

Young Adult Testicular Cancer: Guidelines and Future Directions

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- No relevant disclosures
- I have no relevant financial relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved or investigative use of a commercial product/device in my presentation

Objectives

1. Identify the most common types of testicular malignancies.
2. Understand the various diagnostic and therapeutic approaches to these patients.
3. Remember key urologic principles of care:
 - Inguinal surgical approach
 - High suspicion for testicular primary in males with mediastinal or retroperitoneal masses – scrotal exam, scrotal US, serum tumor markers
 - Checking serum tumor markers prior to any surgery
4. Review topics of emerging research in testicular cancer.



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Introduction

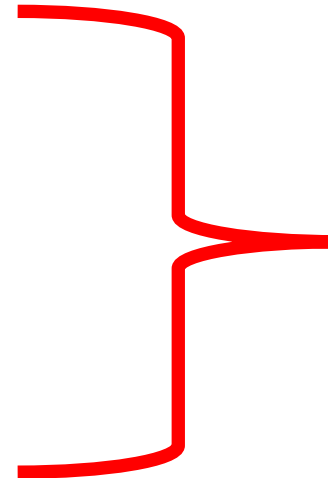
- Primary Testicular Tumors

- Germ Cell Tumors (95%) – AFP, bHCG

- Seminoma
 - Non-Seminoma
 - Yolk Sac Tumor
 - Embryonal Carcinoma
 - Choriocarcinoma
 - Teratoma

- Stromal Tumors (5%) - Inhibin

- Leydig Cell Tumors (Testosterone)
 - Sertoli Cell Tumors (Estradiol)
 - Granulosa Cell Tumors
 - Mixed/Undifferentiated



**Focus of
today's
talk**



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Of course, Dad jokes . . .



Of course, Dad jokes . . .



Background

- Testicular tumors account for 21.4% of all neoplasms in male adolescents and young adults in the U.S.

Most common solid tumor in this age group.

Bleyer A, et al: *Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000*

Prognosis

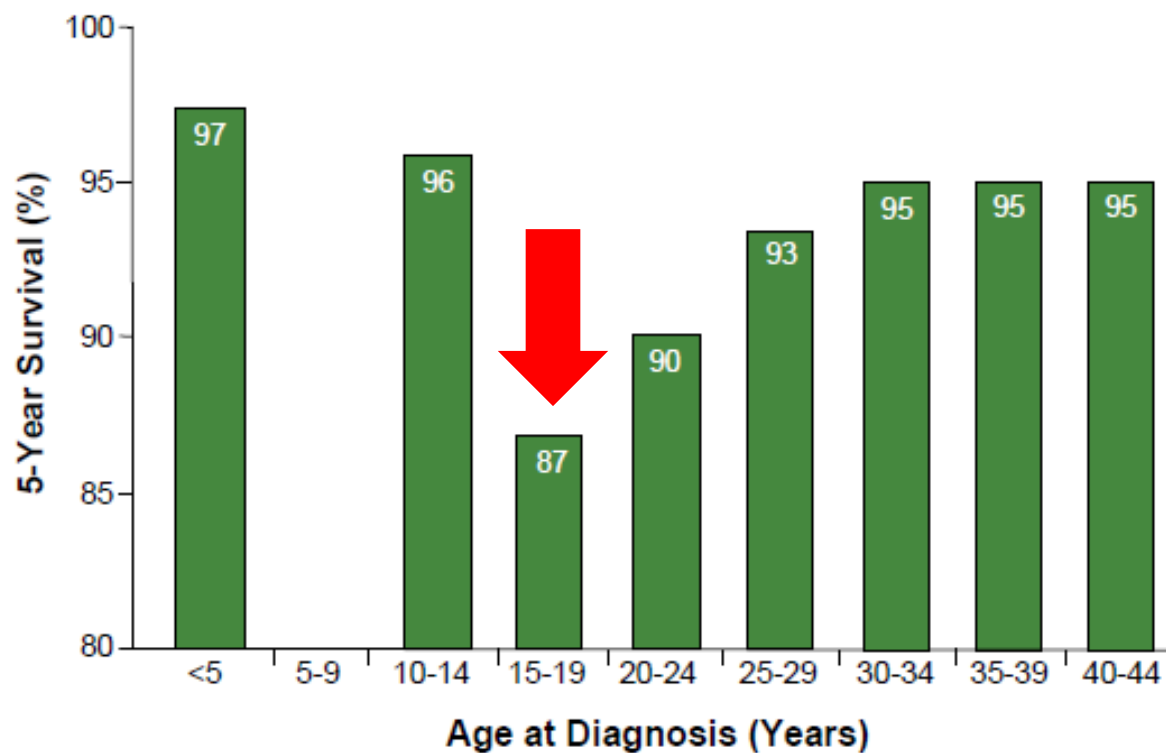


Figure 13.12: 5-Year Survival Rate for Testicular Cancer in Males, SEER 1975-1999

Bleyer A, et al: *Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000*

Background

- The following are well-described risk factors:
 - A prior personal history of cryptorchidism
 - A family history of testicular cancer
 - A prior personal history of testicular cancer
 - Intra-tubular Germ Cell Neoplasia (ITGCN)

Initial Work Up

- First steps
 - **Scrotal US** – assess the lesion and the contralateral testis
 - Serum Tumor Markers: bHCG, AFP, LDH
 - Consideration if those are negative and concern for a stromal tumor: Inhibin, Testosterone, Estradiol
 - Staging Imaging
 - Pre Op CXR before orchiectomy to R/O Massive Pulmonary Mets
 - Consideration of Pre Op CT Chest/Abd/Pelvis
- **Recommend sperm banking**



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Diagnosis

- **Inguinal** surgical approach
 - In general, in a post pubertal male, radical orchiectomy is indicated
 - If markers are negative, <2cm mass, and suspect benign disease or a stromal tumor:
 - Testis sparing surgery may be reasonable
 - Must have pathology available for immediate frozen section analysis
 - If markers are positive or concern on frozen section
 - Inguinal radical orchiectomy

Disclaimer . . . This is my opinion! There are data to support . . .

Staging

- Pathology
- Imaging – CT Chest/Abd/Pelvis
- Serum Markers (based on levels AFTER orchiectomy)
- Clinical versus Pathologic
- T, N, M and S staging
- Group Staging – I, II or III (Note, no Group Stage IV)

Tumor Markers - Keys to Remember

- AFP half life = 5-7days
 - AFP may be elevated in: Yolk Sac Tumor, Embryonal Carcinoma (EC)
 - Physiologic elevation of AFP: Infants, Liver disease
- bHCG half life = 24-36hr
 - bHCG may be elevated in: Seminoma, Choriocarcinoma, EC
 - May see elevation with Marijuana use or elevated LH (hypogonadism)



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Staging

- **Primary Tumor (T-stage):**
 - **pTis:** ITGCN
 - **pT1:** Confined to the testicle and/or epididymis.
 - The tumor may have invaded the tunica albuginea but not vaginalis
 - **pT2:** + LVI or Tunica Vaginalis Invasion.
 - **pT3:** Invasion of the spermatic cord.
 - **pT4:** Invasion of the scrotum.



