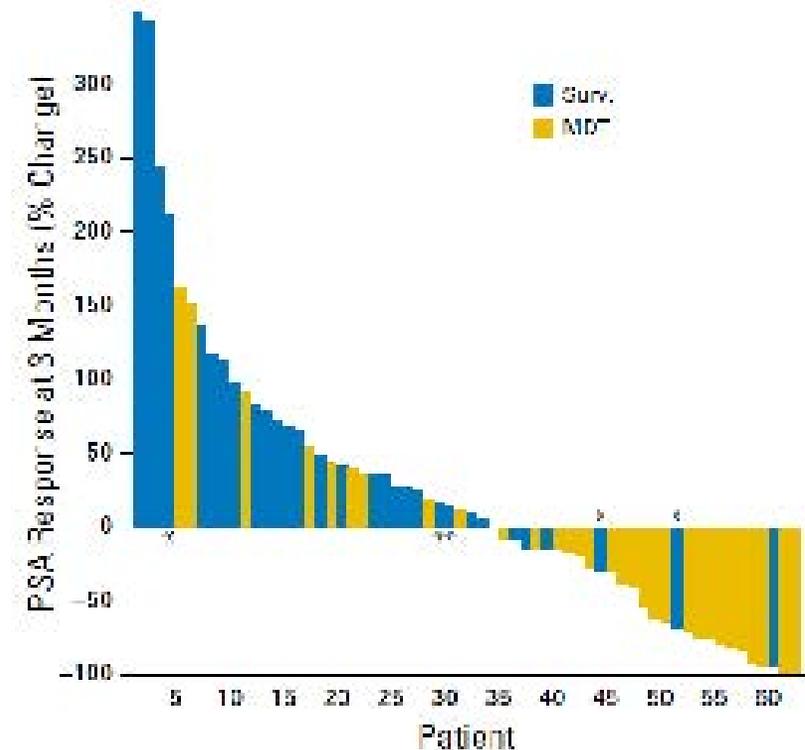
Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Ost P et al; 2018

PRIMO STUDIO RANDOMIZZATO

MDT vs AS

- BCR dopo trattamento curativo
- **≤3 metastasi extracraniche**
- Sorveglianza (PSA ogni 3 mesi) → 31 pz
- MDT di tutte le lesioni (sLND o SBRT) → 31 pz
- Follow up mediano di 3 anni

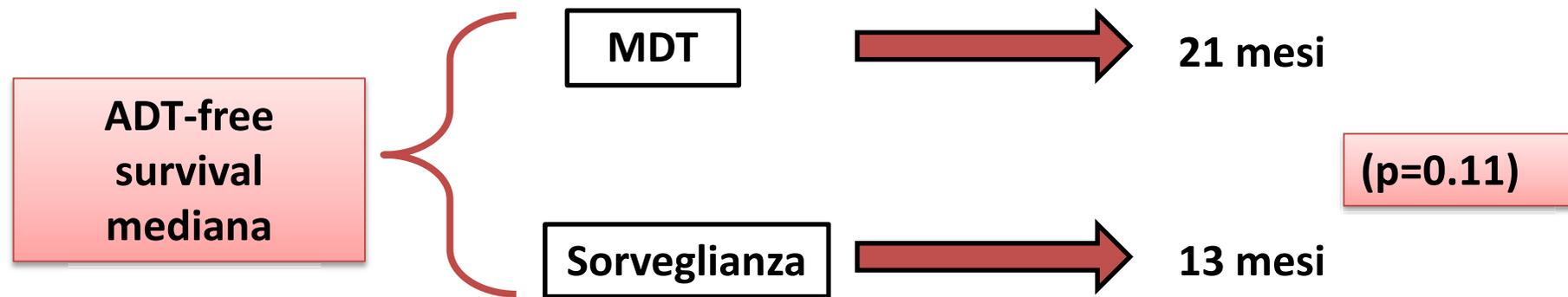


Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

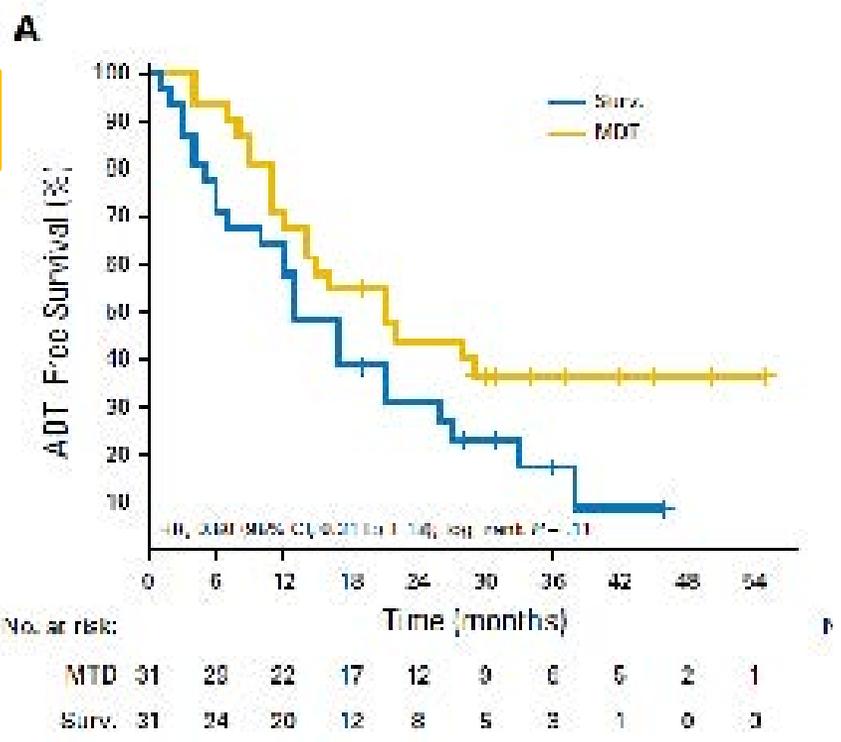
Ost P et al; 2018



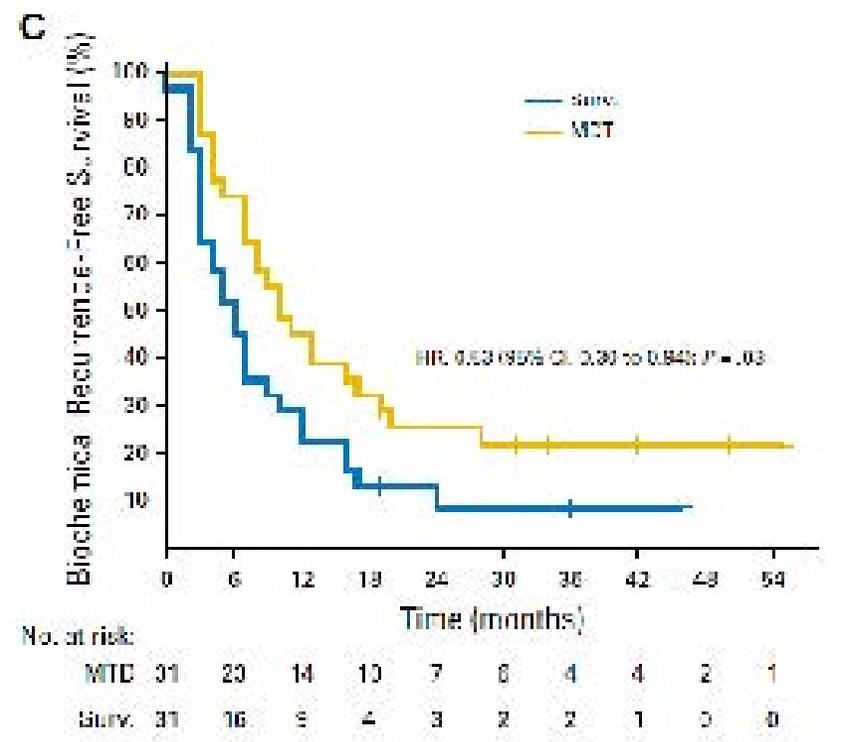
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ADT-free



BCR-free





Contemporary Role of Salvage Lymphadenectomy in Patients with Recurrence Following Radical Prostatectomy

Firas Abdollah^{1,2}, Alberto Briganti³, Francesco Montorsi⁴, Arnulf Stenzl⁵, Christian Stief⁶, Bertrand Tombal⁷, Hein Van Poppel⁸, Karim Touijer⁹

sLND: è quindi possibile curare il paziente?

- *progressione clinica e ricorso a terapia ormonale ritardata in 2/3 dei casi...*
- *>80% avrà ulteriore rialzo del PSA*
- *Solo una % molto esigua può avere un reale beneficio clinico*

Ci sono ancora molti **punti controversi**: ***indicazione!!!***



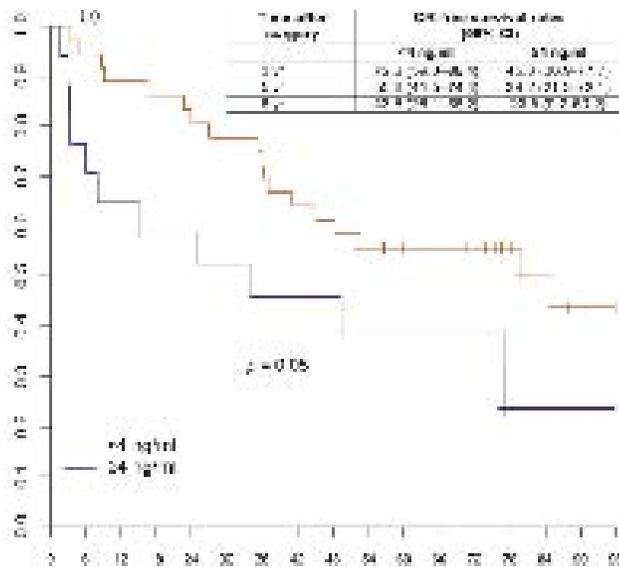
Long-term Outcomes of Salvage Lymph Node Dissection for Clinically Recurrent Prostate Cancer: Results of a Single-institution Series with a Minimum Follow-up of 5 Years

sLND: Come individuare i candidati ideali?

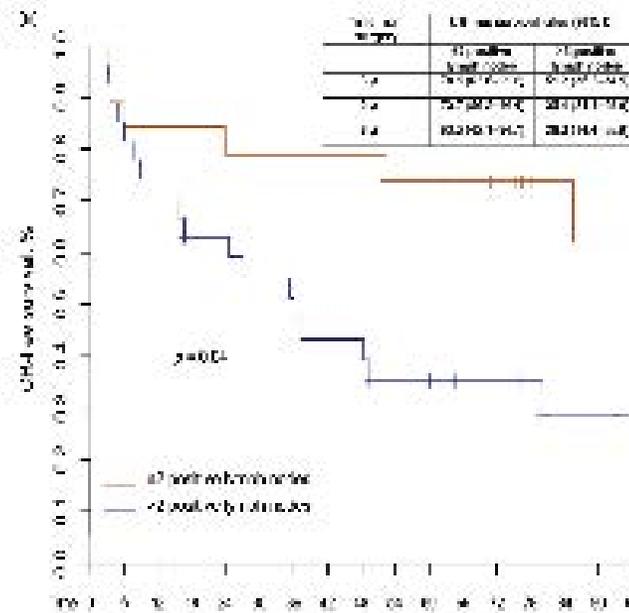
Le recidive linfonodali non sono tutti uguali!

Suardi N et al, 2015

59 Pazienti

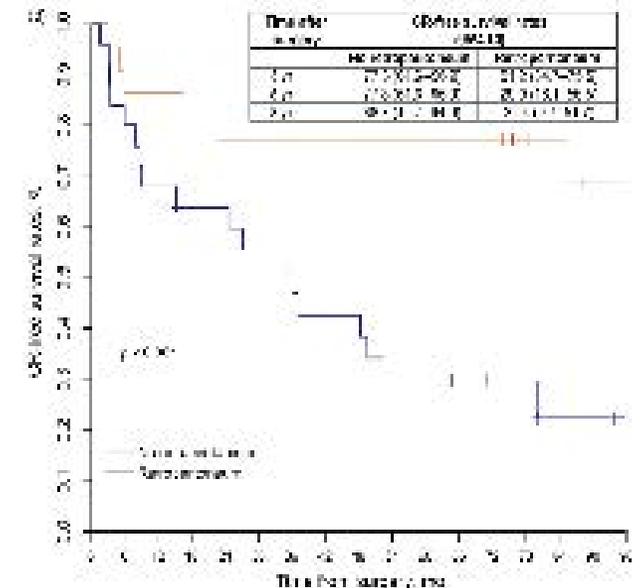


PSA alla sLND
(<4 ng/ml vs ≥4 ng/ml)



N° N+
(≤2 LN+ vs >2 LN+)

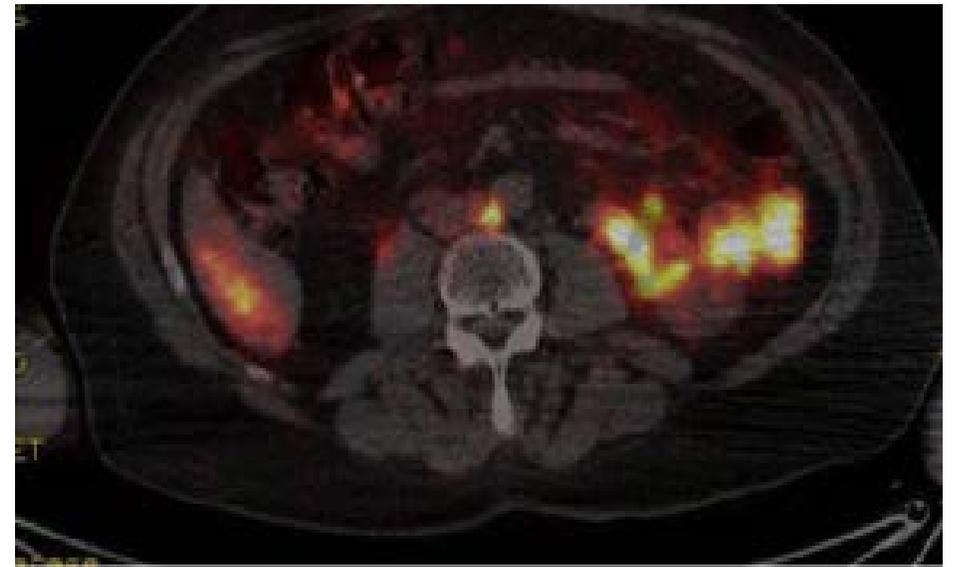
Progressione clinica dopo sLND



Sito di sLND
(pelvica vs retroperitoneale)



Vs.





