

# RPLND for early stage GCTs: Minimizing Treatment related Morbidity

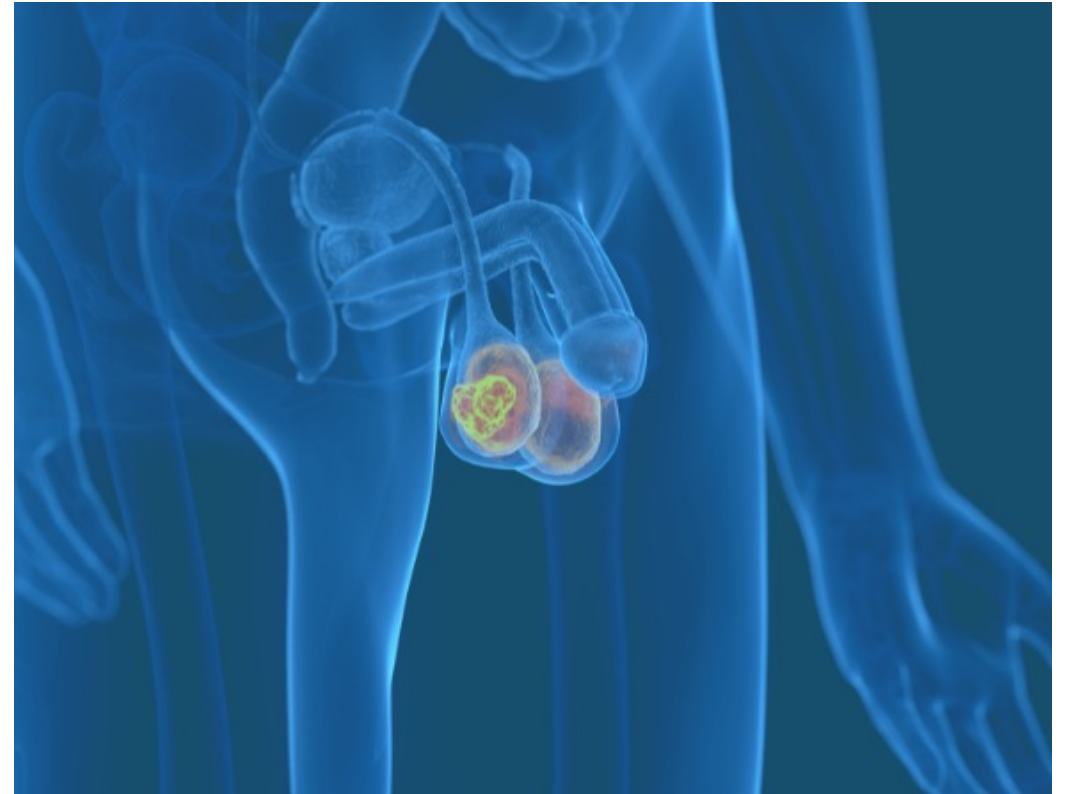
- ADITYA BAGRODIA
- ASSOCIATE PROFESSOR OF UROLOGY
- UC SAN DIEGO
- GU ONCOLOGY TEAM LEADER
- BAGRODIA@HEALTH.UCSD.EDU



@adityabagrodia

## Testicular cancer

- Most life years lost for nonpediatric cancers
- Most common cancer in men between 18-45
- 10,000 new cases/year
- 460 deaths/year



@adityabagrodia

# Testicular cancer shrouded in uncertainty

- Diagnosis
- Stage I disease: **Who will relapse?**
- Stage II:
  - **pN0?**
  - **Develop metastases?**
- Post-chemo NSGCT/seminoma
  - **Fibrosis necrosis only?**



@adityabagrodi

# Testicular Germ Cell Tumors

**Paramount to minimize toxicity while maintaining excellent oncologic outcomes**



[@adityabagrodia](https://twitter.com/adityabagrodia)

# Outline

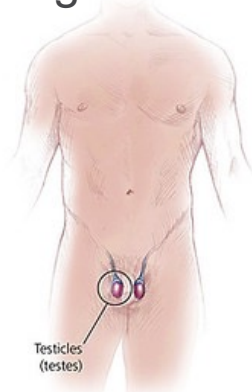
- **Clinical Scenarios (Stage I and Stage II disease)**
- **Introduction to microRNAs for GCT diagnostics**
- **Clinical application across the GCT spectrum**

Pre-orchietomy



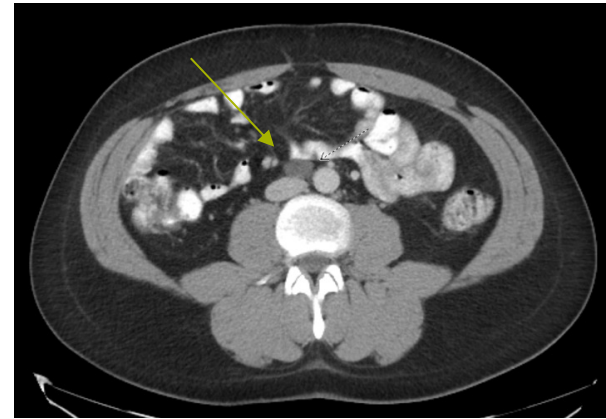
5

Stage I disease

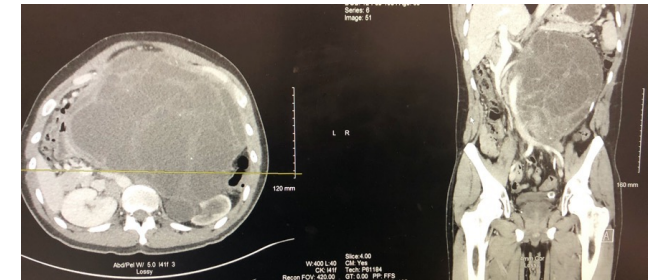


Stage 1

Stage II disease



Post-chemotherapy



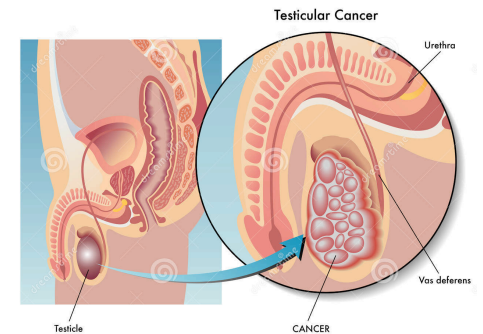
# 5 year survival of patients with testis cancer

	<b>Seminoma</b>	<b>Proportion of cases</b>	<b>NSGCT</b>	<b>Proportion of cases</b>
<b>Stage I</b>	<b>99%</b>	<b>86%</b>	<b>95-99%</b>	<b>70%</b>
<b>Stage II</b>	<b>95%</b>	<b>7%</b>	<b>90%</b>	<b>20%</b>
<b>Stage III</b>	<b>80-85%</b>	<b>5%</b>	<b>70-80%</b>	<b>10%</b>

**THE BULK OF GCT PATIENTS  
HAVE EARLY STAGE DISEASE  
WITH EXCELLENT SURVIVAL**

# Stage I Seminoma

- **Healthy 23 yo male presents with painless enlarging left testis mass**
- **No Hx trauma, infection**
- **No prior Hx UDT**
- **Exam: large palpable firm mass involving left testis**
- **US: 6.5 cm hypoechoic lesion with ↑ flow on Doppler replacing most of left testis**
- **AFP 2; HCG 129**
- **Orchiectomy: 4.5 cm seminoma, + Rete testis invasion**
- **Markers normalize, imaging negative**

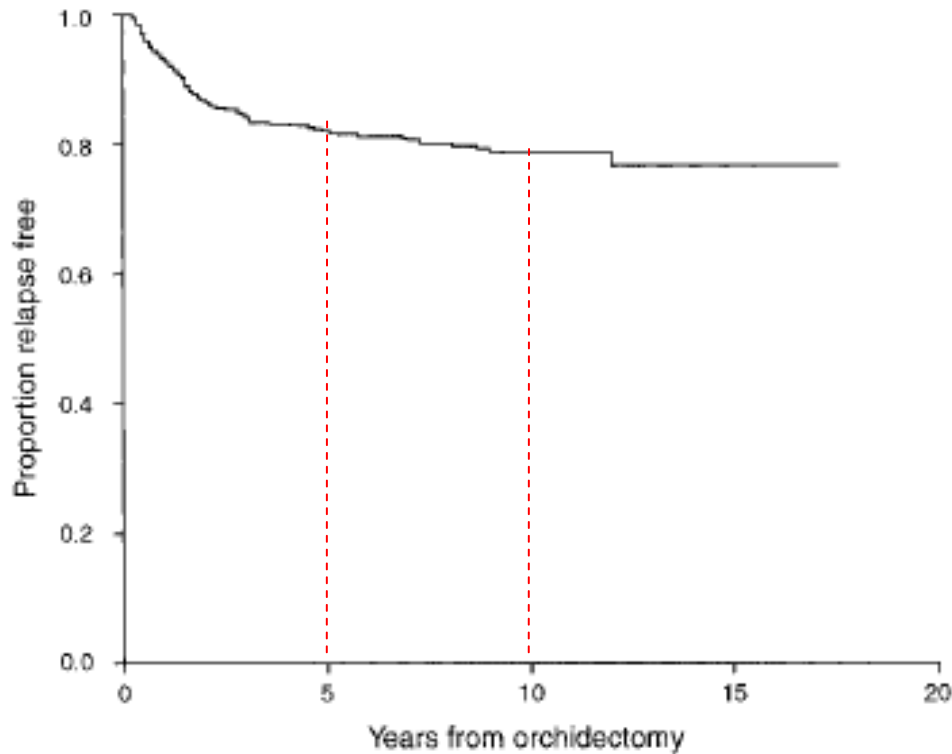




# Stage I Seminoma Treatment Principles

- **Survival approaches 100% independent of timing/type of treatment**
- **Treatment options**
  - **Surveillance**
  - **Single Cycle Carboplatin**
  - **Adjuvant Radiotherapy**
- **Adjuvant therapy “for all” over-treats vast majority of patients**
  - **& associated with acute and chronic toxicities**
- **Risk stratification?**
  - **Size**
  - **Rete testis invasion**

# Stage I Seminoma – Surveillance

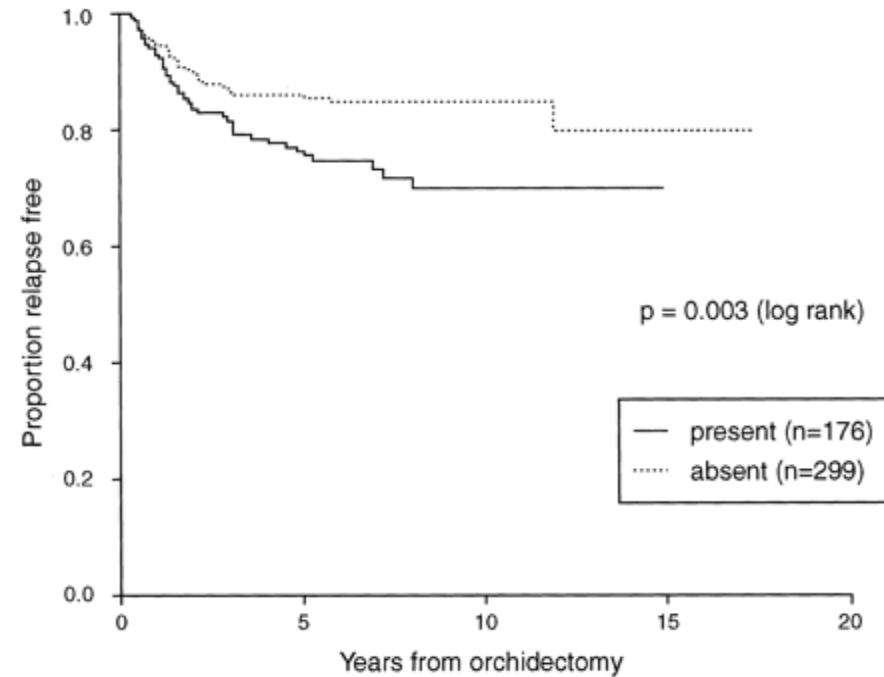
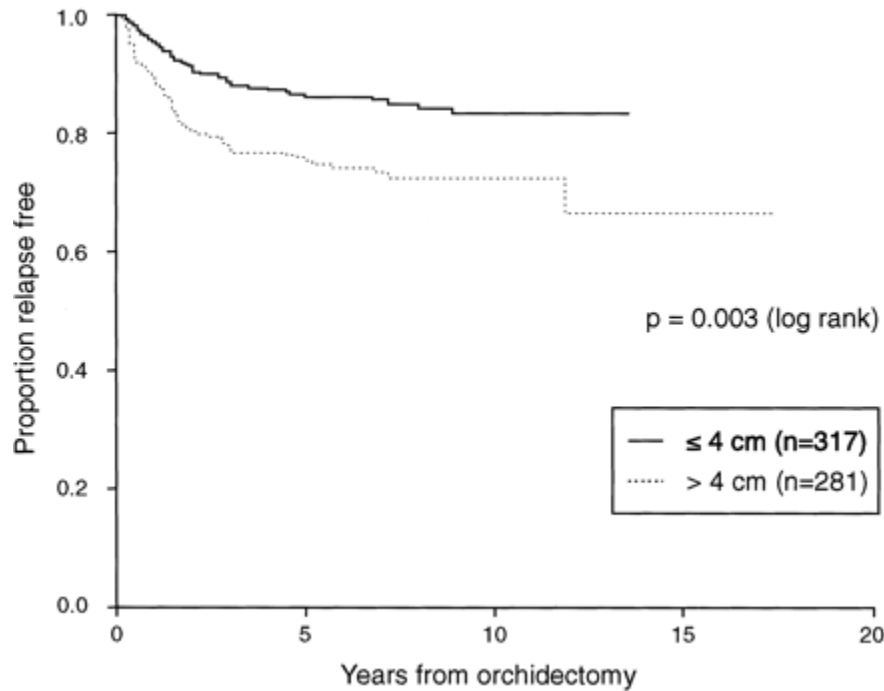


69% of relapses occurred <2 yrs  
7% of relapses occurred >6 yrs

Fig 1. Relapse-free rate for all cases from date of orchidectomy.