Staging

- **Nodal Status (N-stage):** Clinical vs. Pathologic

cN0: There is no spread to regional LNs on imaging.

pN0: There is no cancer found in LNs removed during RPLND.

cN1: Imaging show ≥ 1 enlarged LN in the retroperitoneum but no enlarged LNs > 2 cm.

pN1: There is cancer in 1-5 LNs and none > 2 cm.

cN2: Imaging shows enlarged LNs in retroperitoneum 2-5cm.

pN2: There is cancer in >5 LNs but none are larger than 5 cm. Or, there 1 LN that is 2-5cm.

cN3: Imaging tests show enlarged LN or a LN mass in the retroperitoneum >5 cm.

pN3: There is cancer in 1 enlarged LN or LN mass that is > 5 cm.



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Staging

- **Metastatic Status (M-stage):**

- **M0:** No distant spread (**Different from regional LN spread**)
- **M1:** There is at least one distant metastasis.
 - **M1a:** Spread to distant (non-retroperitoneal) LNs and/or the lungs.
 - **M1b:** Spread to organs other than the lung (the lungs may or may not also be involved).
 - **Example:** Hepatic or Bone Metastases



Staging

- **Serum Marker Status (S-stage):** Nadir levels **AFTER** Orchiectomy

- **S0:** Tumor marker levels are normal.
- **S1:** At least one tumor marker level is above normal
 - hCG <5,000, and AFP <1,000
 - LDH < 1.5 x the upper limit of the normal range
- **S2:** Moderately High
 - hCG 5,000 to 50,000 or AFP 1,000 to 10,000
 - LDH 1.5 to 10 x the upper limit of the normal range
- **S3:** One or more tumor marker level is very highly elevated
 - hCG > 50,000 or AFP >10,000
 - LDH more than 10 times the upper limit of the normal range

Tricks to remember:

A1 . . . AFP

S1 <1,000

S2 1,000 to 10,000

S3 >10,000

Hi 5 . . . HCG

S1 < 5,000

S2 5,000 to 50,000

S3 >50,000



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Group Staging

Stage I (Can be Clinical or Pathologic)

- **Stage I:** any T, N0, M0, SX
- **Stage IA:** pT1 N0 M0 S0
- **Stage IB:** pT2-T4 N0 M0 S0 – Think LVI+
- **Stage IS:** any T, N0, M0, and S1-3 – persistent marker elevation but no clinical evidence of spread on imaging
- **No Spread Seen on Imaging**
- **+LVI, Vaginalis, Cord or Scrotal invasion = Ib**
- **Elevated markers AFTER surgery = Is**

Clinical Stage I

- Imaging:
 - CT scan will be false negative about 30%.
 - Thus, about 30% of men on observation for “Clinical Stage I” disease recur because of occult metastatic disease not evident on imaging at the time of diagnosis.

Group Staging

Stage II: any T, N1-3, M0, S0-1 = Retroperitoneal LN Only Spread

- **Stage IIA:** any T, N1, M0, S0-1
 - **Stage IIB:** any T, N2, M0, S0-1
 - **Stage IIC:** any T, N3, M0, S0-1
-
- N1 = Ila (1-5LNs, Largest <2cm)
 - N2 = I Ib (>5LNs, Largest 2-5cm)
 - N3 = I Ic (>5cm)

Group Staging

Stage III: any T, N0-3, M1, SX = Spread outside of the Retroperitoneal LNs

- **Stage IIIA:** any T, N0-3, M1a, S0-1
- **Stage IIIB:** any T, N1-3, M0, S2; OR any T, N0-3, M1a, S2
- **Stage IIIC:** any T, N1-3, M0, S3; OR any T, N0-3, M1a, S3; OR any T, any N, M1b, any S
- Non Retroperitoneal LN Mets OR Highly Elevated Markers = Stage III
- S2 = Stage IIIB
- M1b or S3 = Stage IIIC



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Metastatic Disease Risk Assignment

<u>Good Risk</u>	
<u>Non-Seminoma</u>	<u>Seminoma</u>
<p><u>No spread to an organ other than the lungs</u></p> <p><u>And</u></p> <p><u>Normal or Low elevated markers (S0-S1)</u> All of the following: AFP < 1,000 ng/mL B-hCG < 5,000 iU/L LDH < 1.5 x ULN</p>	<p><u>No spread to an organ other than the lungs</u></p> <p><u>And</u></p> <p><u>Normal AFP, any B-hCG, any LDH</u></p>



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Metastatic Disease Risk Assignment

<u>Intermediate Risk</u>	
<u>Non-seminoma</u>	<u>Seminoma</u>
<p><u>No Spread to an organ other than the lungs</u></p> <p><u>And</u></p> <p><u>Intermediate markers (S2)</u></p> <p>Any of:</p> <p>AFP $\geq 1,000$ and $\leq 10,000$ ng/mL</p> <p>B-hCG $\geq 5,000$ and $\leq 50,000$ iU/L</p> <p>LDH $\geq 1.5 \times \text{ULN}$ and $\leq 10 \times \text{ULN}$</p>	<p><u>Spread to an organ other than the lungs</u></p> <p><u>And</u></p> <p><u>Normal AFP, any B-hCG, any LDH</u></p>



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Metastatic Disease Risk Assignment

<u>Poor Risk</u>	
<u>Non-seminoma</u>	<u>Seminoma</u>
<u>Spread to an organ other than the lungs</u> <u>OR</u> <u>High markers (S3)</u> Any of the following: AFP $\geq 10,000$ ng/mL B-hCG $\geq 50,000$ iU/L LDH $\geq 10 \times$ ULN	<u>There are no patients with poor-risk seminoma</u>



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Dad joke . . .



Dad joke . . .



Management

- Starts with Orchiectomy
- Exception:
 - Patient with massive pulmonary metastatic disease with fatal potential

Management

- Next, it depends on pathology/staging
 - Histology: Seminoma vs. Non-Seminoma
 - Seminoma is only for 100% pure seminoma
 - Any other histology or any AFP elevation = Non-seminoma
 - Post Orchiectomy Markers (S-status is a post-operative finding)
 - Stage I vs. Metastatic disease
 - If Metastatic, depends on Histology and Risk Classification

Seminoma

- Stage IA, IB: Options
 - Observation (ASCO and NCCN recommended)
 - Radiation
 - Primary Chemotherapy (Carbo x 1 or 2 cycles)
- Risk of occult mets increased by:
 - Size >4cm
 - Rete testis invasion
 - Age >35yr

Seminoma

- Stage IS, IIA and IIB:
 - Radiation – Preferred by NCCN
 - Primary Chemotherapy (BEP x 3 or EP x 4)
- Contraindications to XRT:
 - IBD
 - Prior XRT
 - Pelvic/Horseshoe Kidney

Seminoma

- Stage IIC and III:
 - Good Risk = BEP x 3 or EP x 4
 - Some use EP alone to avoid Bleomycin Pulmonary Toxicity
 - Intermediate Risk = BEP x 4

Seminoma

- Residual Mass after Chemo:
 - 20% Active GCT
 - 80% Fibrosis or Necrosis
- PET is useful in Residual Pure Seminoma
 - **NOTE:** PET should not be used in NSGCT
 - If PET is done, need to wait at least 6 weeks after completion of last cycle of chemotherapy

