Cancer Day for Primary Care

Treatment Complications and Symptom Management for Testicular Cancer

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Presenter Disclosure

- **Faculty / Speaker's name: Piotr Czaykowski**

- **Relationships with commercial interests:**
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Mitigating Potential Bias

- For clinical trials sponsored by an industry partner funding goes directly to the institution; I receive no direct compensation/remuneration
- I receive no direct compensation/remuneration from research funding

Learning Objectives

1. At the end of the presentation, learners will be able to identify common treatment complications and symptoms associated with testicular cancer.
2. At the end of the presentation, learners will be able to describe strategies for managing treatment complications and symptoms in testicular cancer patients.

Symptoms Associated with Testicular Cancer

- Testicular cancer-specific symptoms are rare, and generally do not require specialized management
- In advanced disease:
  - The presence of symptoms depends on the location and extent of the metastatic disease
  - There are rarely “B” symptoms – night sweats, unexplained fever, major weight loss

TREATMENT-RELATED TOXICITY: EARLY

Chemotherapy

- Nausea/vomiting
- Alopecia
- Hypersensitivity reaction
- Leukopenia/febrile neutropenia
- Acute ototoxicity - tinnitus
- Acute nephrotoxicity
  - Hypomagnesemia
- Acute pulmonary toxicity

Radiotherapy

- Fatigue
- Nausea
- Diarrhea
- Dyspepsia

Surgery

- Post-orchiectomy – scrotal hematoma
  - Can be quite distressing for the patient since he often thinks there is a tumor growing in the scrotum again

TREATMENT-RELATED TOXICITY: LATE/CHRONIC

CHEMOTHERAPY

Neurotoxicity

- Peripheral neuropathy
  - Related most commonly to cisplatin
  - Initially distal paresthesias, dysesthesisa
    - Early signs: loss of vibration sense in the toes, loss of DTRs
    - Can be debilitating
  - Advances proximally over time
  - Can worsen for months
  - Recovery can occur and can also take months and may be incomplete

Neurotoxicity

- In 739 testis cancer survivors (TCS), median follow-up 11 years

	Objective PN	Subjective PN
Chemotherapy	21.7%	9.1%
No chemotherapy	12.5%	5.5%

- Risk factors:
  - Cumulative platinum levels > 300 mg/m^2
  - Age, smoking, alcohol use, HTN, pre-existing PN or predisposing conditions (DM)
- There are no evidence-based preventative therapies; management is symptomatic (duloxetine); PT/OT as needed

Ototoxicity

- Cisplatin related
- Tinnitus (spontaneous oto-acoustic emissions)
  - Self-reported in up to 40% of patients
- High-frequency sensorineural hearing loss
  - 488 TCS – formal audiometric analysis at median 4.25 yrs post chemo
  - Self-reported: 30%
  - Objective measurement: 80% have hearing loss, 18% with severe to profound loss

Ototoxicity

- Risk factors: cumulative cisplatin dose (>400 mg/m^2), older age at diagnosis, concurrent use of other ototoxins, noise exposure, HTN, smoking, pre-existing hearing loss
- There are NO evidence-based preventative strategies
  - Minimize noise exposure, avoid other risk factors
  - Baseline testing can be valuable; formal post-chemo audiometric assessment 4-5 years post chemo
  - Tinnitus: difficult to manage

Nephrotoxicity

- Cisplatin-induced tubular cell injury/death; damage to renal vasculature
- ↓GFR can be permanent; can be associated with magnesium wasting
  - 1206 TCS, median f/u 15 yrs: renal function decline was 11.3%, 15.4% and 25.9% after 3, 4 or ≥5 cycles
- Directly tied to dose
- Pre-existing real dysfunction is a risk factor
- Management: hydrate, hydrate, hydrate, avoidance of nephrotoxic drugs

Lung toxicity

- Bleomycin pulmonary toxicity (pneumonitis)
  - Can occur during or after chemotherapy
- Initial symptoms can be subtle: dry cough, dyspnea, occasionally fever
- Incidence varies from 7-12%, 0-1.5% risk of death
- CT: bilateral consolidation, ground glass opacities, infiltrates
- DLCO can decrease significantly, usually recovers post chemo

Lung toxicity

- Norwegian study of TCS:
  - Risk of late pulmonary effects no greater than in those who did not receive chemo; 1/565 died of BPT
- Those at greater risk: very high cisplatin exposure, age > 40, those with diminished renal function, ?smokers
- High-concentration 0_2 post bleomycin (e.g. scuba diving): safety remains unclear
- Recommendations:
  - TCS with prior bleomycin exposure should alert anesthetists pre-anesthetics
  - Wait at least 6-12 months post chemo before scuba diving

