



# **SIU** **UPDATES**

## **ASCO GU**

**ASCO GENITOURINARY CANCER SYMPOSIUM**



**16.15 - 17.00 Penis, Testicle and Uncommon Cancer**

**N. Nicolai, O. De Cobelli, G. Rosti, S. Secondino**

16.15

**RESEARCH**

DISCUSSANTS **N. Nicolai, G. Rosti**

- Testis. New markers on the block? Mi-RNA as predictors of relapse

**S. Secondino**

- Penis. Light (or night) chemotherapy for locally advanced disease: Vinflunine trial

**S. Secondino**

16.35

**DISCUSSION AND CLINICAL CASES**

DISCUSSANTS **N. Nicolai, S. Secondino**

- Testis. Clinical cases context and debate. Role of expert and referral centers for post-chemo surgery: when, which and where PC-RPLND

**O. De Cobelli, G. Rosti**

- Penis. Clinical cases context and debate.

Which is the best sequence for nodal metastases from penile carcinoma?

**S. Secondino, O. De Cobelli**

16.55

Discussion on hot topics

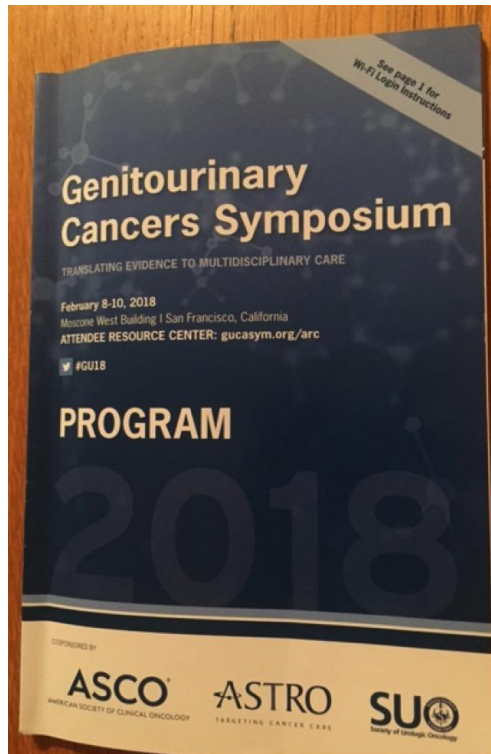
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Conclusions

17.45

Work end

# Testis and penis cancer at Genitourinary Cancers Symposium 2018

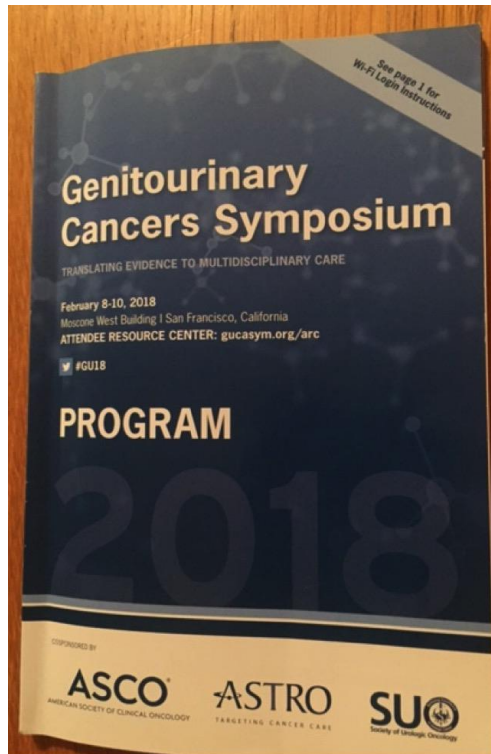


Testis and penis cancers are a rare and very rare disease, respectively.

Research advancements in these diseases do not run as they do in frequent tumours.

Among the small amount of new pieces of information, we picked up **those studies we believe may impact the common practice**, specially focussing on the most critical crossroads.

# Testis and penis cancer at Genitourinary Cancers Symposium 2018



Among these:

- New markers for the diagnosis and monitoring in GCT (miRNA)
- New drugs which may impact favorably (balance efficacy/tolerability) in advanced penis cancer

Then we focus on critical issues in penis and testis cancer management:

- Indication to post-chemo RPLND and role of referral centres for GCT of the testis
- Role and best sequences in patients with nodal metastases from penile cancer.

## Testis. New markers on the blocks?

### Mi-RNA as predictors of relapse

22 Giugno 2018

**Simona Secondino**

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Pavia

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Fondazione IRCCS  
Policlinico San Matteo

Sistema Socio Sanitario



Regione  
Lombardia

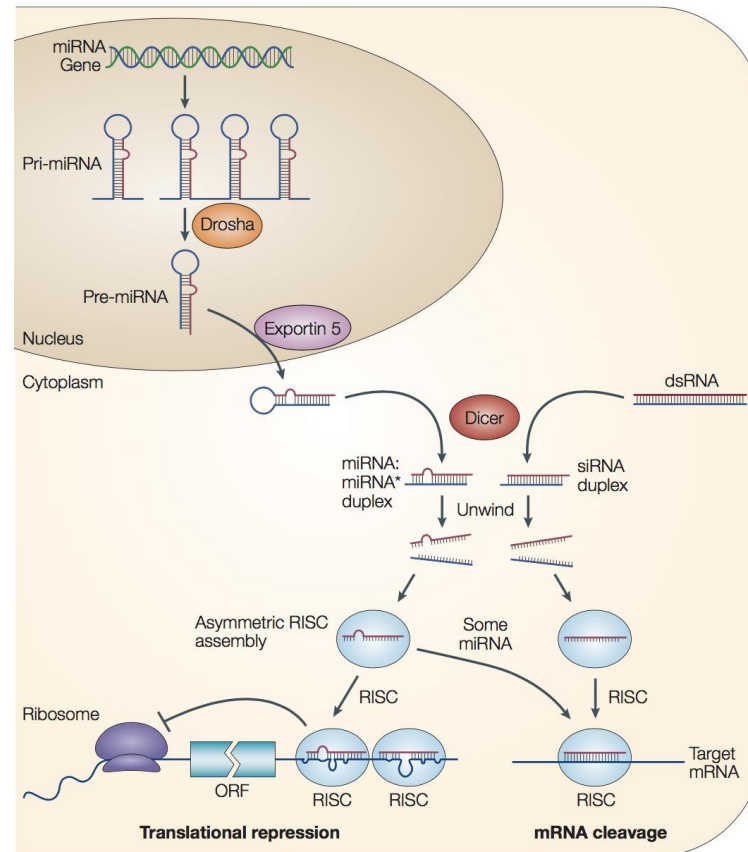
## Mi-RNA: what's their role?

Pri-microRNA (**pri-miRNA**) are first processed into 70 nucleotide **pre-miRNA** inside the nucleus. Pre-miRNA are transported to the cytoplasm, and are processed into mi-RNA.

Only one strand of the mi-RNA is assembled into the RNA-induced silencing complex (**RISC**), which subsequently acts **on its target** by translational repression on **mRNA cleavage**, depending at least in part, on the level of complementarity between the small RNA and its target.

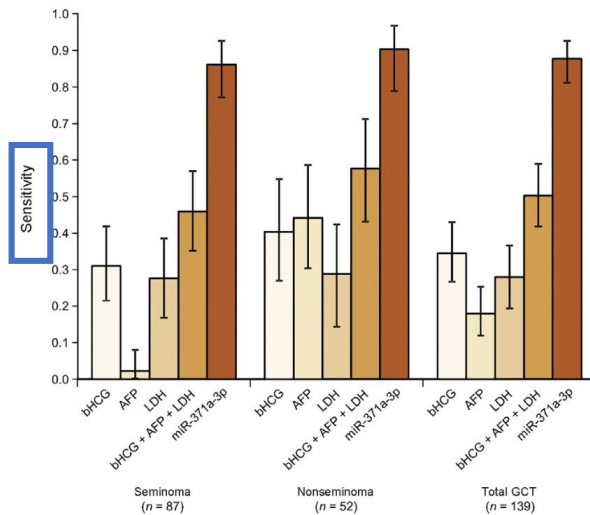
### Translational repression Post-transcriptional gene silencing

*From Lin He, Nature Reviews 2004*



## Mi-RNA: what's their role?

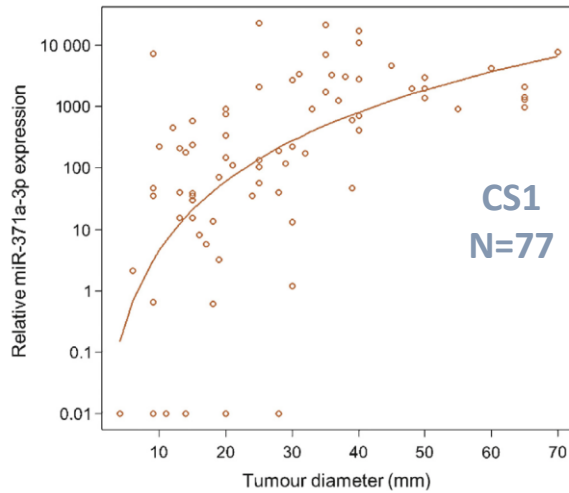
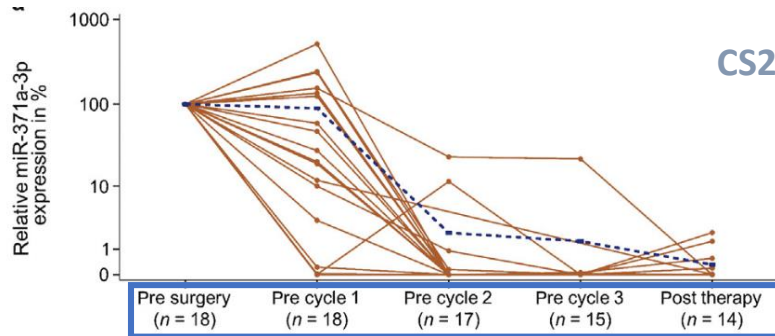
- Markers (alfaFP, BetaHCG, LDH) are expressed in <60% of cases;
- Mi-RNA of the clusters **miR-371-3** and **miR-302/367** were suggested as new serum biomarkers, and were detected in **embryonic stem cell in GCT tissue**;
- They are absent in other malignancies;
- **Sensitivity 92%; specificity 80%;**