Seminoma

- Negative markers and Negative PET = Observation
- Negative markers and Positive PET
 - Post chemotherapy bilateral RPLND
- Persistently elevated markers = 2nd Line Chemotherapy

Seminoma

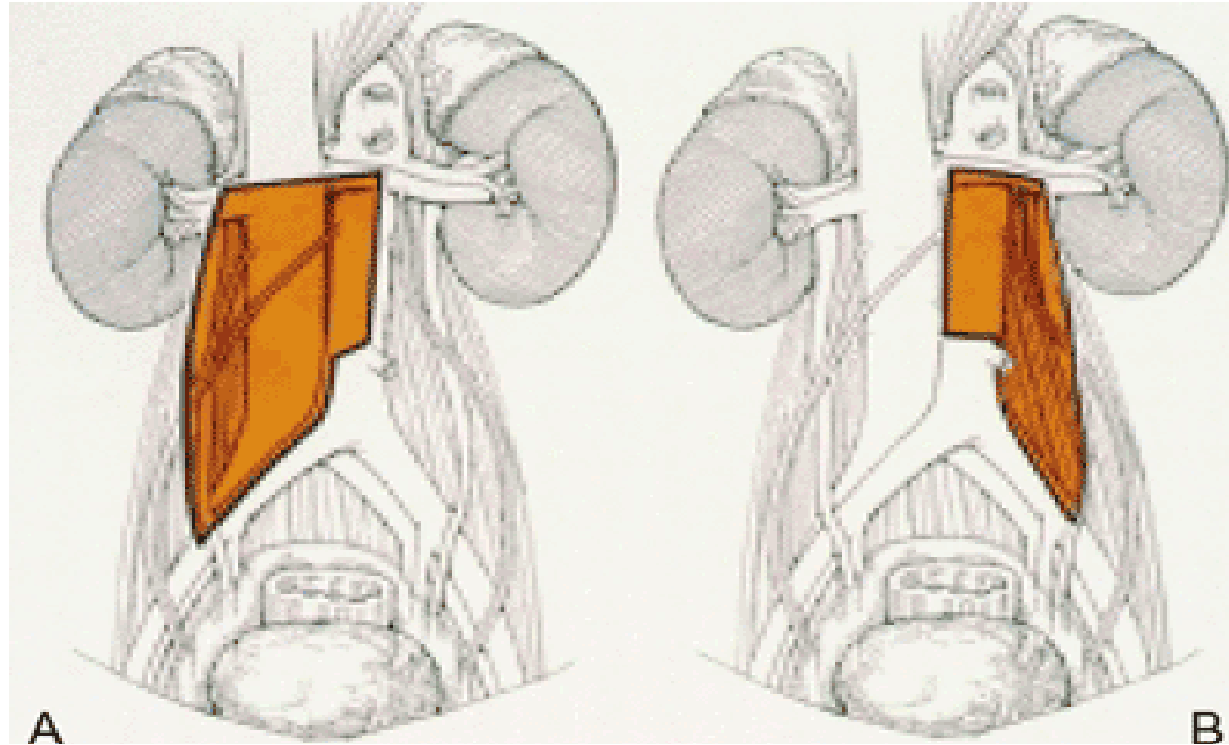
- Active GCT found on Post chemotherapy RPLND
 - Adjuvant Chemotherapy
- Relapse after negative imaging and negative markers
 - Chemotherapy: VeIP or TIP
 - Possibly High dose chemotherapy and autologous BMT

Non-Seminoma

- Stage IA, IB
 - Observation (about 30% will have OMD and “relapse”)
 - Primary Chemotherapy (1 x BEP)
 - Primary RPLND
- Risk of OMD increased by:
 - +LVI
 - >50% Embryonal Carcinoma in the orchiectomy specimen



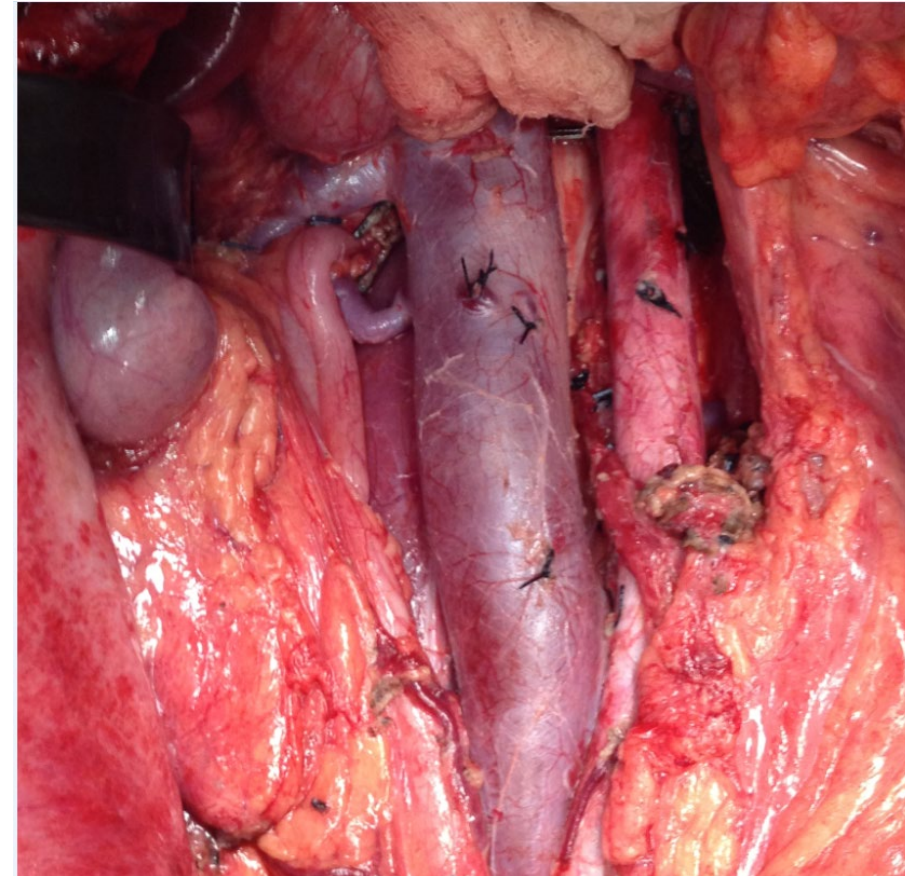
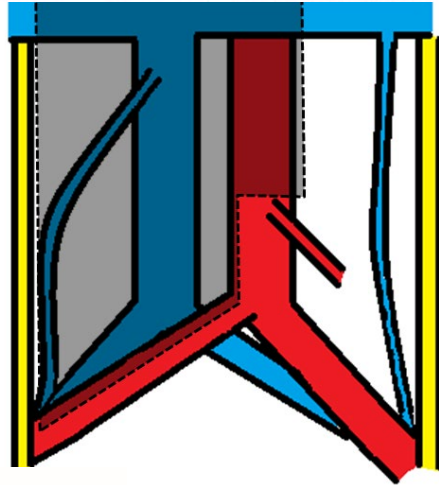
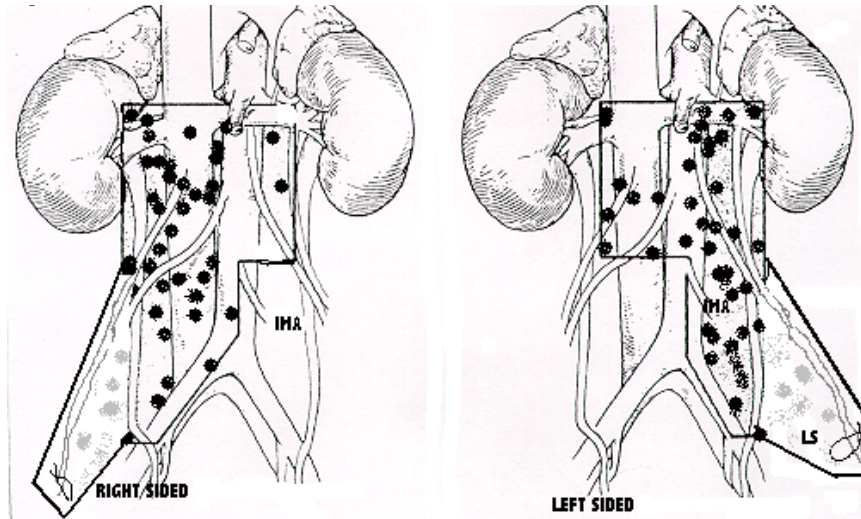
Template RPLND



