Testicular Stromal Tumors

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PUOWG
Pediatric Urologic Oncology Working Group

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Acknowledgement

- Thank you to Dr. Jonathan Ross for the slides!

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Testicular tumors – what does the testis do?

- Make sperm
  - Germ Cell Tumors

- Make hormones and support the germ cells
  - Stromal Tumors – possible markers = Testosterone, Estradiol, Inhibin B
    - Leydig Cell – Testosterone
    - Sertoli Cell – Estradiol
    - Large Cell Calcifying Sertoli Cell Tumor
    - Juvenile Granulosa Cell
    - Mixed/Undifferentiated

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Prepubertal Testis Tumor Registry

- Patients registered primarily between 1980 and 1990

- N=395
  - Younger than 12 years
  - Primary testis tumor

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Primary Testis Tumor Types from Testis Tumor Registry

Tumor Type	Number	%
Yolk Sac	244	62
Teratoma	92	23
Epidermoid Cyst	13	3
Stromal	*42*	*11*
Gonadoblastoma	4	1

Ross et al, 2002

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Primary Testis Tumor Types
Multicenter Study (n=98)

Tumor Type	%
Yolk Sac	15
Teratoma	48
Epidermoid Cyst	14
Stromal	*13*
Other	9

Pohl et al 2003

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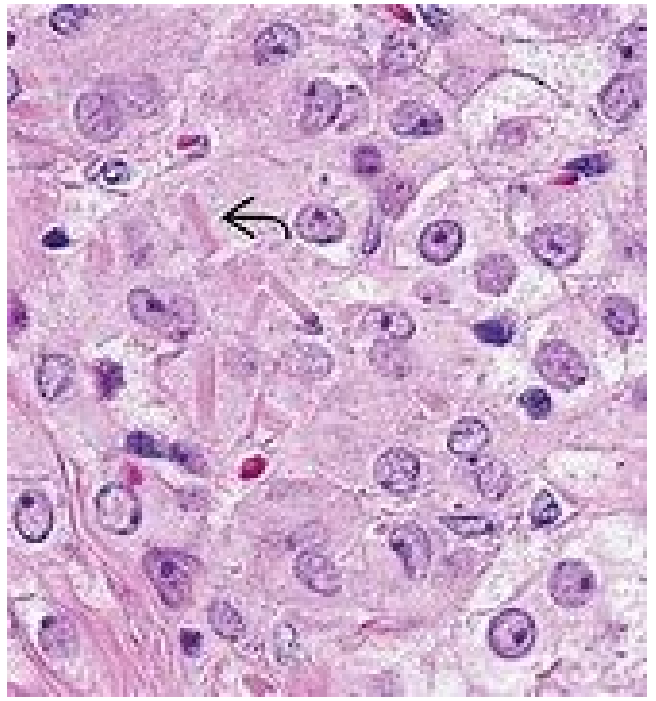
Leydig Cell Tumor

- Reinke crystals are rod-like cytoplasmic inclusions
- Make testosterone



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Leydig Cell Tumor

- Universally benign in children
- Precocious puberty (gynecomastia in adults)
- Testis-sparing appropriate (occasionally multifocal)

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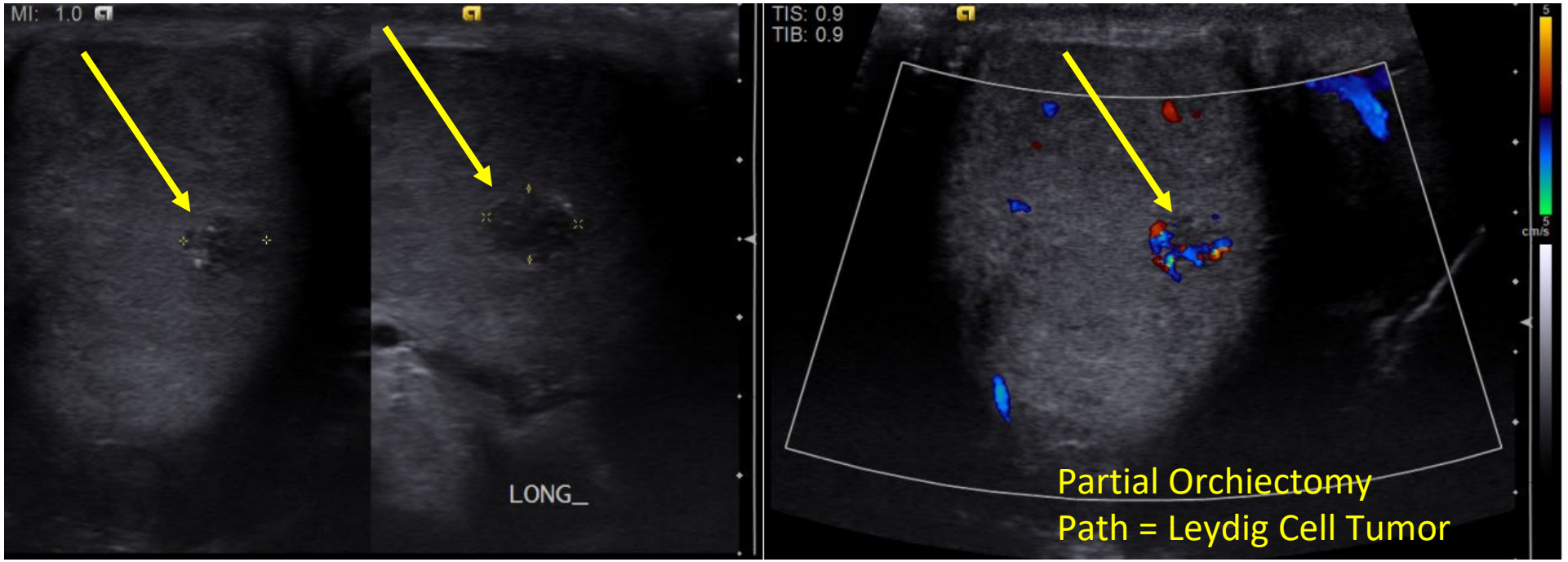
Clinical case