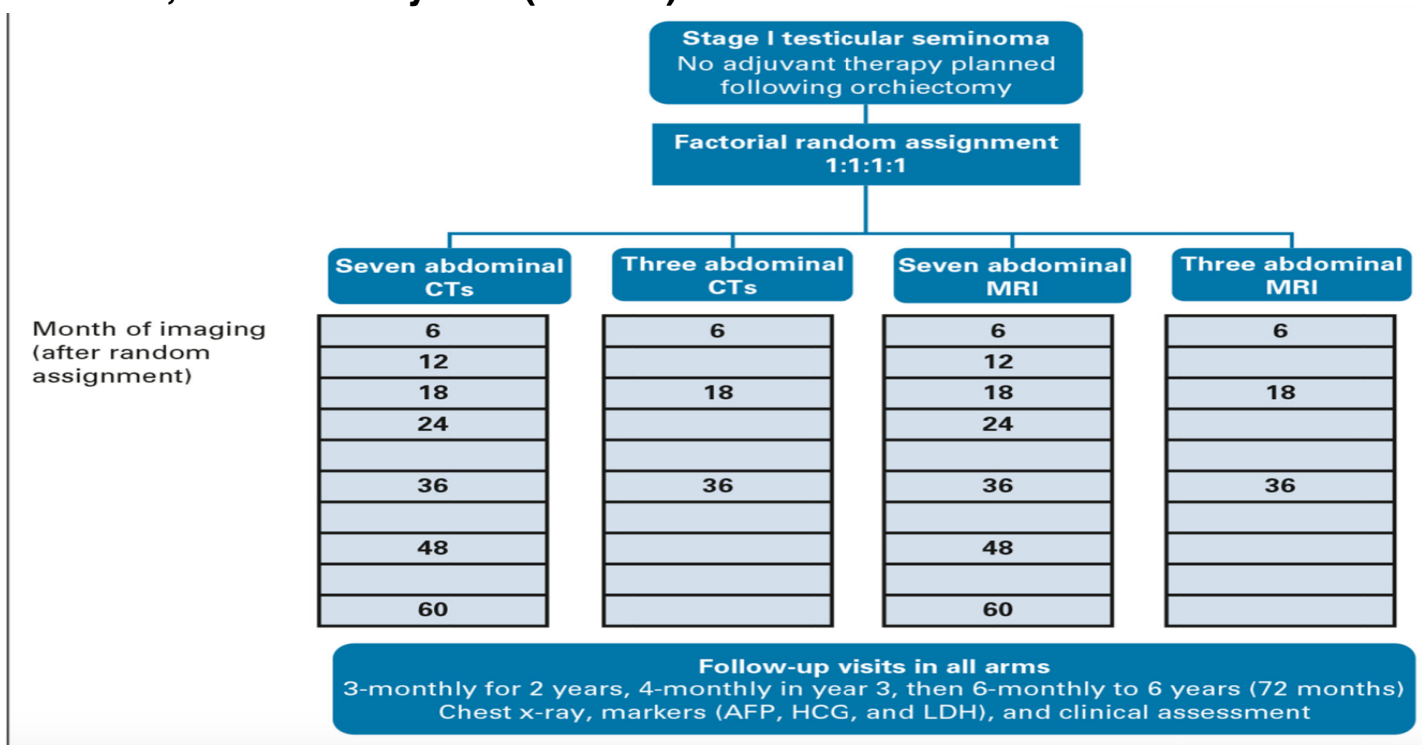
# Stage I Seminoma – Surveillance

**Tumor Size and Rete Testis involvement are risk factors for relapse**



# IMAGING ADVANCES: MRI

## Imaging Modality and Frequency in Surveillance of Stage I Seminoma Testicular Cancer: Results From a Randomized, Phase III, Noninferiority Trial (TRISST)



# TRISST trial

- Design and endpoint: Noninferiority RCT of stage I seminoma surveillance
- Primary endpoint: 6 year incidence of stage  $\geq$  IIC relapse

	3CT (n=166)	7 CT (n=169)	3 MRI (n=167)	7 MRI (n=167)
Relapse >IIC	8 (5.1%)	0 (0%)	1 (0.6%)	1 (0.6%)
Relapse >3cm LN	10 (6.4%)	3 (1.8%)	5 (3.1%)	6 (3.6%)

## Conclusions:

MRI not inferior to CT

3 scans not inferior to 7

**However: MORE recurrences w LN>3cm and stage  $\geq$  IIC with 3 CT.**

# AUA guidelines 2023: Surveillance for stage I seminoma

NCCN (2023)	Year (at month intervals)				
	1	2	3	4	5
H&P	Every 3-6m	Every 6m	Every 6-12m	Annually	Annually
CT ap or MRI	At 4-6, and 12m	Every 6m	Every 6-12m	Every 12-24m	
CXR	As clinically indicated, consider chest CT in symptomatic pts				



Stage I seminoma: updated surveillance schedule (AUA 2023)			
	Years 1-2	Years 3-5	> Year 5
H&P, CT A±P	Every 6m	Every 6-12m	If clinically indicated

# Stage I seminoma: Conclusions

- **Relapse is uncommon (~15%) all comers**
- **Excellent Outcomes with surveillance (treatment at relapse)**
- **In general, surveillance is recommended as the preferred option for stage I seminoma**



## NCCN Guidelines Version 1.2023 Testicular Cancer - Pure Seminoma

Stage  
IA, IB

Surveillance for pT1–pT3 tumors \_  
(strongly preferred)

or

Single-agent carboplatin<sup>k,l</sup>  
(area under the curve [AUC]=7 x 1.  
cycle or AUC=7 x 2 cycles)

or

Radiation therapy (RT)<sup>m</sup> \_\_\_\_\_  
(20 Gy or 25.5 Gy)<sup>n</sup>

# Stage IIA/B seminoma

**Radiation and chemotherapy are standard options for stage II seminoma**

- 30-36 Gy radiation
- Good-risk directed chemotherapy (BEPx3 or EPx4)

**Relapse-free survival at 5 years is excellent (95%)**

**20-30% of patients with clinically detectable nodes will be pN0 at RPLND**



# Another emerging concept for clinical stage II SEMINOMA



## CLINICAL STAGE<sup>w</sup>

Stage IIA

## PRIMARY TREATMENT<sup>o</sup>

RT to include para-aortic and ipsilateral iliac lymph nodes to a dose of 30 Gy<sup>r</sup> | →  
or  
Primary chemotherapy:<sup>z</sup>  
BEP<sup>aa</sup> for 3 cycles or EP for 4 cycles →

Stage IIB

Primary chemotherapy (preferred):<sup>z</sup>  
BEP<sup>aa</sup> for 3 cycles or EP for 4 cycles →  
or  
RT in select non-bulky (≤3 cm) cases to include para-aortic and ipsilateral iliac lymph nodes to a dose of 36 Gy<sup>r</sup> | →

RPLND for isolated <3cm retroperitoneal disease

1. European trials
2. US trial

# WHY RPLND?



**Survival**

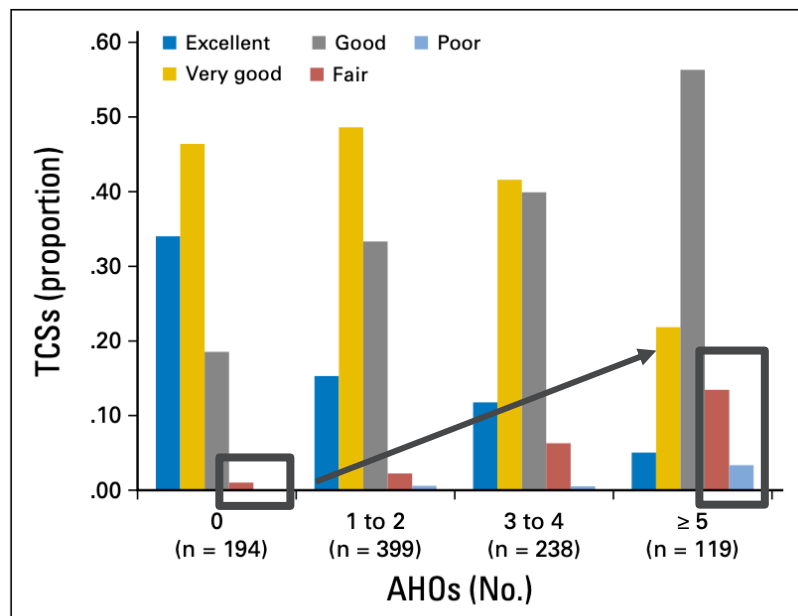
Primary Chemotherapy Primary Radiation	
Cardiac disease	Secondary Malignancies
HTN	Diabetes
Metabolic syndrome	Cognitive impairment
Secondary Malignancies	Anxiety/Depression
Ototoxicity	Hypogonadism/Fertility
Neurotoxicity	Pulmonary complications



**Survivorship**

## Multi-Institutional Assessment of Adverse Health Outcomes Among North American Testicular Cancer Survivors After Modern Cisplatin-Based Chemotherapy

Chunkit Fung, Howard D. Sesso, Annalynn M. Williams, Sarah L. Kerns, Patrick Monahan, Mohammad Abu Zaid, Darren R. Feldman, Robert J. Hamilton, David J. Vaughn, Clair J. Beard, Christian K. Kollmannsberger, Ryan Cook, Sandra Althouse, Shirin Ardeshir-Rouhani-Fard, Steve E. Lipshultz, Lawrence H. Einhorn, Sophie D. Fossa, and Lois B. Travis, for the Platinum Study Group



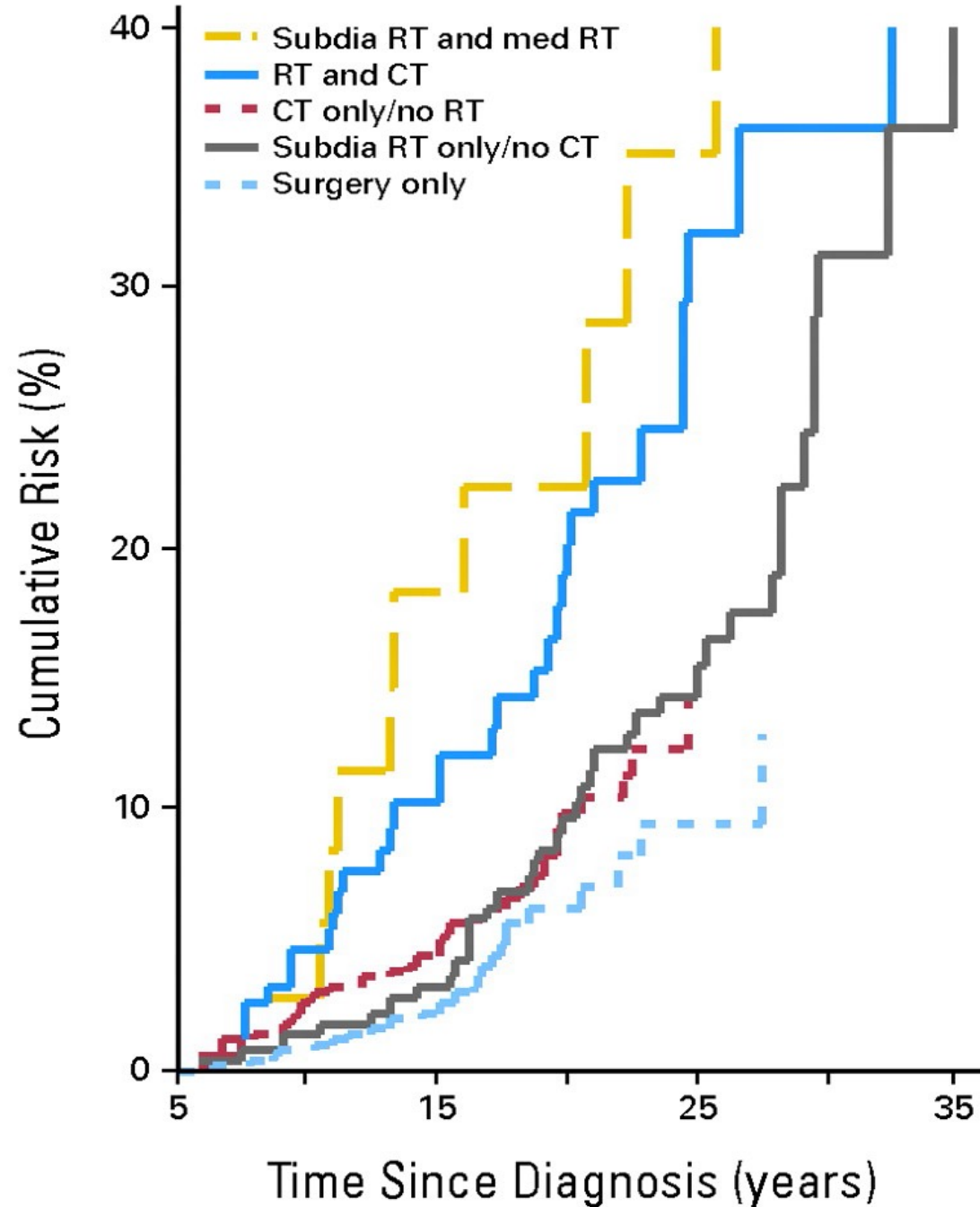
**Fig 1.** Proportion of testicular cancer survivors (TCSs) with excellent, very good, good, fair, and poor self-reported health by number of adverse health outcomes (AHOs). *P* value for association of number of AHOs with self-reported health was  $< .01$  (Mantel 1df  $\chi^2$  test of trend). Self-reported health was not indicated by one participant with one to two AHOs and one participant with three to four AHOs.

- 952 Testis cancer survivors treated with either BEPx3, BEPx4, or EPx4
- Median time since chemotherapy, 4.3 years
- 79.6% reported at least 1 Adverse health outcome
- Self-reported health Fair/Poor
  - 1% with No AHO vs. 16.8% with  $> 5$  AHO's

# Stage II seminoma

***Significant risk of long-term toxicity →***

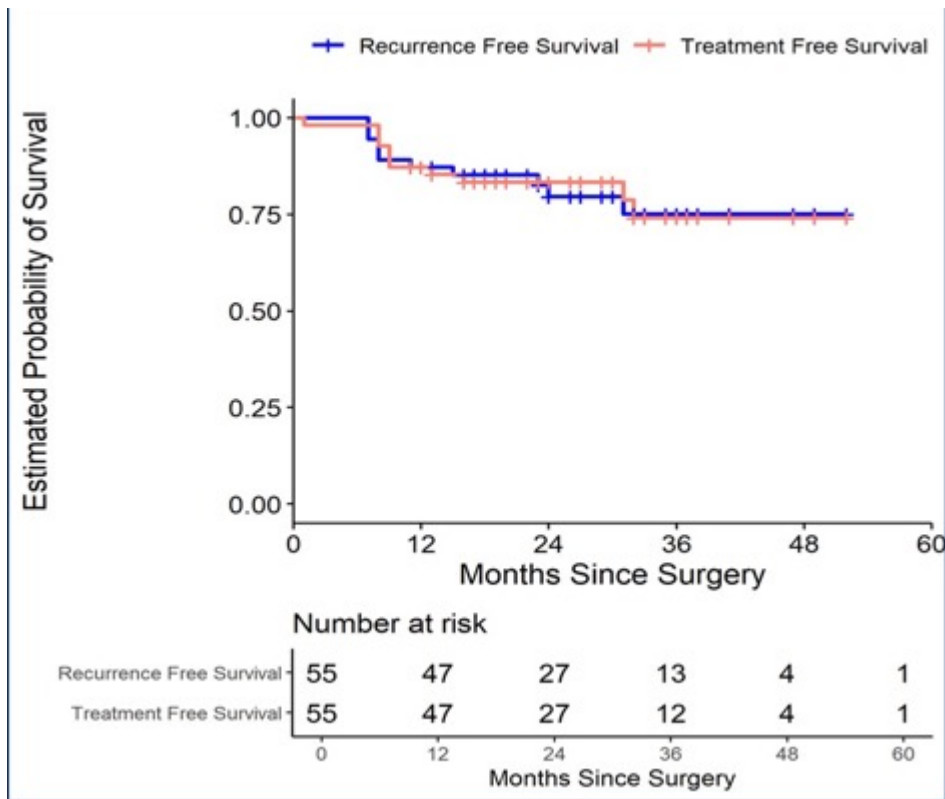
***novel strategies to limit toxicity***



# Surgery for **E**arly Stage **M**etastatic **S**eminoma

- **Phase II trial of RPLND as First-Line Treatment for Testicular Seminoma With Isolated Retroperitoneal Disease (1-3cm)**
- **Pure testicular seminoma**
- **Stage I with 1-3cm relapse**
- **Stage IIA/IIB**
  - **No more than 2 LN (1-3cm) in any dimension**
- **LN must be in RPLND template**
- **Imaging within 6 weeks of surgery**
- **Normal serum markers (1.5X ULN)**