LN drainage is from R to L, thus the extension in the R Template

Goal is to avoid damage to sympathetics and retrograde ejaculation

Template RPLND



Non-Seminoma

- Stage IS
 - Chemotherapy = BEP x 3 or EP x 4
- Stage IIA, IIB
 - Chemotherapy
 - Good Risk = BEP x 3 or EP x 4
 - Intermediate or Poor Risk = BEP x 4
 - If negative markers, some advocate for primary RPLND

Non-Seminoma

- Stage IIC or III
 - Chemotherapy
 - Good Risk = BEP x 3 or EP x 4
 - Intermediate or Poor Risk = BEP x 4

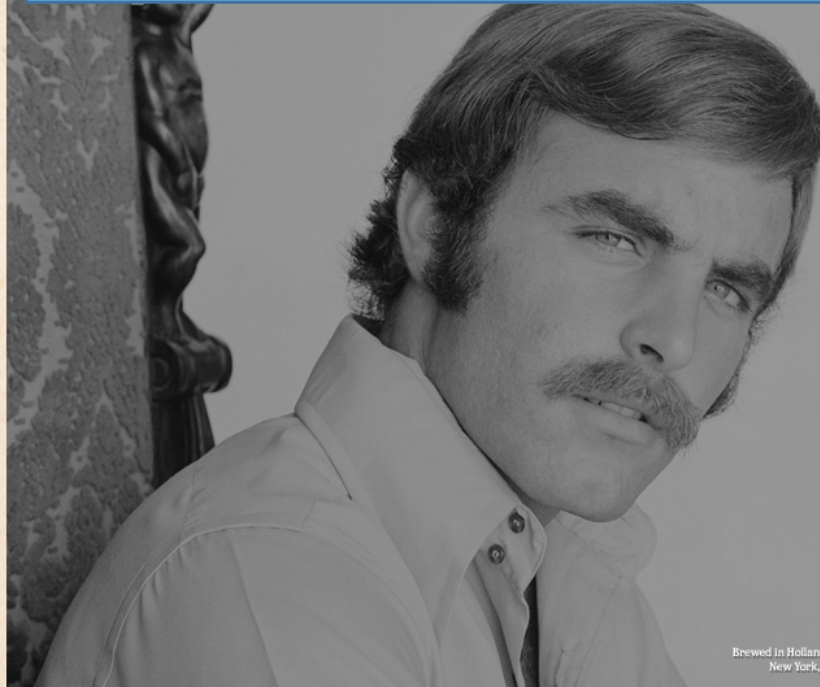
Non-Seminoma

- Residual Mass:
 - 20% Active GCT
 - 40% Teratoma
 - 40% Fibrosis or Necrosis
- PET not helpful since it can't distinguish Teratoma from Fibrosis
- Negative markers, $\geq 1\text{cm}$ Residual = Bilateral RPLND
- Negative markers, $< 1\text{cm}$ Residual = Observation
- Persistent markers = 2nd line Chemotherapy - VeIP or TIP

Non-Seminoma

- Active GCT found on Post chemotherapy RPLND
 - Consider chemotherapy – debated if markers normalize
- Relapse after clinical CR
 - Chemotherapy: VeIP or TIP
 - Vinblastine/Taxol, Ifosfamide and Platinum (Cis > Carbo)
 - Possibly High dose chemotherapy and autologous BMT

DID YOU GET A HAIRCUT?



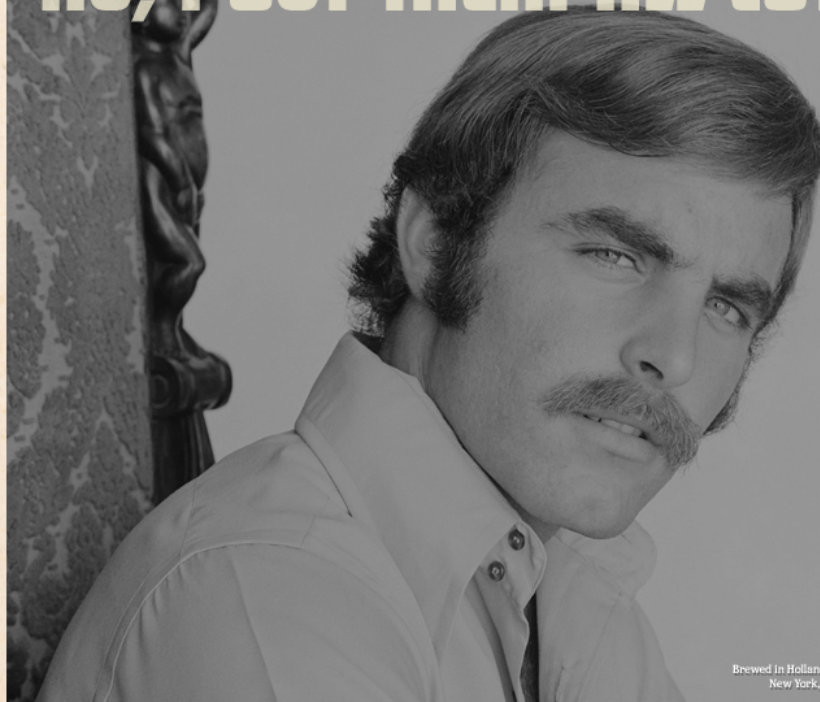
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DID YOU GET A HAIRCUT?
no, I GOT THEM ALL CUT.