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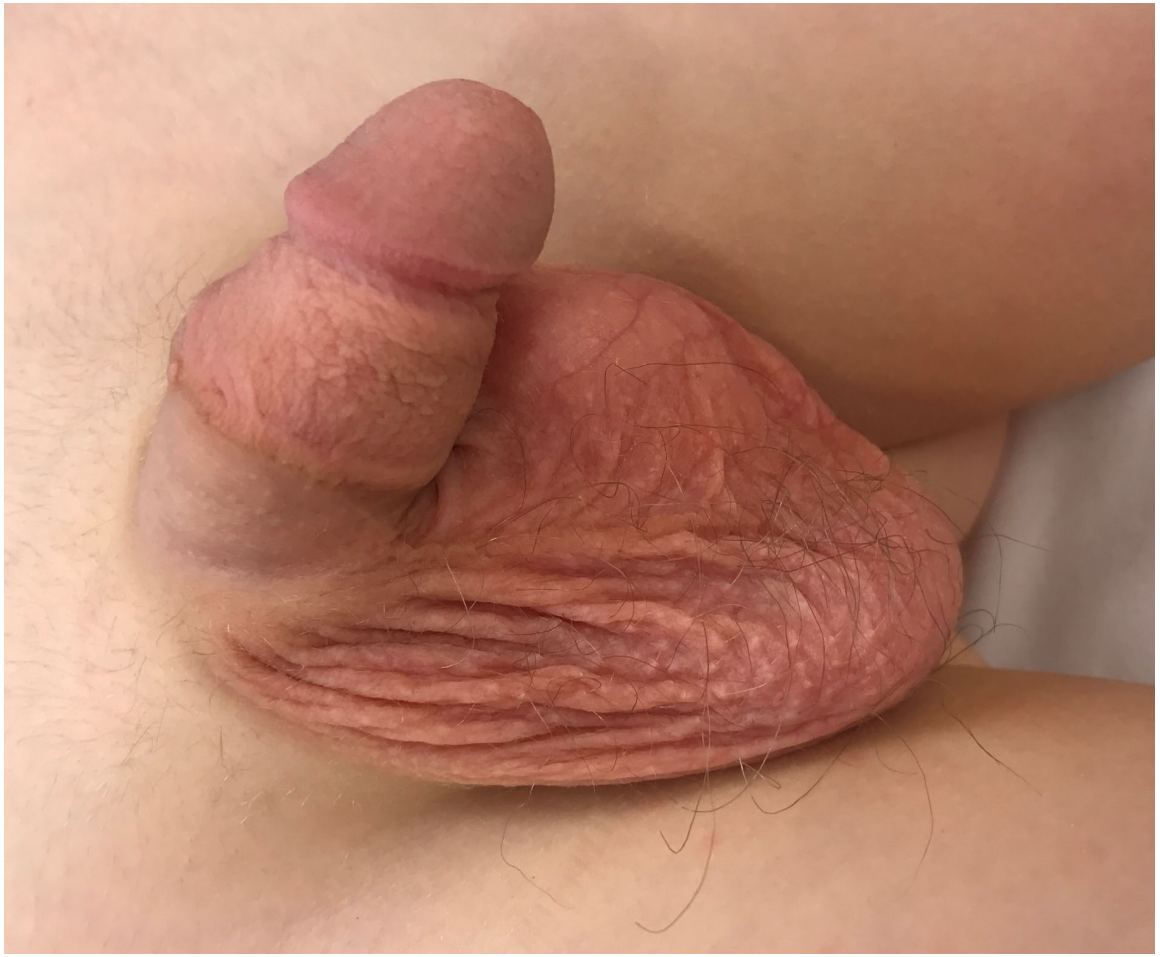
Leydig Cell Tumor – Precocious Puberty