Diagnostic properties

Dieckmann, Eur Urol 2017

## Mi-RNA: what's their role?



Prognostic properties

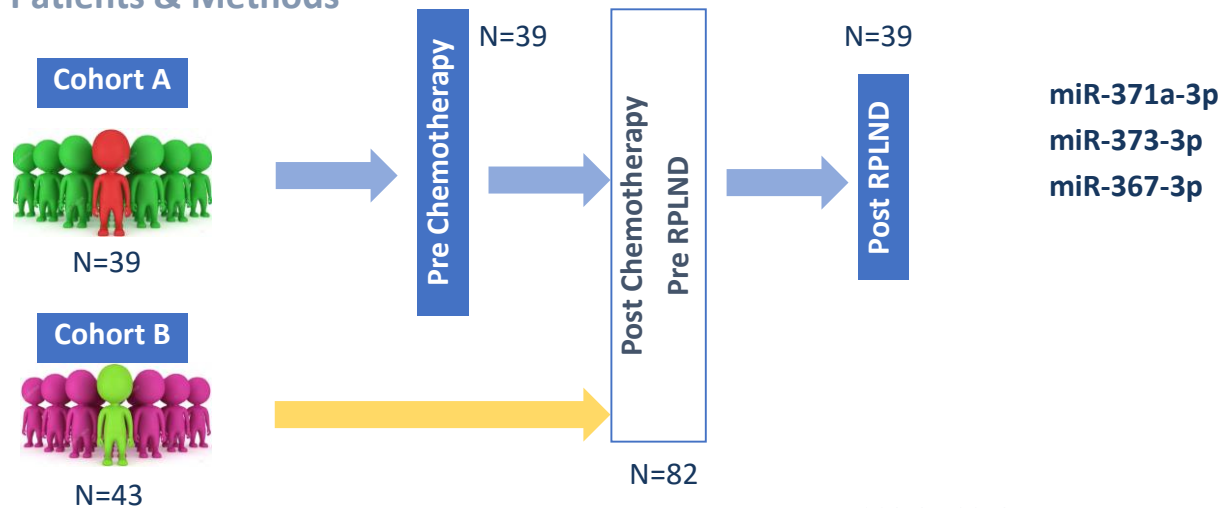
*Dieckmann, Eur Urol 2017*



### Hypothesis

Serum mi-RNAs are predictive markers for viable disease post-chemotherapy

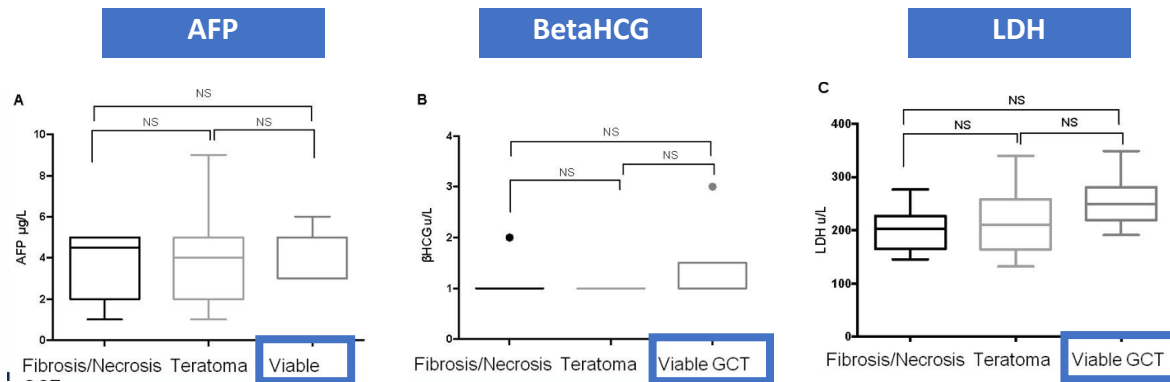
### Patients & Methods



*R. Leao, ASCO GU 2018*

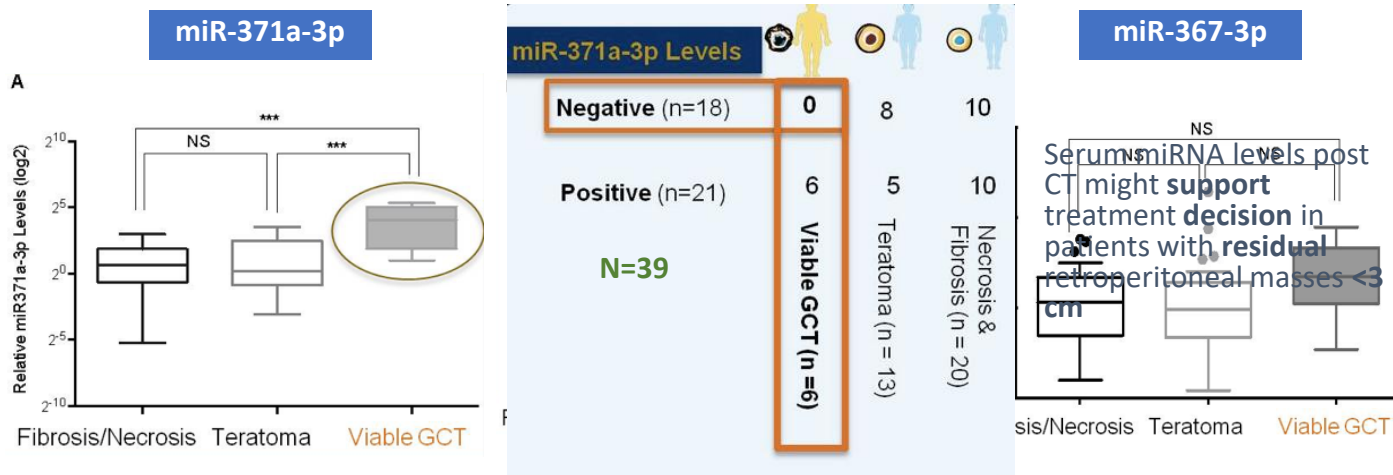
### Results

Classical tumor markers do not predict post-chemotherapy residual masses histology



Results

Serum miRNA levels are higher in the presence of viable GCT post-chemotherapy



Cohort A n=82; A \*\*\*p=0.002; B \*p=0.032

miR-371a-3p cut off level 2.0 (Sensitivity 100%, Specificity 54%; NPV 100%, p=0.02)

- Serum miRNA are associated with **clinical stage, treatment response**;
- **miR-371a-3p** as a single serum marker, highly sensitive and specific, predicts **viable disease**, and **might support** treatment decision;
- More **studies** are needed to confirm these findings;
- Multi-institutional **prospective** studies with **standard miRNA quantification** assays are needed to establish miRNAs as **clinical biomarkers**



## Penis. Light (or night) chemotherapy for locally advanced disease:

### Vinflunine trial

22 Giugno 2018

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Sistema Socio Sanitario



## Systemic therapy in advanced disease

Reference	Regimen	N° patients	ORR	Design
Hussein, 1990	Cisplatin-5FU	6	83%	Retrospective
Shammas, 1992	Cisplatin-5FU	8	25%	Retrospective
Pizzocaro, 1988	VBM (vincristina)	16	56%	Retrospective
Haas (SWOG), 1999	PMB	40	32%	<b>Prospective</b>
Pagliari, 2010	TIP	30	50%	<b>Prospective</b>
Theodore (EORTC), 2008	Cisplatin-Irinotecan	26	31%	<b>Prospective</b>
Nicholson, 2013	TPF	29	38.5%	<b>Prospective</b>
Nicolai, 2016	TPF	47	43%	Retrospective
Necchi, 2017	Dacomitinib	37	28%	<b>Prospective</b>

### Study Design

**Multicentre, single arm, phase II trial**

#### TRIAL CRITERIA:

SCC

Locally advanced disease

- N2-N3
- T4

M1

ECOG (PS0-2)

Misurable disease

No prior CT/RT

#### TREATMENT

Vinflunine 320 mg/mq, q21 for 4 cycles

Patients with SD, RP, CR can continue until PD, or toxicities

#### ENDPOINTS

##### Primary endpoint

- Clinical benefit

##### Secondary endpoints

- ORR, PFS, OS, toxicity

*Pickering, ASCO GU 2018*



### Trial population

25 enrolled patients



22 evaluable patients



17 measurable patients



5 progressed prior to 4 cycles



**7/22 patients** with clinical benefit



### Primary Endpoint

**7/22 patients, 45.5% (ORR+SD)**

90% CI= 27.1-64.7; 95% CI = 24.4-67.8

Study has met primary endpoint

### Secondary Endpoints

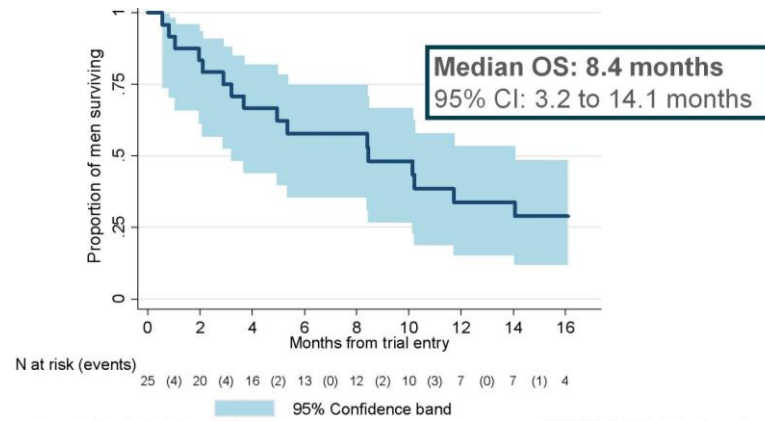
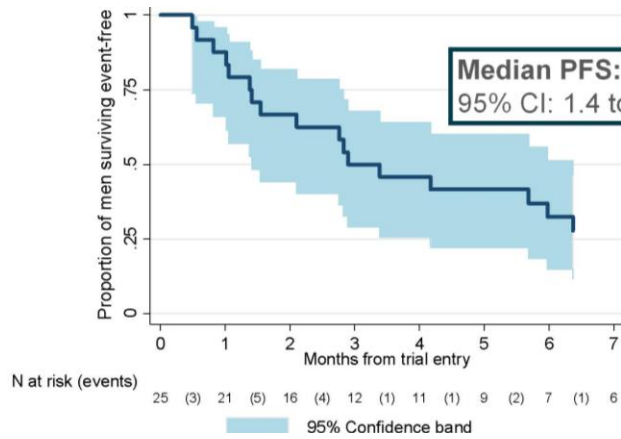
**6/22 patients, 27.3% (ORR)**

95% CI= 10.7-50.2

*Pickering, ASCO GU 2018*



Secondary Endpoints



Pickering, ASCO GU 2018



## Systemic therapy in advanced disease

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<b>Pickering, 2018</b>	<b>Vinflunine</b>	<b>22</b>	<b>27%</b>	<b>Prospective</b>

- The phase II or retrospective nature of the studies, and their small sample size, and the **lack of any randomized clinical trial**, preclude assessment of a superior drug regimen in patients with advanced disease;
- **Multimodal management** that combines systemic therapy with radical surgery yields modest survival rates, in advanced disease;
- More studies are needed to identify also **molecular markers** which could lead to advances in **new therapeutic strategies**, coupled with renewed collaboration initiatives among **high-volume centers**



# Approccio MD e ruolo dei centri di riferimento nei tumori del testicolo

Giovanni Rosti, Simona Secondino

Oncologia, Policlinico San Matteo, IRCCS Pavia

Roma, 22 giugno 2018



Vi sono ancora pazienti che ricevono un trattamento subottimale o inadeguato o eccessivo (20-35%)\*



Rarità della malattia, complessità del trattamento, inesperienza

\* Heidenreich EAU 2017, Feldman ASCO 2018

La parola magica

# Approccio multidisciplinare



Cosa è richiesto

Competenza specifica nella malattia in oggetto

Stima e rispetto per le conoscenze altrui

Essere pronti a valutare le ragioni degli altri

Essere a conoscenza della persona oltre che della malattia

Ma tutti sappiamo fare il PEB !

Verissimo, ma abbiamo una varietà notevole di PEB  
per numero e per tipologia

Che fare con i fattori di crescita?

Che fare con anti-emesi?

Che fare con il riciclo di bleomicina?

Come pensare ai prossimi 40 anni del ragazzo?



Esempio stadio 1 clinico

Radioterapia ? Sorveglianza ? Chemioterapia? Chirurgia?

Nessuna scelta è sbagliata.

Ognuna di queste scelte puo' essere "sbagliata" in quella persona

Che cosa offre un centro di riferimento ?

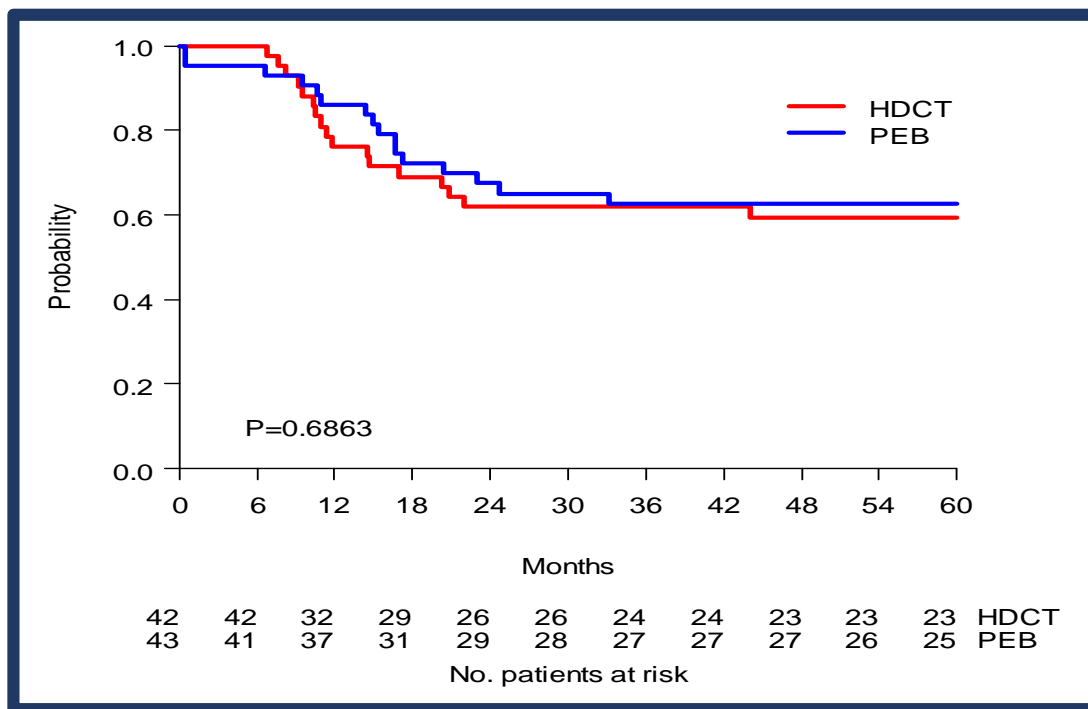
Multi-expertise in malattia rara

Accesso a studi clinici e nuovi farmaci

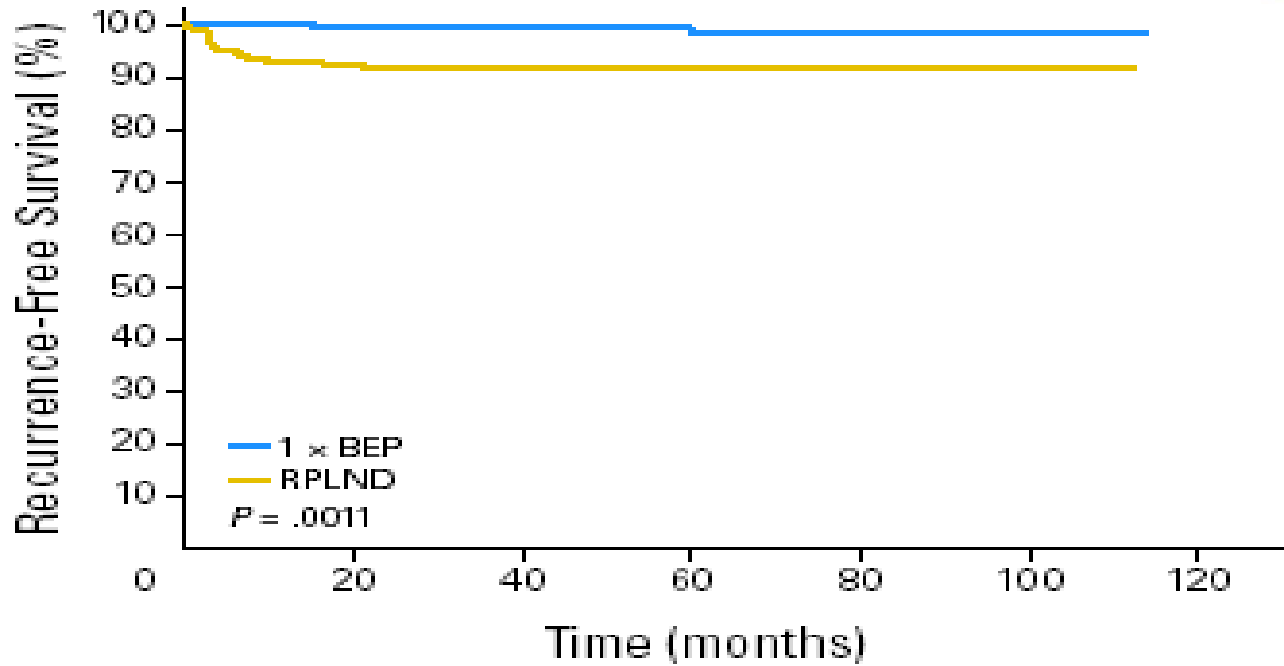
Terapie particolari (es. Alte Dosi e autotrapianto)

Situazioni cliniche particolari : sindrome OBS

## L'esperienza globale di un HV team



Tutti insieme appassionatamente



**Beh! Come si spiega !!!**

## Pitfalls in Advanced NSGCT: Post-chemo imaging and Surgery

- Principle: PET scan has no role in post-chemo evaluation of nonseminoma
  - Pitfall: Using negative PET to justify avoiding surgery
  - Neglects understanding that teratoma is PET-negative
- Principle: RPLND recommended for all residual NSGCT masses > 1cm
  - Pitfall: Avoiding surgery when it is indicated
- Principle: Lack of reduction in size with 3-4 cycles of chemotherapy does not indicate lack of response
  - Pitfall: Giving more chemotherapy b/c “the mass didn’t shrink”
  - Ignores teratoma

«Advanced testis cancer patients of intermediate or poor prognosis and relapsing patients should be managed in tertiary centers only.»