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Survival

5yr Overall Survival

<u>Stage</u>	<u>Risk</u>	<u>Seminoma</u>	<u>NSGCT</u>
I		>98%	>98%
<hr/>			
IIA or IIB		>95%	>95%
IIC or III	Good	86%	92%
	Int	72%	80%
	Poor		48%

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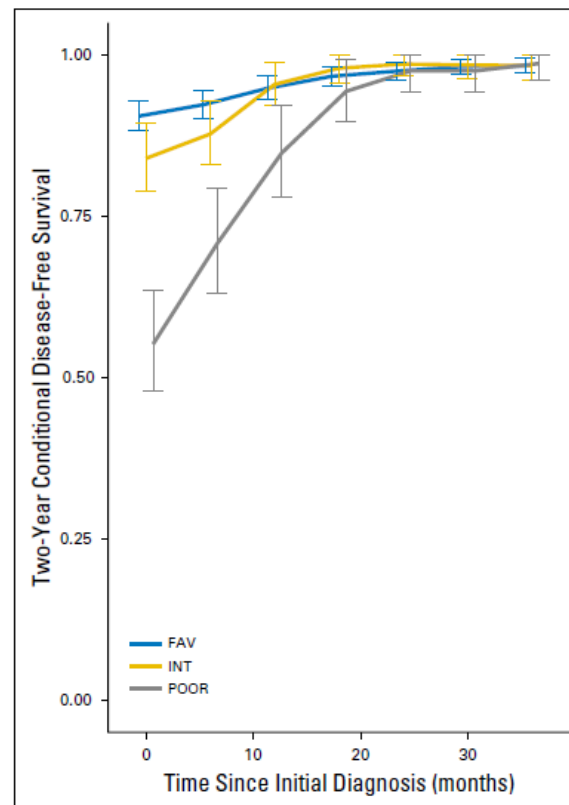
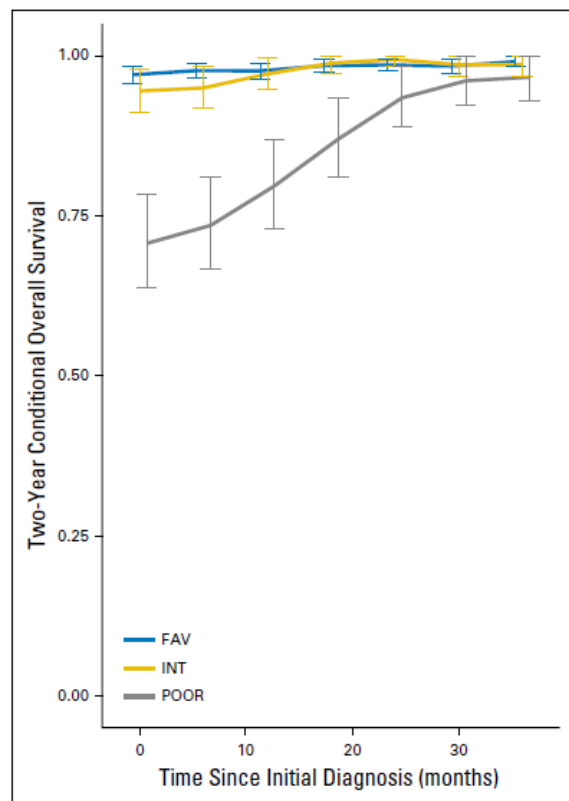
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Conditional Survival of Patients With Metastatic Testicular Germ Cell Tumors Treated With First-Line Curative Therapy

Jenny J. Ko, Brandon Bernard, Ben Tran, Haocheng Li, Tehmina Asif, Igor Stukalin, Margaret Lee, Daphne Day, Nimira Alimohamed, Christopher J. Sweeney, Philippe L. Bedard, and Daniel Y.C. Heng

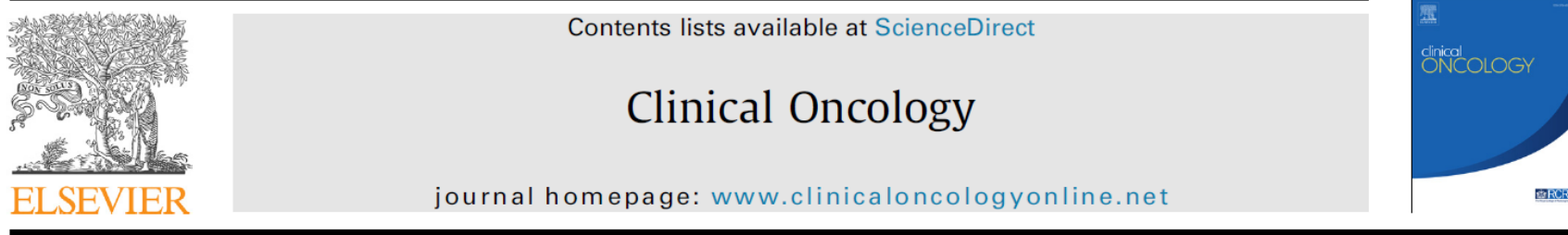


Interlude

- Next stop . . .
 - Emerging Research/Issues in Testis Cancer.

Future Directions

- Local vs. Systemic Control for Stage IIa Seminoma



Original Article

Stage II Testicular Seminoma: Patterns of Care and Survival by Treatment Strategy[☆]

S.M. Glaser^{*}, J.A. Vargo^{*}, G.K. Balasubramani[†], S. Beriwal^{*}

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journal homepage: www.clinicaloncolologyonline.net



Original Article

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[†]Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

- XRT demonstrated better survival compared to Systemic Chemotherapy for Stage IIa Seminoma.
- Local control?
 - XRT vs. RPLND?

Low Volume Stage II Seminoma

- Approximately 15% of all newly diagnosed seminoma patients will be Low-Volume Clinical Stage II at some point.
 - Initial Clinical Stage I and relapse on surveillance: 5-10% of all new diagnoses
 - Initial Clinical Stage II: 10% of all new Diagnoses
- This is analogous to cases considered for primary RPLND in Stage II Non-seminoma or for Stage II Seminoma considered for XRT.

Leung et al. *BJU-I* 2013.
Warde et al. *JCO* 1998.



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Low Volume Stage II Seminoma



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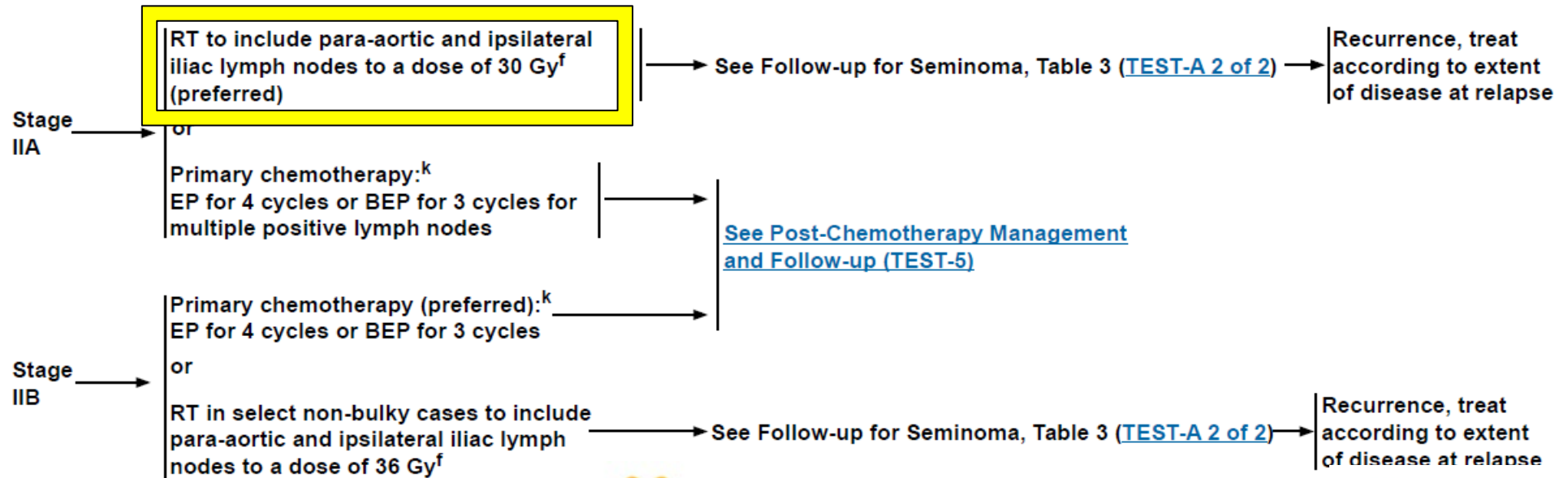
NCCN Guidelines Version 1.2015 Testicular Cancer - Pure Seminoma