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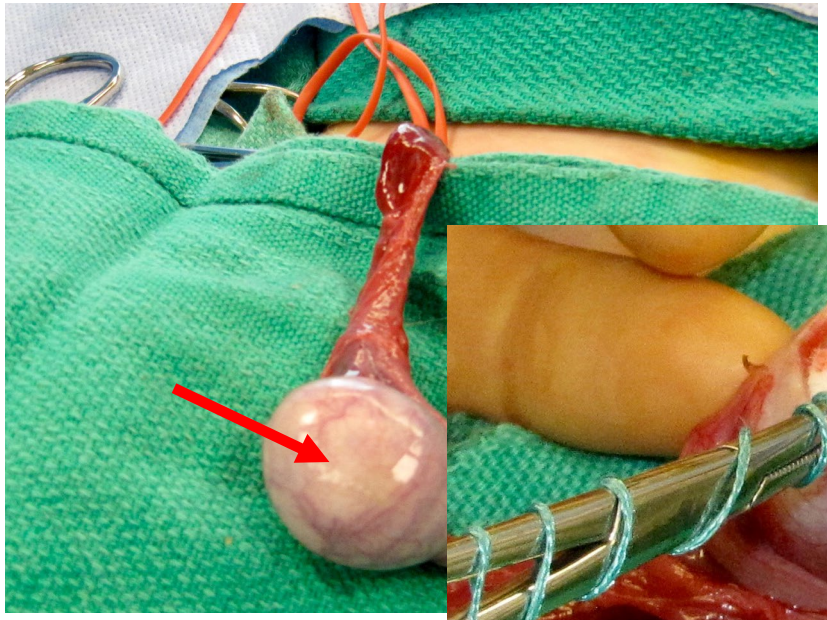
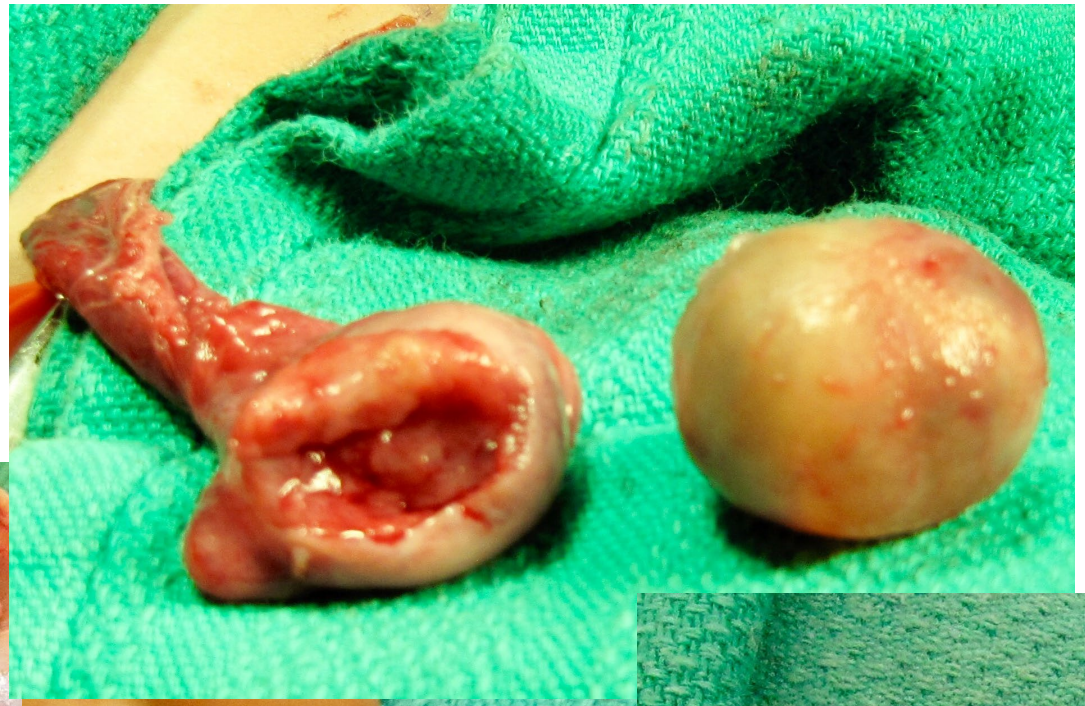
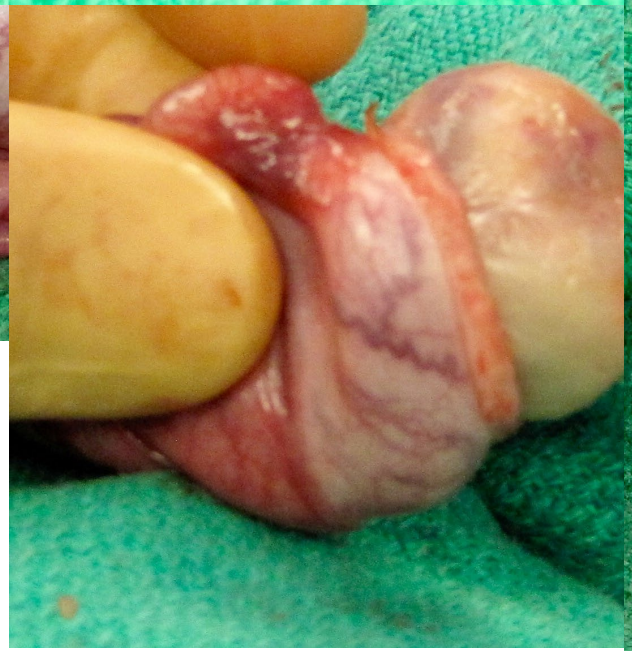
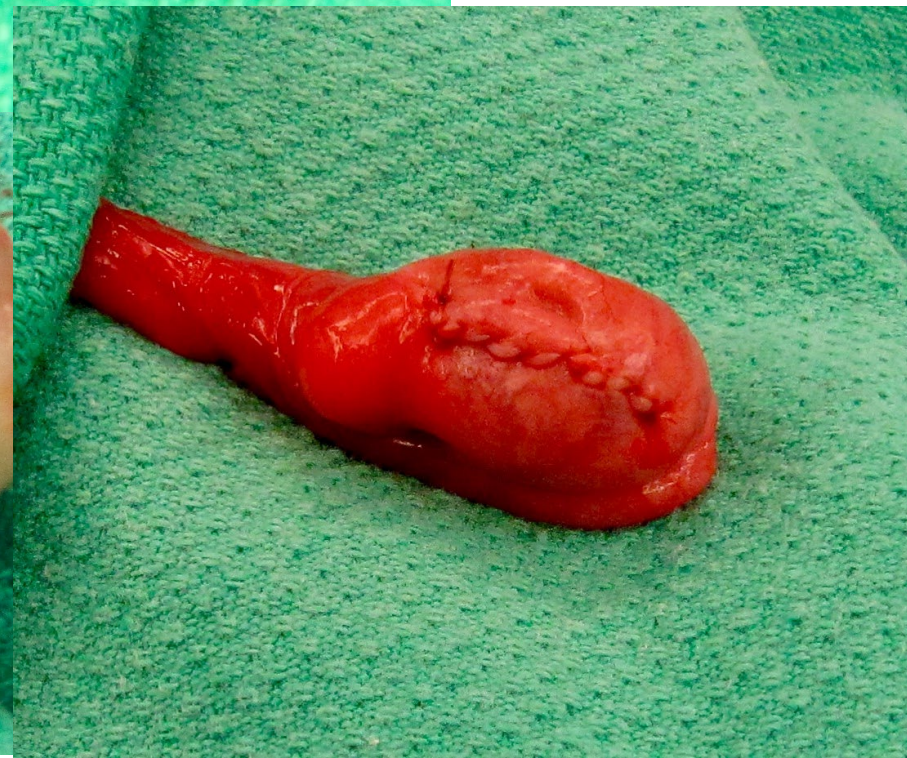
Testis sparing surgery