Recidiva linfonodale: basta la chirurgia?



Approccio multimodale: sLND + radioterapia adiuvante

Adjuvant radiotherapy after salvage lymph node dissection
because of nodal relapse of prostate cancer versus salvage lymph
node dissection only

2015

Hans Christian Ritschke · Wolfgang Schulze-Serannus · Gesche Weyer · Mike Krübig ·
Vanessa Drendel · Petra Stepanovic · Tobias Kraus · Karl Haane · Natalia Vologova Ncher ·
Daniel Seidinger · Simon Kirsie · Anna-Luigi Gross · Corinna Annette Jilg

46 pazienti → sLND

47 pazienti → sLND + RT adiuvante nelle regioni con pN+

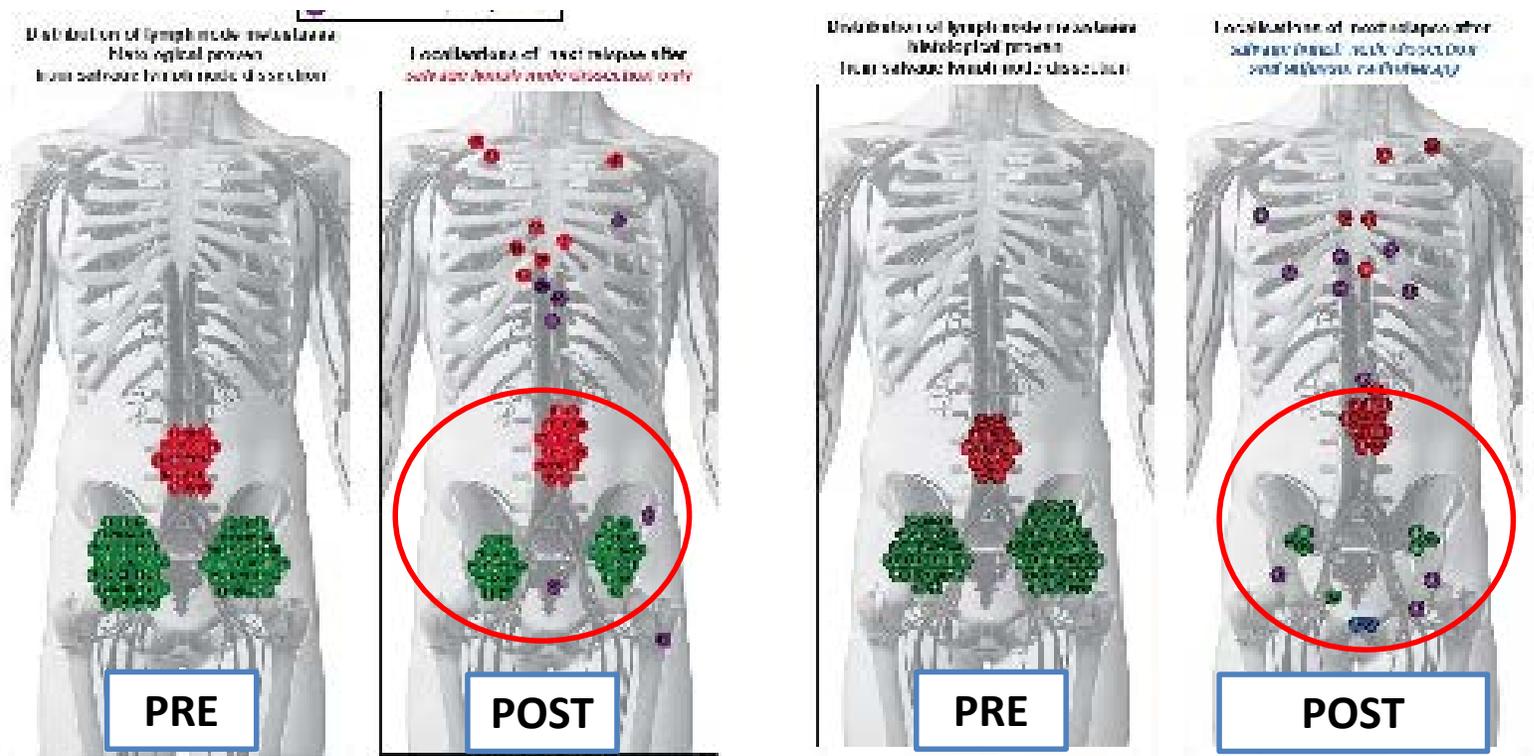
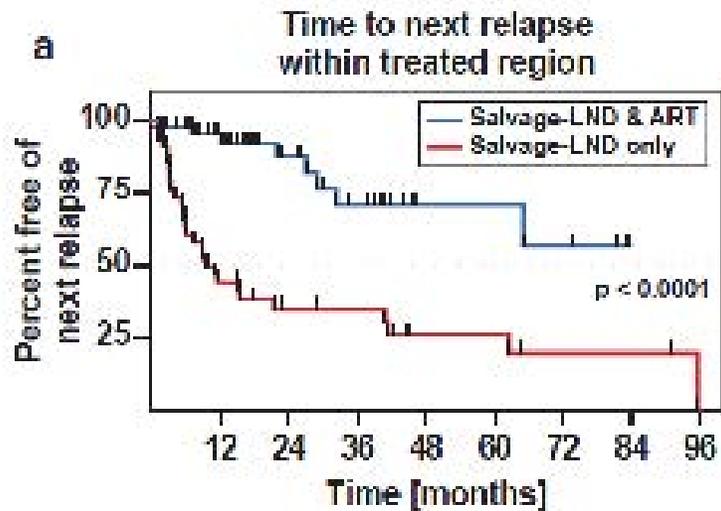


Adjuvant radiotherapy after salvage lymph node dissection
because of nodal relapse of prostate cancer versus salvage lymph
node dissection only

2015

Ilmus Christian Klischke · Wolfgang Schultze-Secundum · Gesche Wiewer · Malte Kahlbig ·
Vanessa Drendel · Petra Stepanica · Tobias Krauss · Karl Ikeme · Natalia Molegova Nidher ·
Daniel Schlager · Simon Kirsse · Anna-Luigi Gross · Corinna Annette Jilg

Aggiungere RT riduce significativamente le
recidive a livello delle regioni trattate con
chirurgia (RFS: 70% vs. 26% a 5 anni; $p < 0.0001$)



CHIRURGIA

CHIRURGIA + RADIOTERAPIA



Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only

2015

Aggiungere RT non riduce la possibilità di avere ulteriori metastasi a distanza

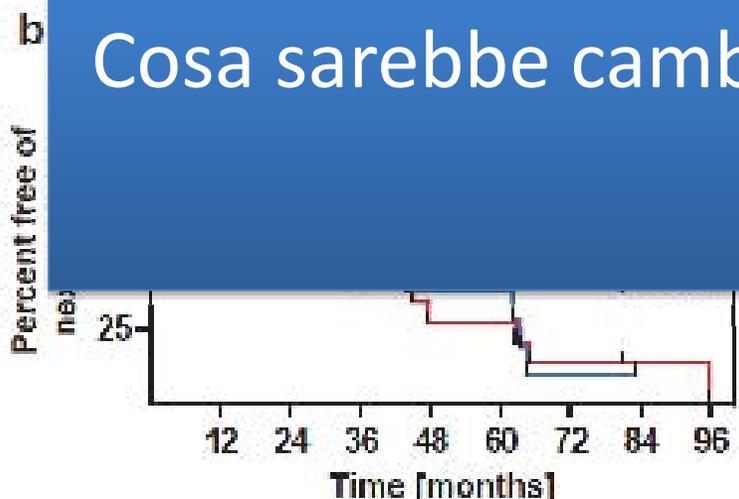
Ilmus Christian Blaskovic · Wolfgang Schultze-Seemann · Gesche Weyer · Malte Kralzig · Vanessa Drendel · Petra Stepanovic · Tobias Krauss · Karl Ikeme · Natalia Volokova Ncher · Daniel Schlager · Simon Kirsic · Anna-Luigi Gross · Corinna Annette Jilg

Distribution of lymph node metastases histological proven from salvage lymph node dissection

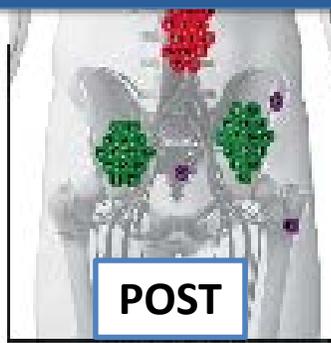
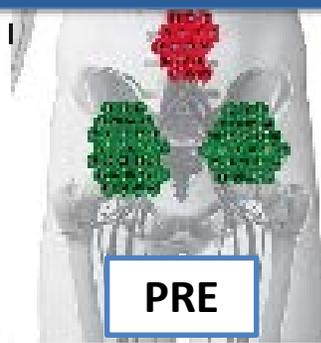
Localizations of next relapse after salvage lymph node dissection only

Distribution of lymph node metastases histological proven from salvage lymph node dissection

Localizations of next relapse after salvage lymph node dissection and adjuvant radiotherapy



Cosa sarebbe cambiato se avessimo trattato questi pazienti con la sola SBRT sulle lesioni?



CHIRURGIA



CHIRURGIA + RADIOTERAPIA



qual è il prezzo in termini di complicanze?



Contemporary Role of Salvage Lymphadenectomy in Patients with Recurrence Following Radical Prostatectomy

2014

Firas Abdollah^{a,*}, Alberto Briganti^b, Francesco Montorsi^a, Arnulf Stenzl^c, Christian Stief^d,
Bertrand Tombal^e, Hela Van Doppel^f, Karim Touijer^g



sLND: Complicanze

La maggior parte sono di **basso grado** (Clavien 1-2):

- Linforrea: **15.3%**
- Febbre: **14.5%**
- Ileo: **11.2%**

Rare complicanze gravi (Clavien 3-5)

- Lesione ureterale: **0.8%**
- Necessità di reintervento: **1,6%**

Dati da centri di terzo livello!!!!



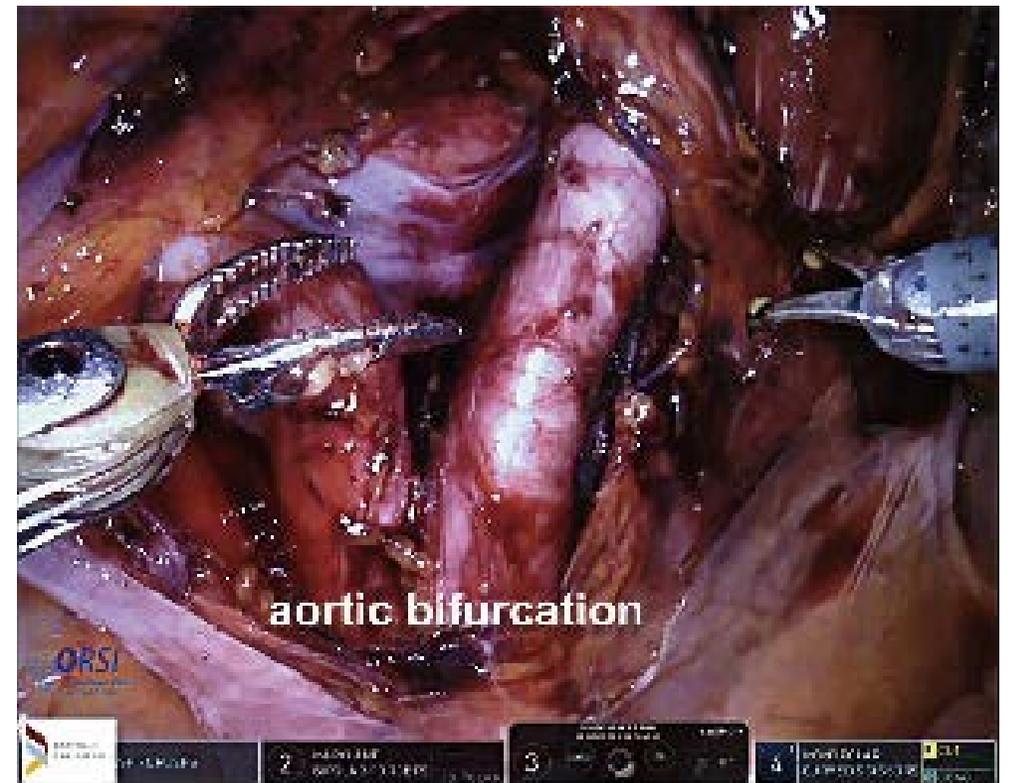
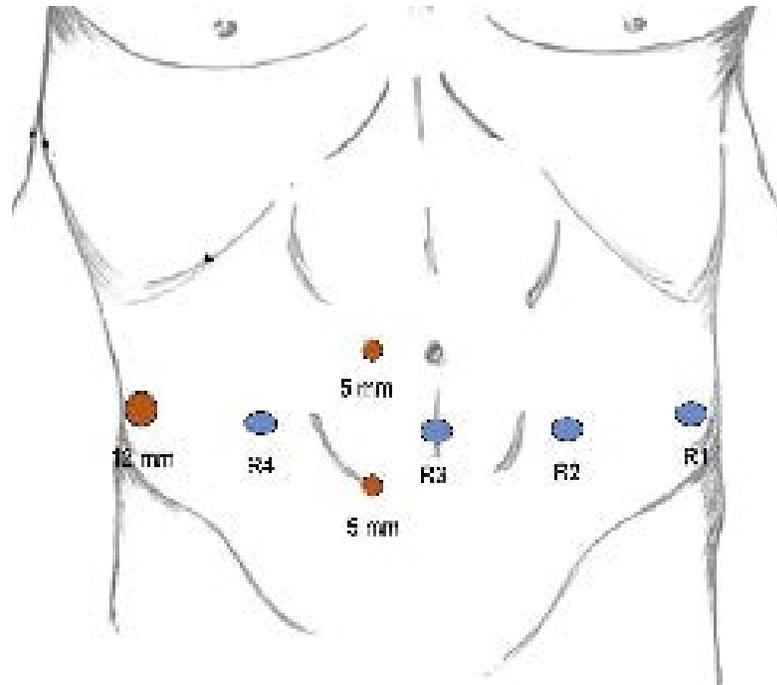
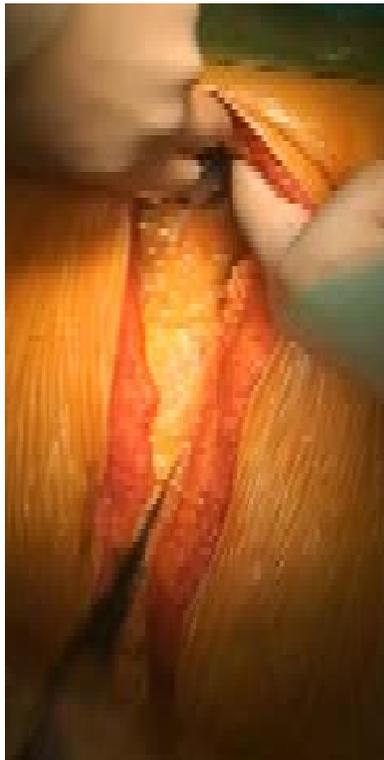
sLND robotica: è un alternativa per ridurre l'impatto di una chirurgia complessa e sperimentale?