Raynaud's phenomenon

- Related to bleomycin +/- cisplatin
- Spasm of small arteries leading to episodes of reduced blood flow, typically in fingers, less in toes
- Numbness, pain, pallor, "red flash"
- Can last minutes to hours, can cause gangrene in extreme instances
- Can occur in up to 30-40% of TCS
  - Chronic, persistently bothersome in ~ 10%
- Risk factor: concurrent smoking
- Management: avoid triggers (e.g. cold); if bothersome, pharmacologic management (Calcium channel blocker)

Cognitive impairment

- The dreaded “”chemo-brain”
- Memory impairment, diminished executive functioning, attention +/- processing speed
- Divergent results in TCS studies:
  - 72 TCS, 60% had test-confirmed cognitive impairment – no clear association with chemotherapy
  - 51 TCS, 14 yrs post treatment – those with chemo had significantly lower neuro-cognitive performance scores; memory complaints 35.7% with chemo, 4.3% without
- No specific monitoring or management

Cardiovascular disease (CVD)
Coronary artery disease (CAD)

- CVD: thromboembolic events, stroke, peripheral atherosclerotic disease and CAD
- SEER Data: NSGCT TCS post-chemotherapy: ~5 fold increased risk of CV deaths within one year of commencing chemotherapy; no apparent increase beyond one year
- Danish study with contemporary chemo: increased risk of MI (6 fold) and CV death (7-fold) in first year (year 0) post chemo, no increased risk in yrs 1-10, slight increase from 10 years onward (~1.5 fold)
  - Increased risk of stroke (6 fold), venous TE (25 fold) in the first year
  - risk of venous or arterial TE event: ~15% during chemo
- Evidence of accelerated vascular aging from cisplatin-induced vascular damage

Metabolic syndrome

- MS: major risk factor for CVD/CAD
- MS: ≥ 3 of HTN, abdominal obesity, hypetriglyceridemia, decreased HDL, elevated total cholesterol, insulin resistance
- European study: 255 TCS treated with orchiectomy +/- chemo (~8 yrs post treatment) versus 360 health men
  - TCS had 1.9 fold greater risk of MS
  - TCS with chemo: 2.2 fold greater risk
    - No increased 10-yr CV risk
- US study: 486 TCS 5-yrs post chemo and age-matched controls
  - TCS survivors had ↑prevalence HTN, LDL, total chol, but not abdo obesity
  - Hypogonadism, chemotherapy likely contributing to MS rather than sedentary behaviour
- Recommendations:
  - TCS need to be actively screened and managed for HTN, abnormal lipid profile, DM
  - Heart health lifestyle
  - Testosterone replacement if symptomatic hypogonadism

Second Malignant Neoplasms

- Swedish study (1980 – 2015) N=8788, Seminoma 55%, NSGCT 42%

SPC[2]s following testicular cancer	N (%)	Median follow-up time IQR (years)
Testicular cancer	830 (9.4)	11 (4–19)
Seminoma	568 (11.6)	11 (4–19)
Non-seminoma	249 (6.6)	13 (4–20)

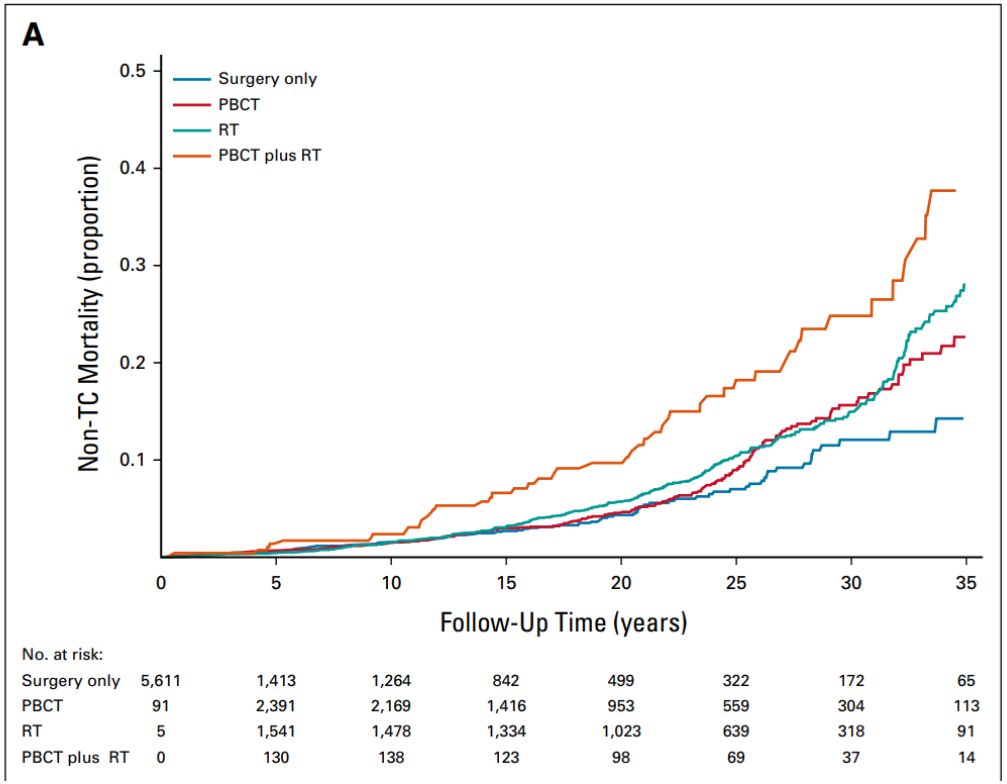
IQR[1] = Interquartile range (lower quartile-upper quartile)
SPC[2] = second primary cancer