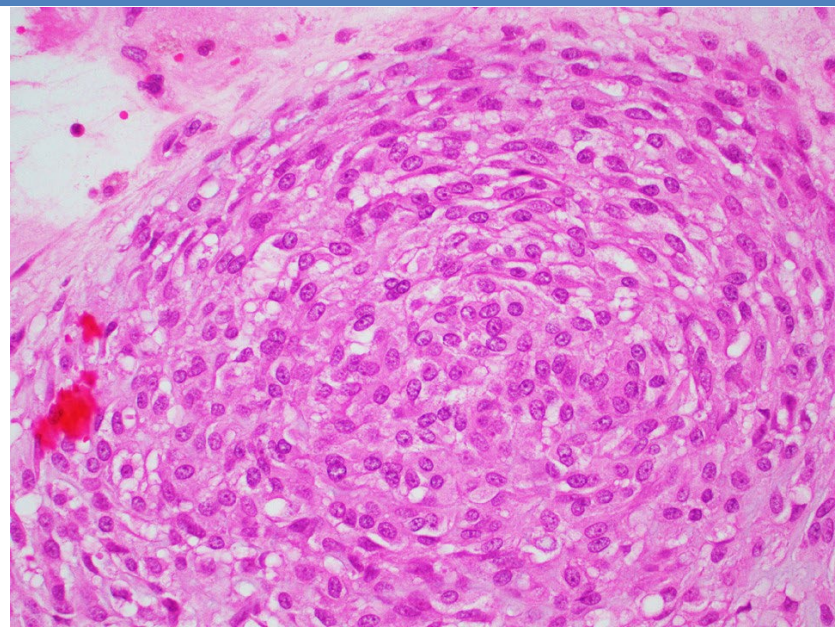






Pictures courtesy of Lynn Woo

Sertoli Cell Tumor



- Orchiectomy or testis-sparing surgery
- Malignant in 10% of adult cases
- Malignancy rare in children (and none reported less than 5 years old)
- Usually hormonally inactive in children