Robot-assisted Salvage Lymph Node Dissection for Clinically Recurrent Prostate Cancer

Francesco Montorsi^{a,b}, Giorgio Gandaglia^{a,b,c,*}, Nicola Fossati^{a,b,c}, Nazareno Suardi^{a,b}, Cristian Pultrone^{a,d}, Ruben De Croote^e, Zach Davey^f, Paolo Untch^g, Andrea Gallina^{h,i}, Alberto Briganti^{a,b}, Alexandre Maitrie^j



Prima esperienza in due centri robotici di riferimento (16 pazienti)



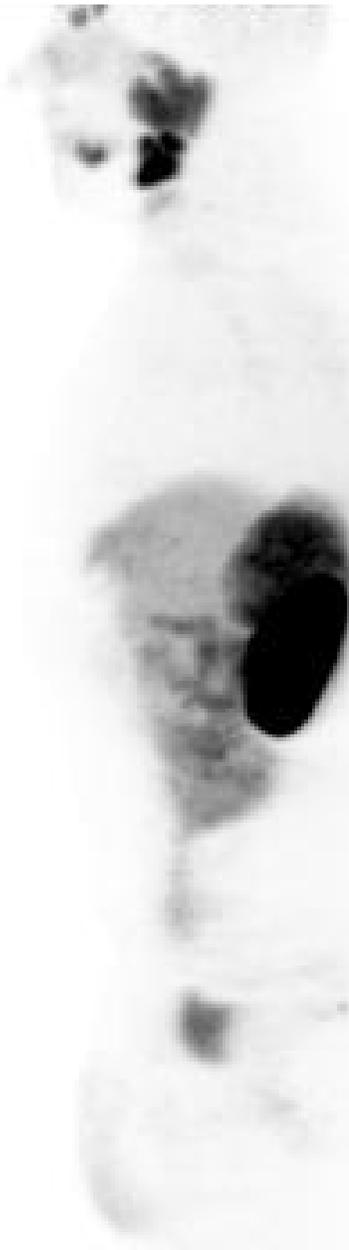
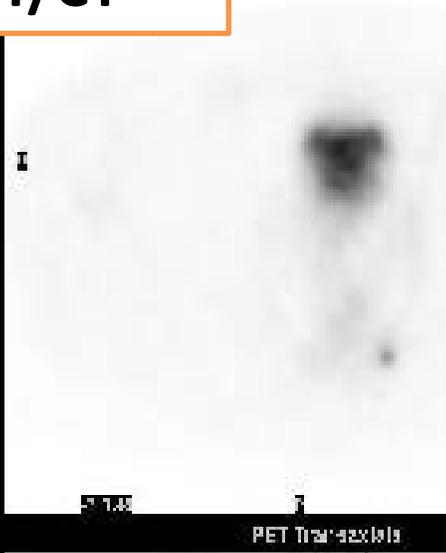
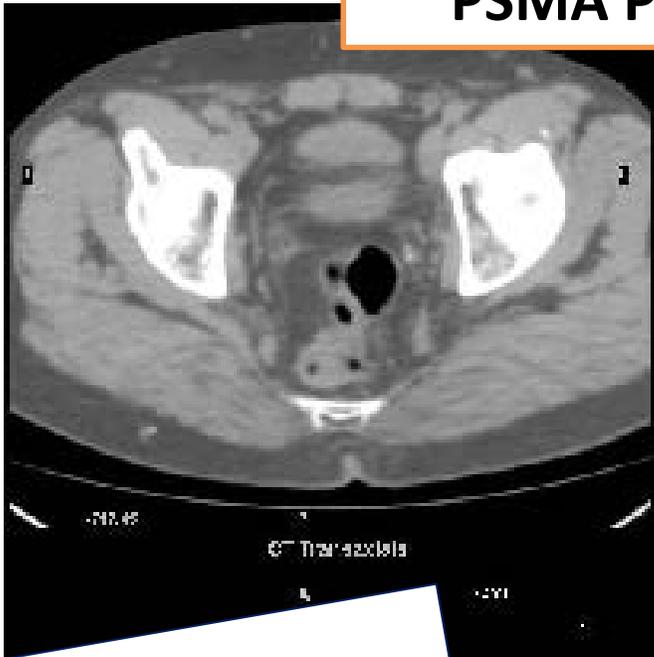


*Spesso è difficile localizzare in corso di intervento
l'esatta sede del linfonodo metastatico **visualizzato
all'imaging!!!***



Gs 4+4 pT3aN0
dopo 5 aa....
PSA: 0.3 ng/ml
PSAdt 4m
TTR 11 m
mpMRI negative

PSMA PET/CT



S-LND → pN0 (0/35)



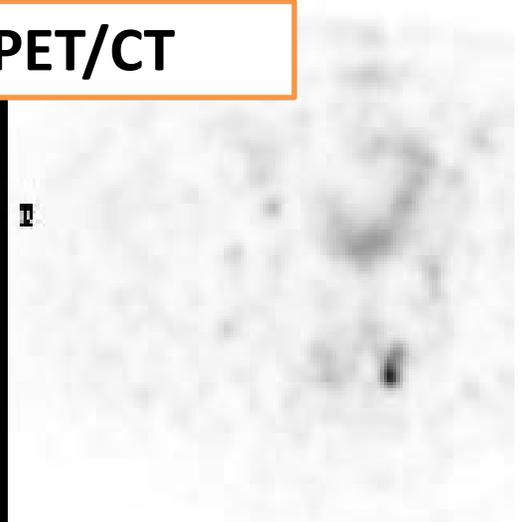
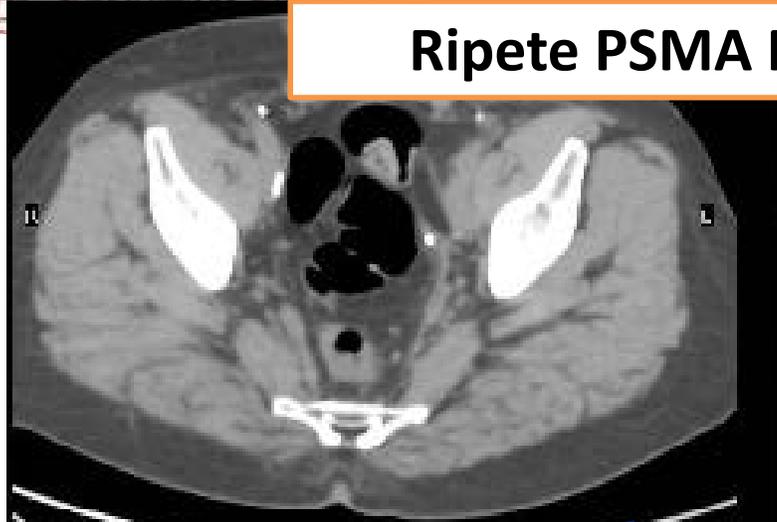


PSA: 1 ng/ml 1 mese dopo sLND
PSAdt 3m

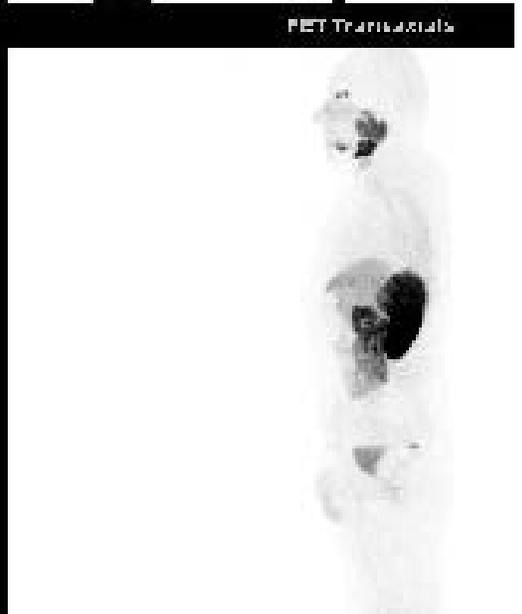
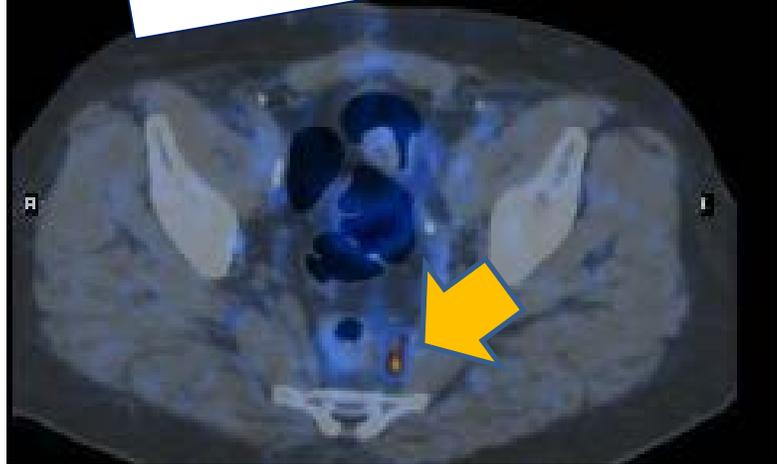


SBRT sul linfonodo + ADT → PSA 0,01 ng/ml

Ripete PSMA PET/CT



???





Futuro della sLND: chirurgia radioguidata con PSMA

Tecnologia PSMA –guided per essere maggiormente selettivi e sicuri di rimuovere esattamente i linfonodi metastatici!!