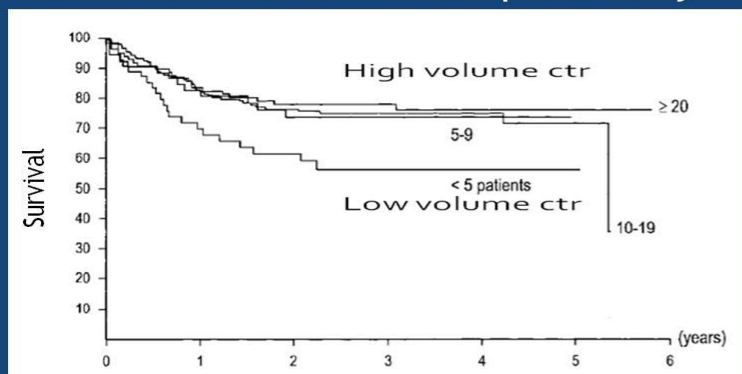
Heidenreich , EAU 2017

Siamo d'accordo? Un po' sì e un po' no

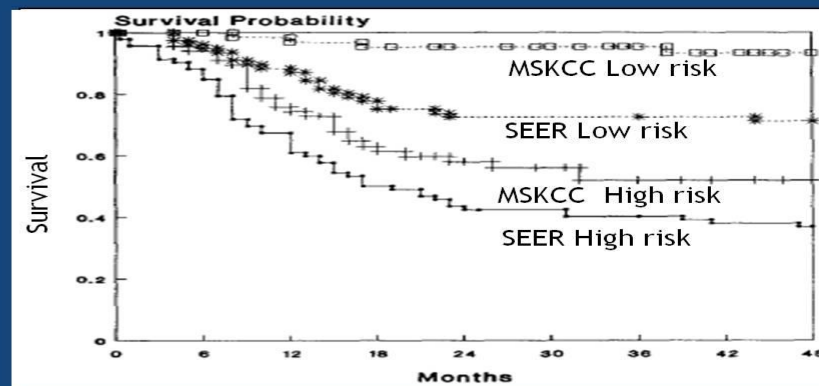
# Pitfalls in Advanced GCT: Referrals

- Principle: Complicated GCT cases require experience and expertise
  - **Pitfall: Not referring pts with complex or relapsed GCT to centers of excellence**

Outcomes better at High volume centers vs. volume centers in European study<sup>1</sup>



Outcomes better at MSKCC vs. SEER<sup>2</sup>



Un ragazzo ha una malattia non seminomatosa  
con metastasi polmonari e retroperitoneali

Alfa-feto da 2050 a 10 in 4 cicli

Resta malattia polmonare piccola (1cm) e RP piccola (2 cm)

Faccio altri due PE.



## Punti critici piu' frequenti

Timing dei marcatori

Imaging adeguate

Sperm banking

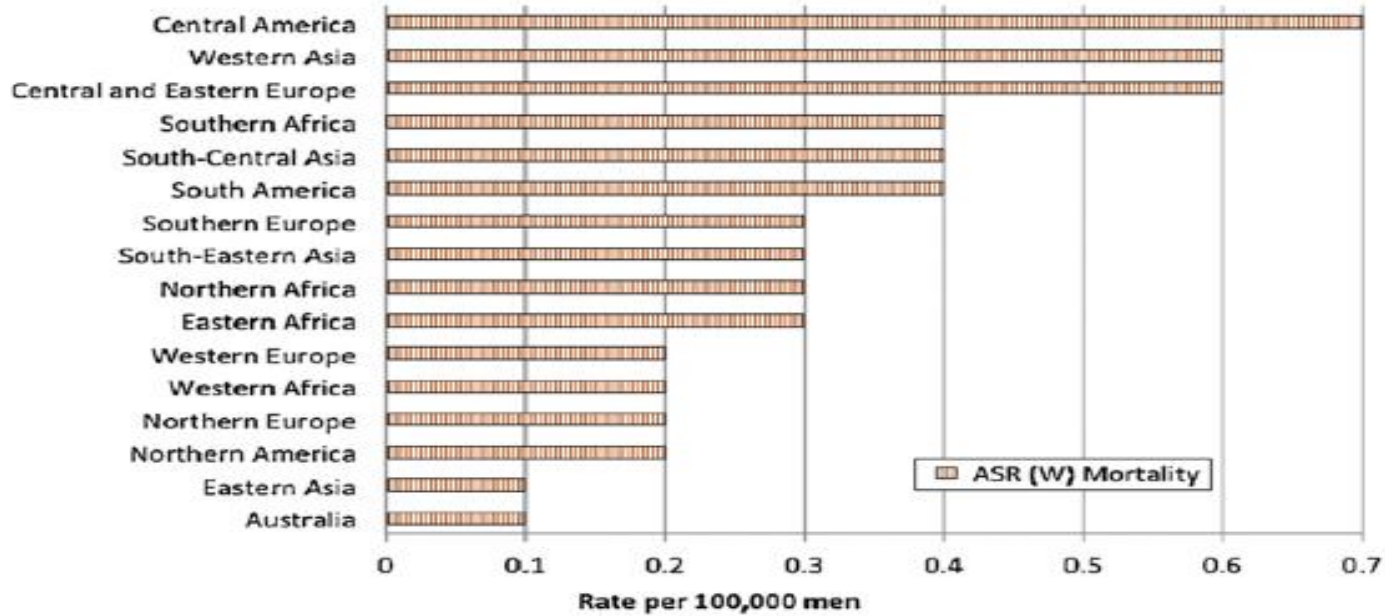
Piccoli linfonodi e sedi «anomale»

Grandi produttori di beta HCG

Fretta nel trattare in seconda linea

Beh! Residuo piccolino lasciamo stare

Tumori del testicolo come misura di performance di un sistema sanitario



Ma dappertutto è uguale?

Alcune parti di Europa sopravvivenza circa 90%

Alcune parti Europa Centro-Orientale < 80%

In alcuni paesi stadi iniziali in minore numero

Estonia non seminoma met. sopravvivenza 47% Italia del Nord 85%

Ipotesi che in certe zone il trattamento sia peggiore

Nicolai N et al EJSO, in press 2018

Paesi Bassi : miglioramento ultimi due decenni se PEB è PEB

allora la chirurgia ottimale fa la differenza (HV centers)

Bulgaria 75% dei pazienti trattati in 19 ospedali con MAV 12

Paesi Bassi 42 centri con MAV di 18 Belgio 40 centri MAV 8

Come mai?

Line Guida Nazionali e network nazionale

Nicolai N et al EJSO, in press 2018

Allora i 2500 casi /anno in Italia devono tutti andare in questi

2 o 3 posti dove sono bravi?

NO

Accesso al centro di riferimento solo per situazioni particolari

Es. Chirurgia del residuo particolare, multistep ecc.

E se usassimo **e-health technology**?

Il MDT deve essere inteso anche come valutazione a distanza

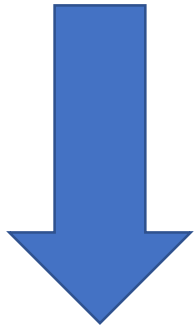
per poi scegliere chi inviare.

Che altro si puo' fare?

Divulgazione dell'approccio diagnostico  
e terapeutico ai tumori del testicolo.



Probabilmente dopo ottenuta la remissione completa da due anni non esistono piu' il buono il brutto ed il cattivo, ma solo il "guarito".



Follow-up



Aspetto psicologico

+ tutto il resto

Dotarsi un goniometro a 361 gradi



The care of the cured ones



# Post-chemotherapy RPLND

Current concepts



## Histology of the residual mass: proportion of viable cancer is about 10%

	Year of surgery				
	1989-1997 (n 291)		1998-2002 (n 213)		P value
RP histology	No of pts	%	No of pts	%	
Fibrosis	148	51	100	47	.8
Teratoma	98	34	101	47	.012
Teratoma with Malignant Transformation	7	3	7	3	
Teratoma ± viable ca	120	41	106	50	.047
<b>Viable ca</b>	<b>45</b>	<b>15</b>	<b>12</b>	<b>6</b>	<b>.001</b>

Carver BS et al, J Clin Oncol 2007 Dec 10;25(35):5603-8.

# FDG-PET in metastatic NSGCT

**Table 3.** Prediction of Viable Tumor With the Different Diagnostic Methods: CT, Serum Tumor Markers, and [<sup>18</sup>F]Fluorodeoxyglucose-PET per Patient (N = 121)

Technique	True Positive		False Positive		True Negative		False Negative	
	No.	%	No.	%	No.	%	No.	%
CT	67	55	54	45	0	0	0	0
PET	47	39	33	27	21	17	20	17
Serum tumor markers*	22	22	11	11	33	33	33	33

Technique	%				
	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Accuracy
CT	100	0	0	55	55
PET	70	48	51	59	56
AFP/HCG	40	73	50	61	56

**NO ROLE OF FDG-PET IN NON-SEMINOMA**

Oechsle K et al. J Clin Oncol. 2008 Dec 20;26(36):5930-5

The special case of the RM < 1 cm in NSGCT following first-line ChT

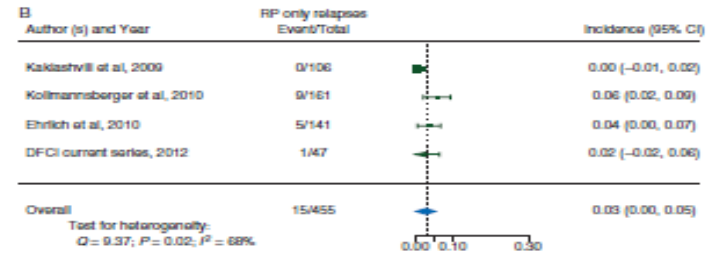
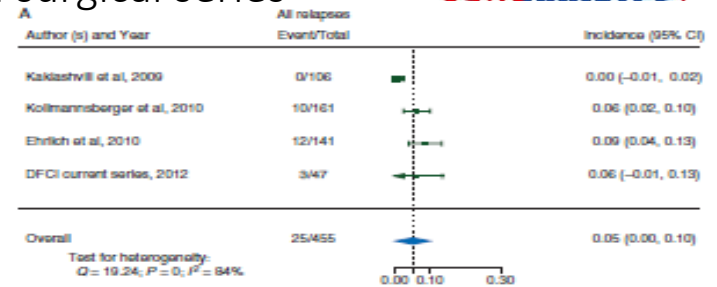
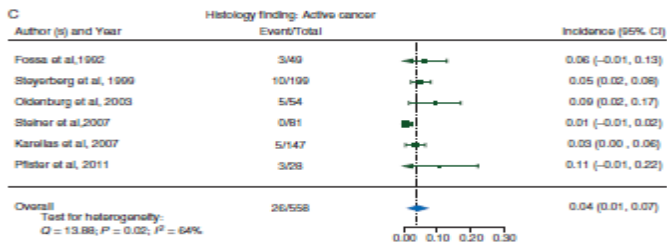
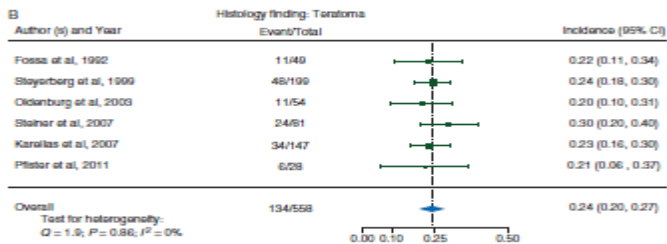
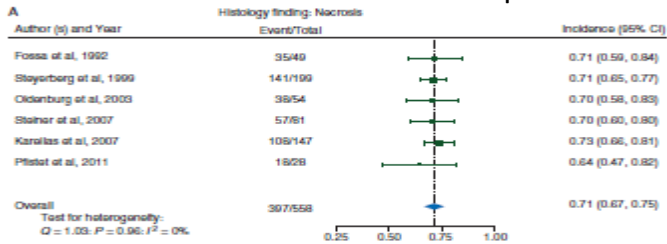
There is unanimous consensus in candidating patients with an appreciable RM ( $\geq 1$  cm) to RPLND

*The (first) dilemma is distinguishing patients with CR from those with a small RM!*

There is consensus in not candidating patients with complete remission to RPLND

# The special case of the RM < 1 cm in NSGCT following first-line ChT

## Comparison between medical and surgical series



# 455 Overall recurrence: 5% (IQR 0-10)  
 RP recurrence: 3% (IQR 0-5)  
 FU from 4 to 15 years

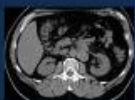
# 558  
 Fibrosis 71% (IQR 67-75)  
 Teratoma 24% (IQR 20-27)  
 Cancer 4% (IQR 1-7)

Ravi P et al Annals of Oncology 25: 331-338, 2014

# The special cases for PC RPLND

- **Residuals from seminoma**
- Following salvage chemo
- **Salvage surgery**
- Late relapses and prognosis
- **Mini-invasive PC-RPLND**
- **Maximal surgery**