[NCCN Guidelines Index](#)
[Testicular Cancer TOC](#)
[Discussion](#)

CLINICAL STAGE

PRIMARY TREATMENT

FOLLOW-UP



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Low Volume Stage II Seminoma

Travis et al. *JNCI* 2005.
van den Belt-Dusebout et al. *JCO* 2007.
Zagars et al. *JCO* 2004.

Background

- RT provides a long-term RFS of 90-95% in Stage II disease.
- But, RT is associated with an increased risk of treatment-induced second malignant neoplasms (SMN).
 - Actuarial risk of developing a SMN at 15-18% 25 years after RT for testicular cancer.
 - Another study of 453 testicular seminoma survivors treated with RT-only quantified that the standardized mortality ratio from SMN was 1.9.



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Low Volume Stage II Seminoma

Data for RPLND - Only 2 reports addressing the issue.

- 17 published cases of patients with low-volume Stage II seminoma treated with RPLND alone, no cases of recurrence reported.

Warszawski et al. *Scan J Nephrol Urol* 1997.
Mezvrishvili et al. *Int Urol Nephrol* 2006.

TESTICULAR CANCER

SEMS trial: Result of a prospective, multi-institutional phase II clinical trial of surgery in early metastatic seminoma.

Background: Chemotherapy or radiotherapy are standard treatments for stage II seminoma, though they are associated with significant long-term treatment-related toxicities. Retroperitoneal lymph node dissection (RPLND) is an established treatment for testicular germ cell tumors but little data exists on its efficacy as a front-line treatment in early metastatic (stage II) seminoma. This is a single-arm, multi-institutional (NCT02537548), phase II study of retroperitoneal lymph node dissection (RPLND) as first-line treatment for

testicular seminoma with isolated retroperitoneal disease. **Methods:** Twelve sites in the United States and Canada prospectively enrolled patients (16 years of age) with testicular seminoma and isolated retroperitoneal lymphadenopathy between 1-3 cm in size. Patients were excluded if they

received prior therapy (except orchiectomy) for testicular cancer. Open, modified-template RPLND was performed by qualified surgeons with a primary endpoint of 2-year recurrence-free survival. Data on complication rates (short and long-term), pathologic up/downstaging, recurrence patterns, adjuvant therapies, and treatment-free survival were assessed. **Results:** A total of 55 patients were enrolled and underwent RPLND. Fourteen patients had initial stage I disease who developed isolated retroperitoneal relapse while 41 patients had clinical stage IIA-B at presentation. With a median follow-up of 24 months (8-52 months), there were a total of 10 recurrences. The overall recurrence rate was 18% with a median time to recurrence of 8 months. Of the recurrences, 8 underwent chemotherapy (6 BEP X 3, 1 EP X 4, 1 carbo/etoposide) and 2 underwent additional surgery. The two-year recurrence free survival was 87% and the overall survival was 100%. There were 7 (13%) patients who experienced short-term complications within 1 year of RPLND. Of these, 5 (9%) were classified as Clavien Dindo I-II and 2 (3.6%) were classified as Clavien Dindo III. No patients have reported long-term complications.

Conclusions: This trial establishes RPLND as a therapeutic option as a first-line treatment in early metastatic seminoma. The surgery offers cancer control rates similar to those seen in non-seminomatous germ cell tumors. [Clinical trial information: NCT02537548.](#)

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TESTICULAR CANCER

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Background: Chemotherapy or radiotherapy are standard treatments for stage II seminoma, though they are associated with significant long-term treatment-related toxicities. Retroperitoneal lymph node dissection (RPLND) is an established treatment for testicular germ cell tumors but little data exists on its efficacy as a front-line treatment in early metastatic (stage II) seminoma. This is a single-arm, multi-institutional (NCT02537548), phase II study of retroperitoneal lymph node dissection (RLND) as first-line treatment for testicular seminoma with isolated retroperitoneal disease. **Methods:** Twelve sites in the United States and Canada prospectively enrolled patients (16 years of age) with testicular seminoma and isolated retroperitoneal lymphadenopathy between 1-3 cm in size. Patients were excluded if they received prior therapy (except orchiectomy) for testicular cancer. Open, modified-template RPLND was performed by qualified surgeons with a primary endpoint of 2-year recurrence-free survival. Data on complication rates (short and long-term), pathologic up/downstaging, recurrence patterns, adjuvant therapies, and treatment-free survival were assessed. **Results:** A total of 55 patients were enrolled and underwent RPLND. Fourteen patients had initial stage I disease who developed isolated retroperitoneal relapse while 41

patients had clinical stage IIA-B at presentation. With a median follow-up of 24 months (8-52 months), there were a total of 10 recurrences. The overall recurrence rate was 18% with a median time to recurrence of 8 months. Of the recurrences, 8 underwent chemotherapy (6 BEP X 3, 1 EP X 4, 1 carbo/etoposide) and 2 underwent additional surgery. The two-year recurrence free survival was 87% and the overall survival was 100%. There were 7 (13%)


patients who experienced short-term complications within 1 year of RPLND. Of these, 5 (9%) were classified as Clavien Dindo I-II and 2 (3.6%) were classified as Clavien Dindo III. No patients have reported long-term complications.