# Surgery for Early Stage Metastatic Seminoma



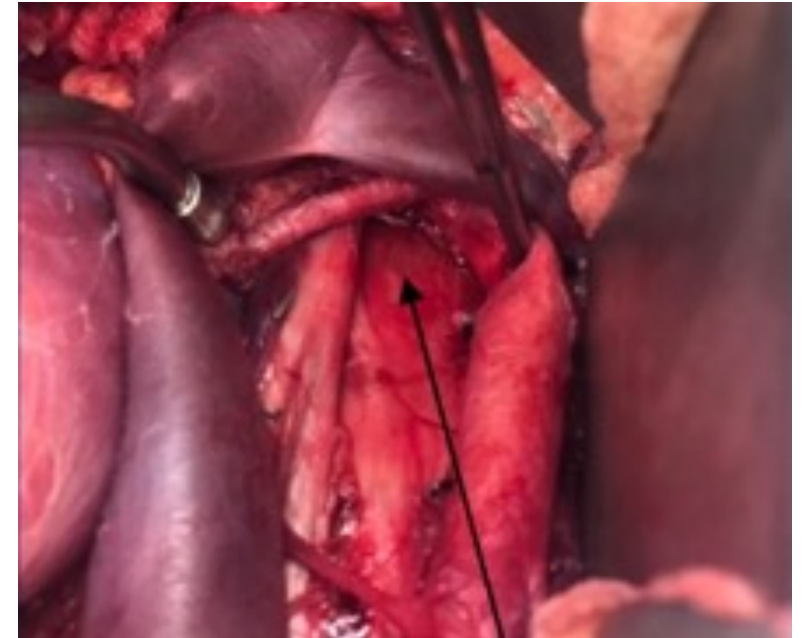
- **33 month follow up**
- **Recurrence in 12 patients (22%)**
  - **Chemotherapy: 10 pts**
  - **Repeat Resection: 2 patients**
- **Time to recurrence: 10.2 months**
- **100% overall survival**

Trial		N	F/U	Relapse	DOD
SEMS <sup>1</sup>	US	55	24	22%	0%
PRIMETEST	Ger	30	21	31%	0%
COTRIMS <sup>1</sup>	Ger	21	21	9.8%	0%
				<b>15.4%<sup>2</sup></b>	

# Surgery for **E**arly Stage **M**etastatic **S**eminoma

Short term (Clavien Dindo grade)	
1	Incision ulceration (I)
2	Ileus (II)
3*	Ileus (II)
4*	Pulmonary embolism (II)
5	Chylous ascites (III)
Long term (>30 days)	
1	Incision hernia- radiographic
2	Anejaculation- bilateral dissection, non-nerve sparing
3	Anejaculation - bilateral dissection, non-nerve sparing
4	Anejaculation - left modified template, non-nerve sparing

\*same patient



# Contemporary RPLND



Historical  
RPLND

Week or more  
hospital stay

Long surgical  
procedure times

NG tubes

Higher morbidity

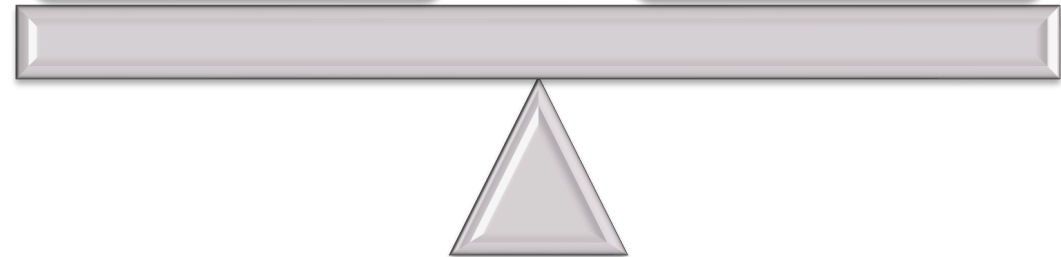
Modern  
RPLND

1-2 day admission

2-3 hour surgery

Complication rates  
low single digits

Most all normal  
ejaculation





## Stage II seminoma considerations

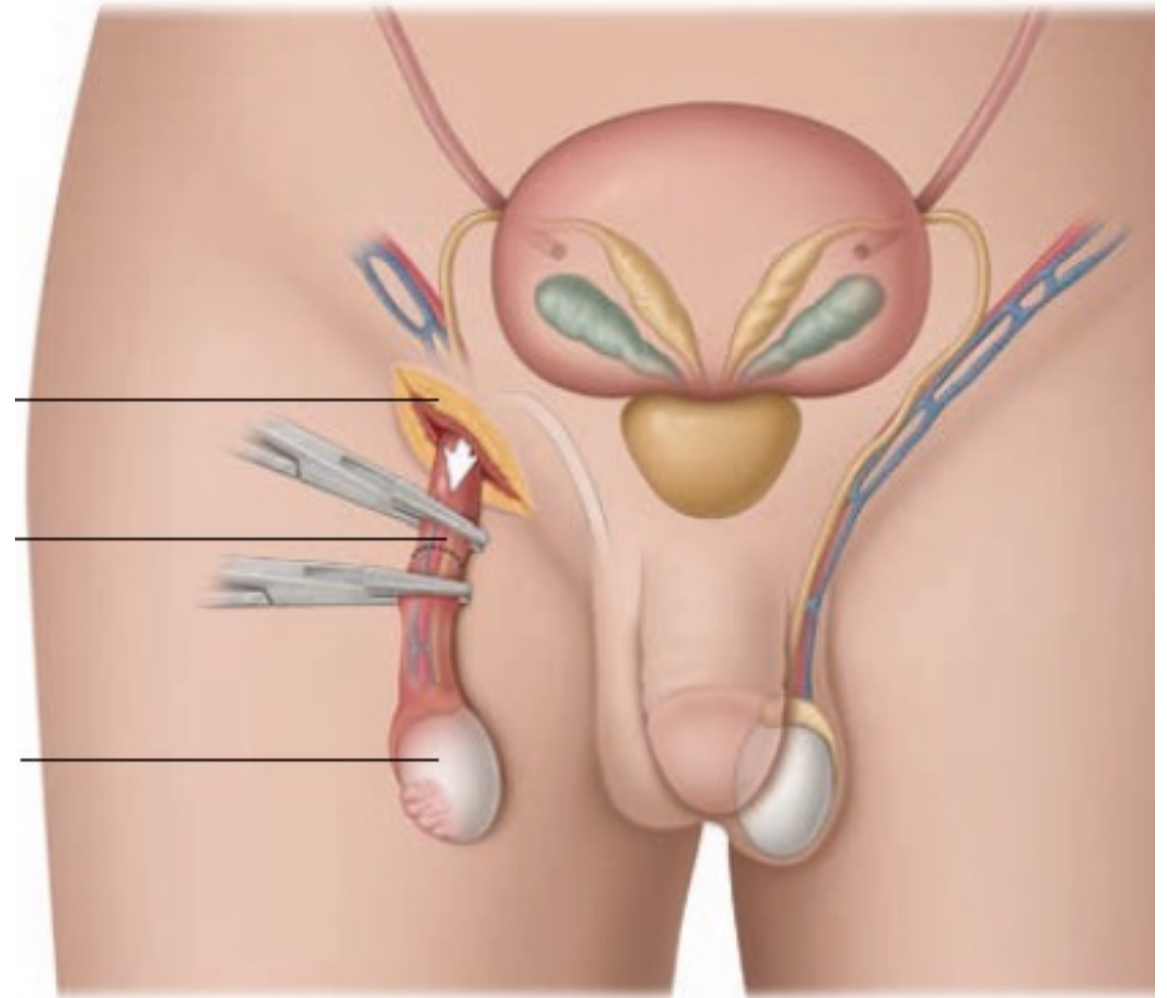
- **Surgery may allow for safe avoidance of chemotherapy/radiation therapy**
- **Very low long-term toxicity**
- **Further optimization**
  - **Stage I with relapse vs Stage II at presentation**
  - **Bilateral templates**
  - **Short-interval imaging to optimize patient selection**

## AUA guidelines 2023

- **Seminoma stage IIA/IIB with LN  $\leq$  3cm; recommend RT or cisplatin-based combination chemotherapy based on shared decision making**
  - **For patients who wish to avoid long term toxicity, RPLND may be offered**
- **Seminoma stage IIB with LN  $>$ 3cm, recommend cisplatin-based combination chemotherapy**

# Stage 1 NSGCT

NSGCT: 30% risk of relapse



©2018 patients.uroweb ALL RIGHTS RESERVED



@adityabagrodia

## Current Predictors

- Current risk stratification is rudimentary at best
  - NSGCT:
    - + LVI and high embryonal carcinoma → 50% occult metastases
- Serum tumor markers only expressed
  - 60% of NSGCT



Stage I without risk factors<sup>h</sup>

Surveillance (preferred) —  
or  
Nerve-sparing RPLND<sup>k,l,m</sup>  
or  
Adjuvant chemotherapy<sup>n</sup>:  
BEP for 1 cycle

Stage I with risk factors<sup>h</sup>

Surveillance —  
or  
Adjuvant chemotherapy<sup>n</sup>:  
BEP for 1 cycle  
or  
Nerve-sparing RPLND<sup>k,l,m</sup>



@adityabagrodia

# Surveillance vs Treatment

## Surveillance

- Pro: Noninvasive
- Con: 15-45% relapse<sup>1</sup>

## Single Cycle Adjuvant BEP

- Pro: Less toxic, <5% relapse
- Con: High overtreatment

## RPLND

- Pro: Diagnostic and therapeutic
- Con: Invasive surgery



@adityabagrodia

1. Nayan M. Eur Urol. 2017
2. Tandstad T. J Clin Oncol. 2009

# Surveillance vs Treatment

## Stage IA

**Observation is the standard**

**Caveat: If malignant transformation**



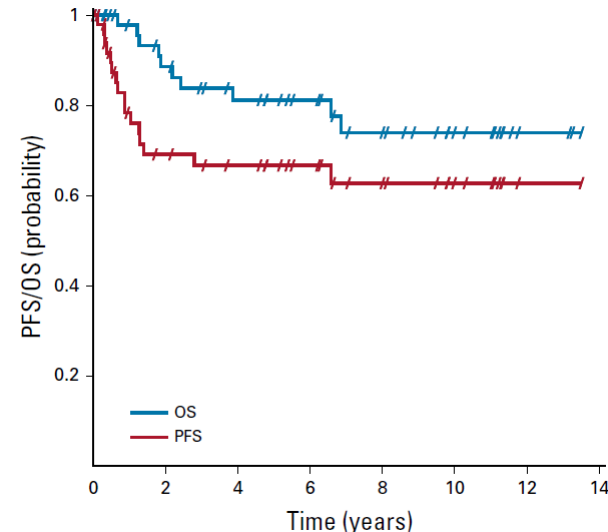
32. Clinicians should recommend RPLND or chemotherapy for patients with stage IIA NSGCT with normal post-orchietomy serum (S0) AFP and hCG. (Moderate Recommendation; Evidence Level: Grade B)

## Stage IB

**Balanced discussion of Surveillance, RPLND, BEPx1**

**Favor surveillance**

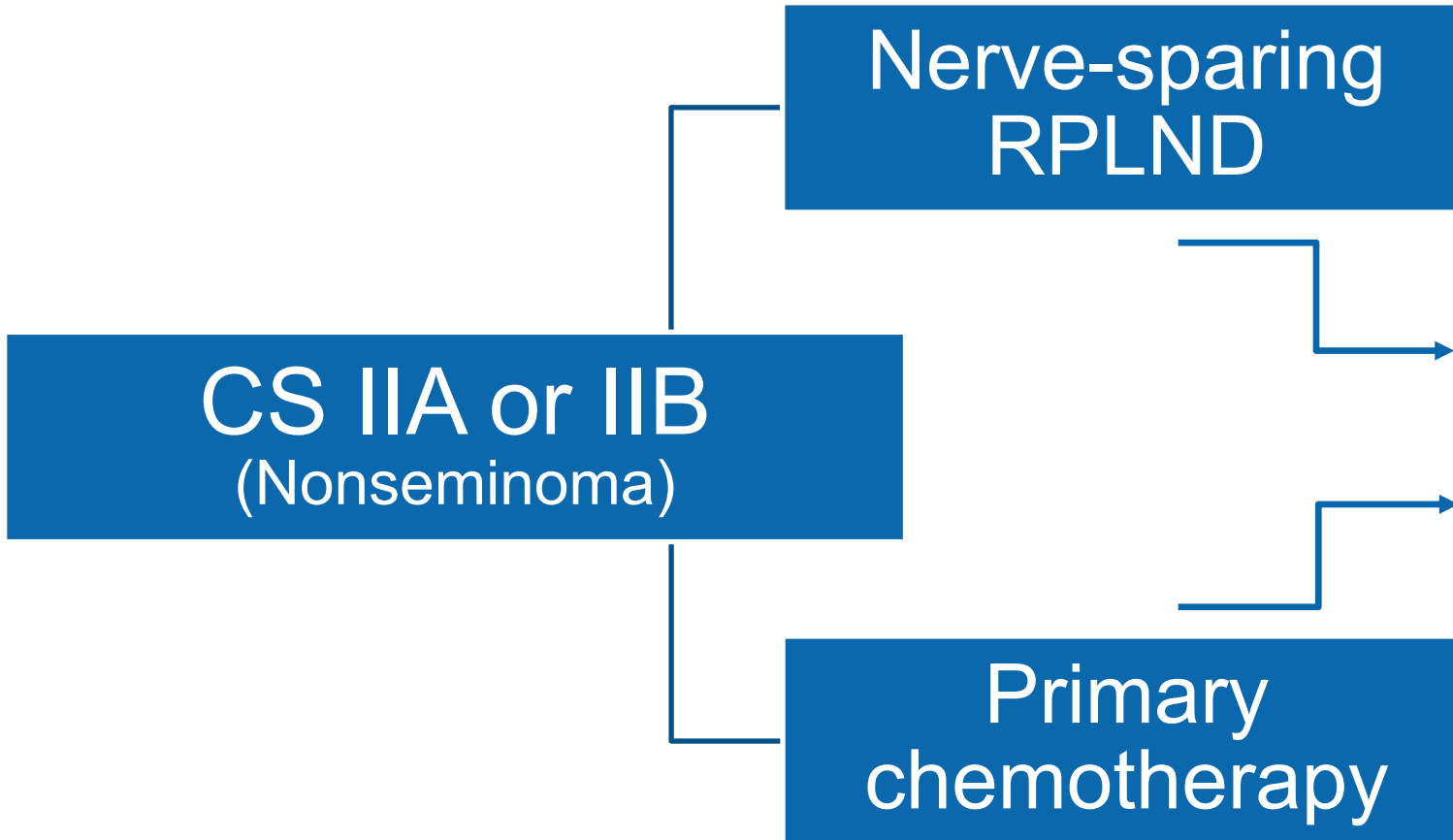
**Outcome of Men With Relapses After Adjuvant Bleomycin, Etoposide, and Cisplatin for Clinical Stage I Nonseminoma**



1. Nayan M. Eur Urol. 2017
2. Tandstad T. J Clin Oncol. 2009
3. Fischer S. JCO 2019



# What do national guidelines say?



## Favor RPLND

- For marker negative IIA
- For selected marker negative IIB

# Stage II Nonseminoma



## Guideline Statement 32

Clinicians should recommend RPLND or chemotherapy for patients with stage IIA NSGCT with normal post-orchietomy serum (S0) AFP and hCG. (Moderate Recommendation; Evidence Level: Grade B)