# Can FDG PET Help in Post-Chemo Seminoma ?



			Sens%	Spec%	PPV%	NPV%	
SEMPET 2003- P	N=56	>3cm 19 <3 cm 37	80 70	100 74	100 37	96 92	
SEMPECON 2011 - R	N=127	>3cm 54 <3cm 73	88 67	92 87	<b>78</b> 50	96 93	<6weeks >6 weeks Acc - 73% 88%
M-analysis 2014	N=357	>3cm 54 <3cm 73	89 47	<b>81</b> 89	<b>58</b>	<b>94</b>	AUC=0.87 AUC=0.7
G3 (A) -R 2018	N=90				<b>23</b>		TP - 24% FP - 77%

## The case of seminomatous RM

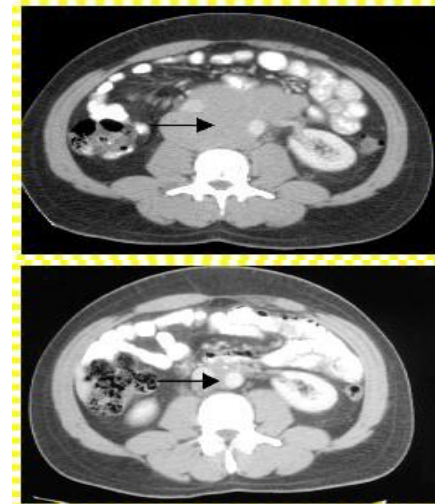
A PC RM in case of SGCT is very frequent (up to 80%)

Rate of vital disease rarely exceeds 10%

RM shape is irregular, very frequently

Surgery is very difficult due to fibrotic scars and the complication rate is high

So far, the recommendation to surgery is very limited to very selected cases



Peterson et al BJUI 2009;104:176-8

Debateble indication →

Strong indication →

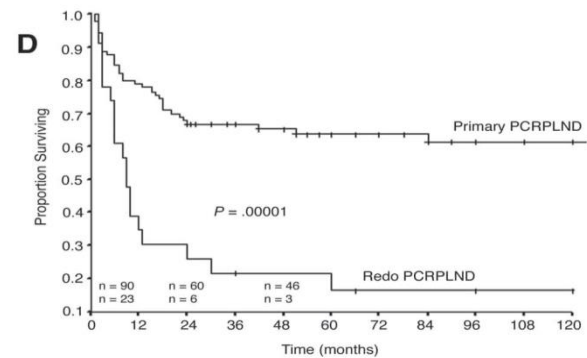
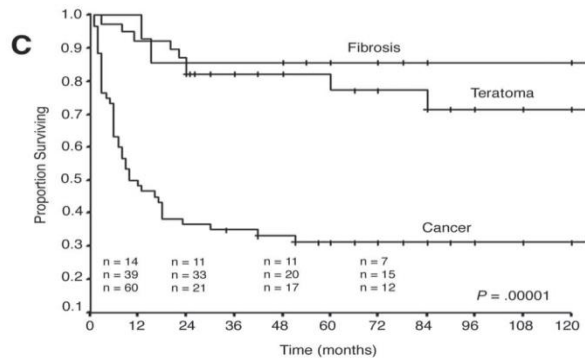
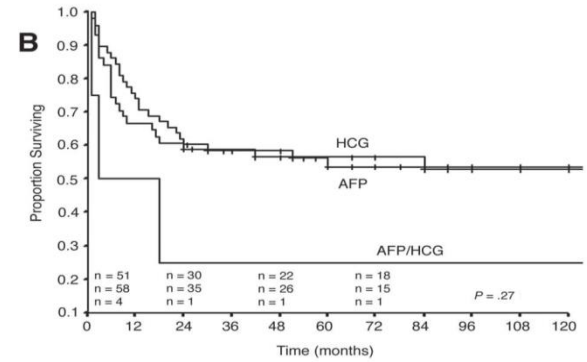
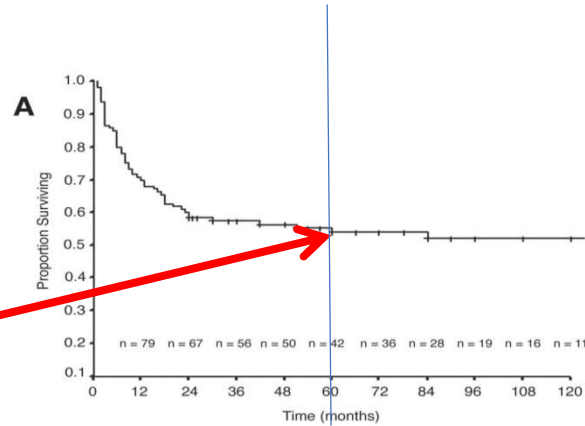
- **Nodular RM (usually of  $\geq 3$  cm) suspicious to contain viable disease (or teratoma!)**
- **RM of seminoma displaying initial AFP elevation (15/40 or 37.5% with viable cancer, 12/40 or 30% with teratoma)**

Mosharafa AA, et al, J Urol 2003;169(6):2126-8

# Salvage RPLND

Surgery performed in case of non-responsive disease (e.g. raised markers)

# 114 pts with elevated tumor markers at PC-RPLND  
 50 1<sup>st</sup> line  
 64 salvage  
 Period: 1977-2000  
**5-year OS: 53.9%**  
 61 (53.5%) alive at a medium FU of 72 mos





# Issues in L-PC-RPLND

- L-PC-RPLND may represent a standard if

It shows to be applicable in a significant (and probably increasing) proportion of patients with a residual mass (not a sequence of special performances)

It demonstrates a better tolerability profile than open PC-RPLND

Oncologic results are comparable with those of open PC-RPLND

Nicolai N et Al, J Endourol 2016, in press

## Available data in MI-RPLND

issue	Lap-RPLND	RA-RPLND	Comments
No of pts	323	57	Significant difference
Stage II B	183	na	Small to medium size residual masses in both techniques
Median size peCht	21-27 mm	na	
Median size pre RPLND	3-60 mm	12-70	
Histology FN/T/Ca	157/137/21	34/22/1	Usually favourable histology
FU	1-222 mos	1-58 mos	Short to medium for Lap, very short for RA
recurrences	8	0 or na	Few recurrences
OT	116-700 min	129-527 min	Similar OT
Major complications	13	na	Few complications in Lap
LAE	3.4%	na	Very low rate in Lap
HS	2-5	2-4	Similar duration

Lap-RPLND

Albqami 2005, Maldonado 2007,  
Permpongkosol 2009,  
Aufderklamm 2009, Steiner 2013,  
Nicolai 2016

RA-RPLND

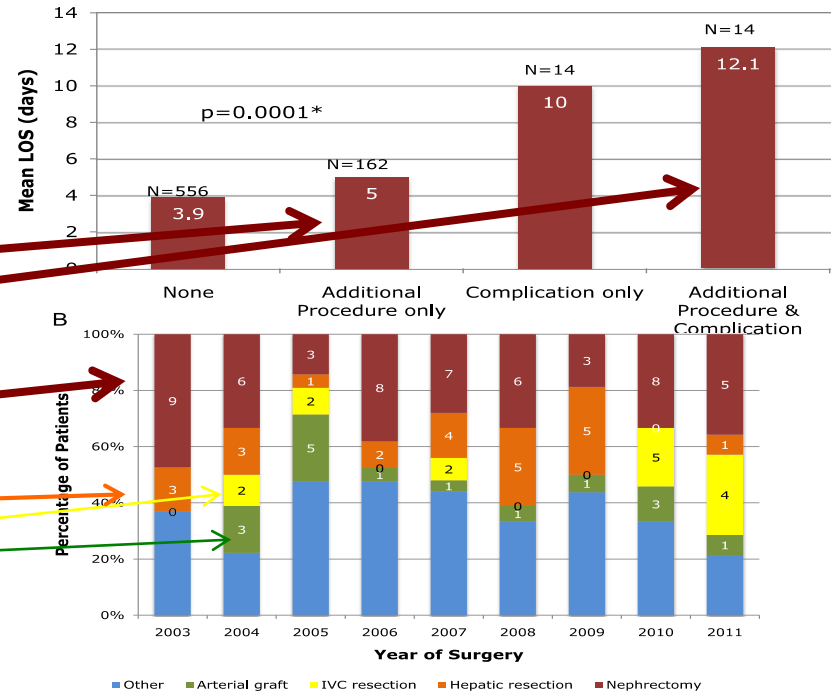
Annerstedt 2008, Kamel 2012, Cost  
2012, Cheney 2014, Harris 2015,  
Stepanian 2017, Singh 2017,  
Doumerc 2018

# Additional procedures (AP)

The concept of maximal surgery

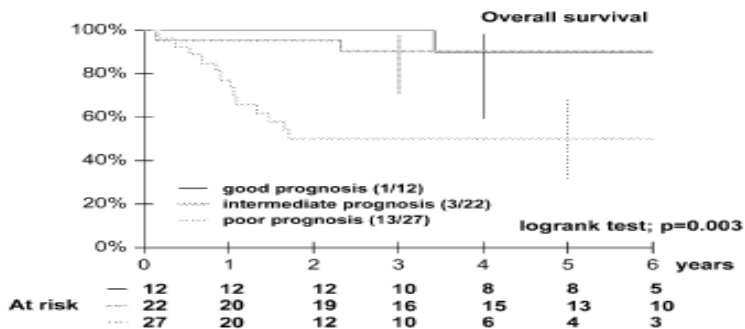
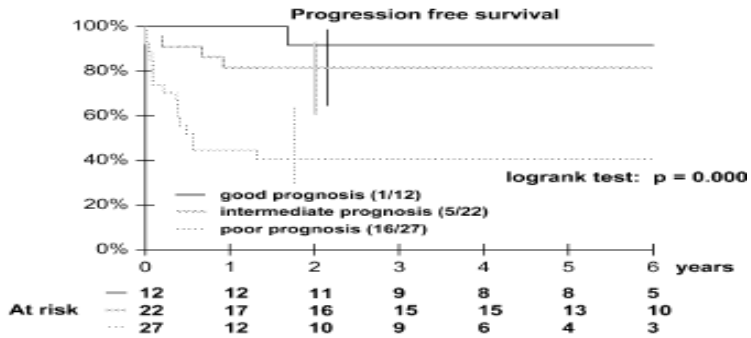
- An AP is required in about 20 to 30% of patients
- Risk Factors for AP: RM size (> 5 cm), histology (viable cancer) and raised markers
- An AP associated with longer hospital stay and complications
- The most frequent APs:
  - Nephrectomy
  - Hepatic resections
  - Vascular resections

• Heidenreich A et al, *Eur Urol* 2009;55:217-226  
 • Cary C et al, *Urol Oncol: Semin Origin Invest*, 2015; in press



## The concept of maximal surgery (2)

Prognostic factors in case of viable cancer



Fizazi K et al. *Ann Oncol* 19: 259–264, 2008

Viable Cancer proportion (%)  
 Risk Category (IGCCC)  
 Radicality



**Maximal Surgery**

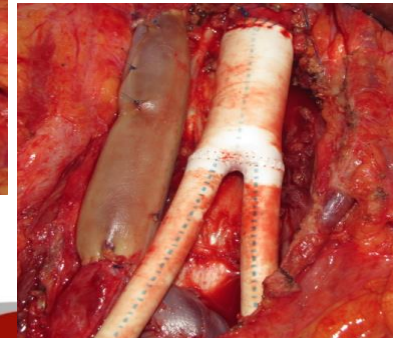
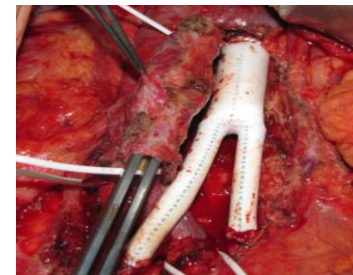
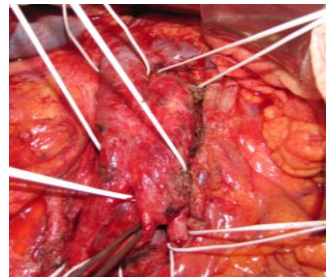
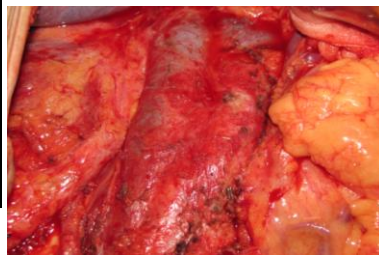
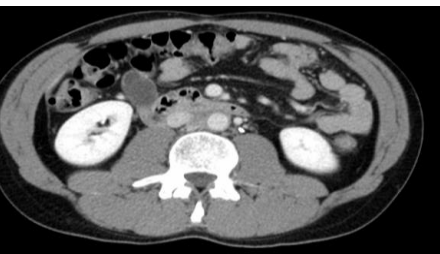
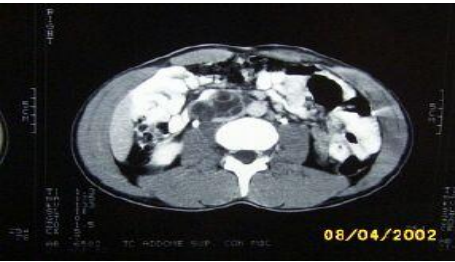
Most of the APs can be foreseen (but some not!)