Zhang et al PLOS One 2019

	Seminoma	Non-seminoma
	RR compared to general population	
Any solid SMN	1.28	1.43
Colorectum	--	1.64
Kidney	2.22	2.20
Bladder	1.57	2.57
Thyroid	3.19	--
Connective tissue	2.39	3.08
Lymphoma	1.96	--
Leukemia	1.96	2.16

Second Malignant Neoplasms
Excess mortality

- Norwe)09,
  media
- SMN a ortality
  rate of no and RT



RADIOTHERAPY

Cardiovascular disease

- Data are conflicting
- Multiple studies suggested TCS who receive RT have increased risk of CV morbidity and mortality
  - Standardized cardiac mortality ratio > 15 yrs post RT: 1.80 (95% CI 1.01 – 2.98)
- Risk almost certainly greater in those who get RT to chest

Second malignant neoplasms

- RT related SMN usually occur 10-15 yrs post RT
- In 10,534 seminoma patients post RT – overall risk of non-testicular SMN was 2.0 (1.8 – 2.2)
  - 36% cumulative 40 year risk compared to 23% in general population (estimated for a 35 yo male)
  - Head and neck cancers, stomach, liver, pancreas, bladder

Gastrointestinal toxicity

- Old data: increased risk of peptic ulcers and chronic diarrhea
- Newer techniques: less obvious long term effects

SURGERY

Disordered ejaculation

- Post retroperitoneal lymph node dissection:
  - "disordered ejaculation" (previously retrograde ejaculation) – damage to, or resection of, sympathetic fibers
  - Primary RPLND (nerve-sparing approach) – antegrade ejaculation in 99%
  - Post chemotherapy: 76%
    - Wide range depending on volume and expertise of the surgical team
  - Mitigation:
    - Pre-RPLND (usually pre-chemotherapy) sperm cryopreservation
    - Post-RPLND: advanced reproductive technology – electroejaculation, microTESE+ICSI

GENERAL

Testosterone deficiency

- Little data about pre-diagnosis testosterone
- Post orchiectomy alone 11% of patients have testosterone < 10 nmol/L
- Post standard chemo: OR 1.8
- Post RT alone: OR 1.6
- Post high dose chemo or chemo + RT: OR 3.1

Testosterone deficiency

- Evaluation usually if symptoms of hypogonadism; check morning testosterone
- Replacement therapy for men who have both low serum T, and symptoms of deficiency
- Exogenous T is contraindicated in TCS seeking future fertility due to negative impacts of T replacement on sperm production

Fertility

- Fertility is often impaired even prior to surgery, chemo or RT
  - ~50% have abnormal semen parameters, and ~25% are azoospermic
  - Inconsistent study findings on recovery of semen parameters after orchiectomy+surveillance
- Cisplatin-based chemo: 20% develop azoospermia at 1 year, with recovery of some spermatogenesis in 48% at 2 yrs, 80% at 5 yrs
- RT effect is dose dependent; direct testicular RT is not a good thing
- Both chemo and RT associated with sperm aneuploidy and sperm DNA fragmentation for up to 24 months
  - Attempted procreation discouraged for first 12 months