## Guideline Statement 33

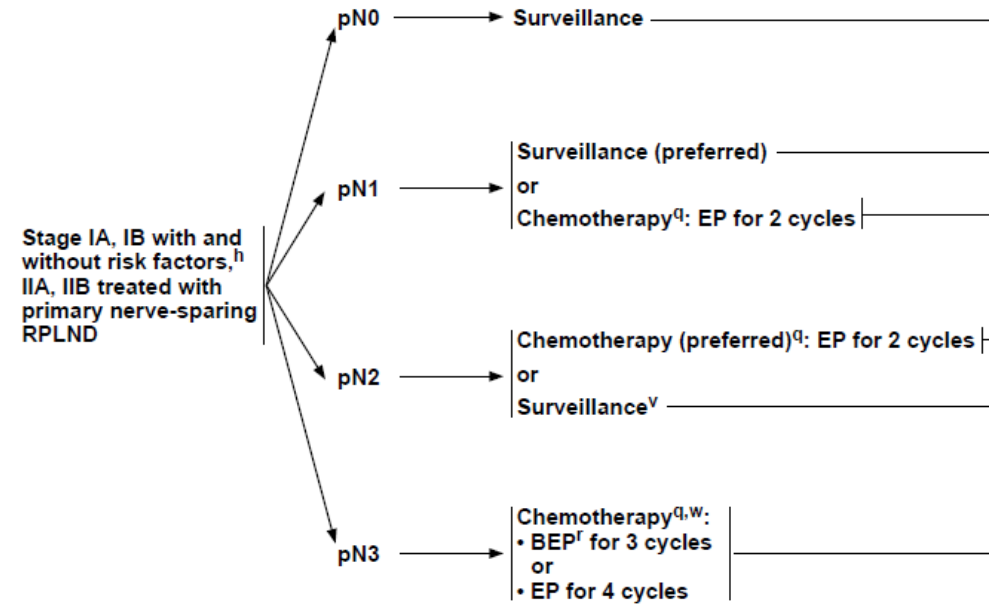
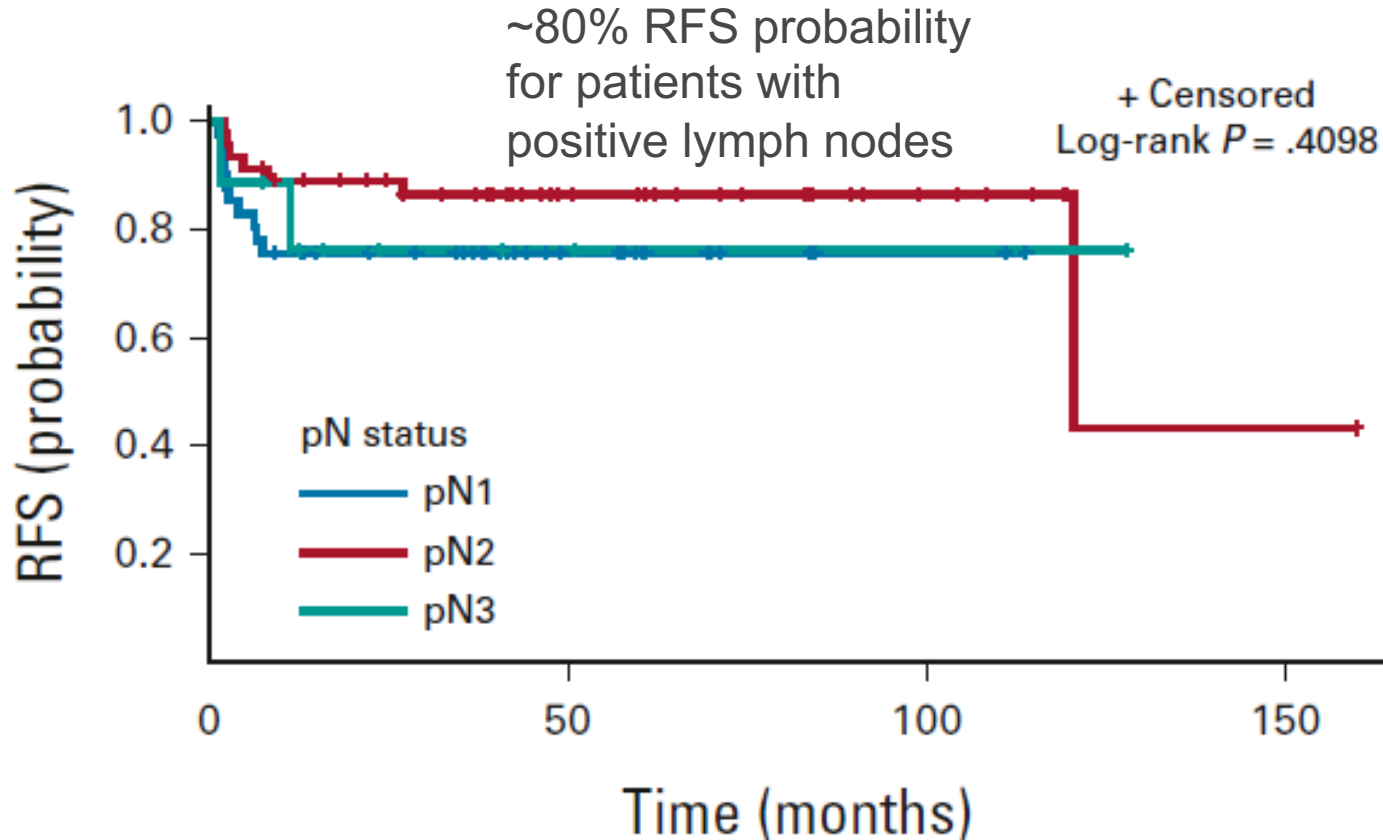
In patients with clinical stage **IIB NSGCT** and normal post-orchietomy serum AFP and hCG, clinicians should recommend risk-appropriate, multi-agent chemotherapy. (Moderate Recommendation; Evidence Level: Grade B). Clinicians may offer RPLND as an alternative to chemotherapy to select patients with clinical stage IIB NSGCT with normal post-orchietomy serum AFP and hCG. (Conditional Recommendation; Evidence Level: Grade C)



# Stage II Nonseminoma

## Primary Retroperitoneal Lymph Node Dissection for Patients With Pathologic Stage II Nonseminomatous Germ Cell Tumor—N1, N2, and N3 Disease: Is Adjuvant Chemotherapy Necessary?

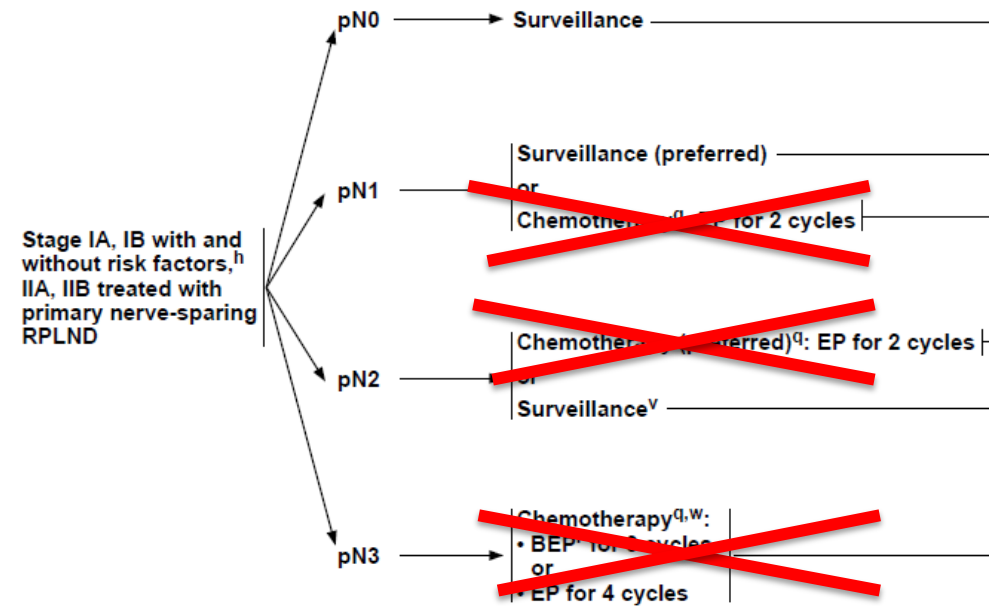
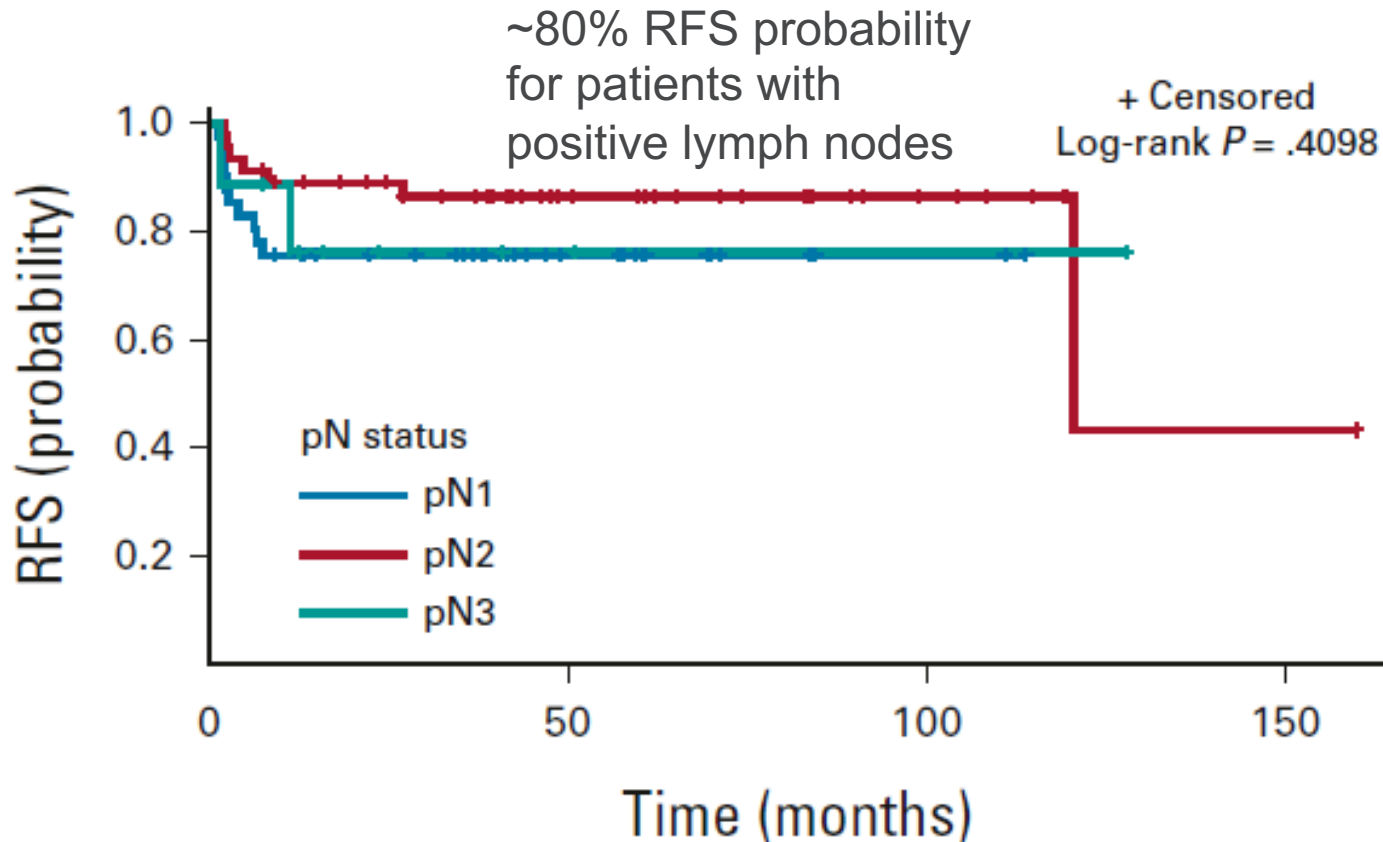
Isamu Tachibana, MD<sup>1</sup>; Sean Q. Kern, MD<sup>1</sup>; Antoin Douglawi, MD<sup>1</sup>; Yan Tong, MS<sup>2</sup>; Mohammad Mahmoud, MD<sup>1</sup>; Timothy A. Masterson, MD<sup>1</sup>; Nabil Adra, MD<sup>3</sup>; Richard S. Foster, MD<sup>1</sup>; Lawrence H. Einhorn, MD<sup>3</sup>; and Clint Cary, MD, MPH<sup>1</sup>



# Stage II Nonseminoma

## Primary Retroperitoneal Lymph Node Dissection for Patients With Pathologic Stage II Nonseminomatous Germ Cell Tumor—N1, N2, and N3 Disease: Is Adjuvant Chemotherapy Necessary?

Isamu Tachibana, MD<sup>1</sup>; Sean Q. Kern, MD<sup>1</sup>; Antoin Douglawi, MD<sup>1</sup>; Yan Tong, MS<sup>2</sup>; Mohammad Mahmoud, MD<sup>1</sup>; Timothy A. Masterson, MD<sup>1</sup>; Nabil Adra, MD<sup>3</sup>; Richard S. Foster, MD<sup>1</sup>; Lawrence H. Einhorn, MD<sup>3</sup>; and Clint Cary, MD, MPH<sup>1</sup>



# Optimizing outcomes of primary RPLND

- Stage I disease
  - Close evaluation of primary landing zones
    - If considering primary RPLND, imaging within 2 weeks markers within 1 week
- Stage II disease
  - De novo stage II versus development of low volume metastases on surveillance
  - Short-interval imaging (6-8 weeks) prior to RPLND
    - Select patients that have involution/pN0
    - Select out patients that may develop metastases
    - Primary landing zone
    - Rule of 3 → suboptimal candidate
      - >3 nodes
      - >3 cm

# Testicular cancer shrouded in uncertainty

- Diagnosis
- Stage I disease: **Who will relapse?**
- Stage II:
  - **pN0?**
  - **Develop metastases?**
- Post-chemo NSGCT/seminoma
  - **Fibrosis necrosis only?**



@adityabagrodi

## Testicular cancer shrouded in uncertainty

**Sensitive and specific biomarkers may allow for precise, individualized treatment recommendations**

**Circulating miR-371a-3p holds the promise to be such a biomarker**



# Current GCT serum markers are underwhelming


- **Conventional tumor markers lack specificity:**
  - **AFP:** HCC, liver disease, familial
  - **hCG:** bladder, renal, gastric, lung, marijuana, cross-reactivity with LH
  - **LDH:** any clinical setting with rapid cell turnover

Table 1 | Serum AFP and hCG levels in GCTs<sup>22</sup>

GCT histological subtype	AFP	hCG
Yolk sac tumour	++	-
Seminoma	-	±
Embryonal carcinoma	±	±
Choriocarcinoma	-	++
Teratoma	±	-

AFP,  $\alpha$ -fetoprotein; GCT, germ cell tumour; hCG, human chorionic gonadotrophin. ++, strongly positive levels;  $\pm$ , levels may be negative or moderately positive; -, negative levels.