An expert surgeons team is needed

*Heidenreich A et al, Eur Urol 2009;55:217-226*

*Cary C et al, Urol Oncol: Semin Origin Invest, 2015;33(9):389*

Standard RPLND



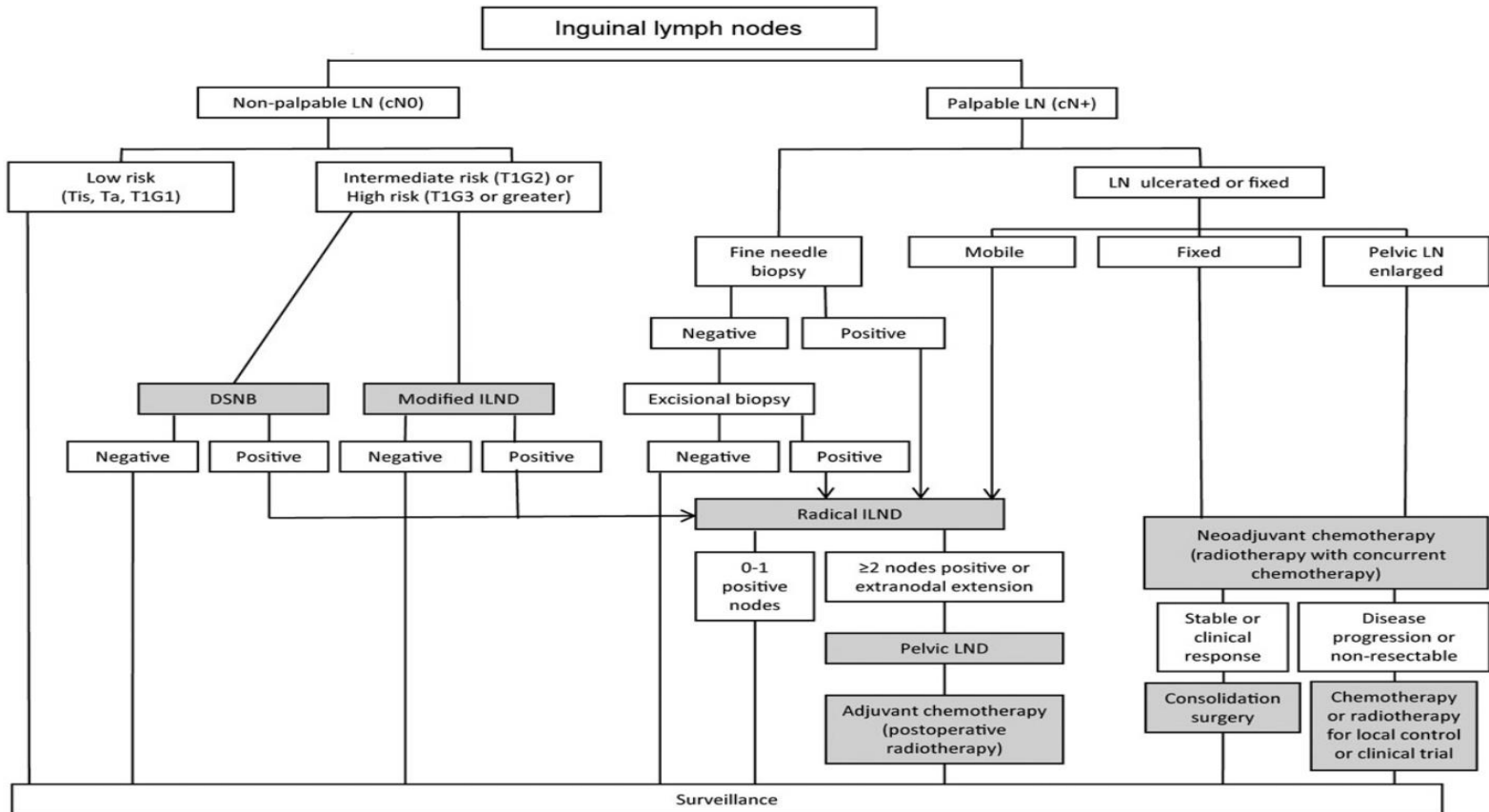
Maximal RPLND with aorta and IVC replacement following salvage therapy

# Penile carcinoma. The best sequence for nodal metastases

Current concepts

Regional lymph nodes	Management of regional lymph nodes is fundamental in the treatment of penile cancer	LE	GR
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	2a	B
	> T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or DSNB.	2a	B
	Palpable inguinal nodes (cN1/cN2)		
Fixed inguinal lymph nodes (cN3)	Radical inguinal lymphadenectomy.		
Pelvic lymphadenopathy	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.		
	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) and if extracapsular nodal metastasis (pN3) is confirmed.	2a	B
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	2b	B
Radiotherapy	Do not use for the treatment of nodal disease in penile cancer.		

## Palpable inguinal nodes (cN1-cN2-cN3)





## Palpable inguinal nodes (cN1-cN2)

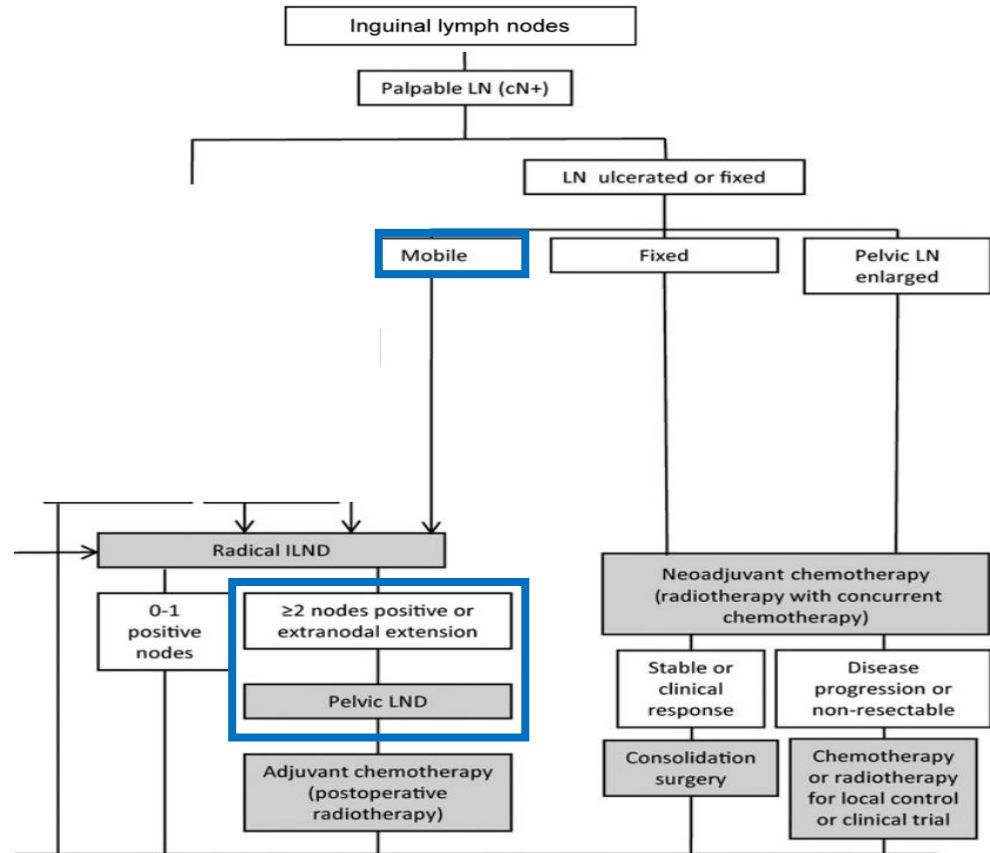
RISK factors for pelvic N+

ILN  $\geq 3$



57,1%

*H Van Poppel, Ann Oncol 2013  
 T Machado, J Urol 2007*



## Adjuvant chemotherapy in N+

### Which drugs?

RR 30% (cisplatin, bleomycin and methotrexate)

Leijte, Eur Urol 2007

Hakenberg, BJU Int 2006

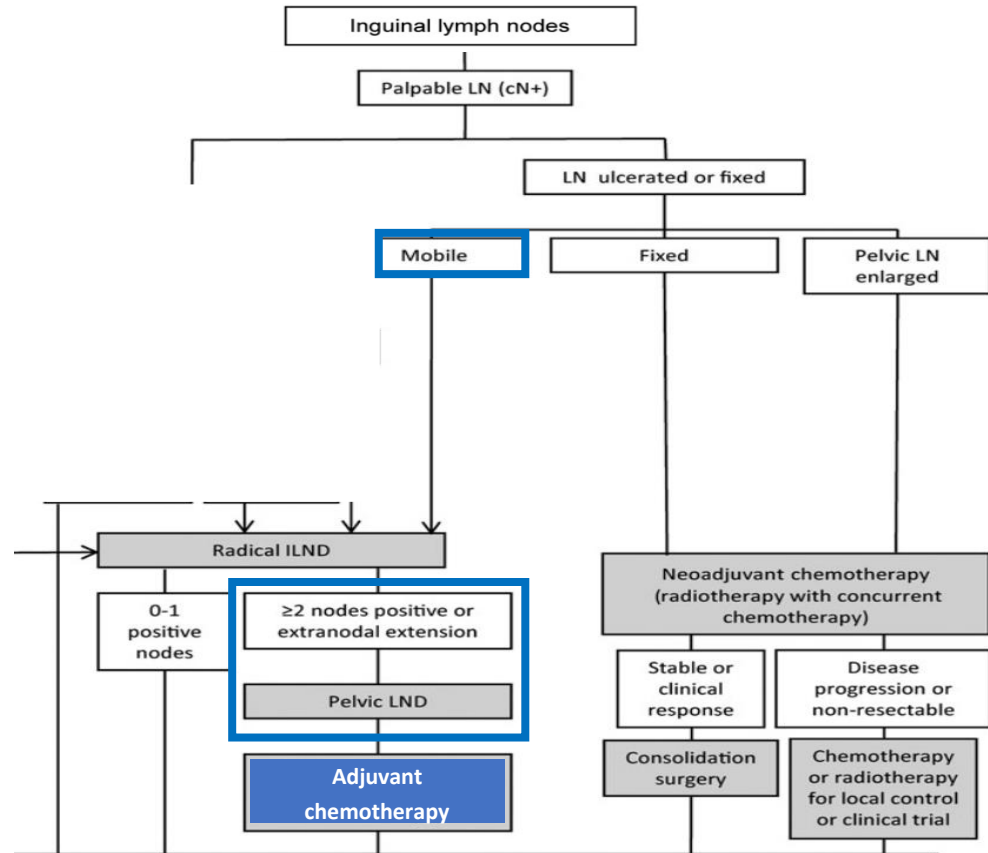


RR 38-50% (T-F or TIP)

Nicholson, Br J Cancer 2013

Nicolai, Clin Genit Cancer 2016

H Van Poppel, Ann Oncol 2013

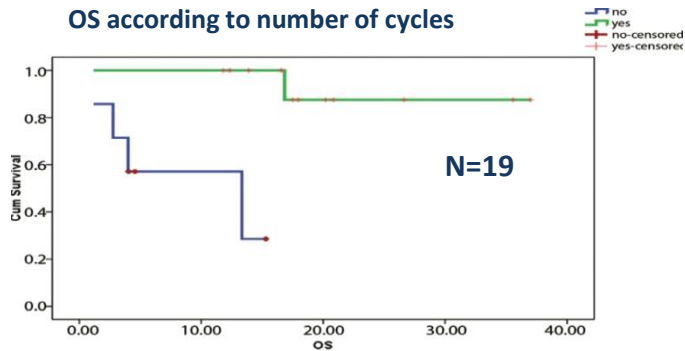


## Adjuvant chemotherapy in N+

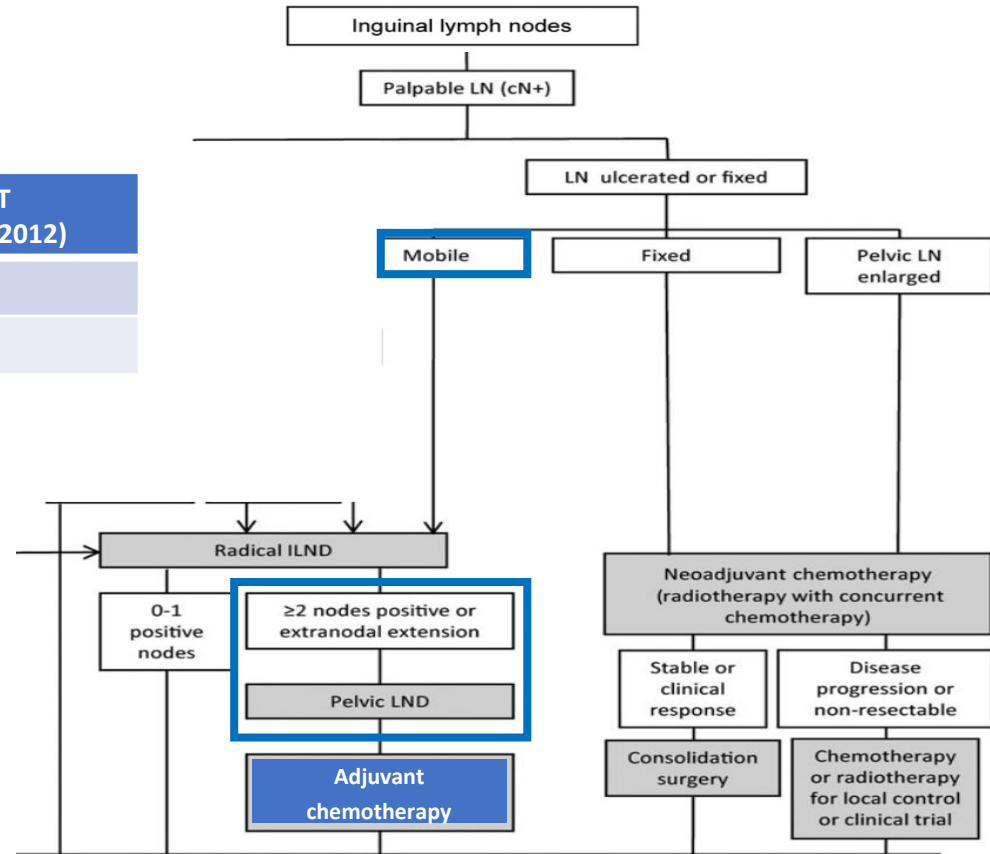
Two-year overall survival

	Only Surgery (Pandey 2006)	Adj CT (Noronha 2012)
Inguinal N+	53.1%	66%
Pelvic N+	28.6%	46%