Surgery in Motion

^{99m}Tc-Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer

Tobias Maurer^{1,2,3}, Stephanie Robu¹, Margret Schortelius¹, Edoardo Schenkelborn⁴, Isabel Rauscher⁵, Nicole S. van den Berg⁶, Pim M.H. van Leeuwen⁷, Bernhard Hutter⁸, Thomas Hain⁹, Matthias M. Heck¹, Jürgen E. Gschwend¹⁰, Markus Schwaiger¹¹, Hans-Jürgen Wester¹, Matthias Eiber¹



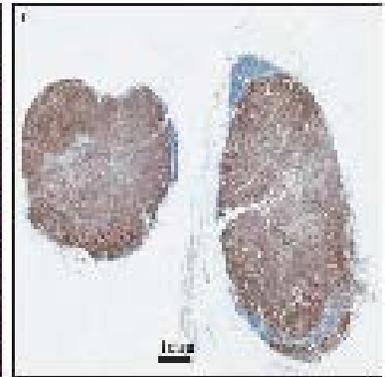
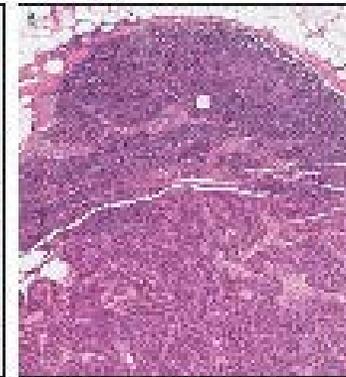
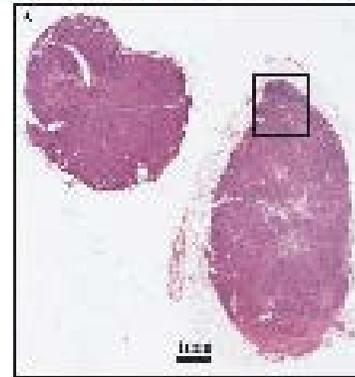
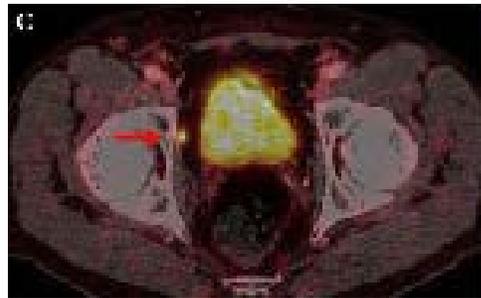
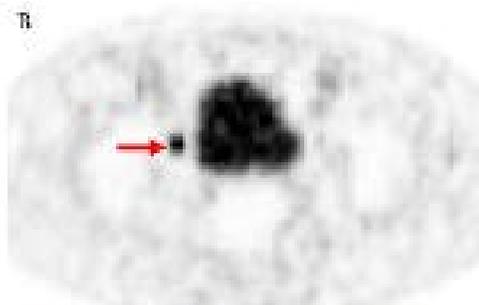
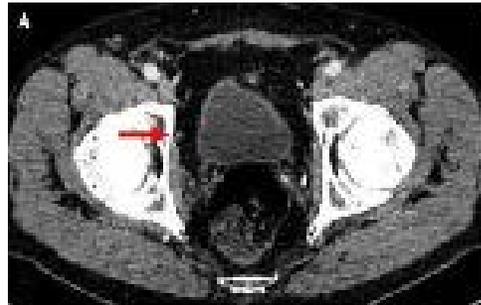
2018

- **31** pazienti con recidiva linfonodale dopo RP evidenziata da PSMA PET/CT
- **sLND** con tecnologia **PSMA-guided**: gamma probe intraoperatoria a dopo infusione endovenosa di **99mTc-PSMA**



Value of ^{111}In -prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up

Isabel Rauscher¹, Charlotte Düvel¹, Martina Wirtz², Margret Schottelius¹, Hans-Jürgen Wester¹, Kristina Schwamborn², Bernhard Haller², Markus Schwager¹, Jürgen F. Gschwend¹, Matthias Filler¹ and Tobias Klöpper¹



- **30/31** pazienti correttamente identificati e **51/145** linfonodi con **metastasi** all'istologico



Value of ^{111}In -prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up

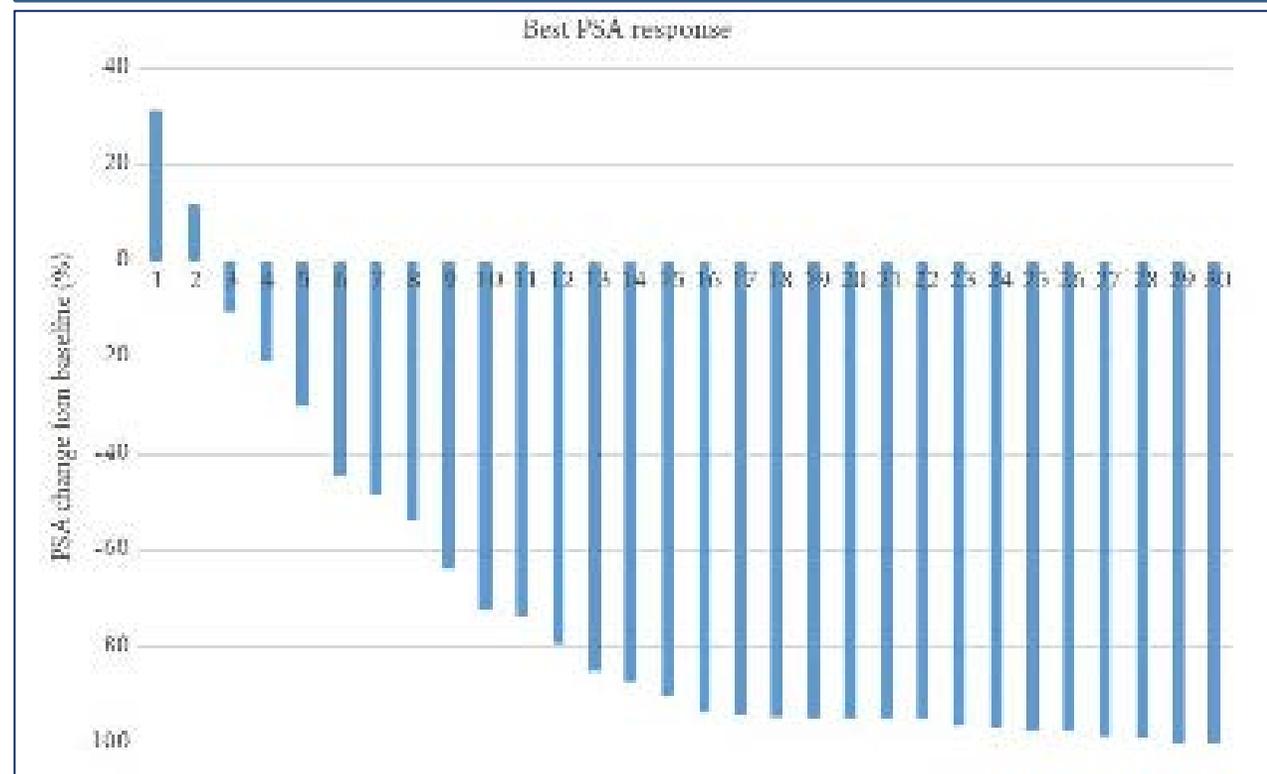
Isabel Rauscher¹, Charlotte Döwle¹, Martina Wirtz¹, Margret Schönfeldt¹, Hans-Jürgen Woster², Kristina Schwamborn², Bernhard Holzer³, Markus Schwaiger⁴, Matthias Biber⁵ and Tobias Maurer¹

BJU Int 2016

- **6 Falsi positivi**
- **1 falso negativo**
- **Identificate 5 lesioni in più rispetto alla PET PSMA preoperatoria**

sLND radioguidata

Ottima risposta biochimica postoperatoria!!



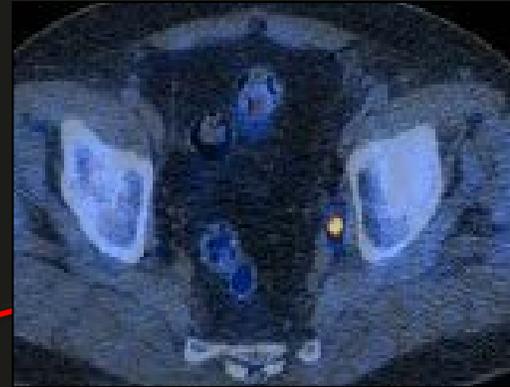
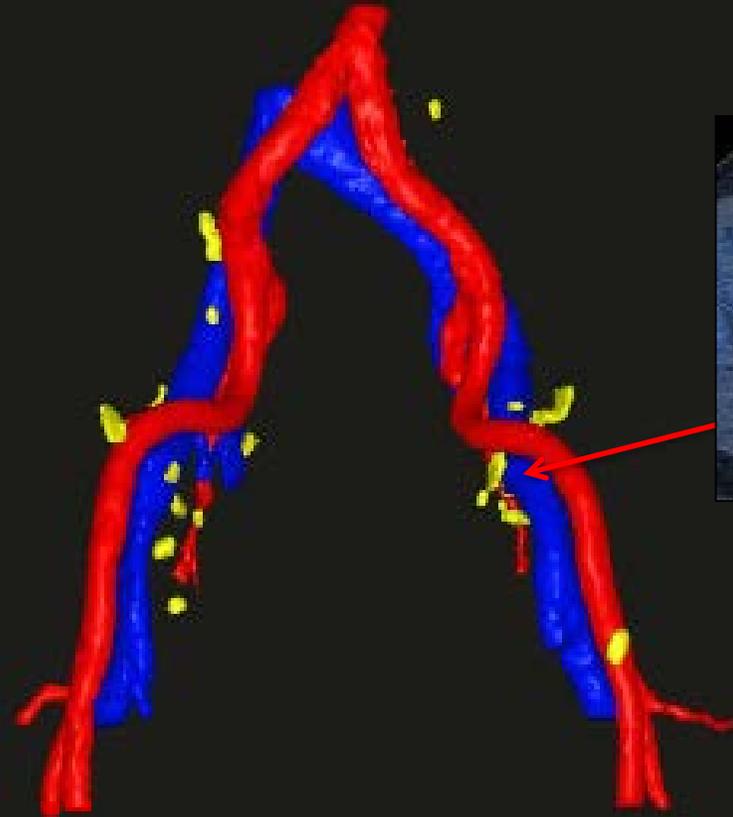


3D sLND

courtesy

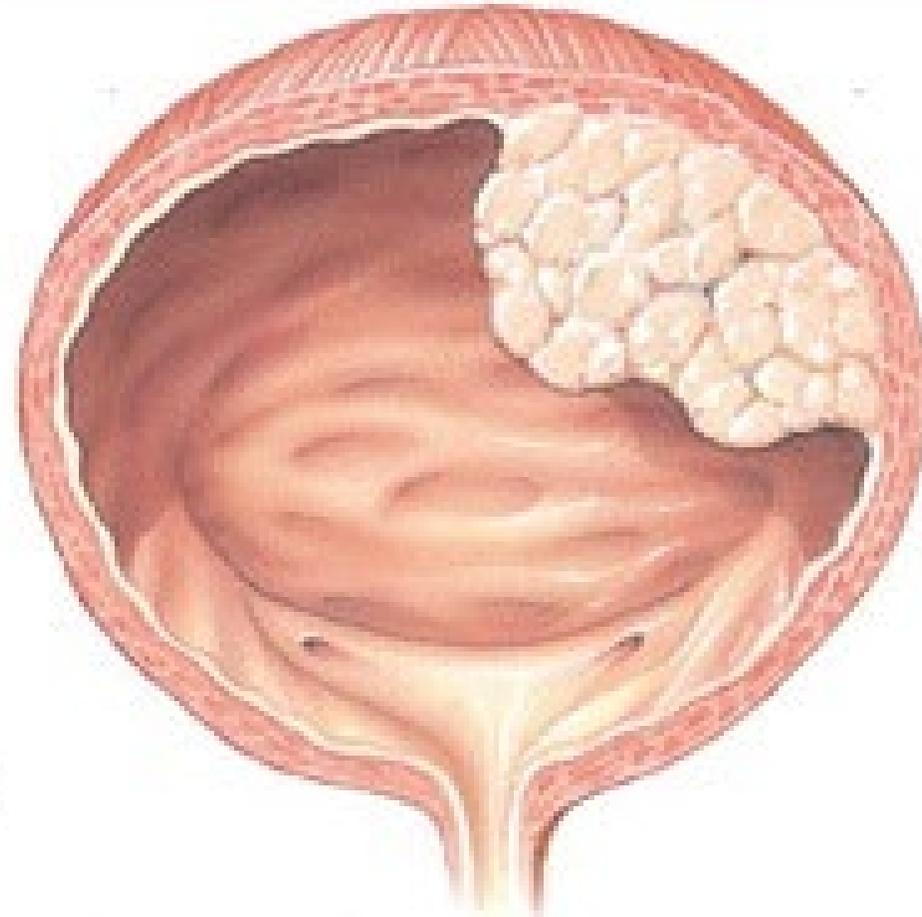
Prof. Emanuela Marcelli

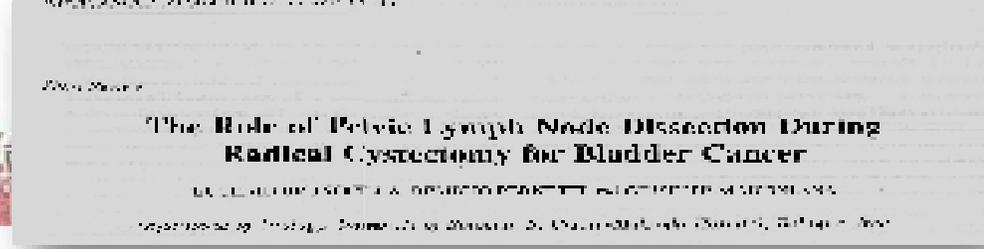
***Laboratorio di Bioingegneria
(Dip. DIMES, Università di Bologna)***





NEOPLASIA VESCICALE





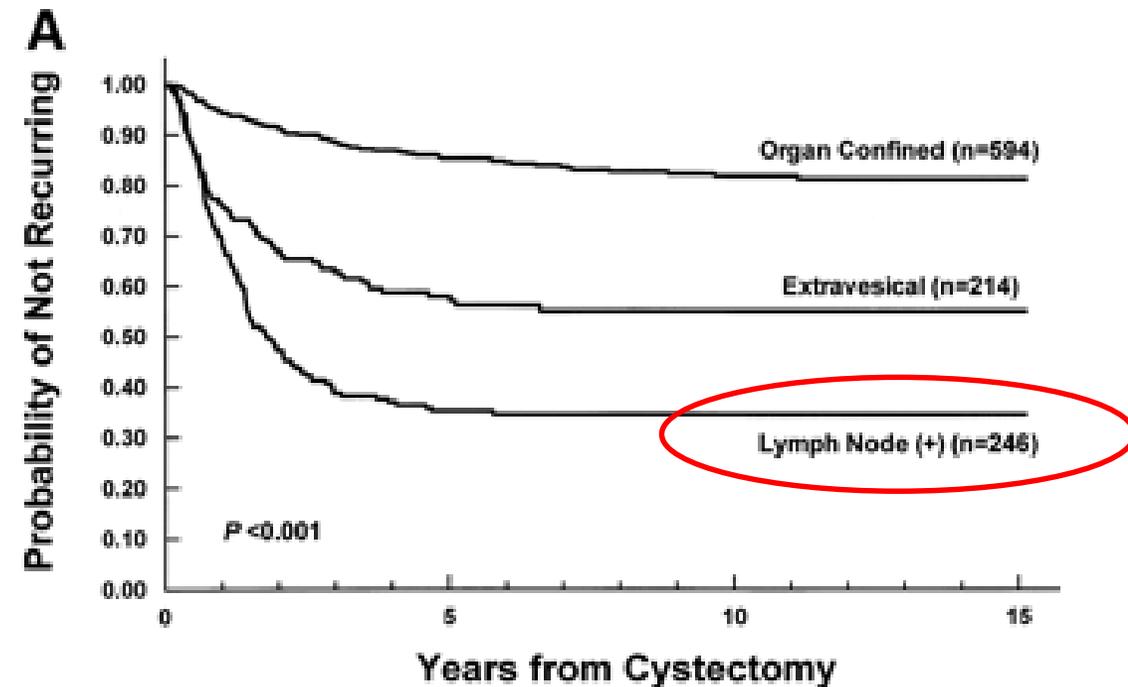
25-30% dei pazienti con tumore infiltrante sono pN+

12% dei T1G3 sono pN+!!!