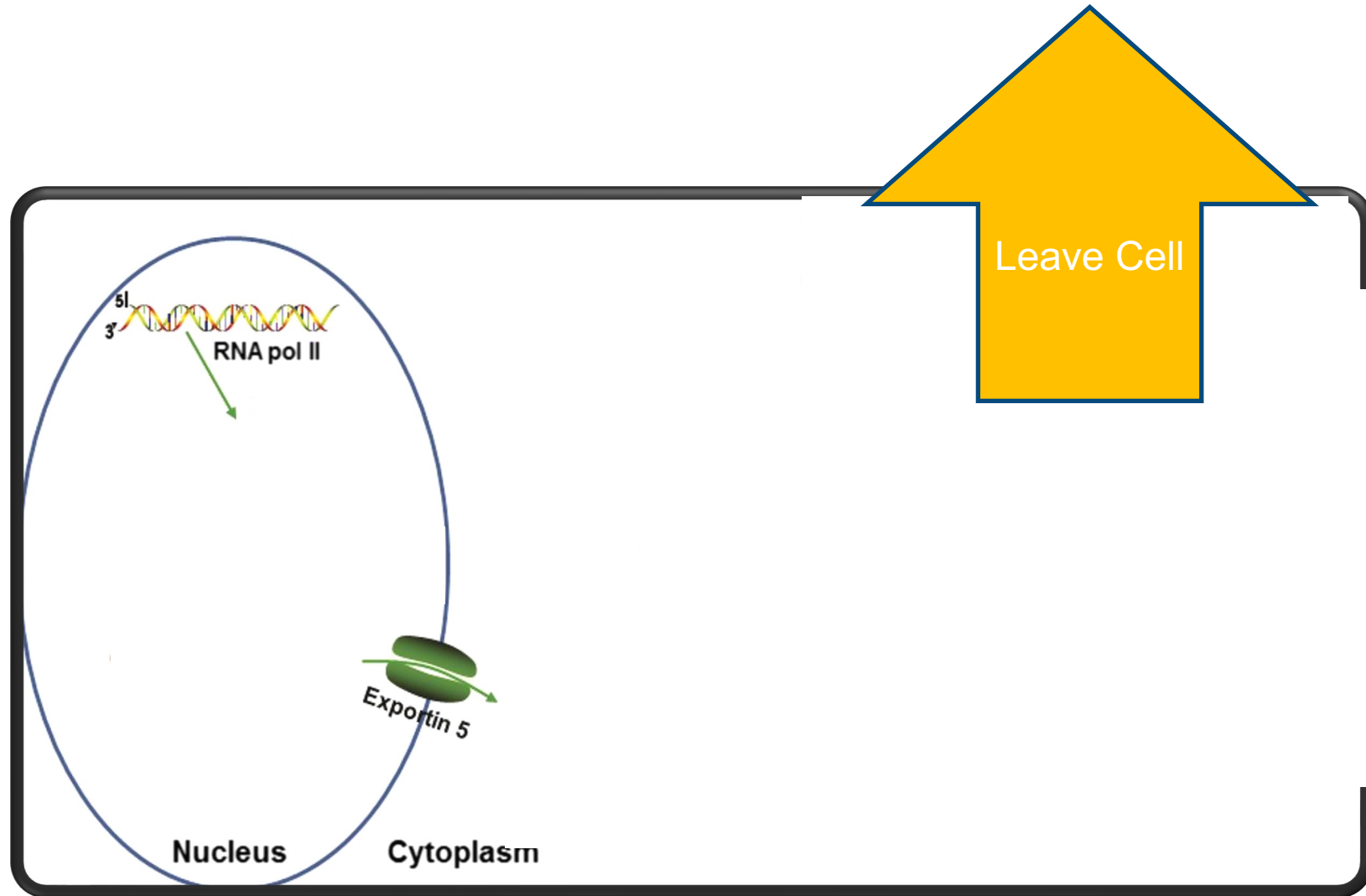




# Micro RNAs (miRNA)

# What are miRNA?

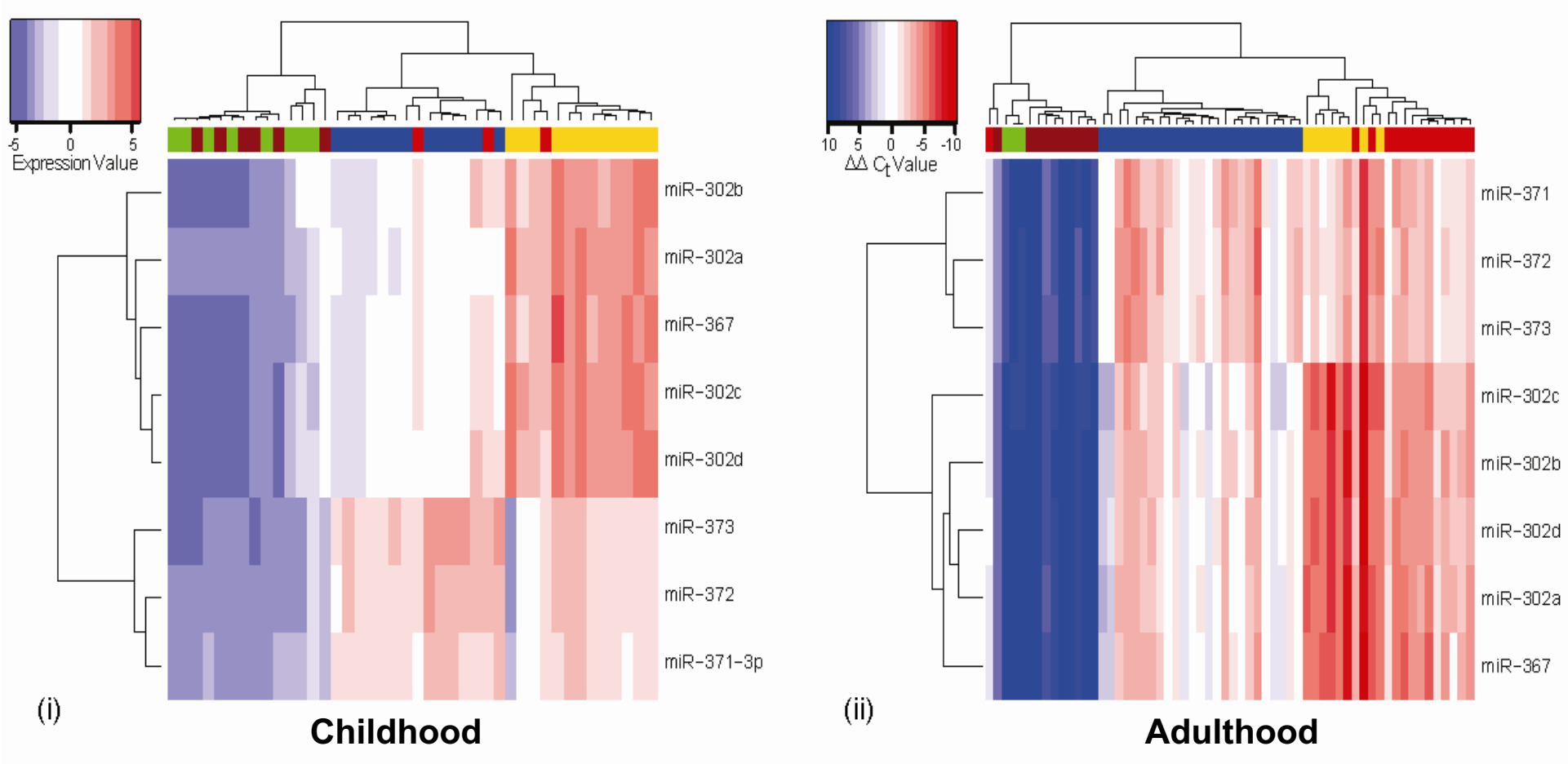
- Small non coding RNAs
- Epigenetic gene regulation
- Released from nucleus
- Intercellular communication
- Dysregulated in many malignancies



1. Mitchell PS. Proc Natl Acad Sci U S A. 2008
2. Li Z Nutr Metab (Lond). 2018



# A panel of 8 miRNAs segregate malignant GCT



■ Yolk sac tumour 
 ■ Germinoma 
 ■ Embryonal carcinoma 
 ■ Teratoma 
 ■ Normal gonad

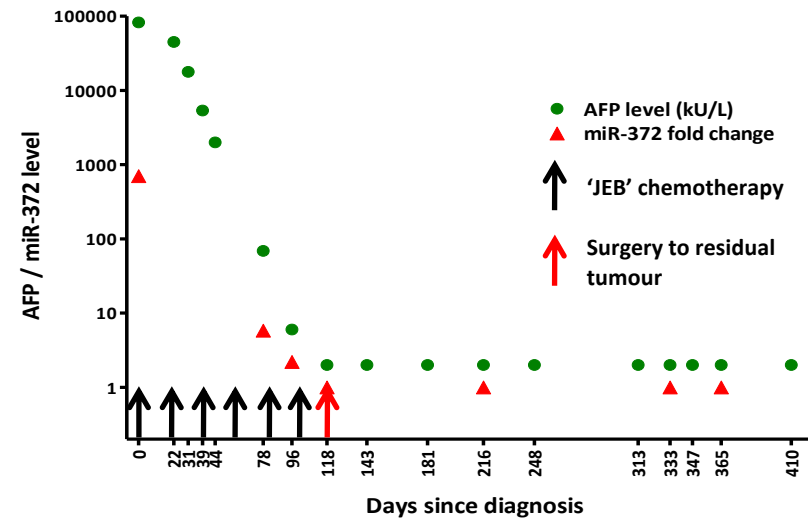
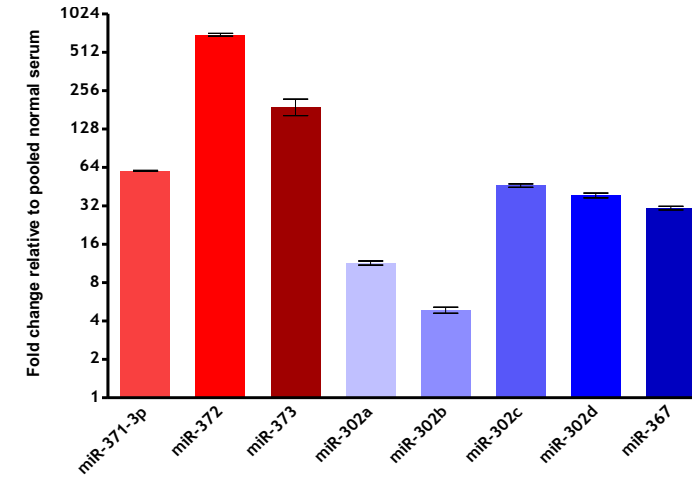
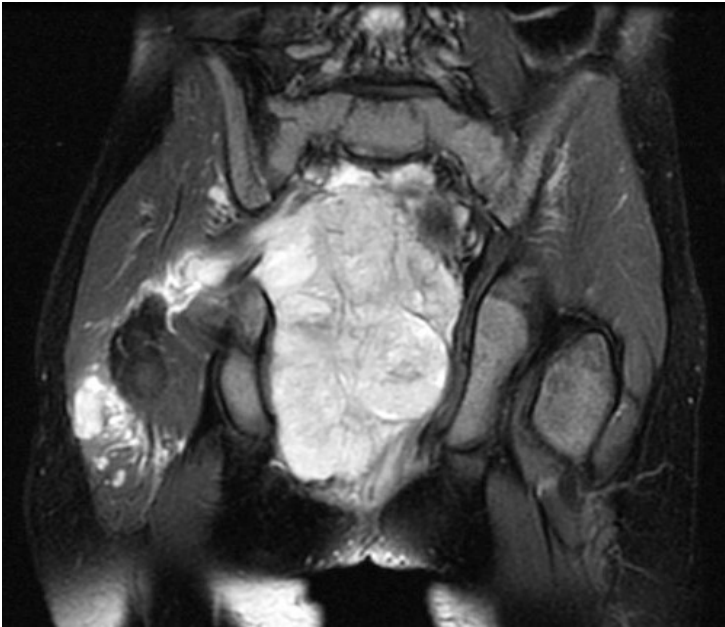
# Serum miRNAs are sensitive to malignant GCT

**4 year old male**

*History* - abnormal gait & constipation

*Serum AFP* - 82,340 kU/L

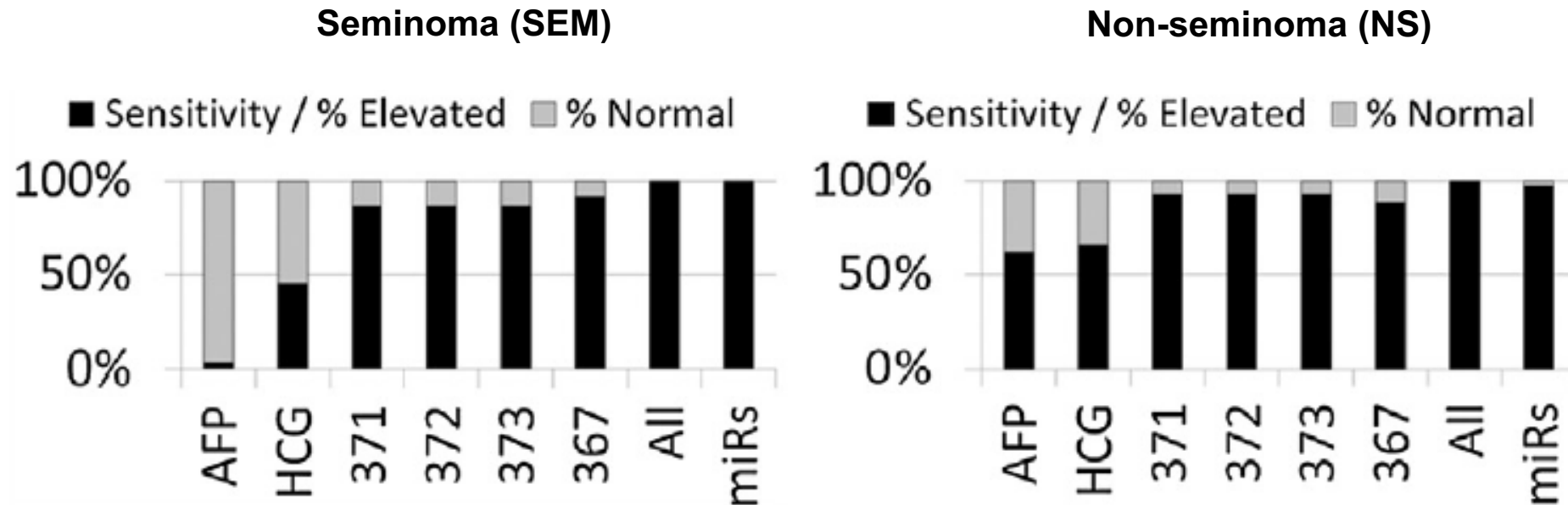
*Histology* - malignant GCT (YST)



@adityabagrodia

# Four serum microRNA signature of malignant GCTs

n=161; 91 malignant GCT vs. 70 controls



**Serum microRNAs outperform conventional AFP and HCG markers**



@adityabagrodia

Gillis et al, *Molecular Oncology*, 2013

UC San Diego Health

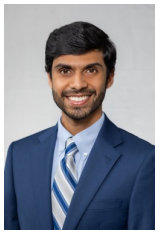
# Histology: miR-371a-3p vs conventional markers

Parameter Studied	AFP	hCG	miR-371a-3p
<b>Seminoma</b>	<3%	18-31%	87%
<b>Non-seminoma</b>	60-70%	53%	94%
<b>Embryonal carcinoma</b>	40%	25%	>90%
<b>Yolk sac tumor</b>	>95%	<5%	>90%
<b>Choriocarcinoma</b>	<5%	>95%	>90%
<b>Teratoma</b>	-	-	<5%
<b>Mixed GCT</b>	Variable	Variable	~90%
<b>Extragonadal</b>	Variable	Variable	>90%
<b>Non-GCT</b>	12%	14%	6%
<b>Half-life after orchiectomy</b>	5-7 days	1.5-3 days	12 hours
<b>Decrease during/after chemotherapy</b>	+	+	+