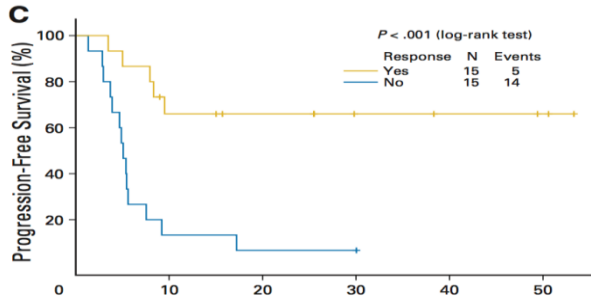
OS according to number of cycles



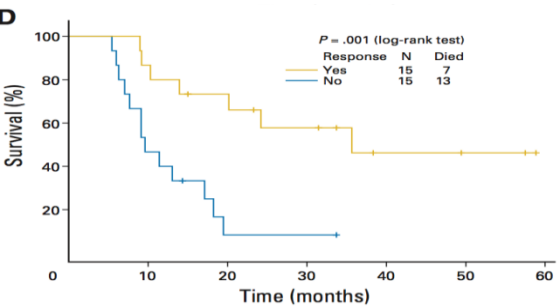
Pandey, *J Surg Oncol* 2006  
 Noronha, *Urol Annals* 2012



## Neo-Adjuvant chemotherapy in N+



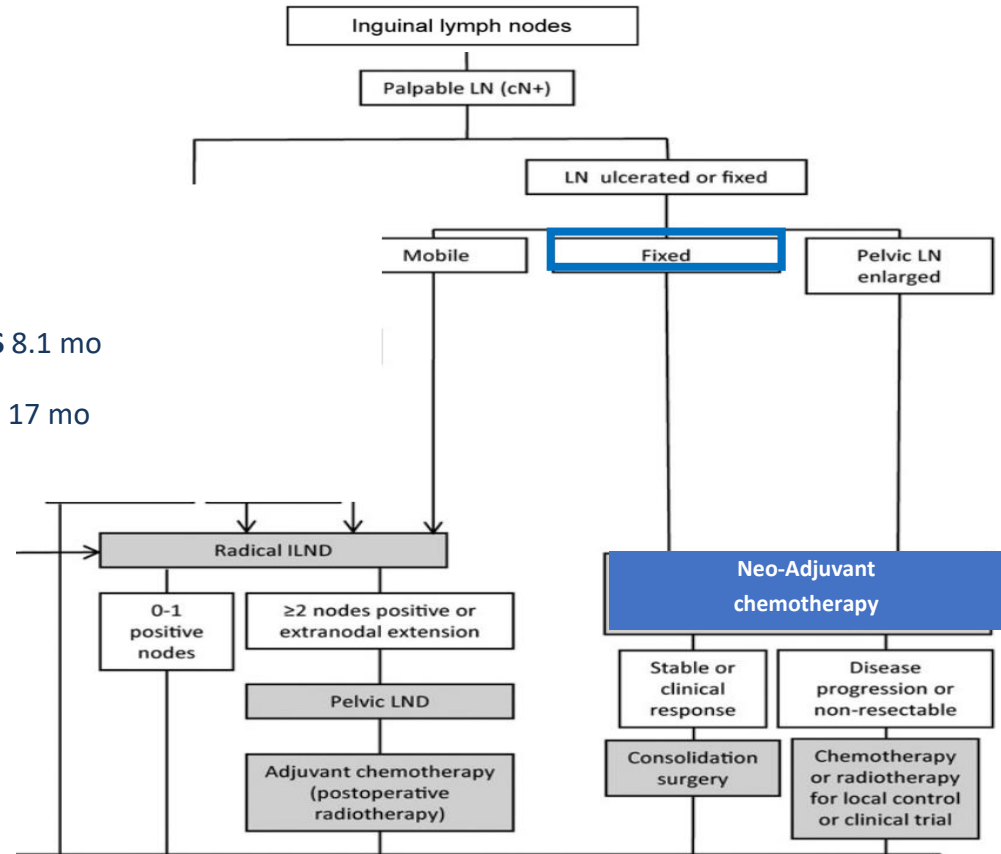
N=30



PFS 8.1 mo

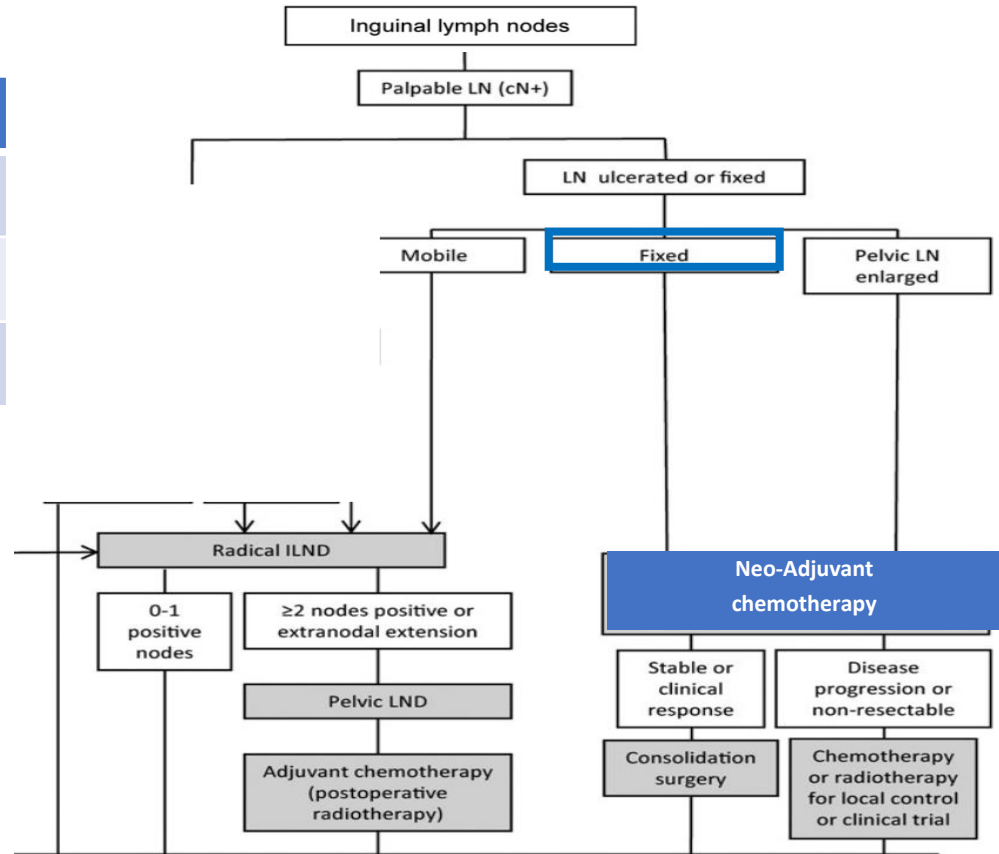
OS 17 mo

Pagliari, JCO 2010

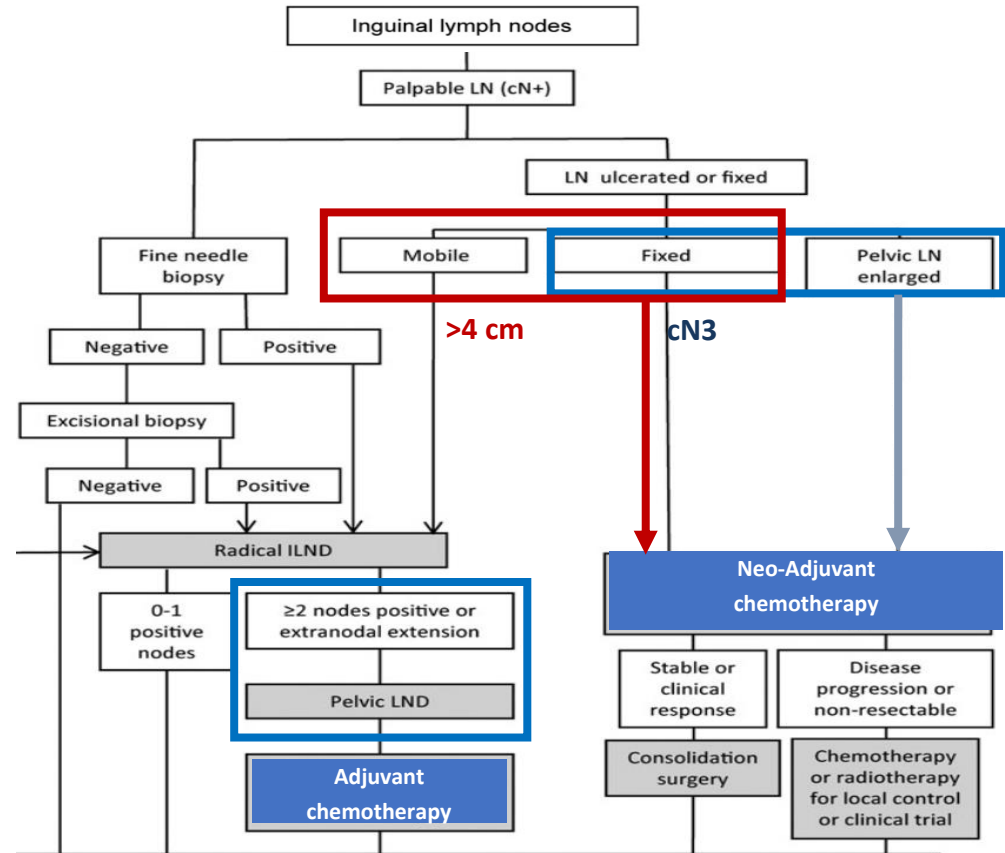


## Neo-Adjuvant chemotherapy in N+

	N	RR	pCR
Leijte 2007	20	63%	10%
Pagliari 2010	30	50%	13%
Nicolai 2016	28	43%	14%



## EAU vs NCCN guidelines

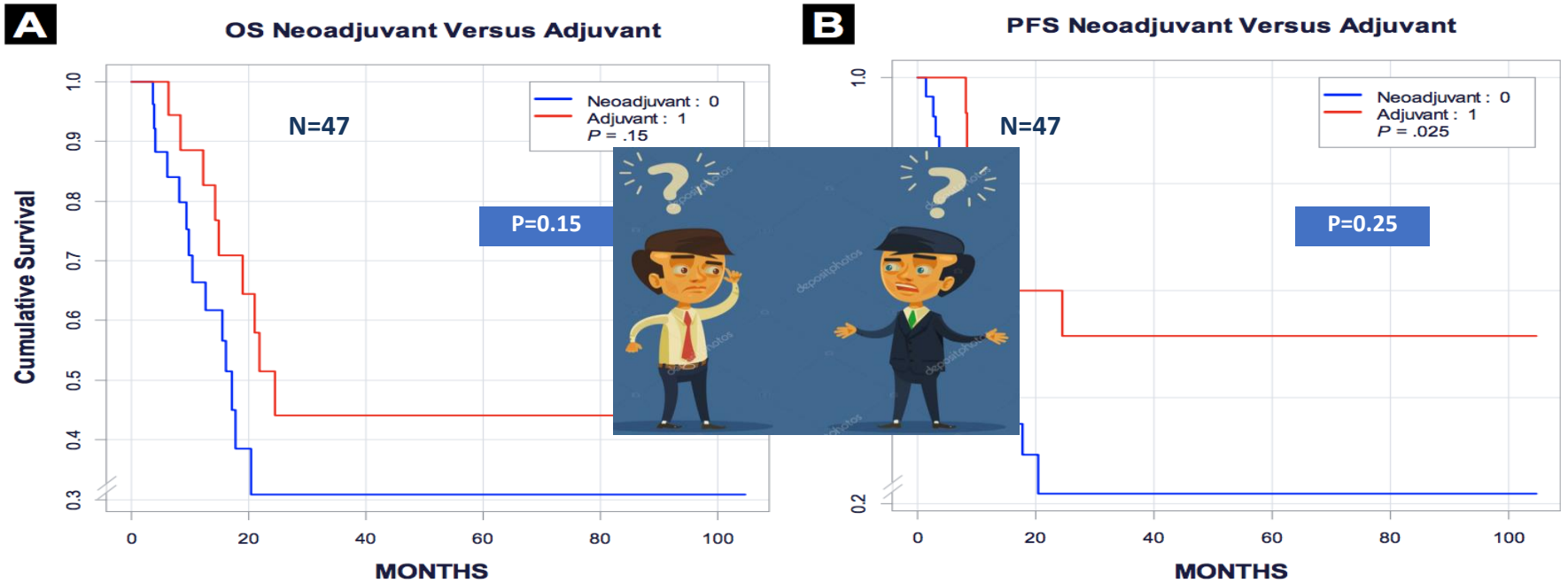


“There are no sufficient data to form conclusions about the use of adjuvant treatment”

*NCCN Guidelines Penile Cancer 2016*

*EAU Guidelines Penile Cancer 2016*

## Adjuvant vs Neoadjuvant chemotherapy



# Clinical cases

SIU-UPDATE June 22<sup>th</sup>, 2018

Testis tumour context





# Clinical presentation

Nov 2016

26 yrs old

Left testicular firm nodule (20 mm)

US: hypoechoic lesion on lower testis pole

STM: AFP 14 ng/ml

January 12 th, 2017

Elevated markers: AFP 242 ng/ml, beta-hCG 367

Left orchidectomy

Definitive pathology: postpubertal teratoma

# Clinical presentation

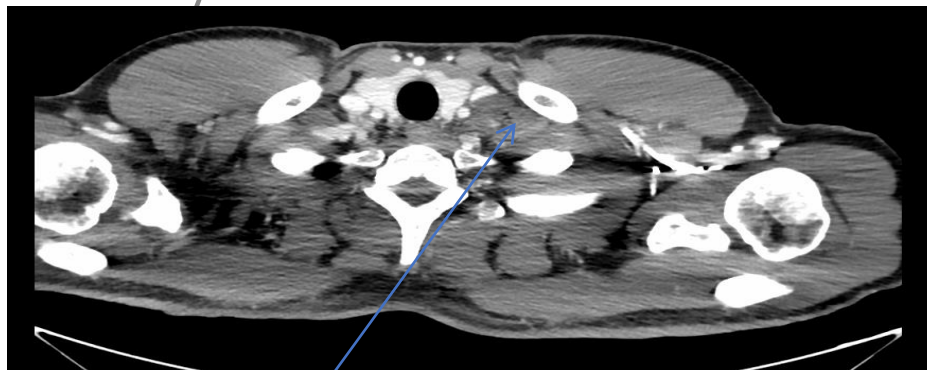
March 2017

AFP and beta-hCG reduced and then increased (AFP 390; beta-hCG 420; LDH N)

whole body CT scans



Two small paraortic enlarged lymph-nodes



One small left supraclavicular lymph-node



# Staging

- Stage pT1, cN2 M0 S1 (good risk)
- Stage II B positive markers

# Which therapy?

- Observation: check again until nodes are clearly larger than 3 cm
- First line chemotherapy
  - 3 courses of PEB
  - 4 courses of PEB
- Primary RPLND
  - Open bilateral
  - Miniinvasive unilateral