1/3 degli N+ sopravvive a 5 aa

Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients

Stein J.P. et al, 2001



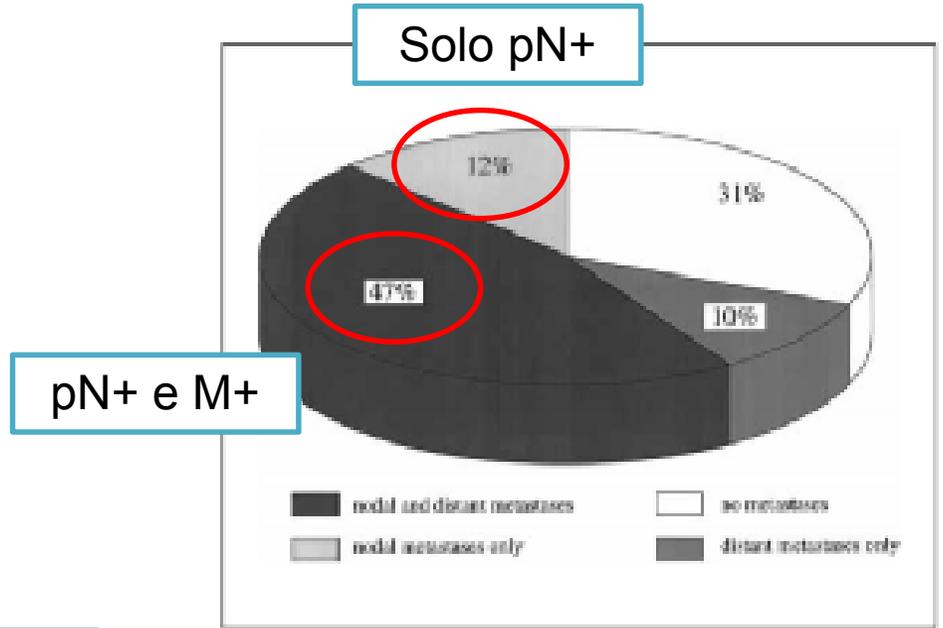
Patterns of Metastasis in Muscle-Invasive Bladder Cancer (pT2-4) An Autopsy Study on 367 Patients

Andreas Wallmeroth^a Urs Wagner^a Halger Moch^a Thomas C. Gasser^b
Guido Sauter^a Michael J. Minatsch^a

Studio condotto su cadaveri di pazienti con MIBC (215)

Distribuzione delle metastasi linfonodali:
92% → linfonodi pelvici
72% → linfonodi retroperitoneali
35 → linfonodi addominali

Alto tasso di M+ in N+





cN0

EAU Guidelines on
**Muscle-invasive
and Metastatic
Bladder Cancer**
2018

Offer radical cystectomy in T2-T4a, N0M0, and high-risk non-MIBC (as outlined above).	Strong
Perform a lymph node dissection as an integral part of cystectomy.	Strong

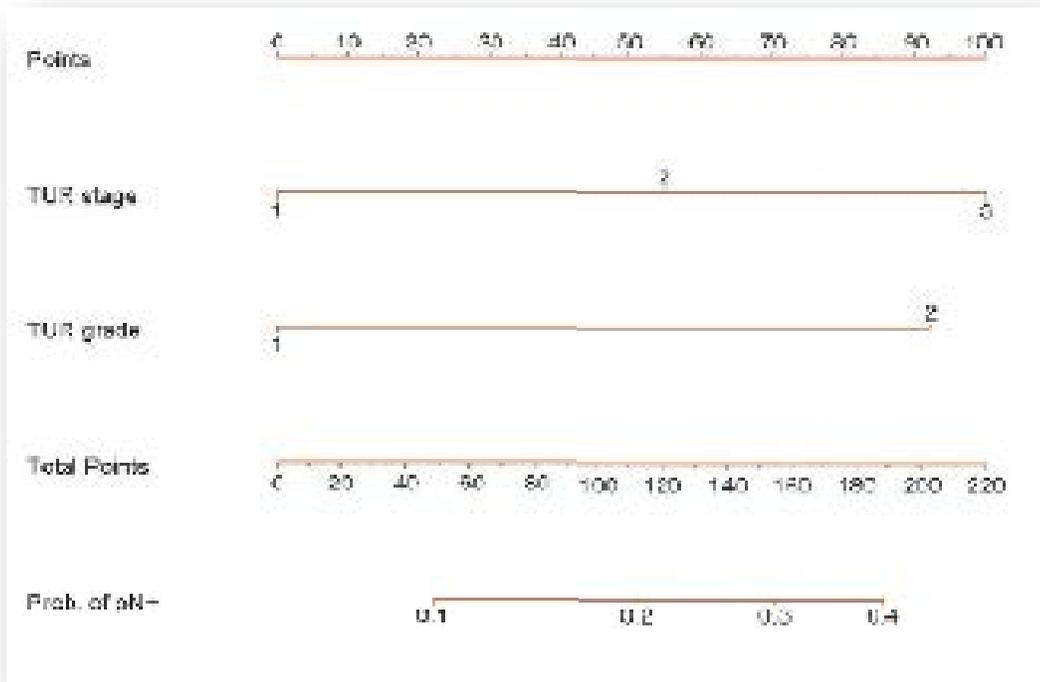
A differenza del carcinoma prostatico in cui il ruolo della PLND è maggiormente dibattuto e vengono utilizzati nomogrammi clinici per decidere se eseguire la PLND, **nella cistectomia radicale la PLND è considerata parte integrante dell'intervento chirurgico in TUTTI i pazienti!!**



Bladder Cancer

Precystectomy Nomogram for Prediction of Advanced Bladder Cancer Stage

Conclusion: Multivariate nomograms are not perfect, but they do predict more accurately than TUR T stage alone.



A differenza della prostata in cui i **nomogrammi** considerano multipli parametri (PSA, Gs primario e secondario, % prelievi positivi...), **nel tumore della vescica si basano solo su 2 parametri (T e grado alla TURB)**

AUC di 63% nella predizione dello stato linfonodale



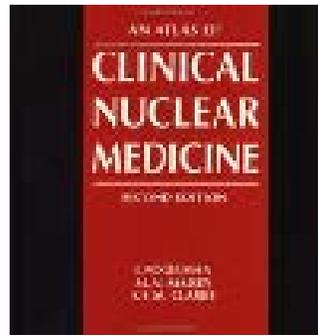
Imaging e stadiazione



Sia la **CT** che la **MR** hanno una **sensibilità relativamente limitata** per lo studio delle metastasi linfonodali (**50-80%**) e si limitano a dare informazioni sul parametro **dimensionale** (8-10 mm).

Recommendations	GR
In patients with confirmed muscle-invasive bladder cancer, CT of the chest, abdomen and pelvis is the optimal form of staging, including excretory-phase CT urography for complete examination of the upper urinary tracts.	B
Excretory-phase CT urography is preferred to MR urography for diagnosing UTUCs in terms of greater diagnostic accuracy, less cost, and greater patient acceptability. MR urography is used when CT urography is contra-indicated for reasons related to contrast administration or radiation dose.	C
Ureteroscopic-guided biopsy is recommended for histopathological confirmation of diagnosis in the pre-operative assessment of UTUC.	C
CT or MRI is recommended for staging locally advanced or metastatic disease in patients in whom radical treatment is being considered.	B
CT and MRI are generally equivalent in diagnosing local and distant abdominal metastases but CT is preferred to diagnose pulmonary metastases.	C

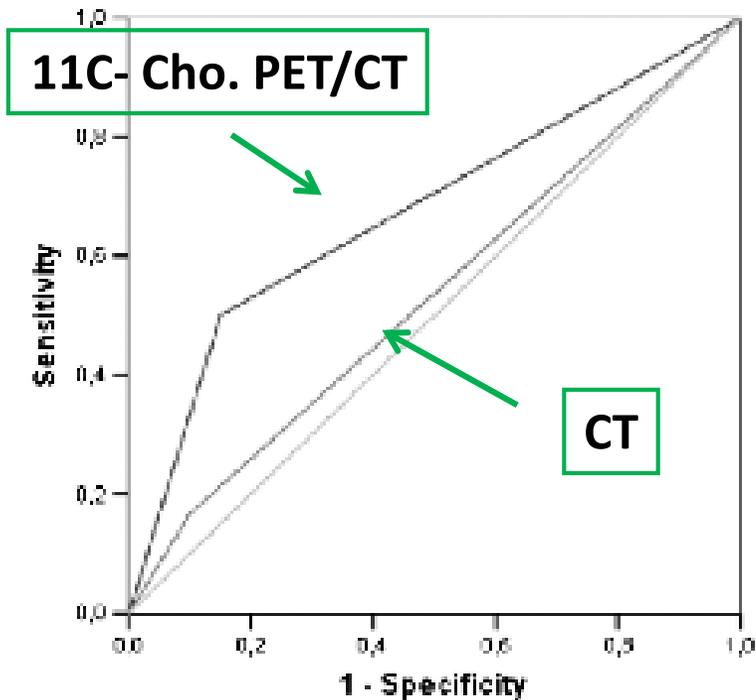
PET/TC e stadiazione



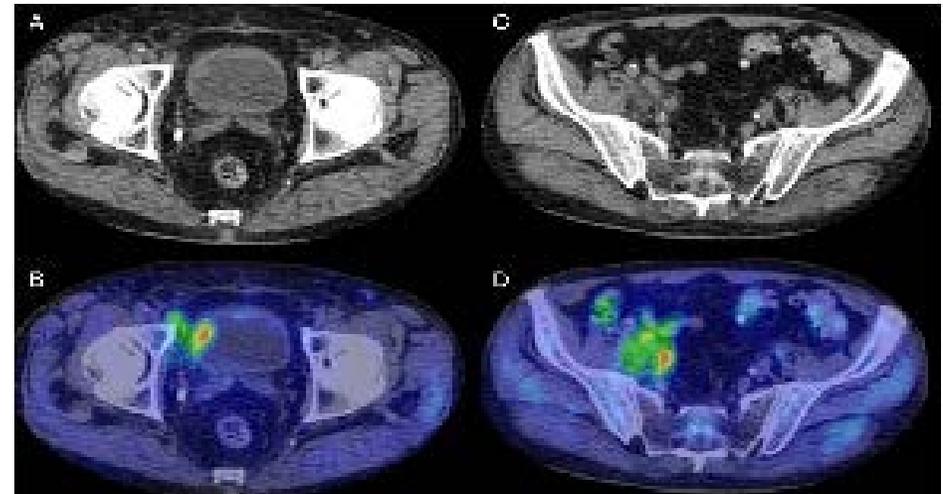
Diagnostic Accuracy of ^{11}C -Choline PET/CT in Preoperative Lymph Node Staging of Bladder Cancer

A Systematic Comparison With Contrast-Enhanced CT and Histologic Findings

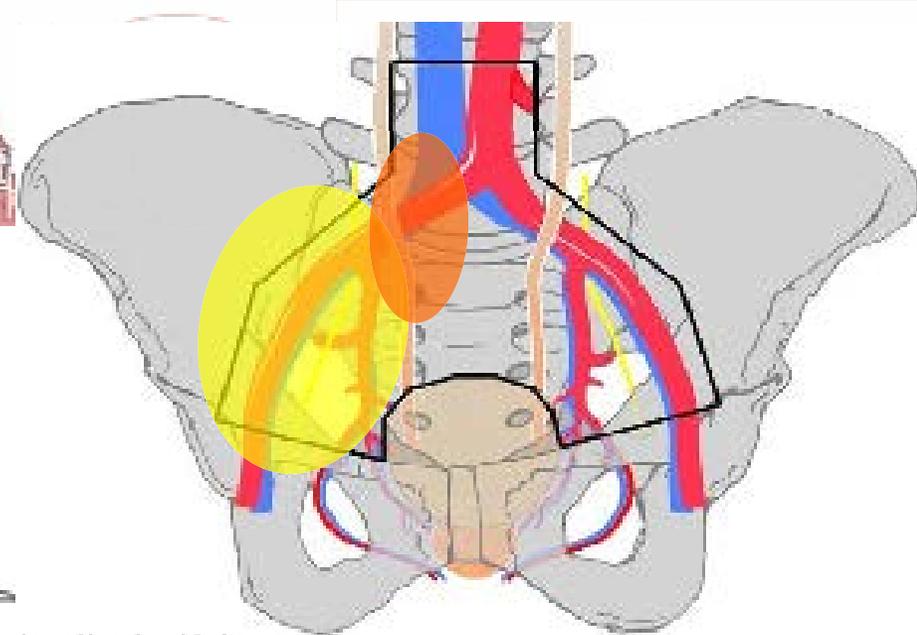
26 casi



	<u>11C- Cho. PET/CT</u>	<u>CT</u>
Sensibilità	42%	14%
Specificità	84%	89%



La **PET/TC-colina** può fornire ulteriori **informazioni diagnostiche** nella stadiazione linfonodale preoperatoria in pazienti con tumore invasive ma l'uso è ancora sperimentale!