@adityabagrodia

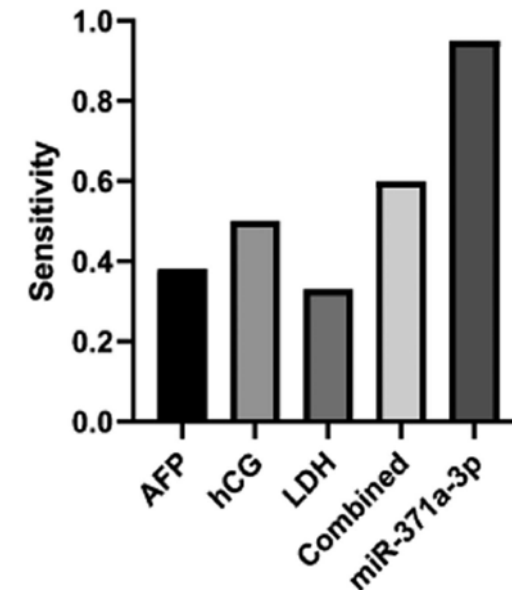
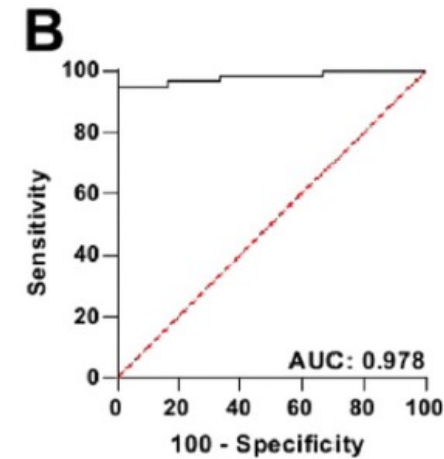
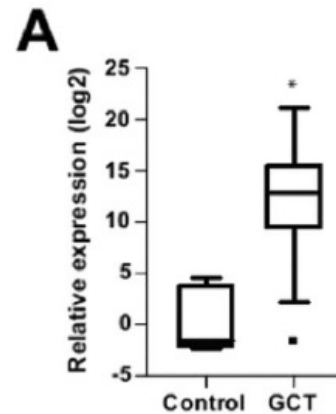
# Clinical Scenario: Pre-orchietomy



## Real-World Application of Pre-Orchiectomy miR-371a-3p Test in Testicular Germ Cell Tumor Management

**Table 1.** Patient characteristics at presentation

	Viable GCT		Control		p Value
No.	58		11		
Median age (IQR)	30	(26–40)	54	(43–56)	<0.0001
% Race (No.):					
White	48	(28)	36	(4)	
Hispanic	48	(28)	36	(4)	
Black	2	(1)	-		
Asian	2	(1)	28	(3)	
% Histology (No.):					
Seminoma	50	(29)	-		
NSGCT	50	(29)	-		
Pure teratoma	-		9	(1)	
Benign	-		55	(6)	
Leydig cell tumor	-		18	(2)	
Secondary metastasis	-		18	(2)	
% Composite stage (No.):					
I	78	(45)	9	(1)	
II	10	(6)	9	(1)	
III	12	(7)	27	(3)	
N/A	-		55	(6)	

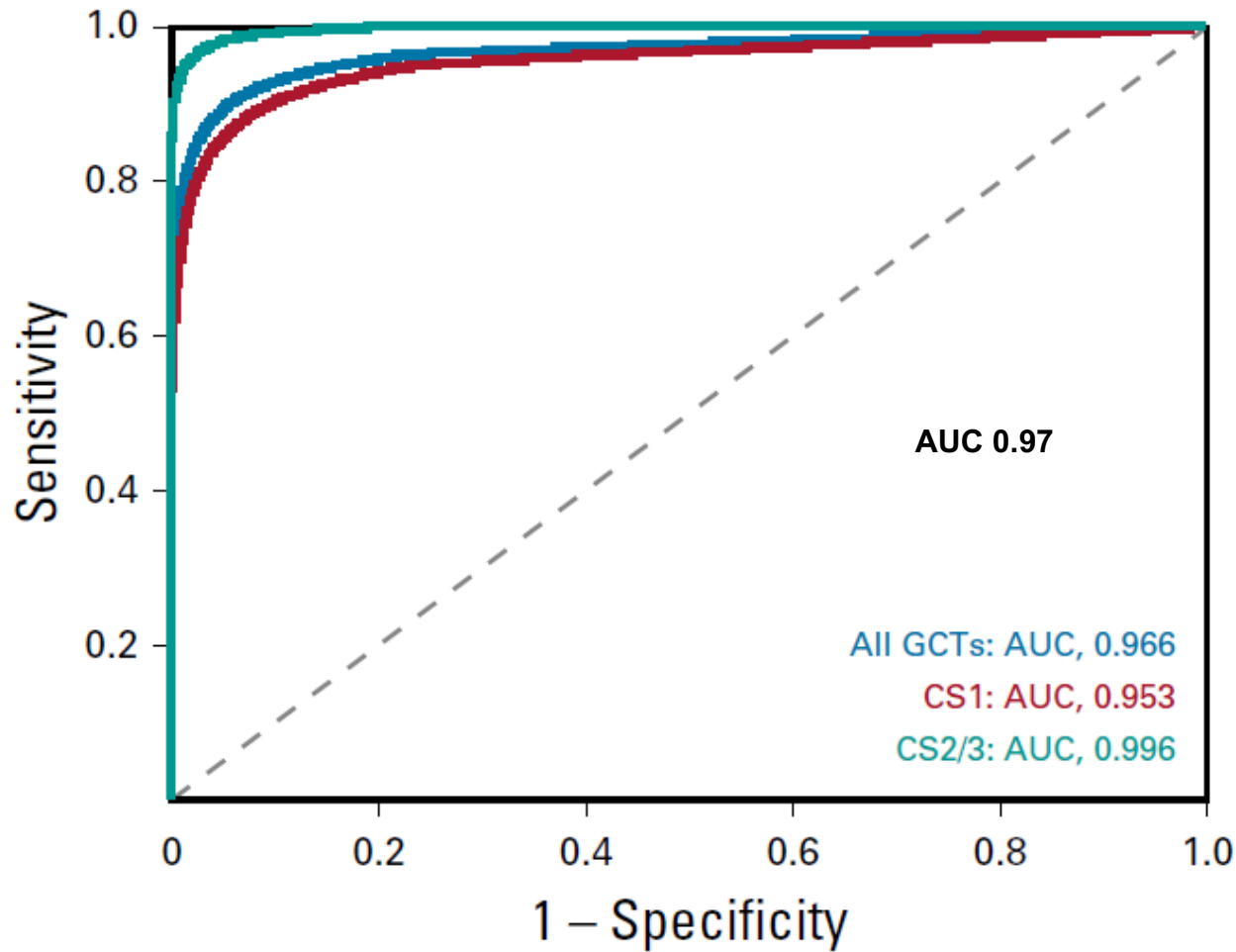


	AUC	Threshold	Sensitivity	Specificity	NPV	PPV	Accuracy
miR-371a-3p	0.978	23.5	0.931	1	0.733	1	0.942
Conventional serum tumor markers	0.79	NL*	0.579	1	0.314	1	0.647



@adityabagrodia

# Serum miR-371a-3p at diagnosis in malignant GCTs



n=874; 616 malignant GCT vs. 258 controls

AUC 0.97

All GCTs: AUC, 0.966

CS1: AUC, 0.953

CS2/3: AUC, 0.996



@adityabagrodia

Dieckmann *et al*, *Journal Clinical Oncology*, 2019

UC San Diego Health

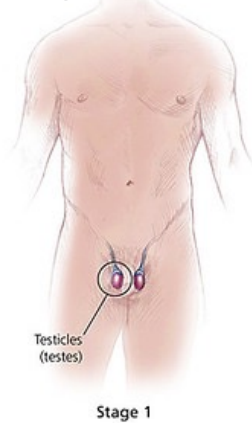
## Conclusion

- miRNA 371 has excellent diagnostic accuracy in the pre-orchietomy setting
- miRNA 371 performs better than conventional STMs to predict pathology

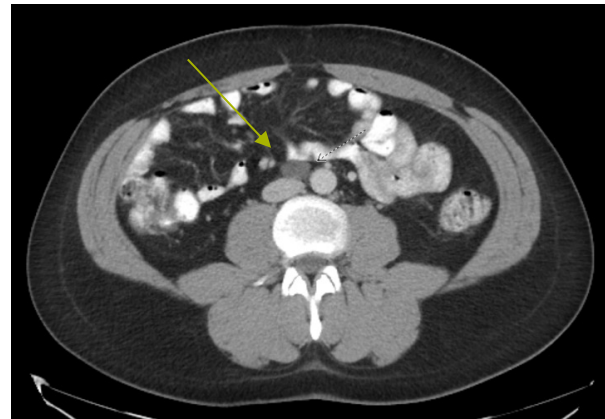
Pre-orchietomy



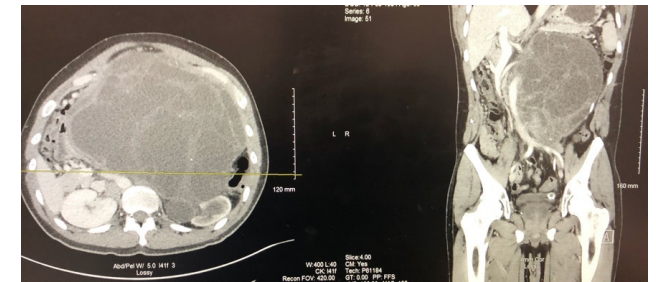
Stage I disease



Stage II disease



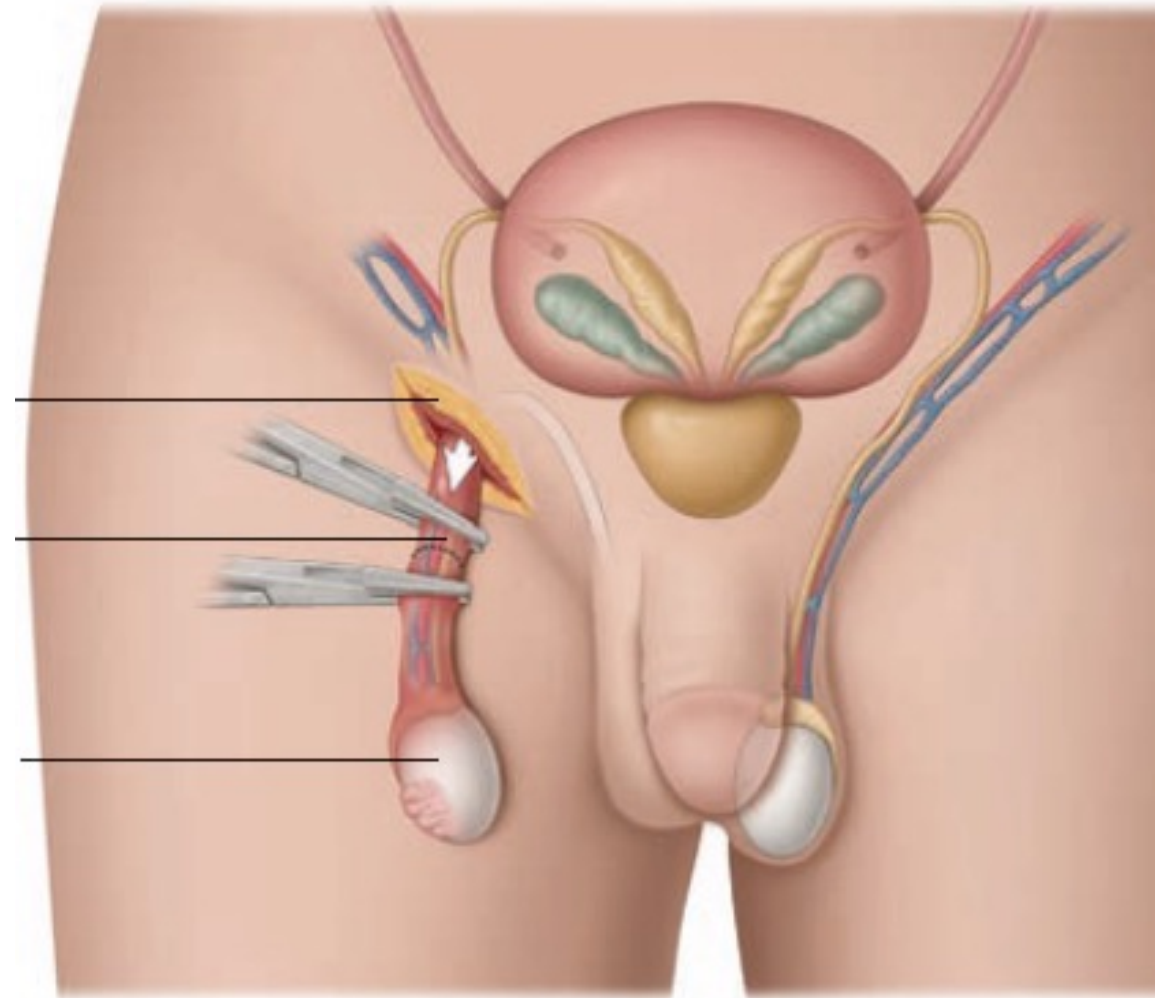
Post-chemotherapy



@adityabagrodia

# Stage 1 NSGCT

NSGCT: 30% risk of relapse



©2018 patients.uroweb ALL RIGHTS RESERVED



@adityabagrodia

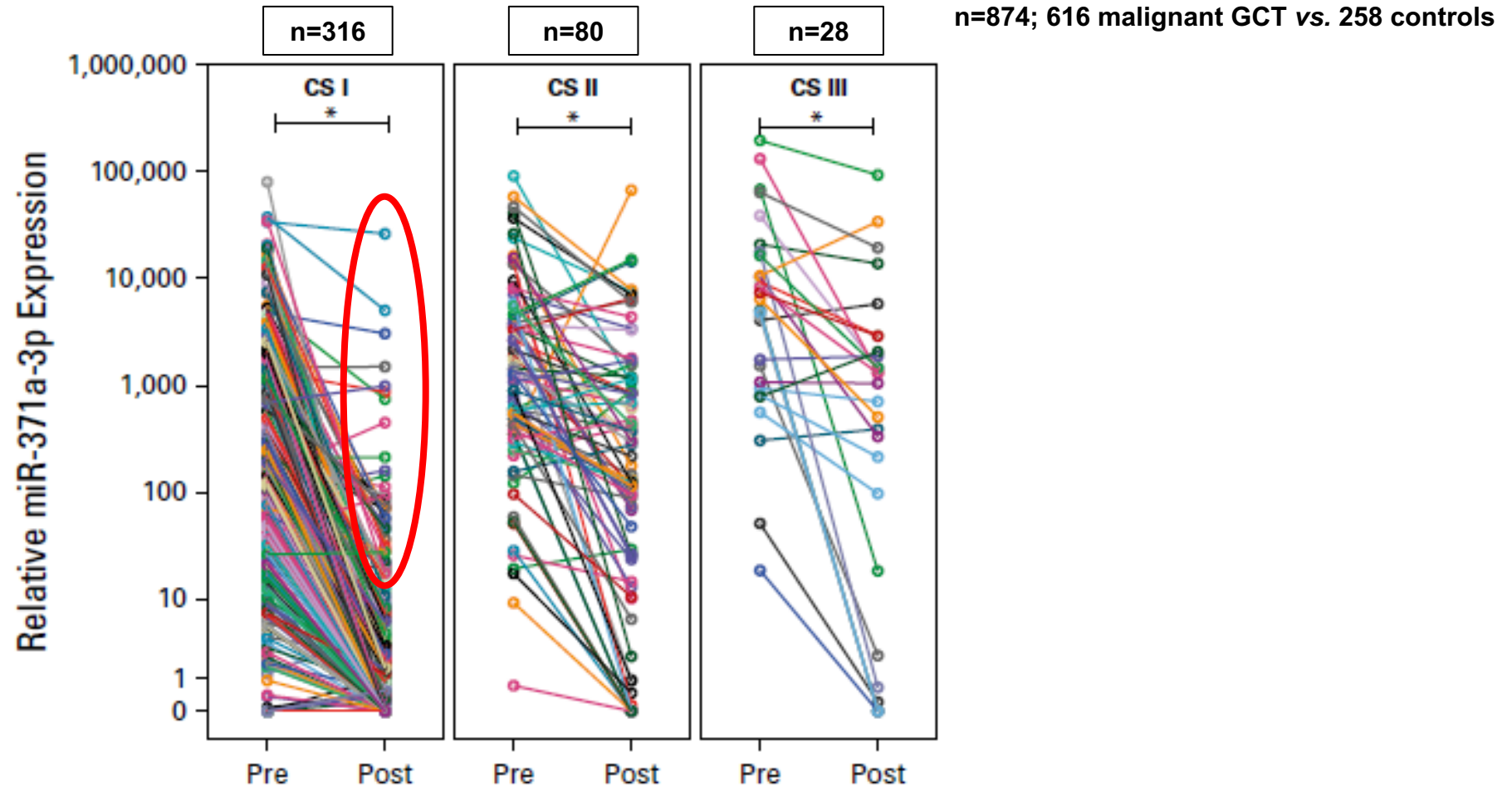


## Case

- **HPI: 24 year old with right T2N0M0S0 NSGCT 50% EC, 45% Teratoma, 5% YST**
- **Elects for RPLND: 1/33 nodes positive 0.5 cm focus of EC**