# Which therapy?

- Observation: check again until nodes are clearly larger than 3 cm
- **First line chemotherapy**
  - **3 courses of PEB**
  - 4 courses of PEB
- Primary RPLND
  - Open bilateral
  - Miniinvasive unilateral

# Actual therapy

- March 2017 → May 2017: 3 courses of PEB (BLM 9/9)
- Markers normalised after 2<sup>nd</sup> course
- Chest and abdominal CT scans

CT scans on July 18 th, 2017



Nodes enlarged of some mm



# What happened?

- Mixed response
- No response
- Progressive disease
- Complete biological response with a residual growing mass
- I do not know



# What to do?

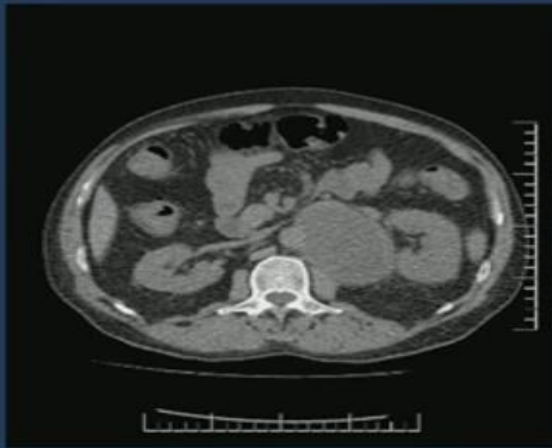
- Continue with another 1-3 courses of PEB
- Salvage Chemotherapy (VIP/TIP/High Dose)
- Surgery (RPLND and neck LND)
- Radiation therapy

# Surgery

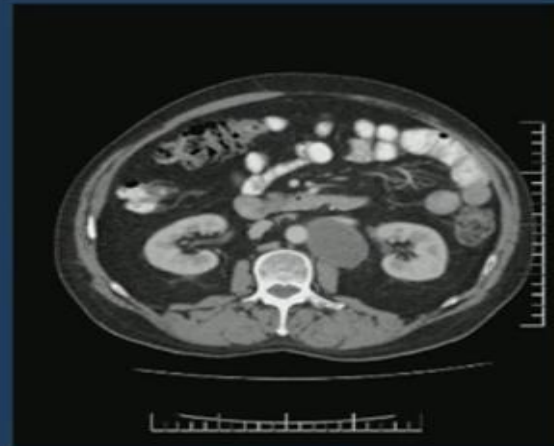
- 10.2017 Mini-invasive (laparoscopic) unilateral RPLND: postpubertal teratoma in 4/18 paraortic and iliac lymph-nodes
- Antegrade ejaculation maintained
- 1.2018 Neck LAD: postpuertal teratoma in 1/20 lymph-nodes

## 2<sup>nd</sup> case (from 2018 GU Symposium)

- Apr 2016 – Age 56, Abdominal Pain
  - CT Bulky Para-Aortic Mass
  - Markers Neg
  - Biopsy consistent with Seminoma
  - U/S testes negative
  - CT Thorax negative
  - Good Prognosis
    - BEP X 3 Completed June 2016
    - Repeat Imaging
      - Left PA Node 5.5 cm
      - Negative PET Scan



April 2016



Jul 2016

## Case # 3 What do you do next

- A. 2 more cycles of BEP
- B. Radiation Therapy
- C. RPLND
- D. Observation

## Case # 3 What do you do next

- A. 2 more cycles of BEP
- B. Radiation Therapy
- C. RPLND
- D. Observation



- A 2%
- B 11%
- C 32%
- D 55%

## Case # 3 What do you do next?

- A. 2 more cycles of BEP
- B. Radiation Therapy
- C. RPLND
- D. Observation



- A 2%
- B 10%
- C 32%
- D 55%

**Clinical cases context and debate.  
Role of expert and referral centers for  
post-chemo surgery: when, which and  
where**

Caso clinico 3  
A.E. 1984

12.2013 Riscontro occasionale nodulo testicolare destro

**27.01.2014 TAC: linfonodo interaortocavale sottorenale 30x30mm**

02.2014 LDH 357, AFP 69, **betaHCG 488**

**10.02.2014 orchifunicolectomia destra con protesi.**

**E.I.:** Il didimo è quasi completamente occupato da

una neoplasia di 5,5 cm di asse maggiore, biancastra, emorragica e necrotica, limitata al didimo.

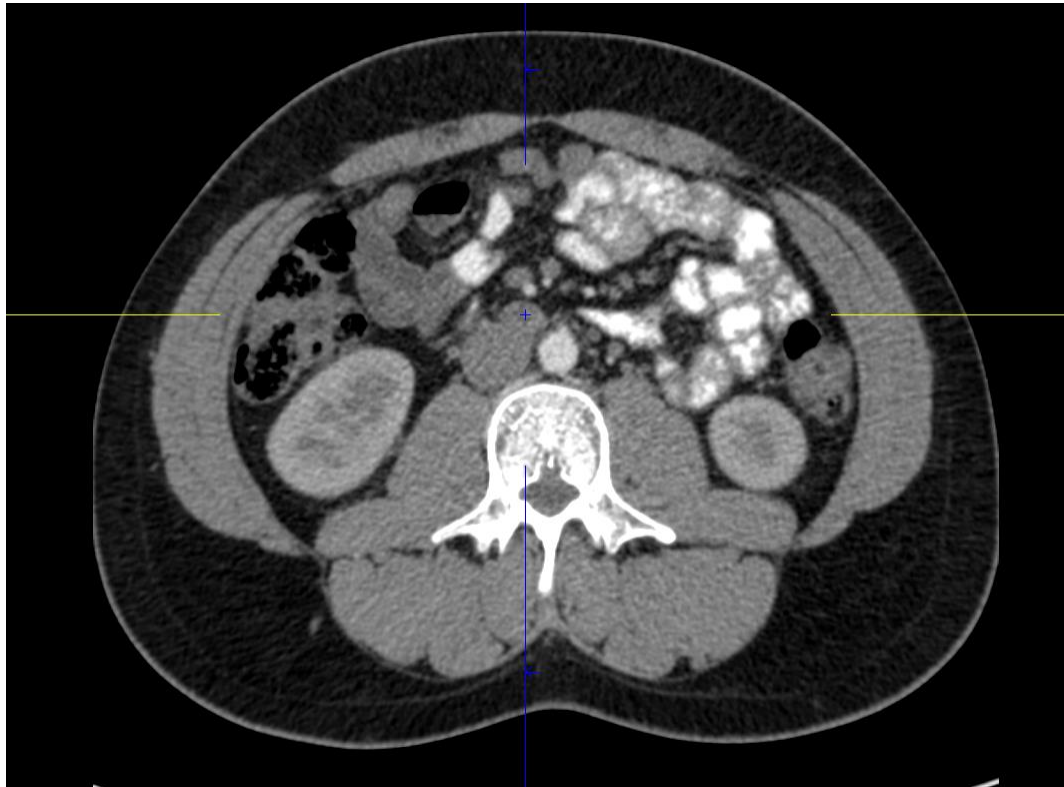
Diagnosi istopatologica:

**Carcinoma embrionario** estesamente necrotico-emorragico con prevalente pattern di crescita di tipo tubulo-ghiandolare e papillare. Rete testis ed epididimo esenti da neoplasia. **Assenza di invasione vascolare.**

**Staging: pT1 pNx**

**MDM: consigliata CT**





10.03.2014 **betaHCG 1298**

Dal 10.03.2014 al 23.05.2014 **4 cicli di PEB**

23.05.2014 Markers neg

**10,07,2014 TAC: linfonodo retroperitoneale  
ridotto a 23x16mm**

**MDM**

**05,08,2014 open RPLND: E.I. focolai  
teratoma cistico**

Da allora FU neg



Caso clinico 4  
D.M. 1990

08.2017 Riscontro occasionale aumento testicolare sinistro

**05.10.2017 TAC: linfadenopatia lomboaortica 3.6cm sottorenale**

19.10.2017 LDH 280, **AFP 92, betaHCG 3,3**

**24.10.2017 orchifunicolectomia sinistra con protesi.**

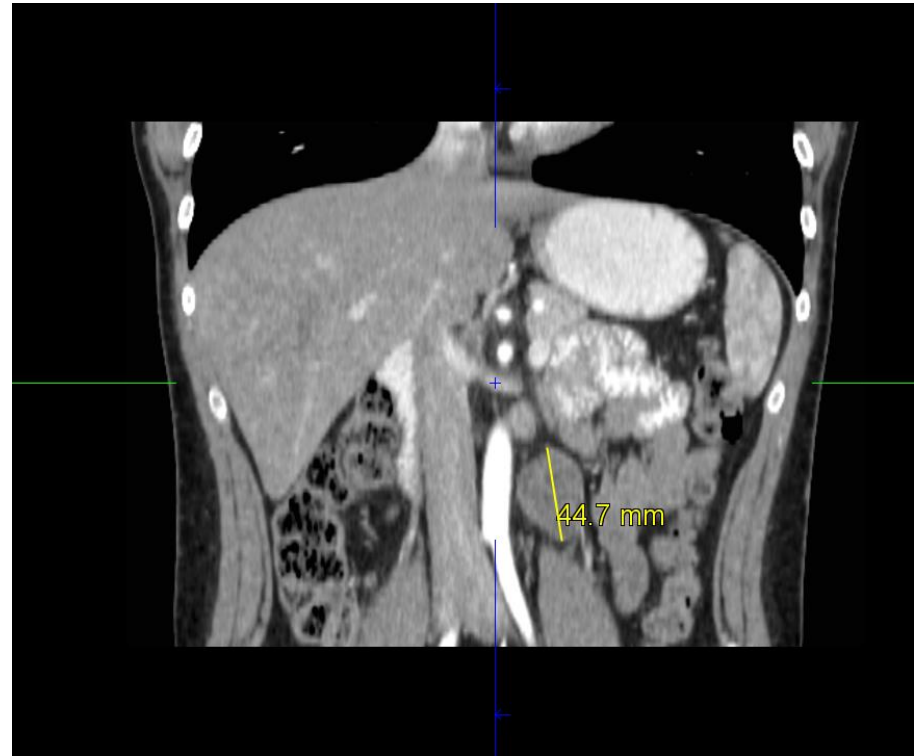
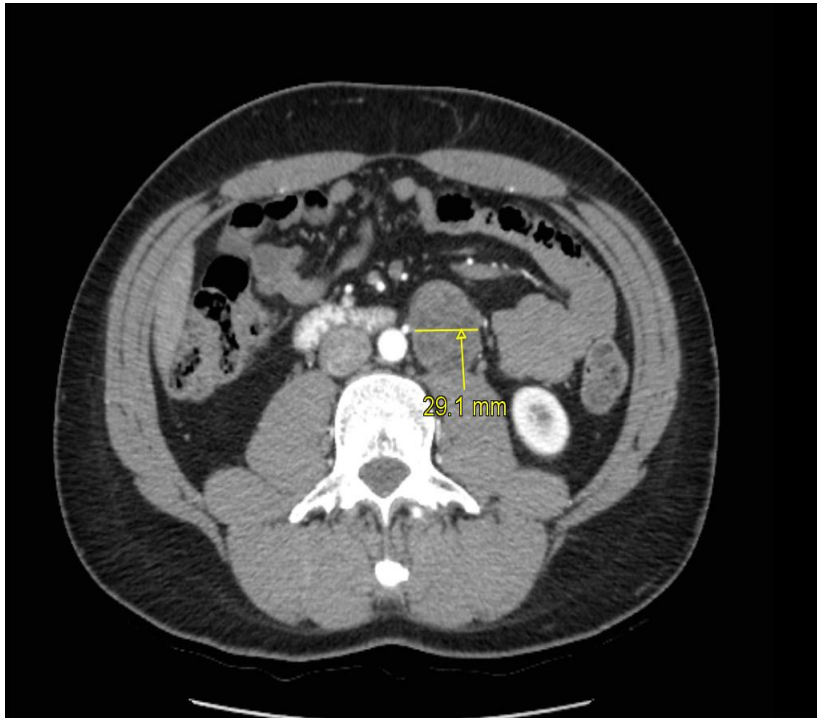
**E.I.:** Testicolo di 5,3x3,5x3 cm con una neoplasia di 3,9 cm di asse maggiore, in parte solida ed in parte microcistica, focalmente emorragica, limitata al parenchima testicolare.

Diagnosi istopatologica:

**A) Tumore a cellule germinali misto limitato al testicolo, con prevalente componente di carcinoma embionario (75%)** associata a ridotta componente di **teratoma postpuberale (20%)** con focolaio di atipia (c.d.: teratoma immaturo) ed a focale tumore del sacco vitellino (5%) associati a neoplasia germinale in situ, necrosi e di focale diffusione pagetoide alla rete testis. Tonaca albuginea esente da neoplasia. **Assenza di invasione vascolare**

Staging: pT1 pNx

**MDM: consigliata CT**



**28.11.2017 AFP 185, betaHCG 1,2**

Dal 28.11.2017 al 14.01.2018 **3 cicli di PEB**

**19.02.2018 Markers neg**

**26.02.2018 TAC: linfadenopatia paraortica sinistra di 30mm di asse corto**

**MDM**

**05.08.2014 RA- RPLND:**

**E.I.:** A) Nodulo solido-cistico di 4,8 cm ed un frammento di tessuto adiposo di 7 cm da cui si isolano B) dodici linfonodi antero e para-aortici.