BJUI

Lymph node mapping in patients with bladder cancer undergoing radical cystectomy and lymph node dissection to the level of the inferior mesenteric artery

Jesun B. Jansen, Benedicte F. Uhai* and Klaus M.-E. Jansen

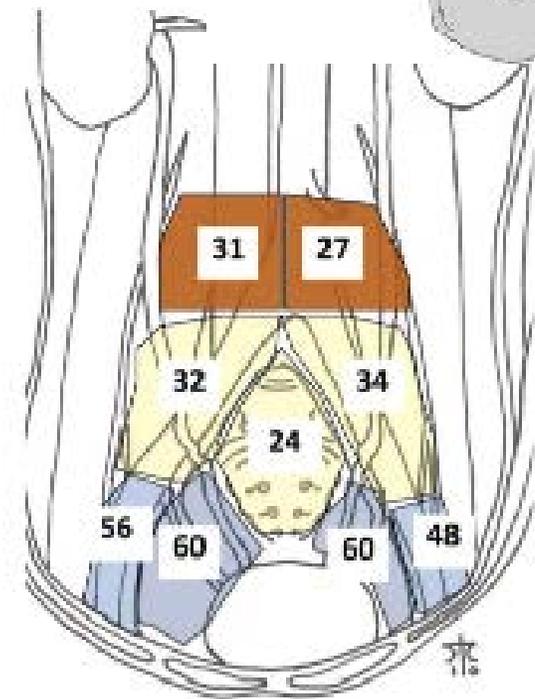
Lymph Node Dissection Technique Is More Important Than Lymph Node Count in Identifying Nodal Metastases in Radical Cystectomy Patients: A Comparative Mapping Study

BJU, 2011

Apar B. Borin*, Steven Denstmond*, Manuel S. Rosenberg*, Steffen Chouhrouzian*, Jin Cai*, Gus Almeida*, Peter W. Nichols*, Basilio G. Maresca*, Ole C. Skjott**

Eur Urol, 2011

No skip lesions



LN+ patients, %, with metastases in each level (n = 151)

Level 3: 28

Level 2: 38

Level 1: 95

Con template esteso si è visto che rare sono le metastasi linfonodali retroperitoneali in assenza di metastasi pelviche



Prima della standardizzazione della **PLND veniva riportata una CSS non superiore al **7%** nei pazienti pN+**



Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference.

Skinner DG. 1982;128:34–6.

The Impact of Lymphadenectomy and Lymph Node Metastasis on the Outcomes of Radical Cystectomy for Bladder Cancer

Alexander Karl^a, Peter R. Carroll^b, Jürgen E. Gschwend^c, Ruth Knüchel^d,
Francesco Montorsi^e, Christian G. Stief^f, Urs E. Studer^f

2009



Study	No. of patients	No. of PLND patients	10y survival %
Skinner et al [1]	104	26	
1979-1981			55
1982-1984			51
pT1			-
pT2			-
pT3			-
pT4			-
pN0			-
pN1			-
pN2			-
pN3			-
pN4			-
pN5			-
1985-1987			57
1988-1990			59
Gezmen et al [2]	180	122	
1979-1982			52
1983-1986			55
1987-1990			58
1991-1994			59
Waller et al [3]	177	111	
1979-1981			51
1982-1984			-
1985-1987			54
Cheng et al [4]	191	127	
1979-1981			51
1982-1984			52
Herrmann et al [5]	146	146	
1979-1981			42
1982-1984			-
1985-1987			-
1988-1990			-
1991-1993			48
Heldmann et al [6]	207	151	
1979-1981			51
1982-1984			51

Sopravvivenza media a 5 anni dei pazienti pN+ è circa il **30%**

PLND: ruolo stadiante o terapeutico?

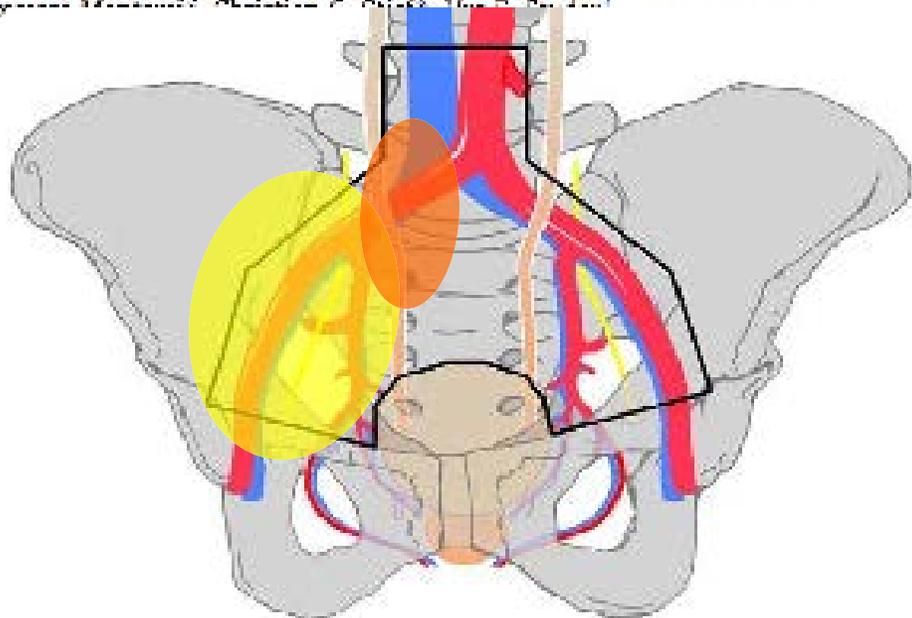
EAU Guidelines on
**Muscle-invasive
and Metastatic
Bladder Cancer**
2018

In studi retrospettivi la **linfadenectomia estesa vs. standard** sembrerebbe **migliorare** la sopravvivenza in pazienti con tumore muscolo-invasivo della vescica

The Impact of Lymphadenectomy and Lymph Node Metastasis on the Outcomes of Radical Cystectomy for Bladder Cancer

Alexander Karl¹*, Peter R. Carroll², Jürgen E. Gschwend³, Ruth Knöche¹,
François Montaudou⁴, Christian C. Gille⁵, Thor B. Pedersen⁶

2009



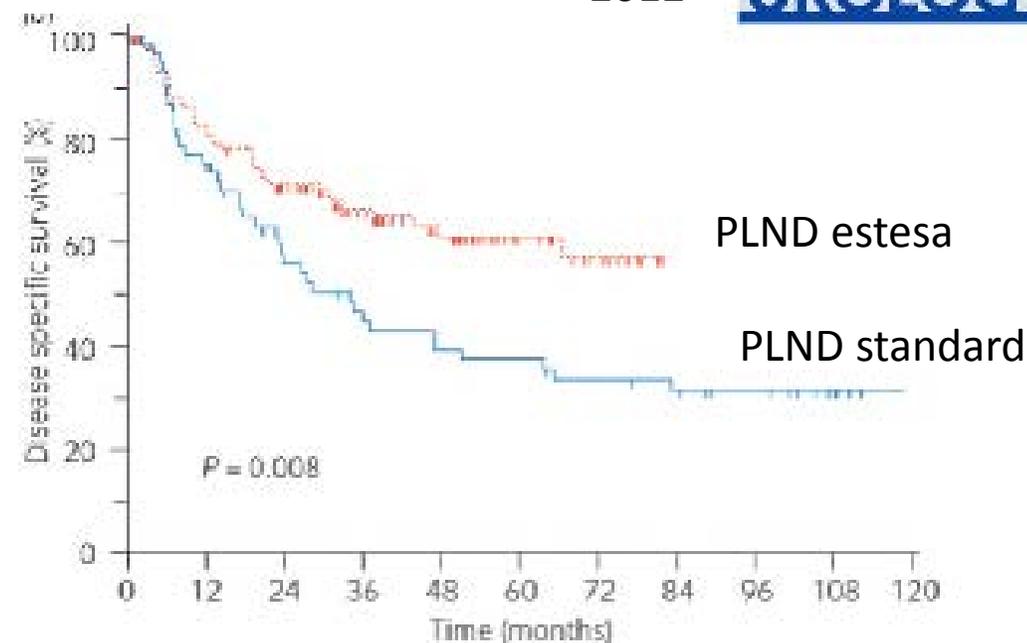
- Standard ■ Iliaci esterni, n. otturatorio, iliaci interni, presacrali, iliaci comuni distali
Esteso ■ ■ 1+ iliaci comuni prossimali, biforcazione aortica

Extended versus limited lymph node dissection in radical cystectomy: Impact on recurrence pattern and survival

Jørgen Beckgaard Jensen,¹ Benedicte Petra Ulhaug² and Klaus Møller-Ernst Jensen¹

2012

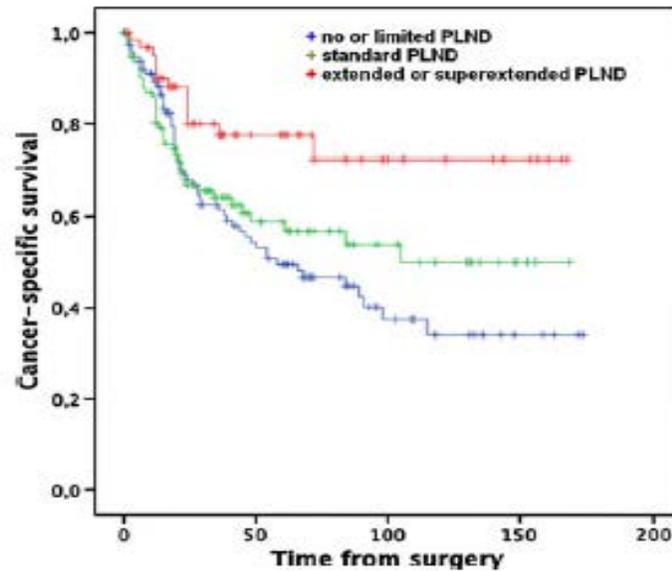
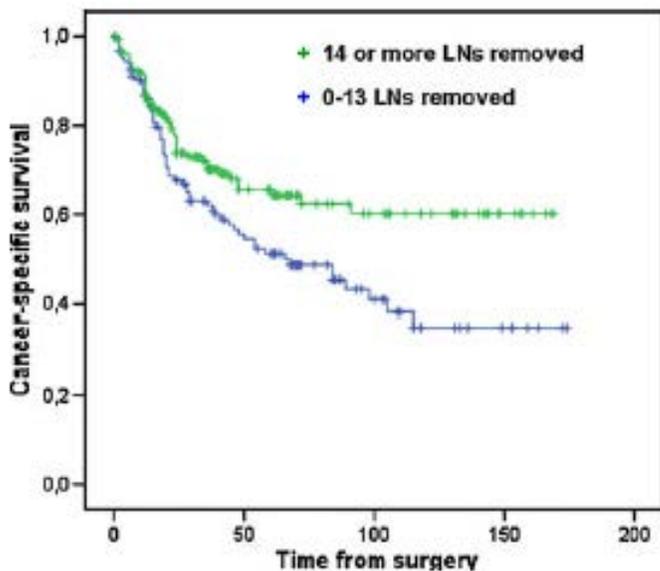
INTERNATIONAL JOURNAL OF
UROLOGY



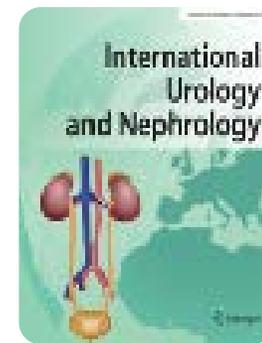
PLND: ruolo stadiante o terapeutico?