Psychosocial issues

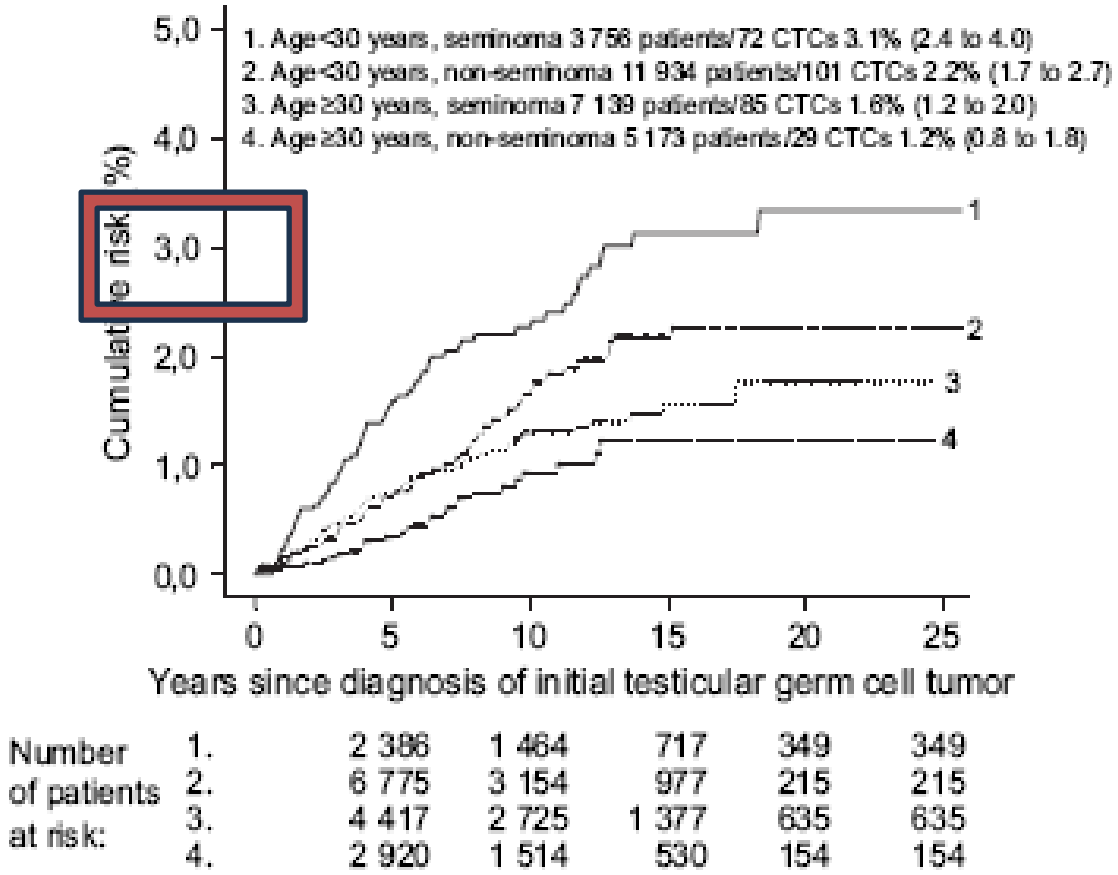
- TCS have similar QoL to age matched controls
- But diagnosis is often in a critical age of development: education, relationships, employment, life goals (autonomy, self-concept)
- Psychological distress
- Fatigue
- Sexual dysfunction and poor body image

Cancer recurrence

- Late recurrence – various definitions
  - Recurrence after 2-5 yrs disease free
  - Norwegian registry: of 5712 GCT patients (1980 – 2009)
    - 472 relapsed (8%)
    - 109 were beyond 2 years (LR) (2%)
    - 50 recurred beyond 10 years (VLR) (<1%)
  - NSGCT more likely to relapse L or VL
  - Median time to LR: 4.7 yrs

Tanstad et al. JCO 2022; 40: 16 suppl 5008

Contralateral testis cancer



Fossa et al JNCI 2005; 97: 1056

Take home message(s)

- If you have a TCS in your practice:
  - Help them avoid Metabolic Syndrome, risk factors for cardiovascular disease
  - Make sure they participate in available cancer screening programs (e.g., Colon Check); minimize risk factors (smoking, sun exposure, alcohol, sedentarianism)
  - Remember that late recurrences can happen, as can contralateral testicular cancers – investigate symptoms

Barriers to Change

The biggest barrier is lack of familiarity due to the rarity of this type of cancer

We are not planning to increase incidence if we can help it.

Sorry.

References

- Testicular cancer survivorship: long-term toxicity and management. *Shrem, Wood, Hamilton, Kuhathaas, Czaykowski et al.*

  Can Urol Assoc J 2022; 16 (8) 257-72