**Diagnosi istopatologica:**

**A) Metastasi di tumore delle cellule germinali del testicolo in forma di teratoma.**

Istiocitosi dei seni nei linfonodi esaminati

# Clinical cases

SIU-UPDATE June 22<sup>th</sup>, 2018

Penis tumour context



- 66 yrs old
- Glans lesion treated with corticosteroid for three months
- Rapid growth in one month
- Appearance of bilateral groin masses
- Comorbidities: smoker (20 per day), mild diabetes, mild hypertension



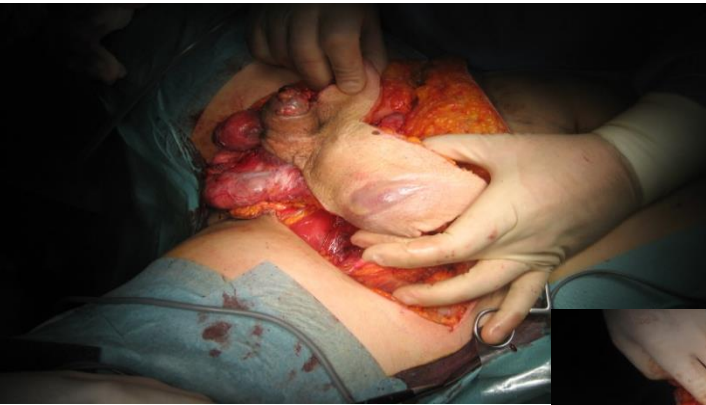


# What to do?

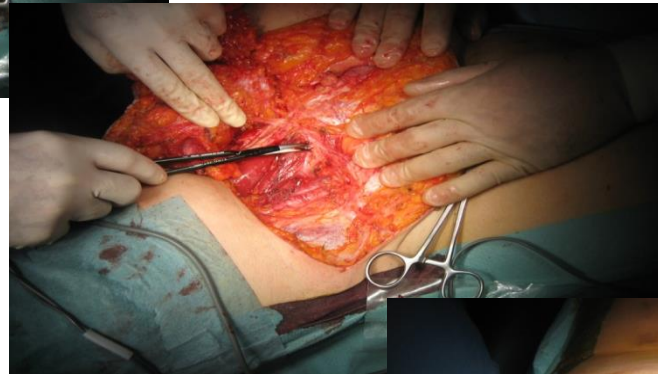
- Primary chemotherapy
- Clinical trial
- Chemotherapy followed by RT
- Primary surgery
  - Amputation and groin dissections
  - Amputation, groin and pelvic dissection
  - Emasculation and inguinopelvic dissection

# What to do?

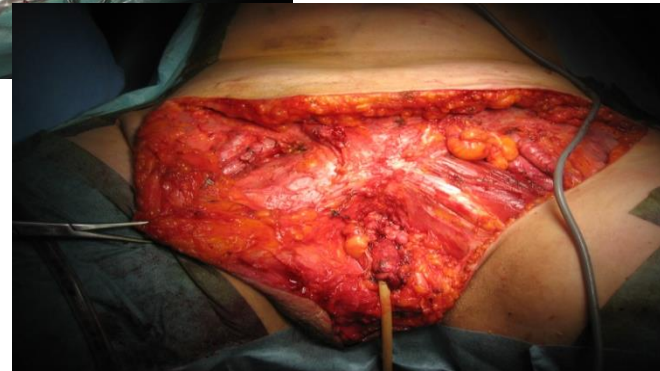
- Primary chemotherapy
- Clinical trial
- Chemotherapy followed by RT
- Primary surgery
  - Amputation and groin dissections
  - Amputation, groin and pelvic dissection
  - **Emasculatation and inguinopelvic dissection**



En-bloc excision of primary tumour (total amputation),  
Bilateral orchiectomy, skin and left groin mass



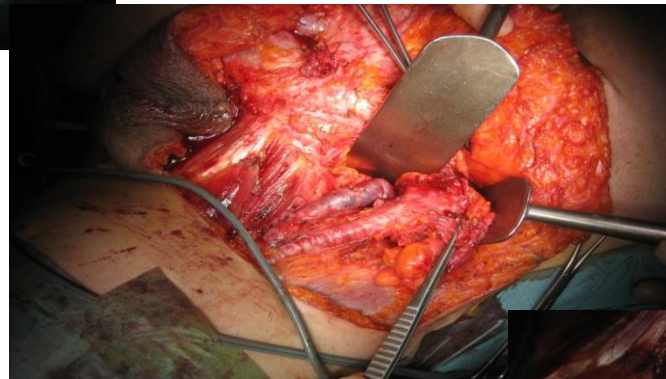
Completion of inguinal LND



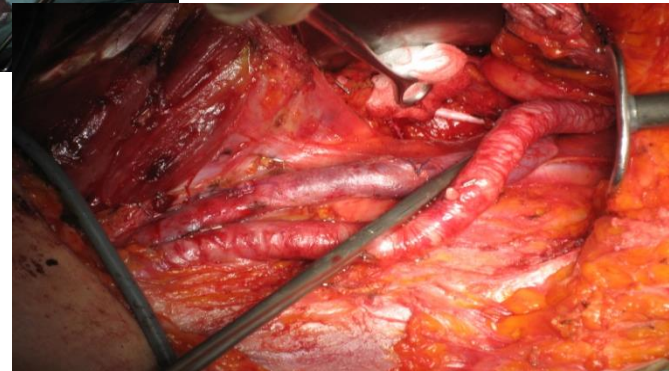
Final aspect of  
bilateral ILND and  
emasculation



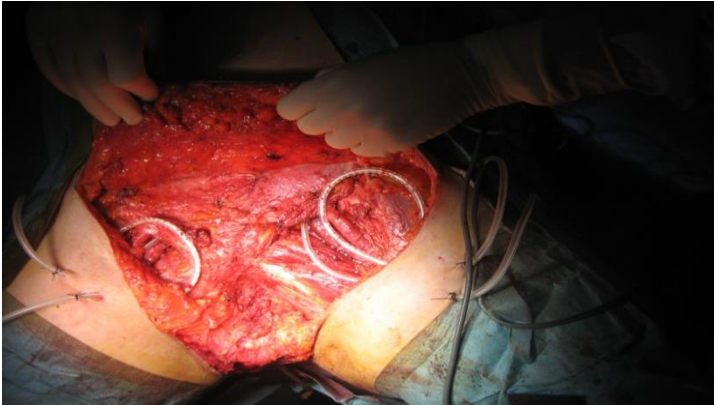
Pelvic LND



Pelvic LND



Final aspect of  
pelvic LND



End of intervention and closure



**Which is the best sequence for nodal metastases from penile carcinoma?**

**CASE 2  
PENILE SCC WITH SINGLE PALPABLE NODE  
(cN1)**

**Staging**

Inguinal ultrasound: positive node on the right side.  
Chest + abdomen CT: negative.

**Management**

- ✓ Glansctomy
- ✓ Bilateral inguinal lymph node dissection.

**Pathology**

Squamocellular carcinoma, involving the corpus spongiosum (max depth 6 mm) with peritumoral vascular invasion. Free surgical margins.  
Node metastasis in **1/15 nodes** (right side)

Staging: **pT2 pN1**

Grading: **G2**



## Which is the best sequence for nodal metastases from penile carcinoma?

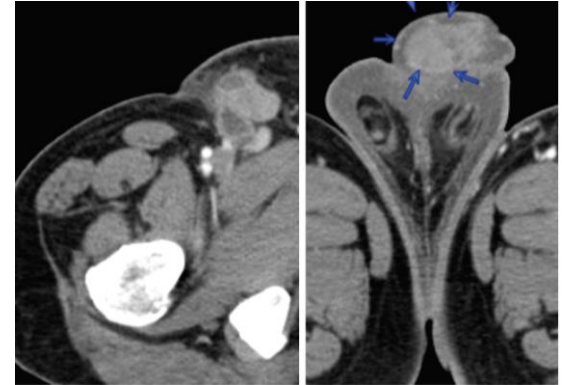
### CASE 3 - PENILE SCC WITH FIXED NODES (cN3)

#### Physical examination

- ✓ Necrotic lesion involving the glans penis.
- ✓ Large, fixed, palpable nodes involving both inguinal regions.

#### Staging

- ✓ Inguinal ultrasound: bilateral enlarged nodes.
- ✓ Chest + abdomen CT  
chest: negative;  
gross bilateral inguinal adenopathies.
- ✓ PET/CT scan  
positive inguinal nodes bilaterally;  
no pelvic positivities.



**Which is the best sequence for nodal metastases from penile carcinoma?**

**CASE 3 - PENILE SCC WITH FIXED NODES (cN3)**

**Management – Step 1**

Neoadjuvant chemotherapy with **paclitaxel, ifosfamide and cisplatin**.  
→ Objective and radiologic response.



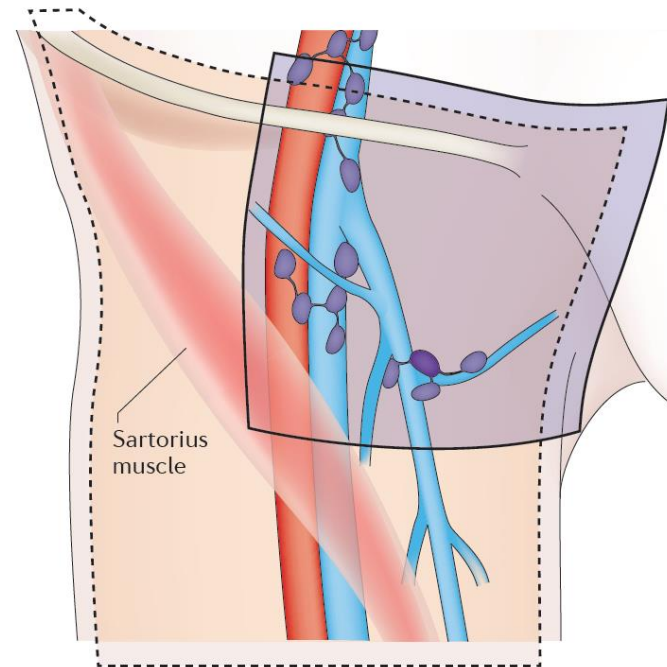


## Which is the best sequence for nodal metastases from penile carcinoma?

### CASE 3 PENILE SCC WITH FIXED NODES (cN3)

#### Management – Step 2

- ✓ **Glansectomy**
  - intraoperative positive margins
  - **radical penectomy with perineal urethrostomy**Squamocellular carcinoma involving the distal urethra and both corpora cavernosa.  
**pT3 G3**
  
- ✓ **Radical bilateral inguinal lymphadenectomy**
  - 3/11 positive nodes on the right side
  - 2/15 positive nodes on the left side**pN2**



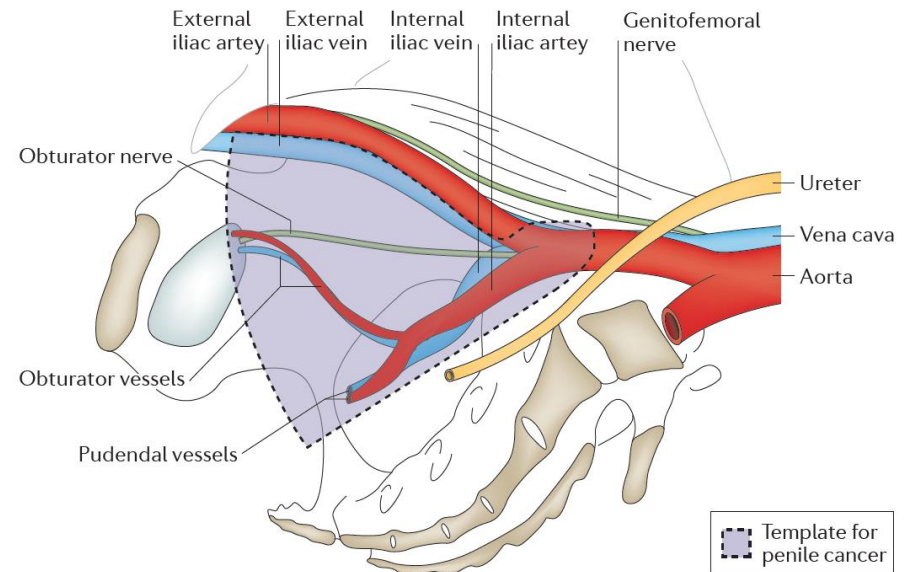
Standard groin dissection      Modified groin dissection

**Which is the best sequence for nodal metastases from penile carcinoma?**

**CASE 3  
PENILE SCC WITH FIXED NODES (cN3)**

**Management – Step 3**

Bilateral pelvic lymph node dissection  
→ **25 negative nodes**



# Conclusions

## Testis Cancer

mi-RNAs may represent a new device for staging and FU of markers negative GCT of the testis (80% of S and 40% of NS)

Post-chemo RPLND should be performed in referral centres.

RPLND is not usually indicated in seminoma

MI-RPLND is admitted in selected situations.

Maximal surgery must be planned prior to surgery with multidisciplinary surgical team.

## Penile Cancer

Systemic chemotherapy (CHT) has a moderate efficacy and displays a relevant toxicity. 'New' drugs (Vinflunine) are awaited in this setting.

Neo-adjuvant CHT is active in inducing responses and adjuvant CHT maintains complete remissions in some N+ case. Surgery remains the milestone of treatment in N+ patients and neo-adjuvant or adjuvant chemotherapy should be considered according to resectability and following final histology.



Thanks to



## Panelists

**Prof. Ottavio De Cobelli, IEO Milano**

**Dott. Giovanni Rosti, Policlinico San Matteo Pavia**

**Dott. Simona Secondino, Policlinico San Matteo Pavia**



**Raffaella Longhi**

**Federica Baldrighi**

**Andrea Canton**



**Società Italiana di Urologia**

*Dott. Nicola Nicolai, INT Milano*