Conclusions: This trial establishes RPLND as a therapeutic option as a first-line treatment in early metastatic seminoma. The surgery offers cancer control rates similar to those seen in non-seminomatous germ cell tumors. [Clinical trial information: NCT02537548.](#)

TESTICULAR CANCER

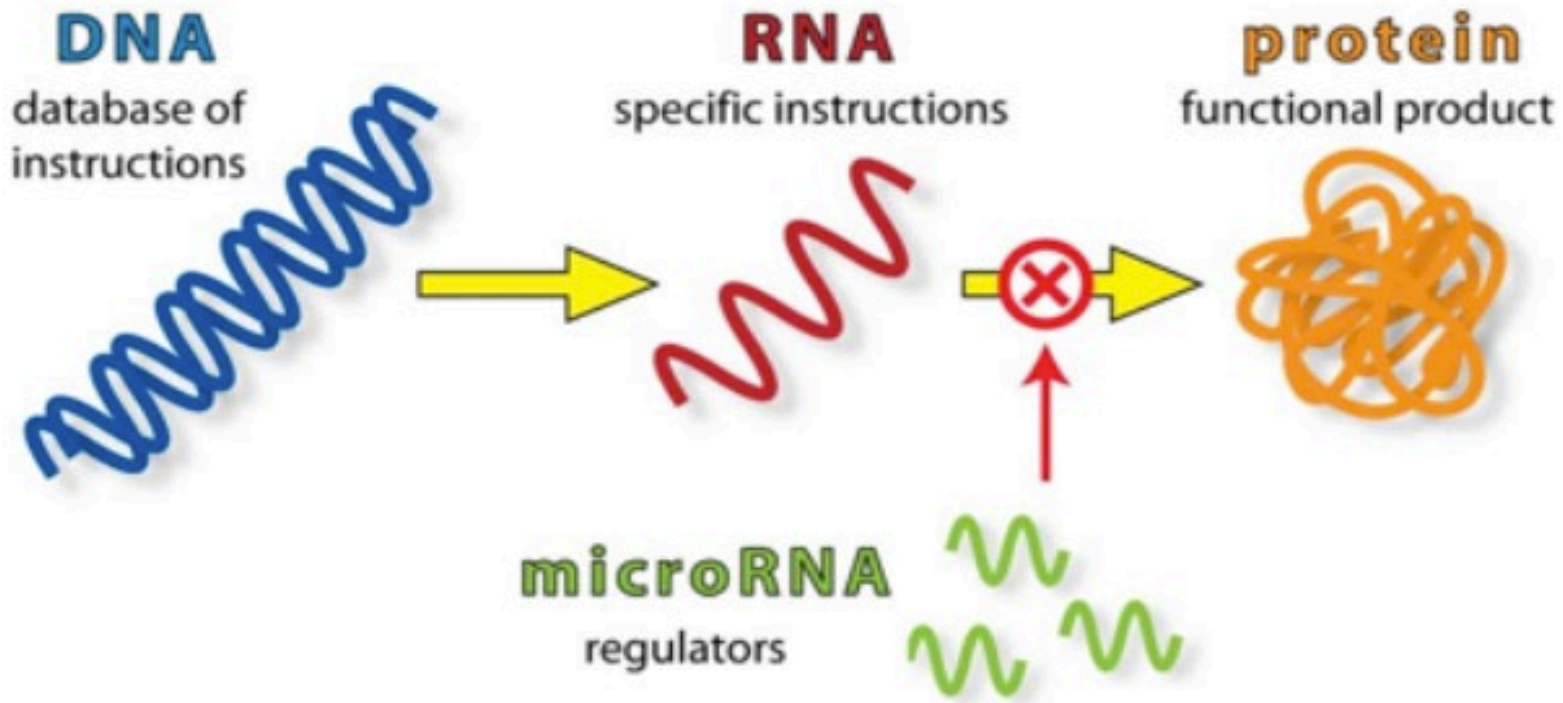
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What is a micro RNA?

- Short
- Non-c
- Funct



Early formative work

Original Paper

High-throughput cell tumour

miRNA	Histology	Mapping	Target
34aN	TE	1p36.22	—
133b	TE	6p12.2	<i>POU4F1, MEIS2</i>
140	TE	16q22.1	<i>BCL11A, SOX4</i>
145	SE/EC	5q32	<i>PLAGL2, E2F3</i>
367	EC	4q25	<i>PLAG1</i> <u>LATS2</u>
371	SE/EC	19q13.41	<i>ZIC4</i>
372	SE/EC	19q13.41	<u>LATS2, LEFTY1, DAZAP2, TNFAIP1, PLAGL2</u>
373	EC	19q13.41	<u>LATS2, LEFTY1, MLL3, TNFAIP1</u>

in human germ

Various histological elements within germ cell tumors can be identified based on expression of 156 miRNA

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J Baeten,² P

¹Department of
Netherlands

²Applied Biosystems, Foster

³Department of Bioinforma

⁴Integromics, Madrid, Spain

eltman,¹

am, The

Gillis et al. *J Pathol* 2007:213;319

Serum Levels of MicroRNAs miR-371-3: A Novel Class of Serum Biomarkers for Testicular Germ Cell Tumors?

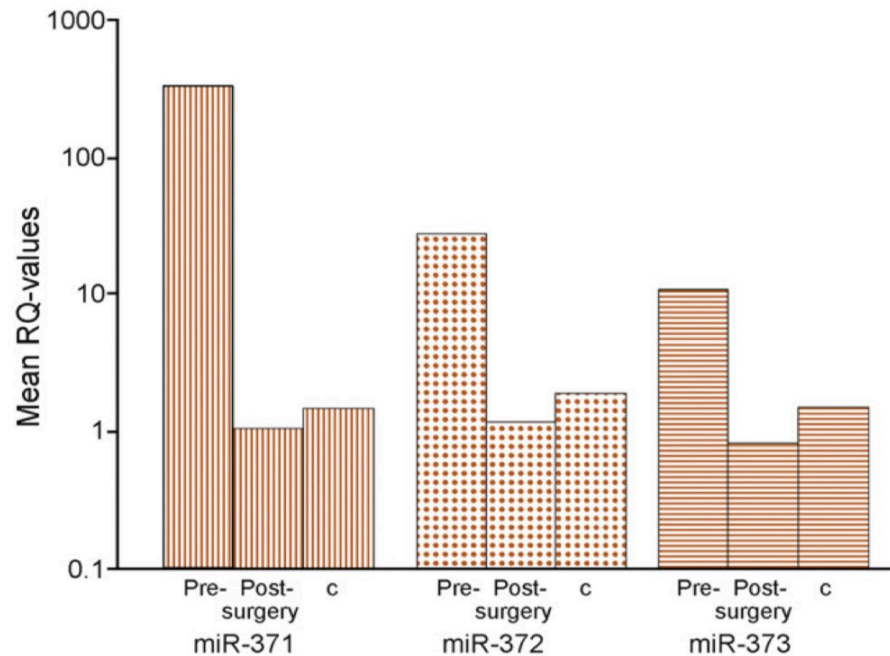


Fig. 1 – Results of the relative microRNA (miRNA) quantifications in serum of germ cell tumor (GCT) patients and controls. Mean values of three miRNAs—miR-371, miR-372, and miR-373—in serum samples of 11 GCT patients pre- and postoperatively. c: mean value of 12 controls; the y-axis is plotted on a log¹⁰ scale.