**Pre-RPLND miRNA-371a-3p  
POSITIVE**

# Serum miR-371a-3p declines after orchiectomy in stage 1 disease



@adityabagrodia

# Serum MicroRNA-371a-3p Levels Predict Viable Germ Cell Tumor in Chemotherapy-naïve Patients Undergoing Retroperitoneal Lymph Node Dissection

John T. Lavin<sup>a,1</sup>, Nirmish Singla<sup>a,1</sup>, Solomon L. Woldu<sup>a</sup>, Yair Lotan<sup>a</sup>, Cheryl M. Lewis<sup>b</sup>, Kuntal Majmudar<sup>b</sup>, Anna Savelyeva<sup>a</sup>, Payal Kapur<sup>b</sup>, Vitaly Margulis<sup>a,c</sup>, Douglas W. Strand<sup>a</sup>, Matthew J. Murray<sup>d,e</sup>, James F. Amatruda<sup>f</sup>, Aditya Bagrodia<sup>a,\*</sup>



- Serum collection in chemotherapy-naïve patients prior to RPLND
- Bilateral full-template or extended modified template RPLND
- RPLND histology classification:
  - Benign
  - Viable GCT (seminoma or NSGCT)
  - Teratoma only



@adityabagrodia

## Results: Clinicopathologic characteristics

<b>Number of patients</b>	<b>24</b>
<b>Median age at RPLND (IQR), years</b>	<b>27 (21-33)</b>
<b>Orchiectomy histology # (%):</b>	
-Benign	2 (8.3)
-Pure seminoma	4 (16.7)
-Pure NSGCT	2 (8.3)
-Mixed NSGCT	16 (66.7)
<b>pT stage # (%):</b>	
-pT0	2 (8)
-pT1	13 (54)
-pT2	9 (38)
<b>Clinical N stage # (%)</b>	
-cN0	12 (50.0)
-cN1	9 (37.5)
-cN2	3 (12.5)
<b>Composite clinical stage # (%):</b>	
-I	12 (50.0)
-II	12 (50.0)



@adityabagrodia

## Results: Clinicopathologic characteristics

<b>RPLND histology # (%):</b>	
-Benign	10 (41.7)
-Viable GCT (seminoma or NSGCT)	11 (45.8)
-Teratoma only	3 (12.5)
<b>pN stage # (%):</b>	
-pN0	10 (41.7)
-pN1	6 (25.0)
-pN2	7 (29.2)
-pN3	1 (4.2)



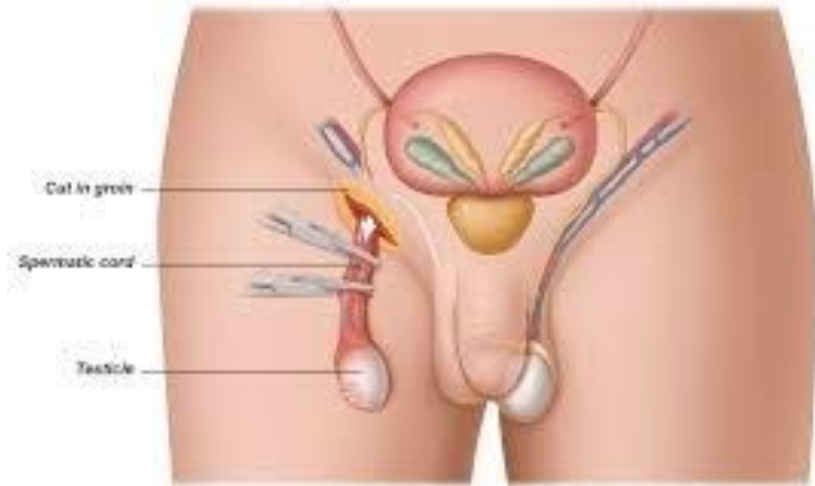
# Performance characteristics of serum miRNAs in detecting viable GCT

miRNA	Sensitivity	Specificity	PPV	NPV	Accuracy
miR-371a	100%	92%	92%	100%	96%
miR-367	73%	85%	80%	79%	79%
miR-372	100%	31%	55%	100%	63%
miR-373	55%	92%	86%	71%	75%
miR-375	0%	95%	0%	75%	69%



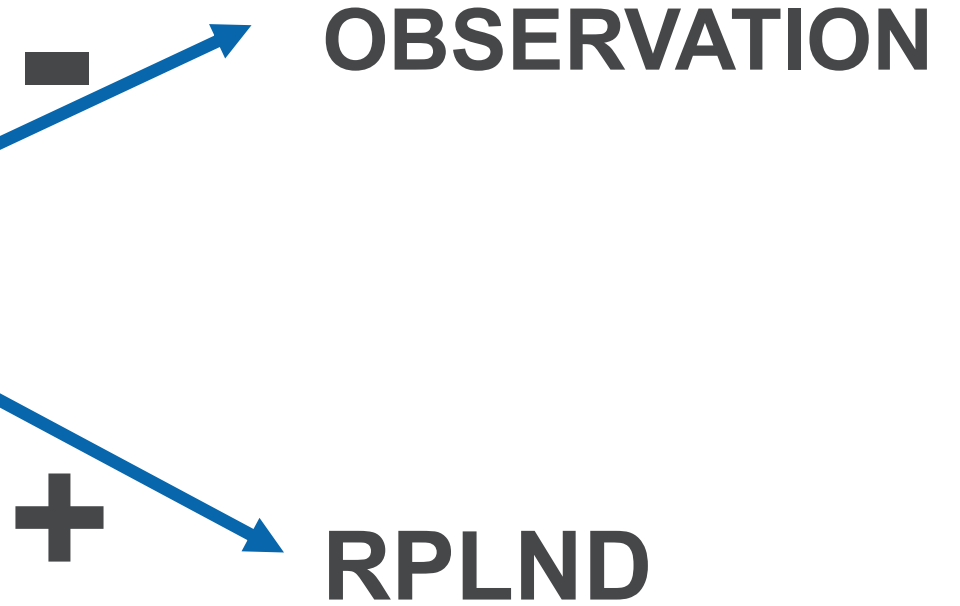
**Next steps:  
incorporate miRNAs  
into a clinical trial**

# miR-371a-3p based clinical trial: EA8221



ORCHIECTOMY

serum  
miR371



@adityabagrodia



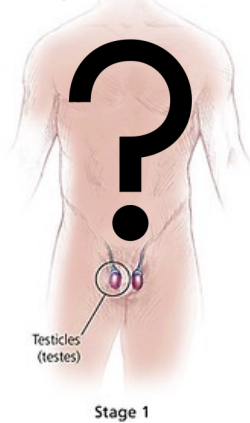
## Conclusion

- miRNA 371 is promising in post-orchietomy setting
- Early post-orch miR-371 may not predict relapse
  - Likely a sensitivity issue

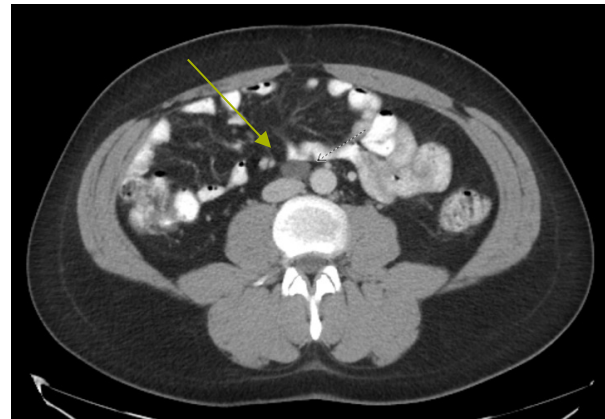
Pre-orchietomy



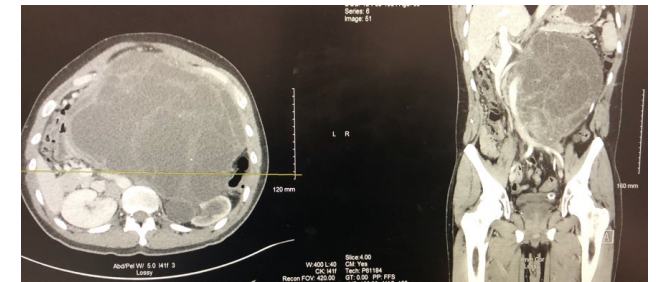
Stage I disease



Stage II disease



Post-chemotherapy



@adityabagrodia

## Case

- 44 year old with right testicular mass: 45% sem, 30% YST, 20% EC, 5% teratoma
- Repeat imaging in 8 weeks
  - No change



# Case

- **Scheduled for RPLND in 8 weeks with repeat imaging 1 week prior**
- **Bilateral Full template RPLND**
  - **0.5 cm focus of seminoma in 1/18 paraaortic LNs**
  - **3 mm focus of seminoma in 1/14 interaortocaval LNs**

**Pre-RPLND miRNA-  
371a-3p POSITIVE**

## miR in Stage II Disease

- Prospective serum collection from 32 consecutive chemotherapy-naïve patients immediately prior to RPLND
- Bilateral full-template or extended modified template RPLND performed
- RPLND histology classification:
  - Benign
  - Viable GCT (seminoma or NSGCT)
  - Teratoma only



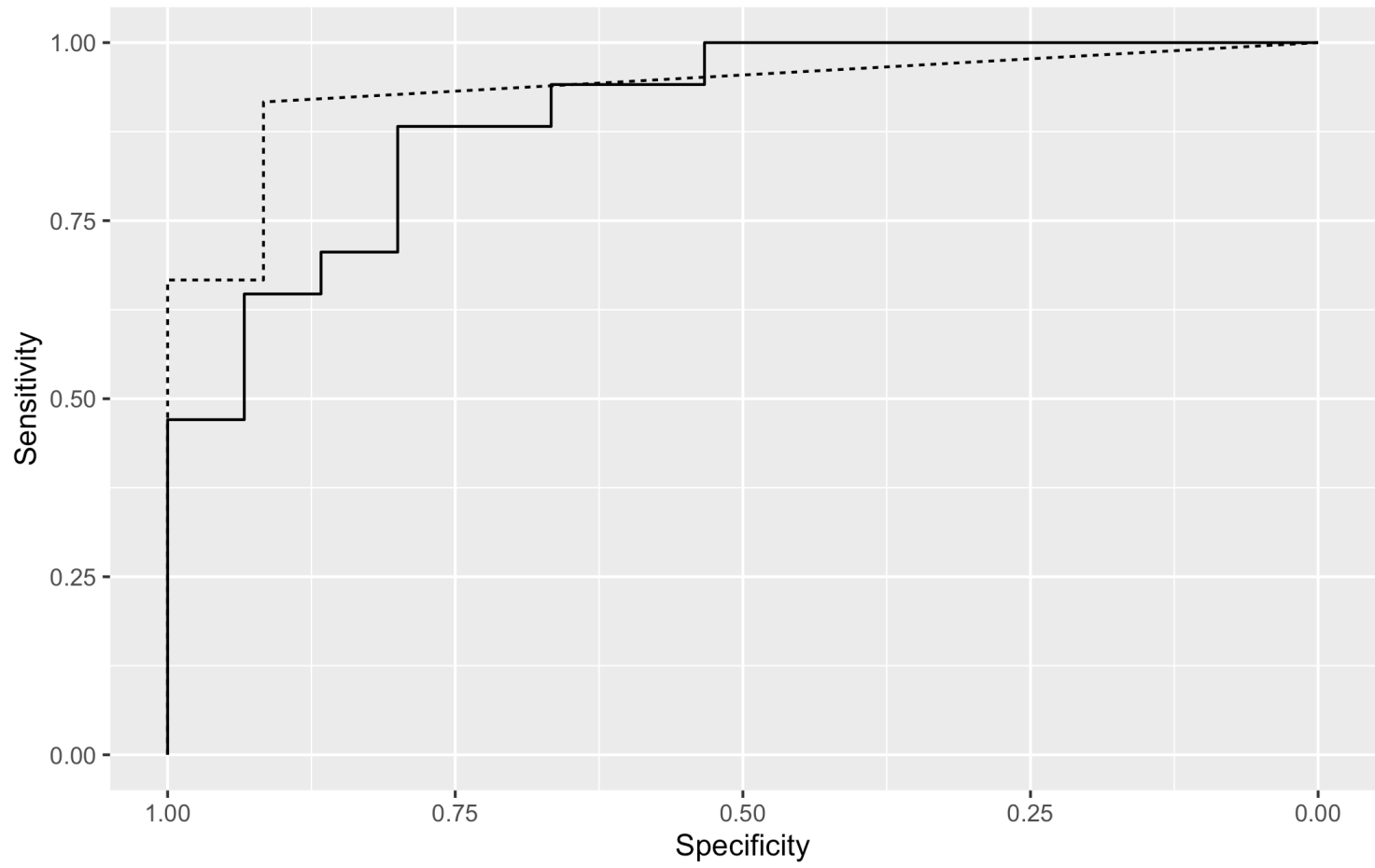
# Patient characteristics (n=32)

Age	Years	Median (IQR)	28 (23.5-35.0)
pT Stage	pT0	N (%)	2 (6.3)
	pT1		14 (43.8)
	pT2		16 (50.0)
cN Stage	cN0	N (%)	12 (37.5)
	cN1		15 (46.9)
	cN2		4 (12.5)
	cN3		1 (3.1)
Clinical Stage (CS)	CS I	N (%)	12 (37.5)
	CS II		20 (62.5)
RPLND Histopathology	Benign	N (%)	9 (28.1)
	Seminoma		12 (37.5)
	Non-Seminoma		11 (34.4)
pN Stage	pN0	N (%)	9 (28.1)
	pN1		11 (34.4)
	pN2		11 (34.4)
	pN3		1 (3.1)
Pathologic Stage (PS)	PS I	N (%)	9 (28.1)
	PS II		23 (71.9)