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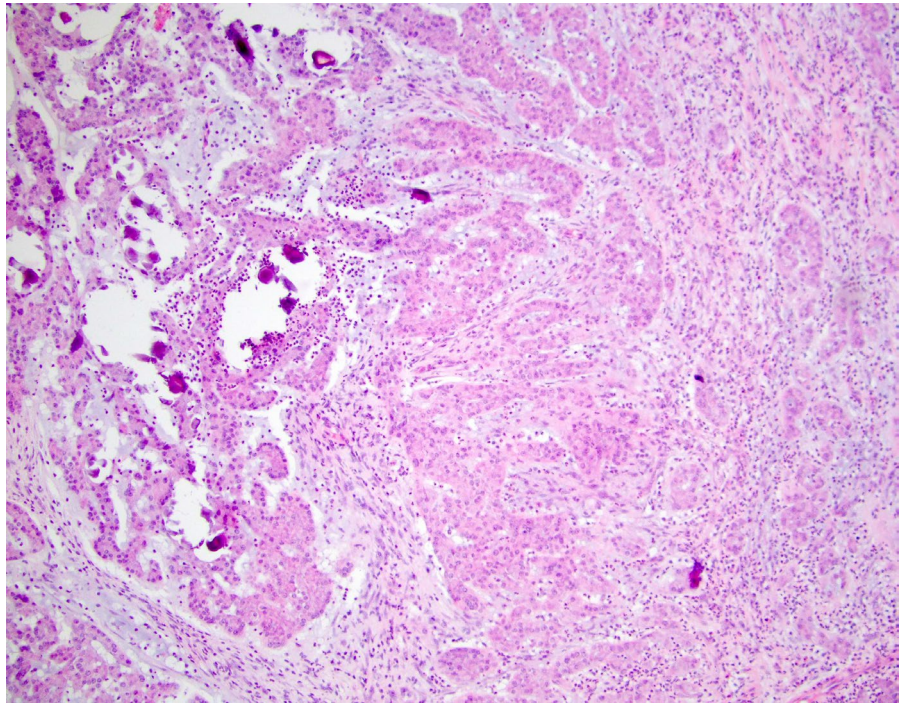
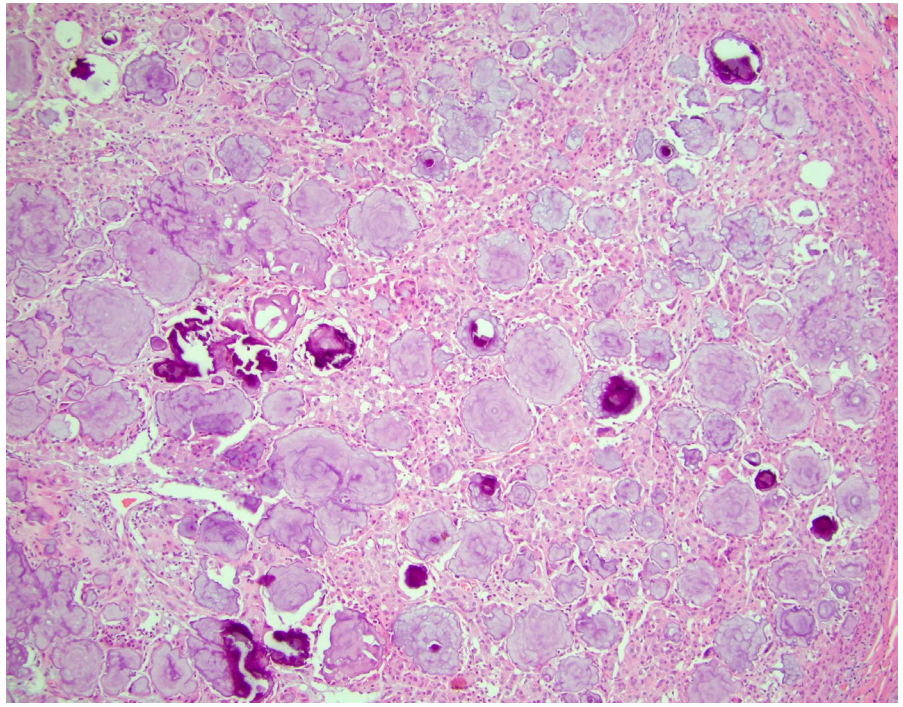
Large cell calcifying Sertoli cell tumor





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Large cell calcifying Sertoli cell tumor

- Present with mass
- 1/4 bilateral/multifocal
- 1/3 have an associated syndrome
  - Peutz-Jegher
  - Carney's
- Universally benign under 25 years old
  - Testis-sparing reasonable

