University of Kentucky
Department of Urology

Testicular GCT – COG vs NCCN (Focus on Primary Treatment)

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Objectives

1. Introduction
2. COG vs. NCCN (staging, nuances)
3. Teratoma “fate”
4. Surgical management nuances
    a) PC-RPLND
    b) TSS
5. Chemotherapy
6. Toxicities
7. MaGIC and Current trials

Introduction

- Generally treated similar to adult testis cancer
- In pediatrics, COG and NCCN guidance is available → need to know both
  - Pre-pubertal → COG algorithms (not as good with post vs pre-pubertal patients)
  - Post-pubertal → NCCN algorithms
- Personal take:
  - NCCN is excellent for post-pubertal patients, GU very familiar
  - Peds oncology much more comfortable with COG, favor these protocols
  - COG groups all GCT together, differences between sites are complex/nuanced and make navigation clunky

COG vs. AJCC/NCCN

Stage	COG	AJCC
I	Limited to testis/neg margin Excisional biopsy with FS and completion orchiectomy at same setting NED beyond testis LNs <1cm	N0 → I
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IV	Distant mets	M1 → III

COG vs. IGCCC Risk Groups

	Low	Standard 1	Standard 2	Poor
Age (y)	0-50	0-<11	11-<25	11-<25
COG stage	I	II-IV	II-IV	II-IV
IGCCC risk	-	-	Good	Intermediate/poor

Age

	Pre-Pubertal	Adolescent/Adult
Malignant potential	70-75% Benign	75% Malignant
Predominant type of malignancy	Pure YST or pure teratoma	Mixed, NSGCT
Metastatic potential	5% at presentation	20-30% at presentation
Teratoma	Common (40%) as pure teratoma, uniformly behaves in a benign manner	Part of a mixed tumor, higher potential for metastatic spread and malignant degeneration

Woo L & Ross JH. "Testicular Tumors in Children and Adolescents." *AUA Update Series* 2019;38:381-9.

Teratoma

- Can be found at any age
  - Commonly mixed and immature in post-pubertal patients
- Behavior depends on age/pubertal status of patient
  - Benign in pre-pubertal (focal insult, no GCNIS)
  - Mets and malignant degeneration in post-pubertal (field effect, with GCNIS)
- Post-surgical management depends on pubertal status of patient
  - Post-pubertal patient with “pre-pubertal teratoma” on path report → malignant NSGCT

Teratoma "Fate"

- Growing teratoma syndrome:
  - Enlarging mass despite normalization of STMs
  - Can happen anywhere
  - Path → pure teratoma only
  - Chemo resistant → require surgical resection

- Malignant transformation:
  - Co-occurrence and/or development of non-GCT with teratoma
  - Distinct from SMN that is treatment-related
  - May be seen at diagnosis or in new/persistent mass
  - Occurs in <2%, usually seen at diagnosis

PC-RPLND

- Rare to have residual PC mass in pre-pubertal patients
  - Excision of mass only, not formal RPLND
- Much more common in teens/AYAs

- NCCN guidelines with excellent information
  - PC mass = >1cm with normal STMs
  - Referral to high volume center (including ADULT centers) is advised

- COG recs:
  - Full RPLND for patients ≥11y
  - Excision only for patients <11y
  - Ok for normal or stable elevated (not rising) STMs

TSS in Teens/Young Adults – Controversial

- Orchiectomy is the standard of care for all malignant testicular cancers

- 2019 AUA guideline on testicular cancer
  - Post-pubertal patients should be treated per adult algorithms (ex. NCCN)
  - TSS recommended only in certain scenarios (solitary testis, B tumors, etc.)

TSS in Adult Men – Controversial

- German Testicular Cancer Study Group → TSS in select situations
  - Adult males (>20y)
  - Mass <2cm
  - Normal markers
  - Tumor bed biopsy negative, intraoperative frozen section to verify
  - Use of cold ischemia
  - Must receive adjuvant XRT if GCNIS present
- At 7y follow up:
  - 98% NED
  - Preserved T in 85%
  - 50% paternity rate without ART

Heidenreich A, *et al.* *J Urol* 2001;166(6):2161-5.