Inoltre la **sopravvivenza** sia globale sia cancro-specifica sembra **correlata con il numero di linfonodi asportati durante la chirurgia**

È stato ipotizzato che l'asportazione di un **numero maggiore di 15-20 linfonodi** sia da una parte **sufficiente alla valutazione dello stato di coinvolgimento linfonodale**, dall'altra comporterebbe un **aumento della sopravvivenza**



The number of nodes removed as well as the template of the dissection is independently correlated to cancer-specific survival after radical cystectomy for muscle-invasive bladder cancer





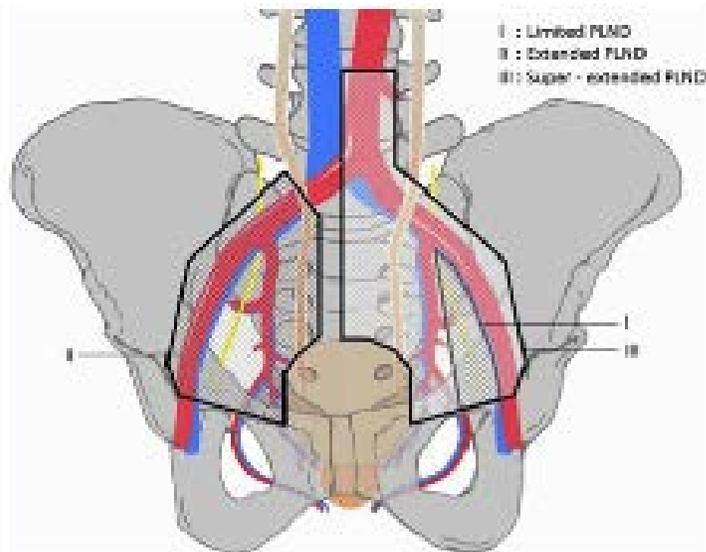
The Impact of Lymphadenectomy and Lymph Node Metastasi on the Outcomes of Radical Cystectomy for Bladder Cancer

Alexander Karl^{a,*}, Peter R. Carroll^b, Jürgen E. Gschwend^c, Ruth Knüchel^d,
Francesco Montorsi^e, Christian G. Stief^a, Urs E. Studer^f

2009



- Una **dissezione** linfonodale pelvica **estesa** può avere un **ruolo curativo** (minor rischio di recidive), **in pazienti con metastasi (pN+) o micrometastasi (pN0)**



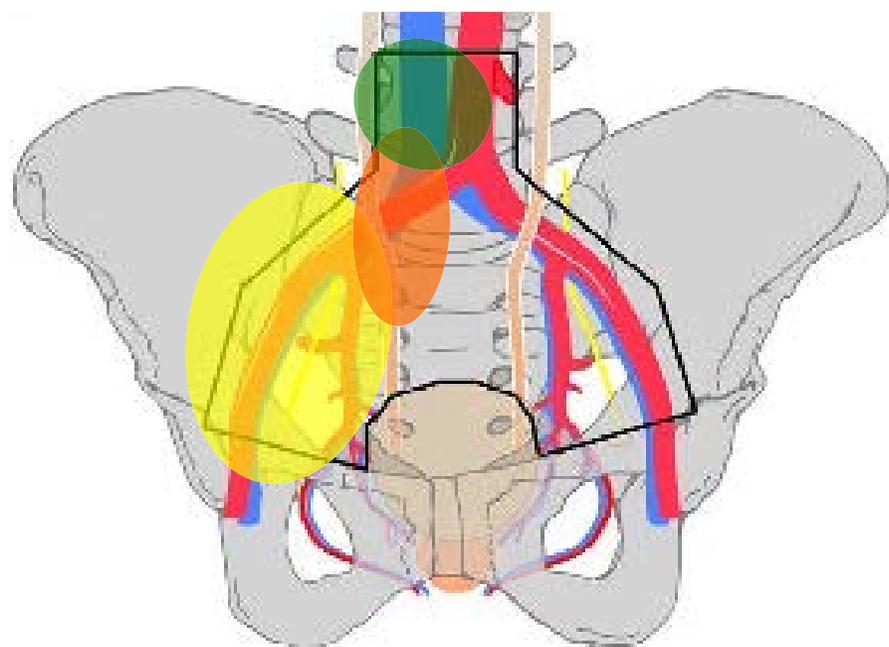
- **Concetto che si basava su dati retrospettivi!!!**

Super Extended Versus Extended Pelvic Lymph Node Dissection in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Comparative Study

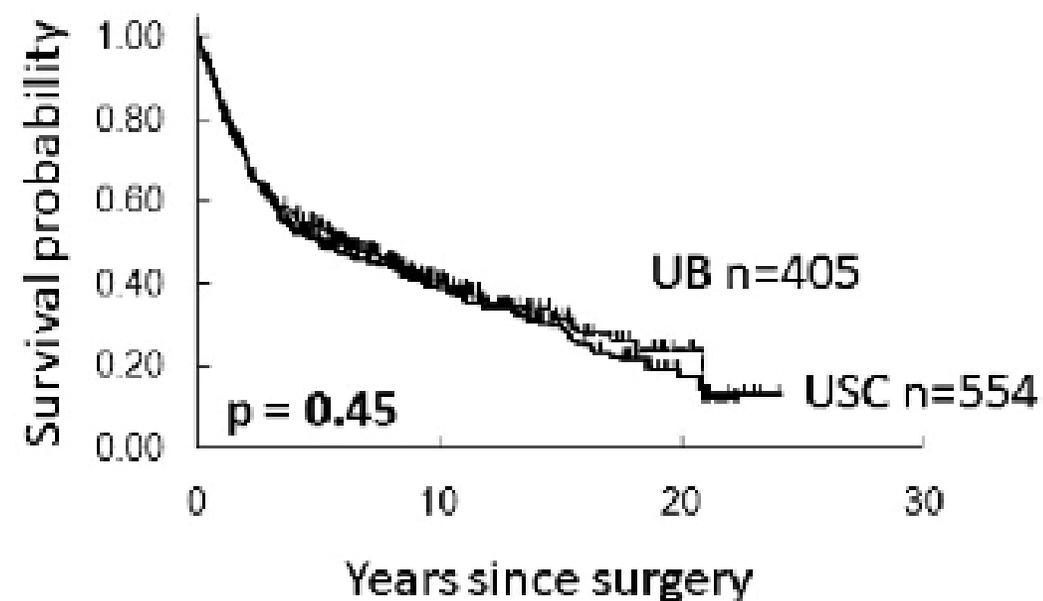
Passer Zelinger,* Urs E. Studer, Eric C. Skinner, Ryan P. Dunn, Jie Cao, Beat Roth, Gus Miranda, Frédéric Birkhäuser, John Stein,† Fiona C. Burkhard, Sanjiv Hansotia,‡ George N. Thalmann, Federico S. Hill and Donald S. Skinner



Non sono state osservate differenze significative tra PLND estesa e superestesa



Overall survival



- 1) Standard
- 2) Esteso
- 3) supeesteso

- Iliaci esterni, n. otturatorio, iliaci interni, presacrali, iliaci comuni distali
- ■ 1+ iliaci comuni prossimali, biforcazione aortica
- ■ ■ 2+ preaortici e precavali fino all'a. mesenterica inferiore



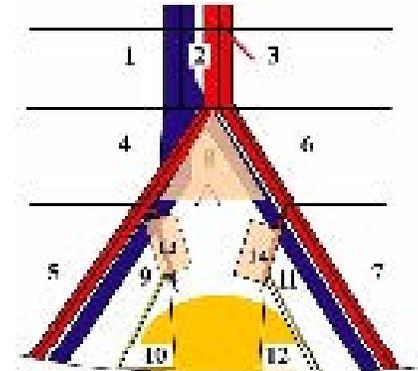
Primo trial randomizzato

2018

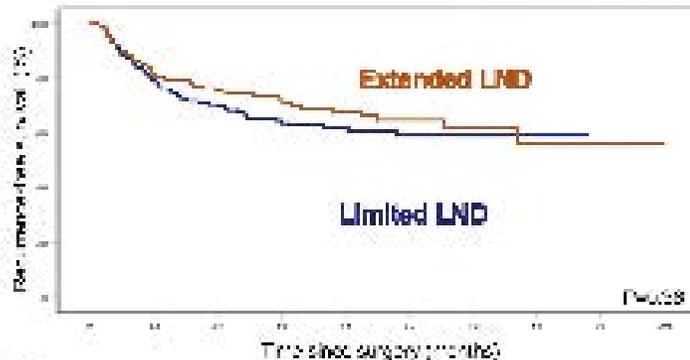
Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results From a Prospective, Randomized Trial

Jürgen E. Gschwend^{1,2,*}, Matthias M. Heck^{1,3}, Jan Lehmann⁴, Herbert Hübner⁵, Peter Albers⁶, Johannes M. Kroll⁷, Detlef Trantjeberg⁸, Patrick de Coester⁹, Axel Hentzenreich¹⁰, Günter Kubiak¹¹, Michael Stöckle¹², Thomas Schmoller¹³, Arnulf Stenzl¹⁴, Markus Wüller¹⁵, Michael Truss¹⁶, Stephan Ruth¹⁷, Uwe-Detlef Liehr¹⁸, Joachim Leifner¹⁹, Thomas Dregenzner²⁰, Margitta Reitz²¹

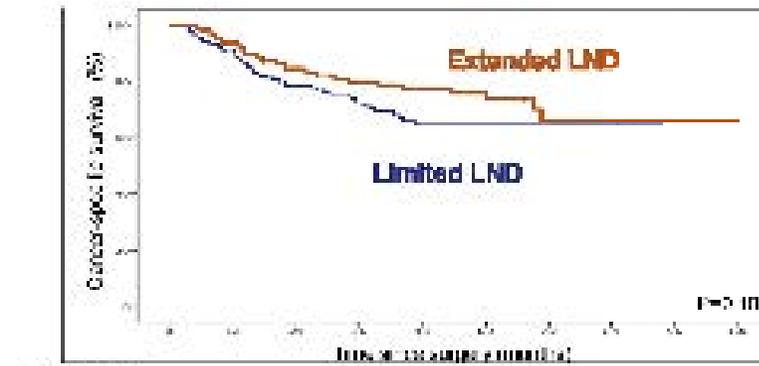
401 pazienti randomizzati: limited LND vs. extended LND



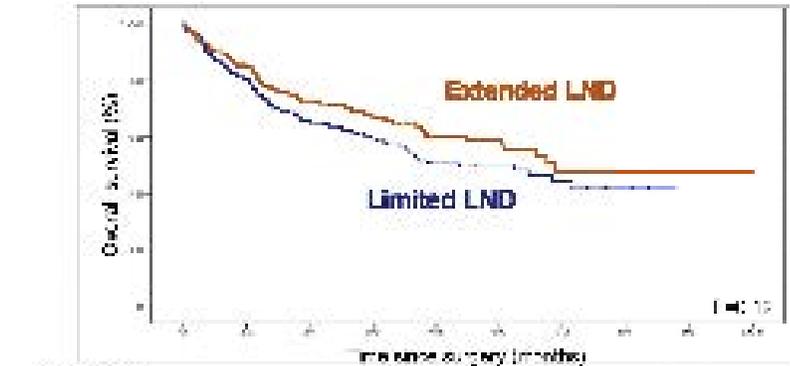
A Recurrence-free survival



B Cancer-specific survival



C Overall survival



Number of patients	0	3	6	9	12	15	18	21	24
Extended LND	192	187	185	181	177	173	168	163	158
Limited LND	209	197	181	167	151	135	119	103	87

Number of patients	0	3	6	9	12	15	18	21	24
Extended LND	192	187	178	168	157	145	133	121	109
Limited LND	209	195	175	158	138	118	98	78	58

Number of patients	0	3	6	9	12	15	18	21	24
Extended LND	192	184	170	156	142	128	114	100	86
Limited LND	209	193	170	150	130	110	90	70	50



PLND: Complicanze

- **La PLND estesa aumenta, in media, i tempi operatori di circa 60 minuti**
- **Rispetto alla PLND standard, NON si registra un aumento di morbidità o mortalità con approccio esteso (ma aumenta il rischio di linfoceli)**
- **In studi con elevata numerosità, il tasso di complicanze precoci e di mortalità registrato è stato del 28% e del 3% rispettivamente**



Possibile ruolo per la robotica?

Nonostante diffusa da 10 anni, è considerata ancora una **tecnica «sperimentale»** e **studi comparativi sono limitati da importanti bias (età pazienti, CHT neoadiuvante e stadio <T2 nel 50-60%)**

Systematic Review and Cumulative Analysis of Perioperative Outcomes and Complications After Robot-assisted Radical Cystectomy

Giacomo Novara^{a,*}, James W.F. Catto^b, Timothy Wilson^c, Magnus Annerstedt^d, Kevin Chan^e, Declan G. Murphy^f, Alexander Motttrie^g, James O. Penbody^h, Ella C. Skinner^h, Peter N. Wiklundⁱ, Khurshid A. Guru^k, Bertram Yuh^{o1}

2015



Best Practices in Robot-assisted Radical Cystectomy and Urinary Reconstruction: Recommendations of the Pasadena Consensus Panel

2015

Systematic Review and Cumulative Analysis of Oncologic and Functional Outcomes After Robot-assisted Radical Cystectomy

Bertram Yuh^{o1,*}, Timothy Wilson^c, Bernie Hochner^b, Kevin Chan^e, Joan Palau^g, Arnulf Stenzl^d, Francesco Montorsi^c, George Thalmann^f, Khurshid Guru^h, James W.F. Catto^h, Peter N. Wiklundⁱ, Giacomo Novara^{k1}

- **Tempi operatori maggiori** con RARC (1-1,5 ore in più)
- **Minor complicitanze grado 3 e sanguinamento**
- **Degenza paragonabile**
- **Esperienza chirurgica e volume chirurgico sono fondamentali** per ottenere outcomes adeguati (>30 casi/anno)
- **PSM simili tra ORC e RARC**
- A 5 anni DFS (53–74%), CSS (66–80%) e OS (39–66%)
- Mancano dati a lungo follow up



Possibile ruolo per la robotica?

Evolution of cystectomy care over an 11-year period in a high-volume tertiary referral centre

Aldo Brassetti¹, Axel Möller², Oscar Laurin³, Jonas Høijer⁴, Christoffer Adding⁵, Ayako Miyakawa⁶, Abolfazl Hosseini⁷ and Peter Wiklund⁸



		Overall	ORC	RARC	p-value
Patients		814	347 (42.6%)	467 (57.4%)	
Lymphadenectomy (n = 813)	none	66 (8%)	57 (16%)	9 (2%)	< 0.001
	limited-standard	346 (42.5%)	224 (65%)	122 (26%)	
	extended	401 (49.5%)	66 (19%)	335 (72%)	

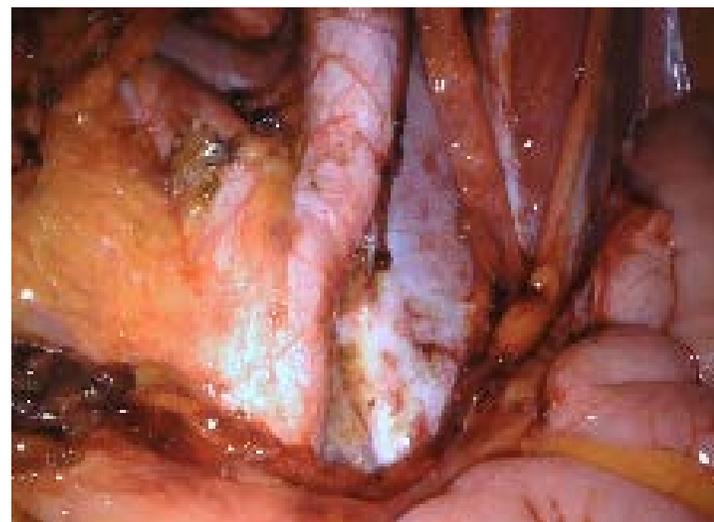
Robot-assisted Versus Open Radical Cystectomy in Patients Receiving Perioperative Chemotherapy for Muscle-invasive Bladder Cancer: The Oncologist's Perspective from a Multicentre Study

2018

Andrea Necchi¹, Gregory B. Pond², Marc C. Smaldone³, Sumanta K. Pal⁴, Kevin Chan⁵, Yu-Ning Wong⁶, Rosalia Viterbo⁷, Guru Sonpayde⁸, Lauren C. Harshman⁹, Simon Crabb¹⁰

	Median number of lymph nodes removed (IQR)		p value
	RARC	ORC	
Overall	21 (14–34.5)	13 (8–21)	<0.001
Selected RARC centres only	21 (14–34.5)	15 (8–23)	<0.001

In centri di riferimento, con la tecnica robotica la linfadenectomia viene eseguita più frequentemente con template esteso!