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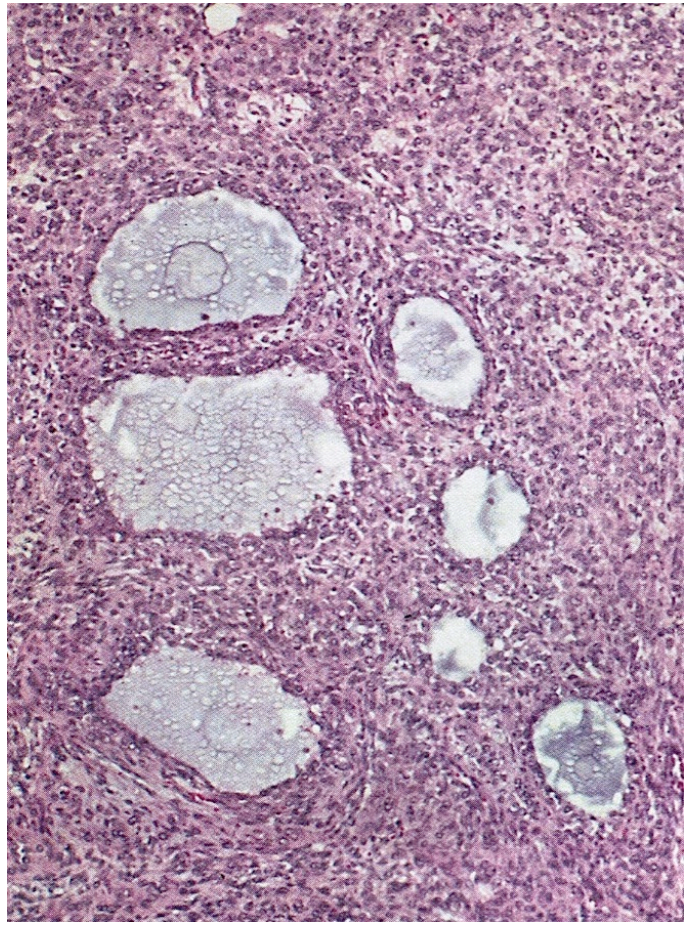
Juvenile Granulosa cell tumor

- Tumor of infancy
- Universally benign
  - Testis-sparing surgery if possible
- Y chromosome abnormalities common and ambiguous genitalia has been seen
- Hormonally inactive



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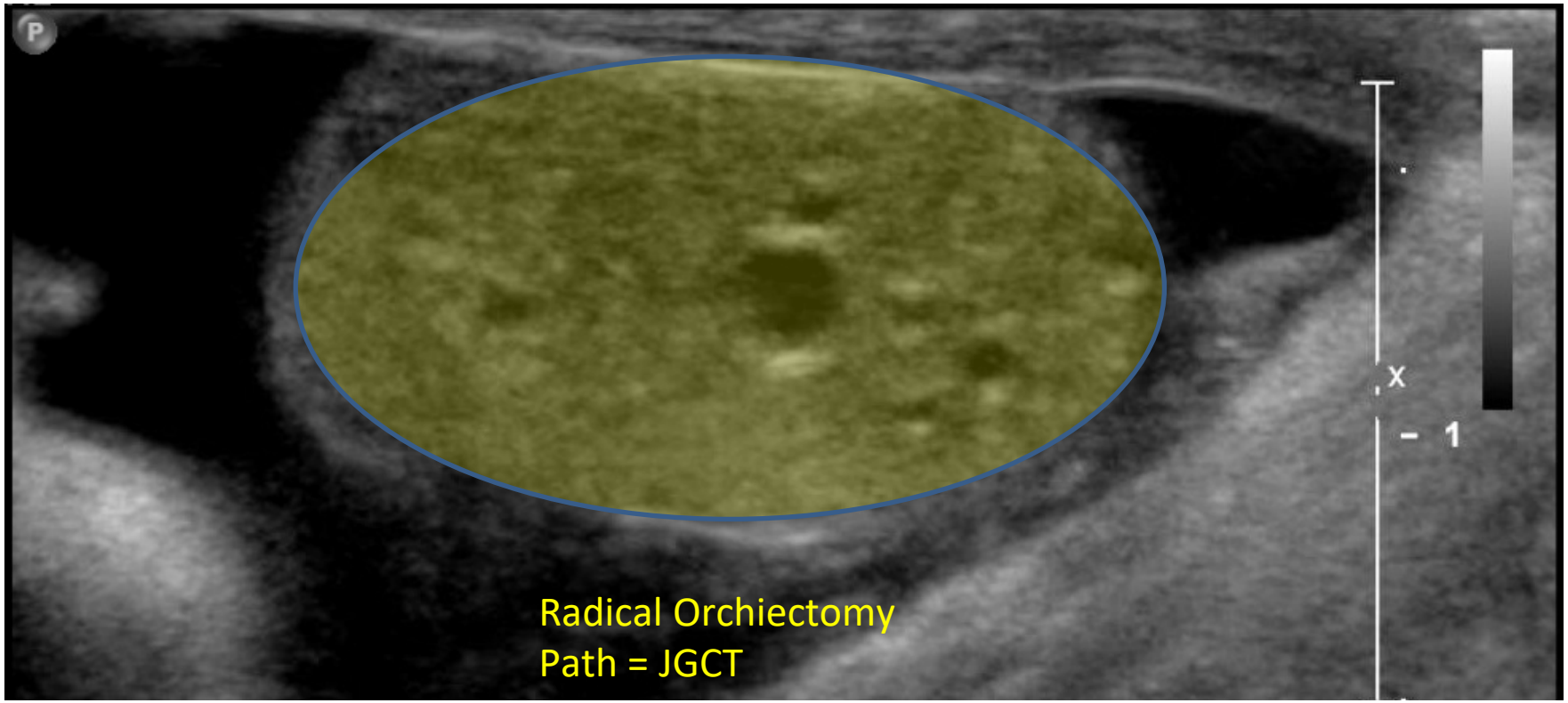
Large mass in 21 day old male