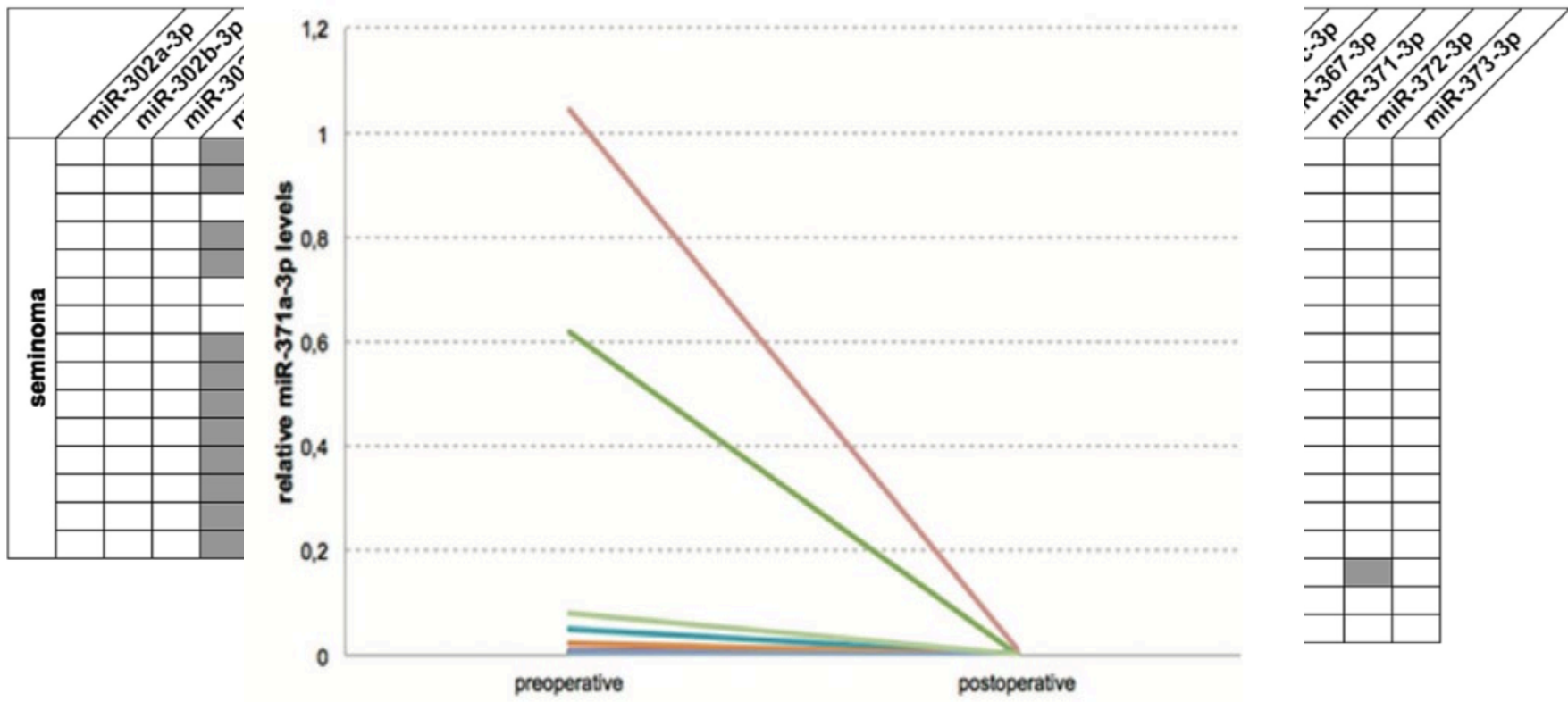
- 11 clinical stage I patients
-6 seminoma & 5 non-seminoma
- Blood drawn preorchietomy and 5 days post
- Small sample size
- Unclear about specificity (thyroid cancers)
- Correlated with earlier report in a 4 year old with YST

Belge et al. *Eur Urol* 2012;61;1068

Circulating Serum miRNA (miR-367-3p, miR-371a-3p, miR-372-3p and miR-373-3p) as Biomarkers in Patients with Testicular Germ Cell Cancer

Syring et al. *J Urol* 2015;193;331

Isabella Syring,* Joanna Bartels, Stefan Holdenrieder, Glen Kristiansen, Stefan C. Müller and Jörg Ellinger



Can we move into clinical practice?

Expanding into clinical trials

- SWOG S1823 trial
- AGCT 1531 trial

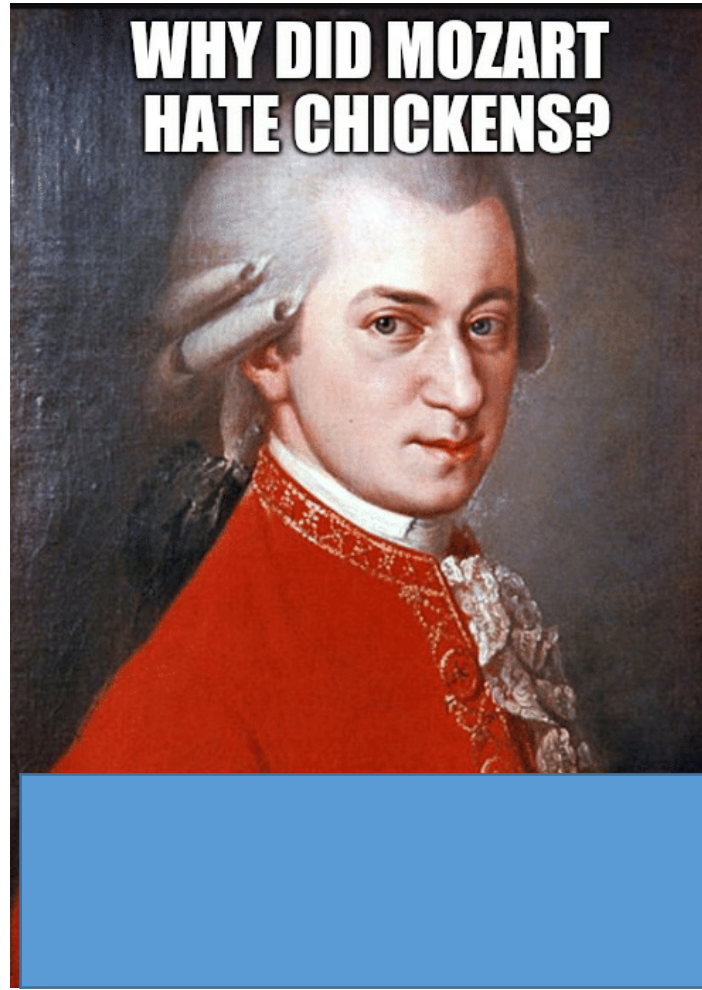
Clinical Pearls

- On observation, most relapses in 1st year and almost all by 2nd year
- Watch for Pulmonary Congestion in post-chemotherapy RPLND patients b/c of Bleomycin exposure
 - Pre Op PFTs if ≥ 4 cycles of Bleomycin
 - No O₂ >21%
 - Judicious use of IVFs

Clinical Pearls

- No role for XRT in Non Seminoma
 - Seminoma “exquisitely” sensitive to XRT
- Role of PET limited to Post Chemotherapy Residual Seminoma
- No “Poor Risk” Seminoma
- Remember to consider testicular primary in males with a retroperitoneal or mediastinal mass

Time for One Last Dad Joke



Time for One Last Dad Joke



Conclusions

- Thank you!
- Questions? Comments?
- Please reach out!

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- @cost_nicholas

Please be interactive!!! Ask questions!!!

***Please promote the meeting
on social media:***

***#PAYAUroOncCourse
@PedsUroOnc***



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Cancer Center



PUOWG
Pediatric Urologic Oncology
Working Group



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