@adityabagrodia

# Performance of serum miR-371a-3p test in patients with minimal residual disease.



	value
Threshold	35
Sensitivity	0.92
Specificity	0.92
AUC	0.934 (0.835-1)
PPV	0.92
NPV	0.92
Accuracy	0.92

Method — Original - - - Revised



@adityabagrodia

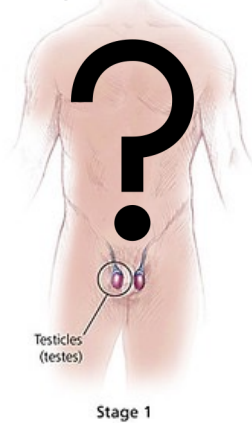
# Conclusion

- miRNA 371 is promising for stage II disease

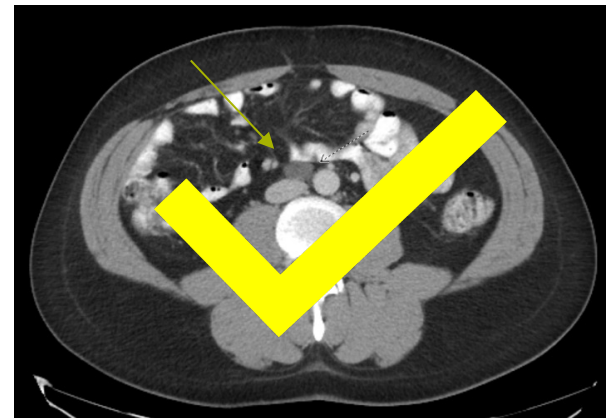
Pre-orchietomy



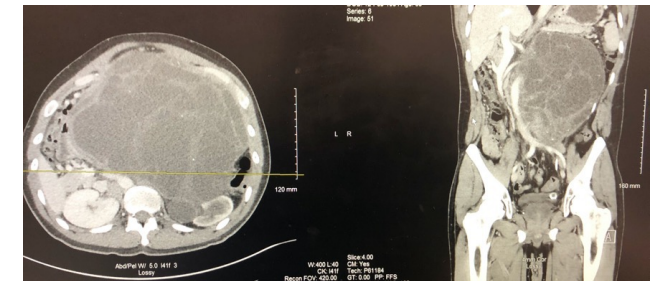
Stage I disease



Stage II disease



Post-chemotherapy



@adityabagrodi

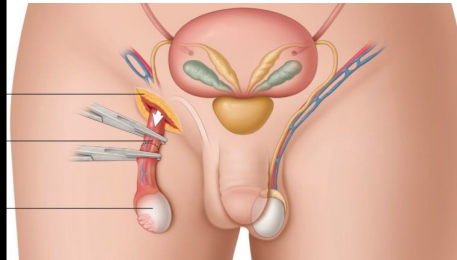
# AGCT 1531: A Phase III Study of Active Surveillance for Adult and Pediatric Patients with Germ Cell Tumors

## ● Inclusion Criteria:

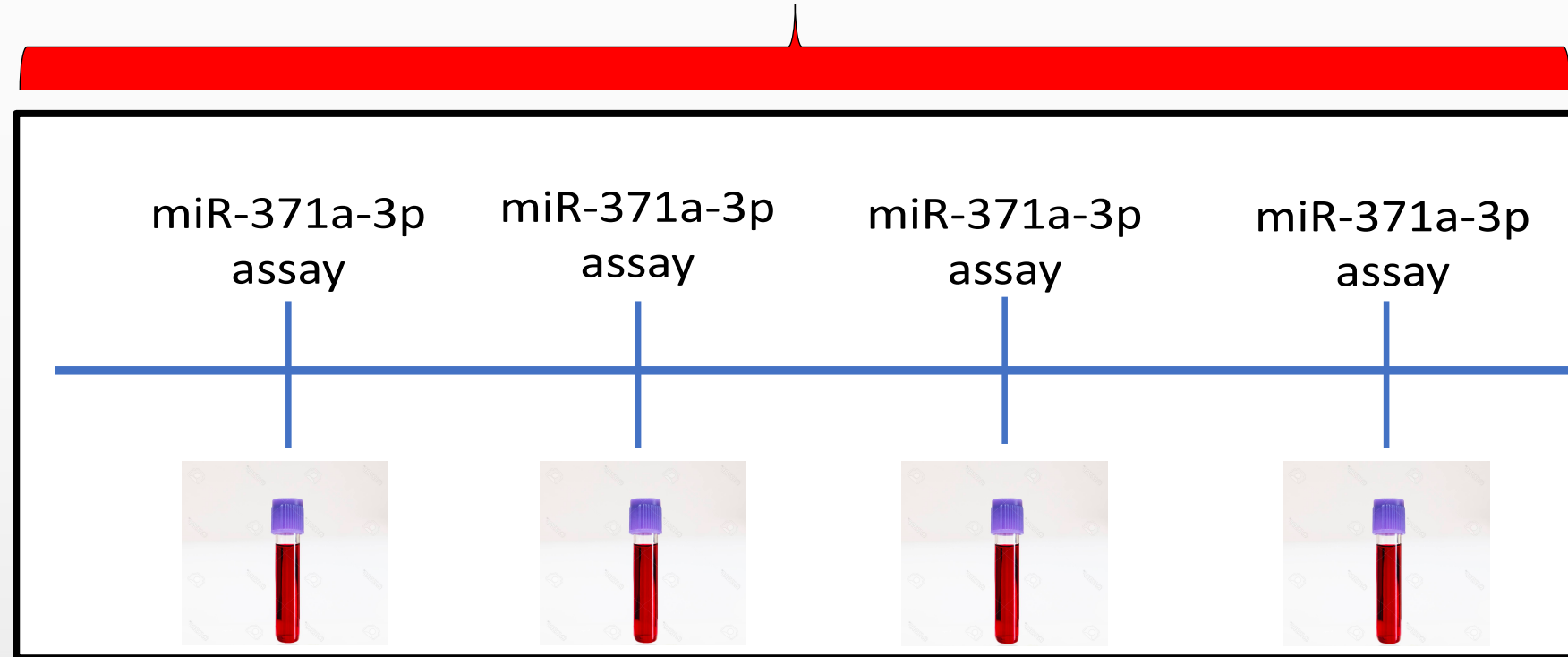
- Stage IA/B: Seminoma/NSGCT
  - TanyNOMOS0
- Any age

Standard Surveillance imaging/labs/follow up per NCCN guidelines

Orchiectomy



Stage I  
GCT



@adityabagrodiya



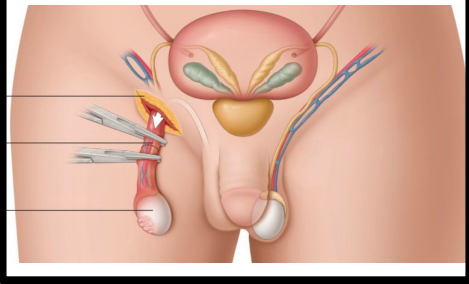
# S1823: A PROSPECTIVE OBSERVATIONAL COHORT STUDY TO ASSESS miRNA 371 FOR OUTCOME PREDICTION IN PATIENTS WITH NEWLY DIAGNOSED GERM CELL TUMORS

- Inclusion Criteria:

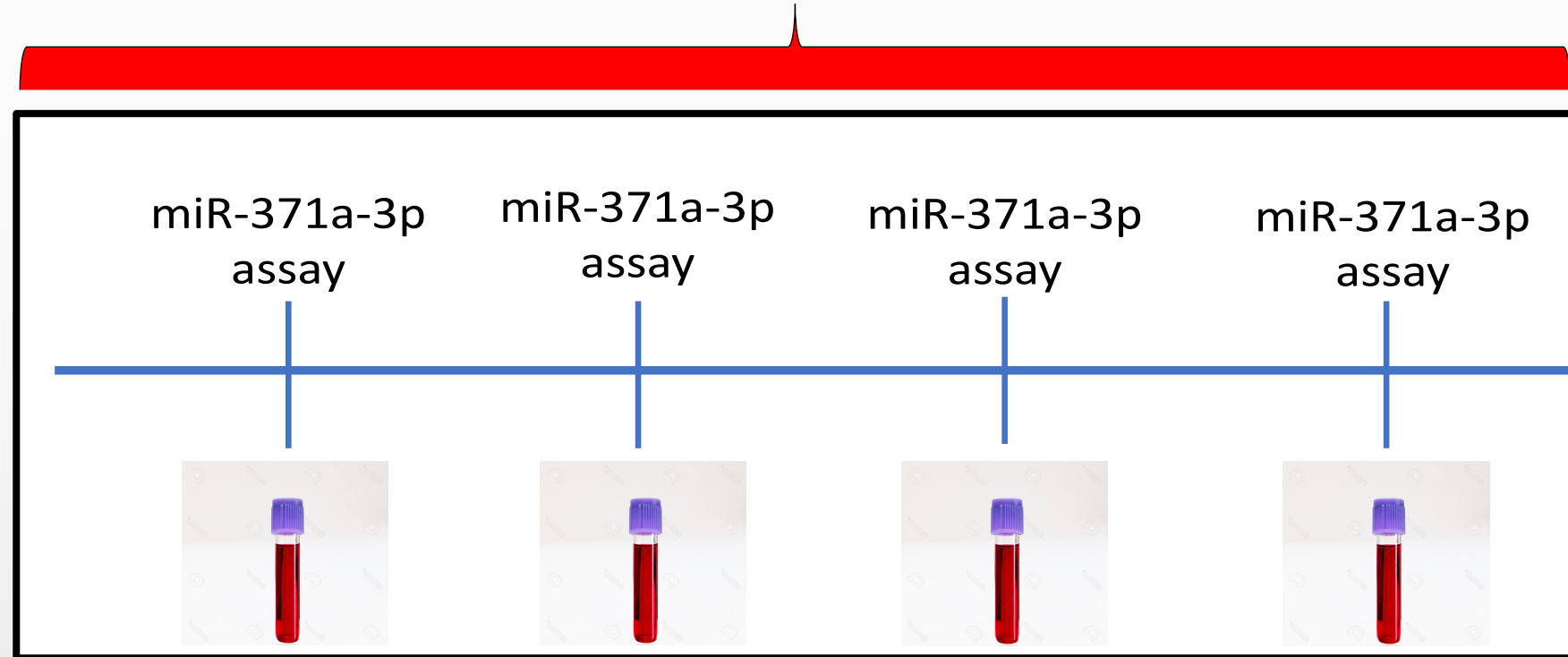
- Stage I-IIA: Seminoma/NSGCT

Standard Surveillance imaging

Orchiectomy



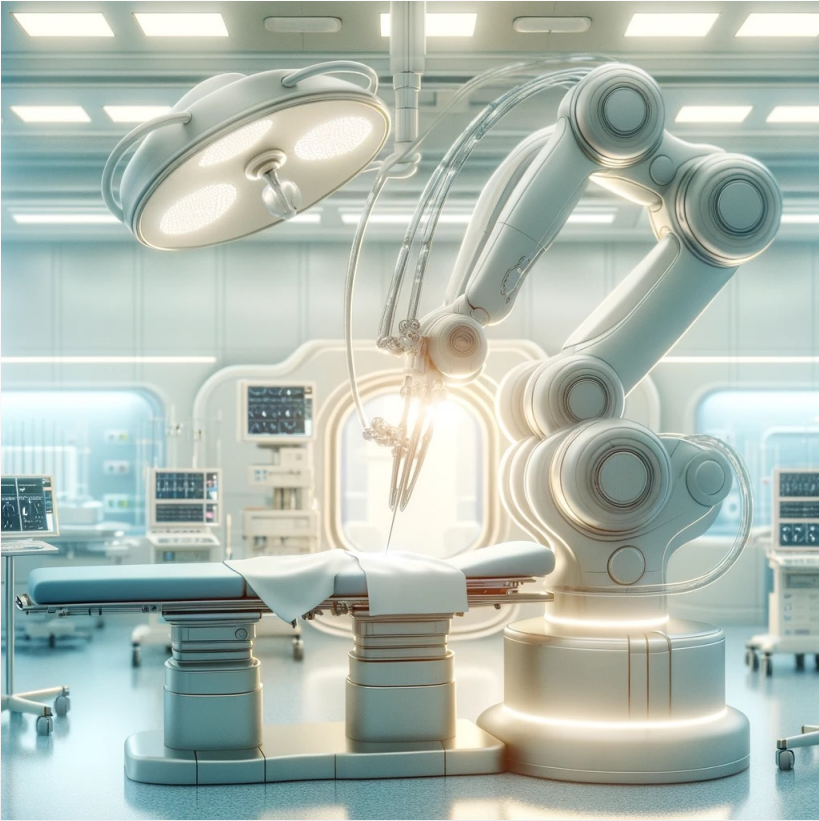
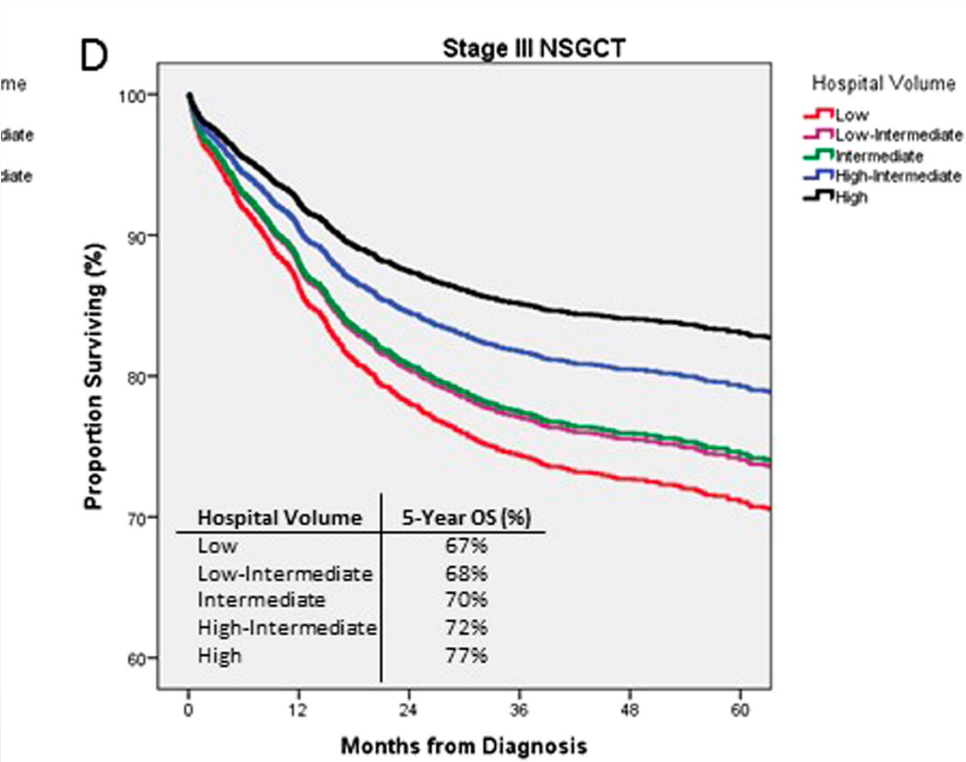
Stage I-IIA GCT



Germ cell tumor multi-disciplinary clinic every Tuesday



Robotic RPLND in appropriately selected patients



@adityabagrodia

## Conclusions

Early-stage testicular cancer management must maintain oncologic outcomes and prevent long term toxicity

Surgery for early-stage disease is curative in most patients at high volume centers

microRNAs likely change the way we diagnose and manage patients

Thank you!

Aditya Bagrodia

[bagrodia@health.ucsd.edu](mailto:bagrodia@health.ucsd.edu)

423-967-5848



@adityabagrodia