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Mixed/Undifferentiated stromal tumors

- Malignancy uncommon, but can occur in older children
- Metastatic evaluation/surveillance in older children and those with worrisome histological features

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Behavior of Stromal Tumors in kids

- Leydig cell, LCCSCT, and JGCT are benign*
  - Consider follow-up for 2 years

- Occasional Sertoli > 5 years old and poorly differentiated stromal may be malignant
  - Resection when at all possible
  - PEB is recommended systemic treatment but lack of good data/responses

Thomas et al, 2001, Schultz et al, 2012, Schneider et al, 2021

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Behavior of Stromal Tumors – Pediatric/Adolescent

Pathologic Risk Factors in Pediatric and Adolescent Patients With Clinical Stage I Testicular Stromal Tumors

Kyle O. Rove, MD, Paul D. Maroni, MD,* Carrye R. Cost, MD,†*
Diane L. Fairclough, DrPH, MSPH,‡ Gianluca Giannarini, MD,§
Anne K. Harris, MPH,‖¶ Kris A. P. Schultz, MD,‖¶
*and Nicholas G. Cost, MD**

(*J Pediatr Hematol Oncol* 2015;37:e441–e446)

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Behavior of Stromal Tumors – Pediatric/Adolescent

Pathologic risk factors
- ≥3 mitoses per HPF
- Positive margins
- Rete testis invasion
- LVI
- Cellular atypia
- Necrosis
- Largest tumor diameter > 5 cm

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Behavior of Stromal Tumors – Pediatric/Adolescent

Results: A total of 100 patients from 31 publications were included with a median age at diagnosis of 5.7 years (range, 1.2 mo to 21 y). Seventy-nine patients were 12 years and below (median 7.2 mo) and 21 patients were 13 to 21 years (median 16 y). No patients in either group were identified to have OMD at retroperitoneal lymph node dissection or during follow-up surveillance (median follow-up 45.6 y; range, 4 to 360 mo). 99% of those 12 years and below versus 95% of those above 12 years had 0 to 1 pathologic risk factors, and 1% versus 5% had 2 + pathologic risk factors ($P = 0.38$).

Conclusions: Clinical stage I TSTs in adolescent, postpubertal patients appear to behave in a benign manner with few pathologic risk factors, similar to prepubertal patients. Given the low risk of relapse in this population, low-impact surveillance strategies are paramount. Prospective study of these patients is needed, and entry into a tumor registry such as the International Ovarian and Testicular Stromal Tumor Registry is important to learning more about this rare disease.

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Behavior of Stromal Tumors – Post pubertal

Oncology

Pathologic Risk Factors for Metastatic Disease in Postpubertal Patients With Clinical Stage I Testicular Stromal Tumors

Kyle O. Rove, Paul D. Maroni, Carrye R. Cost, Diane L. Fairclough, Gianluca Giannarini, Anne K. Harris, Kris Ann P. Schultz, and Nicholas G. Cost

UROLOGY 97: 138–144, 2016.

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Behavior of Stromal Tumors – Post pubertal

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Behavior of Stromal Tumors – Post pubertal

OBJECTIVE To systematically review the existing literature to analyze the impact of previously identified pathologic risk factors on harboring occult metastatic disease (OMD) in patients with Clinical Stage I testicular stromal tumors (TSTs).

MATERIALS AND METHODS A literature search using PubMed was conducted using the following terms: "testicular stromal tumors," "testicular Leydig cell tumors," "testicular Sertoli tumors," "testicular interstitial tumors," "testicular granulosa tumor," and "testicular sex cord tumors." For analysis, we included only studies with data on available recurrence, survival, and time-to-event. We hypothesized that patients with ≥2 risk factors would experience lower 5-year OMD-free survival (OMDFS) than those with <2 risk factors.