Problema del seeding: locally advanced e cN+

- **Aggressività e stadio locale avanzato del tumore**
- Immunodepressione del paziente
- **Contatto del tumore con la ferita/porte laparoscopiche**
- **Manipolazione chirurgica**
- «nebulizzazione” di cellule tumorali nella cavità peritoneale secondaria al pneumoperitoneo
- **Perdita di gas** dalle porte laparoscopiche con accumulo di cellule neoplastiche a livello delle porte (**effetto camino**)
- **Contaminazione da strumenti laparoscopici** con cellule neoplastiche a livello delle porte
- **Studi autoptici** dimostrano **carcinosi peritoneale** nel **19%** dei pazienti con neoplasia vescicale per lo più **multimetastatica!**



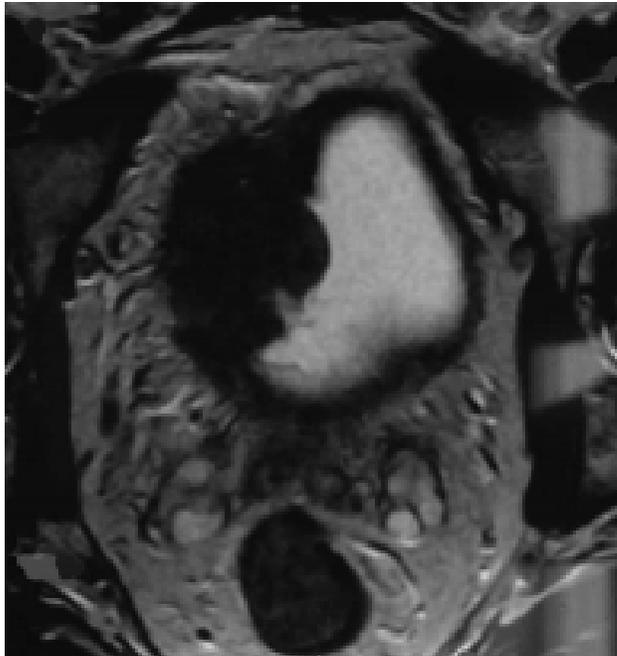
Problema del seeding: locally advanced e cN+

PORT SITE METASTASES AFTER ROBOT-ASSISTED
LAPAROSCOPIC RADICAL CYSTECTOMY

NASR A. EL-TABEY and AHMED M. SIOMI

10 mesi dopo.....

cT3b N0 M0





Problema del seeding: locally advanced e cN+

Early Recurrence Patterns Following Totally Intracorporeal Robot-assisted Radical Cystectomy: Results from the EAU Robotic Urology Section (ERUS) Scientific Working Group

Justin W. Collins^a, Abolfazl Hosseini^a, Christopher Aading^a, Tommy Nyberg^b, Anthony Koupparis^c, Edward Rowe^c, Matthew Perry^d, Rami Issa^d, Martin C. Schumacher^e, Carl Wjiburg^f, Abdulkah E. Canda^g, Melvin D. Bulboy^h, Karel Decosterckerⁱ, Christian Schwentner^j, Arnulf Stenzl^j, Sebastian Edeling^k, Saša Pokupić^l, Fredrik D'Hondt^l, Alexander Mottrie^l, Peter N. Wiklund^m



2017

RARC: 717 pazienti
FU minimo 12 mesi

5 pazienti (0.7%) → carcinosi peritoneale (4/5 recidiva multimetastatica; 80% up-staged a malattia non-organo confinata)

2 pazienti (0.3%) → port site metastasis

Pattern di recidiva simile alle cistectomie open



Problema del seeding: locally advanced e cN+

Recurrence Patterns After Open and Robot-assisted Radical Cystectomy for Bladder Cancer

Daniel P. Nguyen^{1,2,3,*}, Basfir Al Hussein Al Awaridh², Xian Wu³, Padraic O'Malley⁴, Igor M. Inayarov⁵, Abimbola Ayanbesan⁶, Bishop M. Faltus⁴, Paul J. Christos³, Douglas S. Scherr^{1†}



2015

ORC: 120
RARC: 263
FU: 30 mesi

RARC non aumenta il rischio di recidiva rispetto a ORC, ma le **metastasi linfonodali extra-pelviche e carcinosi peritoneale** sono **maggiori con la tecnica robotica!!**

Table 2 – Distribution of locations among patients with recurrence and secondary urothelial carcinomas within 2 yr after open (ORC) and robot-assisted radical cystectomy (RARC)

Variable	ORC	RARC
Any recurrence ^a	33/79 (42)	57/158 (36)
Local recurrence ^a	15/65 (23)	24/136 (18)
Cystectomy bed	11 (73)	14 (58)
PLND template	6 (40)	12 (50)
Distant recurrence ^a	26/73 (36)	43/147 (29)
Lung	9 (35)	14 (33)
Liver	9 (35)	10 (23)
Bone	12 (46)	16 (37)
Extrapelvic lymph node	4 (15)	10 (23)
Peritoneal carcinomatosis	2 (8)	9 (21)
Other (brain, adrenal)	3 (12)	0
Secondary urothelial carcinoma	0	4
Upper urinary tract	0	3 (75)
Urethra	0	1 (25)

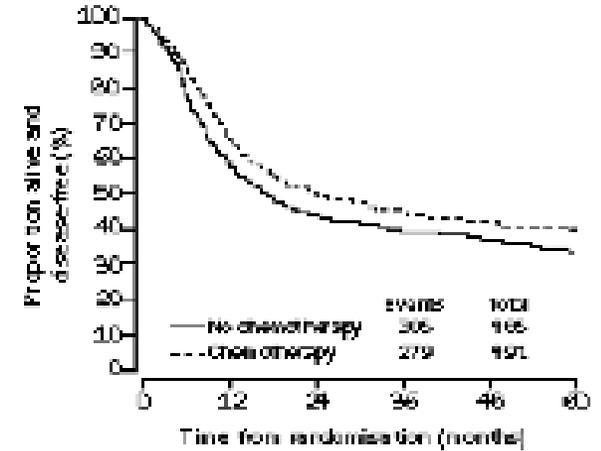


Soluzione per locally advanced e cN+: CHT neoadiuvante?



CHT neoadiuvante

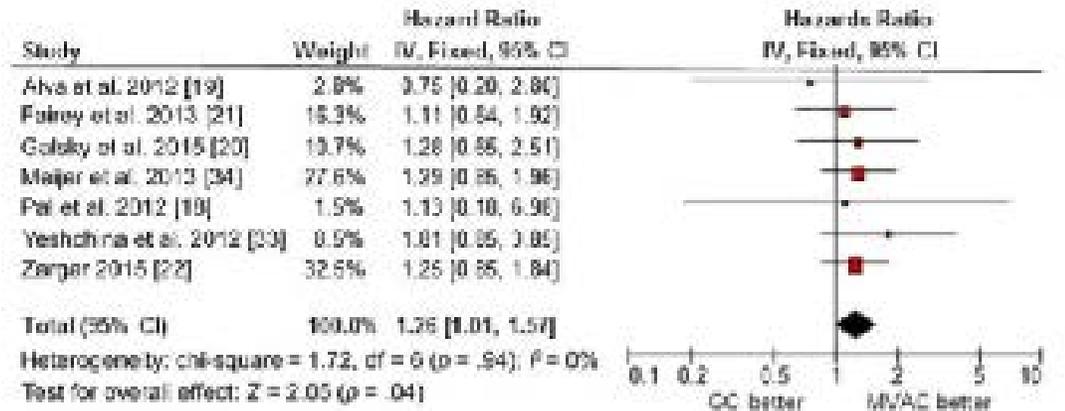
Recommendations	Strength rating
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cNM0 bladder cancer. In this case, always use cisplatin-based combination therapy.	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong



- Aumenta la sopravvivenza globale dell' 8% a 5 anni
- Aumenta il downstaging a pT0, N0 e R0 con migliori outcomes oncologici

The Oncologist Controversy Letter

Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis 2016



cN+

POST-CHEMOTHERAPY SURGERY IN PATIENTS WITH UNRESECTABLE OR REGIONALLY METASTATIC BLADDER CANCER

HARRY W. HERR, S. MACHELE DONAT AND DEAN F. BAJORIN

- 92% dei pazienti sottoposti a CHT senza chirurgia deceduti per neoplasia
- 1/3 dei pazienti sottoposti a chirurgia dopo CHT neoadiuvante sopravvive a 5 anni

Comparative Effectiveness of Treatment Strategies for Bladder Cancer With Clinical Evidence of Regional Lymph Node Involvement

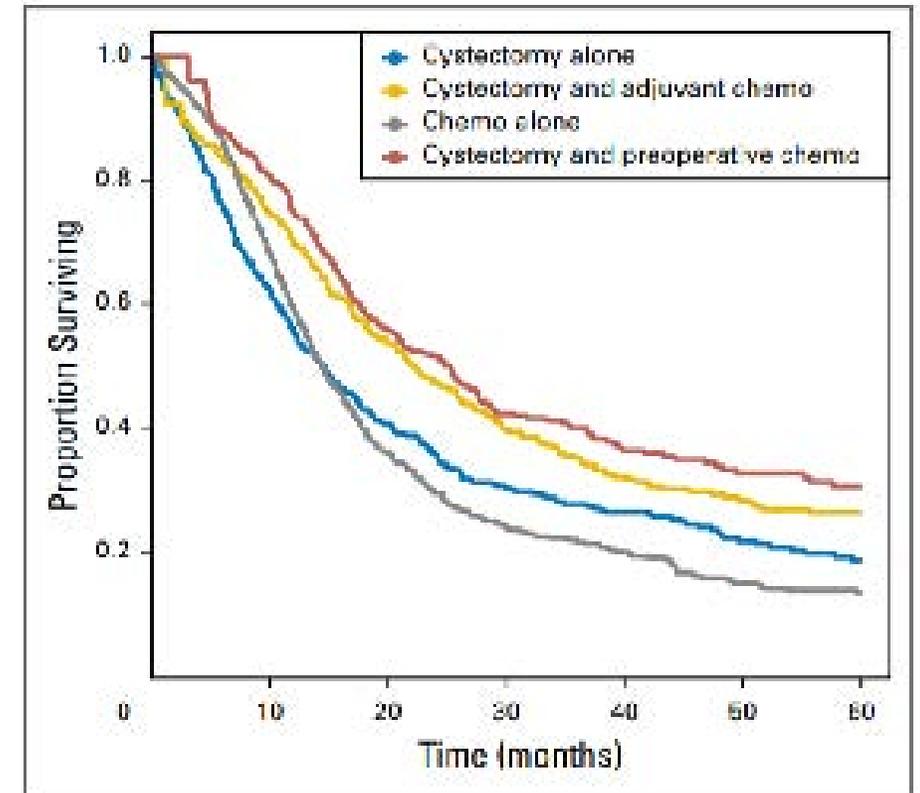
Matthew D. Galley, Nicholas Soper, John F. Maloney, Ross Mansour, Michael D'Amico, Nabil M. Hamed, Chih-Kai Tsai, Paolo Zuffanti, Peter H. Pisters, William K. Kelly, Alfredo Martinez, and Bart Selzer

JOURNAL OF CLINICAL ONCOLOGY

2016

1,739 pazienti (cN1-2-3):

- 1,104 chirurgia (363 con CHT neoadiuvante)
- 635 CHT esclusiva





T4b e cN+

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b).	Weak
Offer palliative cystectomy in patients with symptoms.	Weak

- **Cistectomia palliativa** come alternativa a trattamento conservativo (ex. RT)
- **Sintomi invalidanti: dolore, sanguinamento, disuria e anuria ostruttiva**
- **Nessun ruolo per la PLND (aumento tempi chirurgici e morbidità, nessun vantaggio di sopravvivenza per pazienti a scarsa prognosi)**

BLADDER CANCER WITH OBSTRUCTIVE UREMIA: ONCOLOGIC OUTCOME AFTER DEFINITIVE SURGICAL MANAGEMENT

NASR A. EL-TADAY, YASSER OSMAN, AHMED MOHIB, TAREK MEHSEN,
and HASSAN ABOL-ENEN

2005

- **61 pazienti con uremia ostruttiva** sottoposti a cistectomia
- **10 cistectomie di salvataggio** → **tutti 10 pazienti recidiva pelvica entro 1 anno dalla chirurgia!!**

CONCLUSIONI

- **PLND in Cap: ruolo stadiante ma tutt'ora problema non risolto della nostra chirurgia**
- **Salvage PLND: solo in casi ben selezionati può essere curativa**
- **PLND in BC: ruolo curativo? probabilmente non da sola**