TSS in Teens/Young Adults – Controversial

- In adults, 2cm cutoff predicts risk of malignancy
- What about in patients <18y old?
  - Review of 24 patients who underwent TSS
  - Negative markers, unilateral masses, any age
  - 2cm size cutoff did not predict benign vs. malignant final pathology

Chemotherapy

- NCCN:
  - EPx4 = BEP x3
  - Insufficient evidence to favor specific regimen

- COG:
  - Must include bleomycin
  - Main source is French study from 2007
    - No evidence that regimens achieve statistically significant difference
    - Study underpowered so until there is better study, BEPx3 should remain standard

Toxicity of Treatment

- Hypogonadism, infertility
- Cardiovascular disease
- SMN
  - Cumulative 1%/y
  - 20yo with testis cancer → 47% chance SMN by age 70y

- Bleomycin – lung toxicity
- Etoposide – SMN development
- Cisplatin – renal, neuro, ototoxicity

MaGIC

- Malignant GCT International Collaborative
- COG + CCLG (UK) = MaGIC
- Application of IGCCC to pediatric GCT → poor correlation with outcomes
- Goal → create pediatric specific GCT risk stratification
- Found increase likelihood of cure with:
  - Age <11y
  - Stage II/III vs IV
  - Testis vs ovary/EG site
  - Histology, STMs were not prognostic
- EFS >80% → standard risk group (subdivided by age)
- EFS <70% → poor risk

AGCT 1532

- Phase 3 study
  - Safety, feasibility and tolerability already determined
- **Efficacy/toxicity** of accelerated vs standard BEP for post-pubertal mets GCT
  - COG – poor risk
  - NCCN – stage III intermediate/poor risk
- Difference is timing and # of doses of bleomycin
  - More doses and more often with accelerated
  - GSF supplementation allows BM recover faster → less waiting between?
  - Accelerated regimens successful with other tumors
  - Improved compliance, patients prefer shorter duration of therapy

AGCT 1531 (SWOG, ECOG, Alliance, NRG, JCCG)

- Goals: minimize toxicity while maintain current survival
  - Evaluate miRNAs
  - Create biobank
- AS for low risk GCTs (adult and peds, seminoma and non)
  - Eliminate toxicity of therapy beyond initial surgery; salvage is nearly 100%
  - More applicable to ovary, other sites
- EFS of carbo vs cisplatin for standard risk NSGCT patients
  - PEb vs CEb x4 for SR1
  - BEP vs BEC x3 for SR2

AGCT 1531 (SWOG, ECOG, Alliance, NRG, JCCG)

- No longer recommend additional chemotherapy as “consolidation”
- Carbo vs cisplatin for GCT:
  - Carbo with fewer AEs
  - Carbo inferior to cisplatin in adult men with good risk mets testis GCT
  - CRCTU (UK) uses JEb (carbo instead of cisplatin) x >30y
    - Outcomes ≈ countries using cisplatin
  - Key difference between above studies is carbo dose/freq (much higher in UK)
- MaGIC compared COG vs UK (cisplatin vs carbo) for SR:
  - No difference in outcome by risk group
  - Small numbers (79 vs 13 testis patients total)
  - Treatment not randomized

Frazier L, *et al. Eur J Can* 2018.

Conclusion

- Several nuanced differences between COG and NCCN
- MaGIC seems to be bridging this gap

- Try to be familiar with both protocols to discuss pros/cons/recs with oncologists
- Familiarity of nuances important when advocating for treatment

- Encourage teens/AYAs to enroll onto COG trials
  - Paucity of data/participation (transitional phase of care)
  - Outcomes are worse
  - Rich area for study to improve outcomes

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