RESULTS Two hundred ninety-two patients from 47 publications were included with a median age at diagnosis of 35 years (range 12-76). Five-year OMDFS and overall survival in patients with Stage I TSTs were 91.2% and 93.2%, respectively. When comparing those who harbored OMD to those who did not, we observed an increased risk of OMD for each additional risk factor ($P < .001$). Five-year OMDFS was 98.1% for those with <2 risk factors vs 44.9% for those with ≥2 risk factors ($P < .001$).

CONCLUSION The existing literature on pathologic risk factors for OMD in this population is insufficient to make broad clinical recommendations. However, these factors appear to risk-stratify patients and may be useful for future research investigating adjuvant therapy in higher-risk patients. This review indicates that such a stratification system has a rational basis. UROLOGY 97: 138–144, 2016.

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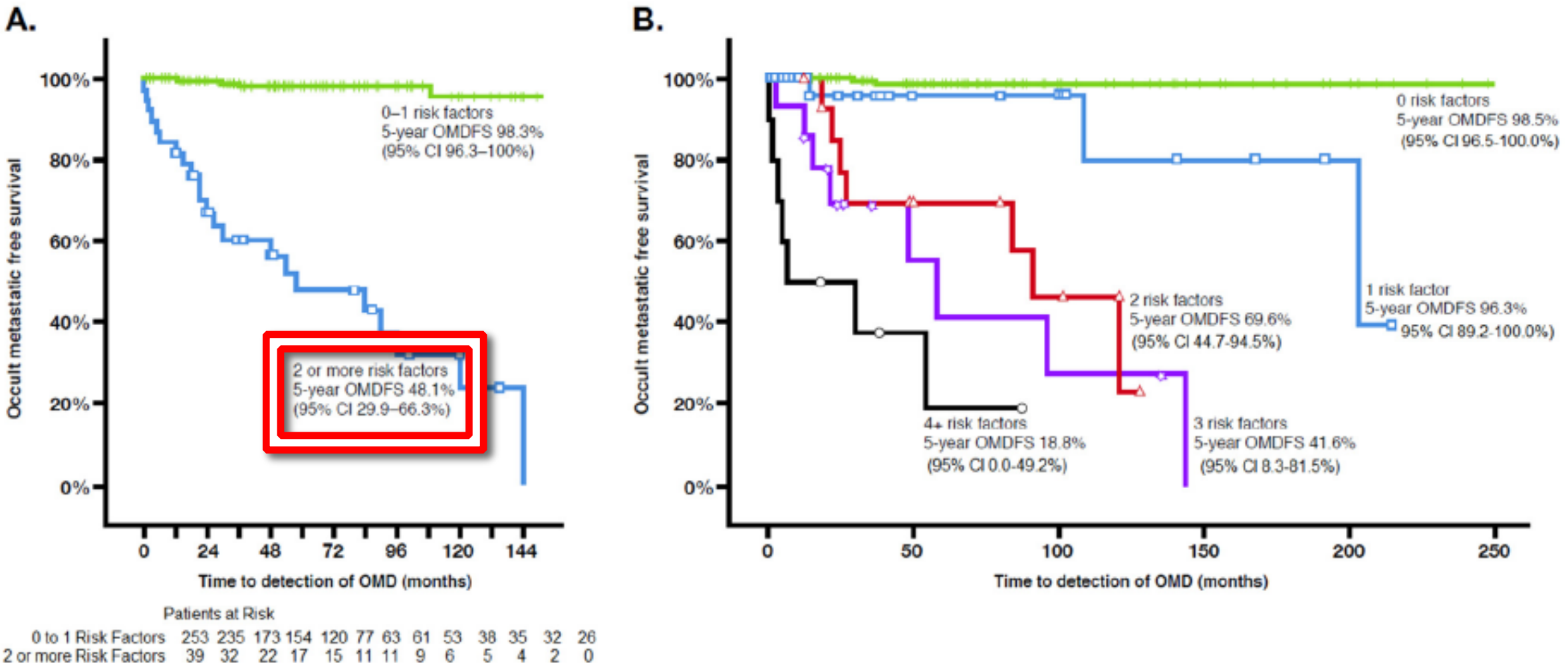

Figure 1. **(A)** Kaplan-Meier curve demonstrating worse occult metastatic disease-free survival (OMDFS) in patients with 2 or more pathologic risk factors as opposed to those with only 0 to 1 risk factor. Difference in 5-year OMDFS between the curves significant to *P* value <.001 by log-rank comparison. **(B)** Kaplan-Meier curve demonstrating worse OMDFS in patients with increasing numbers of risk factors. Difference in 5-year OMDFS between the curves significant to *P* value <.001 by log-rank comparison. (Color version available online.)

Take-home Points

- Testis-sparing appropriate for most prepubertal patients
- Leydig cell tumor, LCCSCT and JGCT released from oncologic follow-up
- Sertoli cell (over 5 yo) and undifferentiated stromal tumors require metastatic evaluation
- Best treatment for metastatic disease is resection
- Consider genetic testing?
  - DICER-1?

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