Navigating Fertility Preservation for the Testicular Cancer Patient

Premal Patel, MD FRCSC

Male Infertility, Microsurgery & Sexual Medicine

Medical Director & Co-Founder, Men's Health Clinic Manitoba www.mhclinic.ca

Assistant Professor, Department of Surgery

Presenter Disclosure

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  - **Grants/Research Support:** Coloplast
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Mitigating Potential Bias

- Not Applicable

Equity Commitment

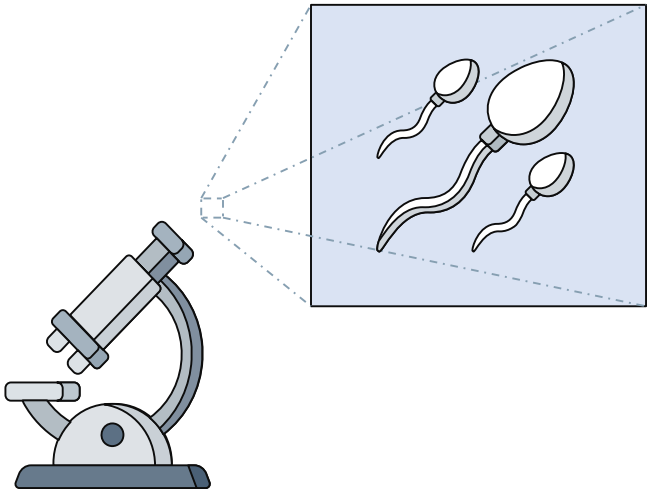
- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

Fertility

- Introduction
  - Testicular cancer is the most common malignancy in young males *(1/250 lifetime risk)*
  - Peak age of presentation: 25 – 29
  - Often overlapping with the ages men are interested in conceiving children

- Men with testicular Ca
  - >50% initially present with oligospermia *(< 15 mill/ml)* prior to treatment
  - Post cisplatin, only 48% successfully father a child *(vs 90% in post-orchiectomy surveillance group)*
  - <50% of oncology providers regularly counsel men on fertility preservation prior to initiating treatment



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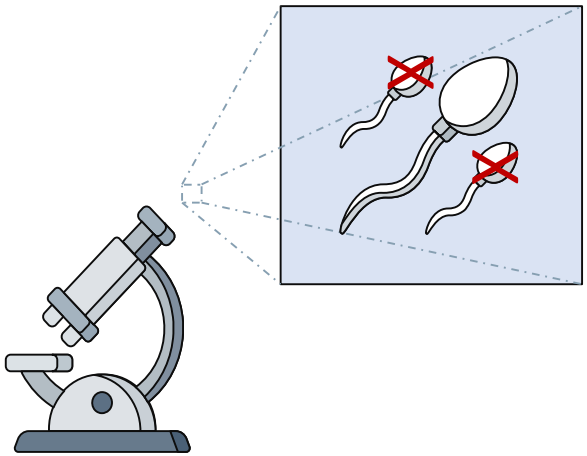
Fertility



- Mechanism of infertility in testicular Ca
  - Multifactorial
    - direct parenchymal damage by tumor
    - *correlative etiologies* i.e. cryptorchidism
    - *causative etiologies* i.e. HPG axis deviation
  - Hypothalamic-pituitary-gonadal axis)HPG):
    - directly controls testicular function
    - elevated AFP or BHCG can interfere with the feedback mechanisms
    - disruption in LH / FSH / testosterone levels correlate with spermatogenesis and decreased [sperm]
  - Cancer associated:
    - systemic inflammation, elevated oxidative stress and DNA fragmentation, fevers, disruption of blood-testis barrier, and formation of anti-sperm antibodies
  - In combination with treatment *(particularly chemo)* fertility is often greatly affected

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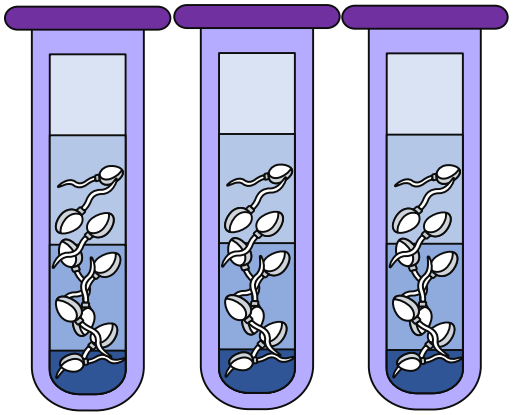
Fertility

- Strategies for fertility preservation prior to tx
  - Cryopreservation is the primary method
    - When performed prior to chemo or radiation Tx, it is currently the most cost effective and efficacious technique
  - Collection methods
    - masturbation
    - postejaculatory alkalinized urine specimen *(retrograde ejaculation)*
    - penile vibratory stimulation (PVS) *(SCI or young pt)*
    - electroejaculation **GA required *(impaired ejaculatory reflex)*
    - perc. aspiration of the epididymis (PESA) *(sufficient for ICSI but not IUI)*
    - testicular sperm aspiration (TESA) *(sufficient for ICSI but not IUI)*
      - *surgical TESE may be required if pt has nonobstructive azoospermia (NOA)*
      - CAN be done at time of orchiectomy (onco-TESE)
  - Pre-pubertal male?
    - spermatogonial stem cell cryopreservation via testicular tissue…
    - still considered experimental, requires two invasive procedures as they need a delayed autotransplant in hopes of restoring spermatogenesis



- Fertility preservation uptake
  - despite options, only ~50% offered preservation
  - >70% of these pts forgo banking
  - often citing cost, being overwhelmed c/ new dx
  - some centers now have "oncofertility programs"
    - increased access / awareness
    - auto prompts to providers for referral
    - hotline for interested pts
    - standardized care pathway
    - counselling and support for future paternity

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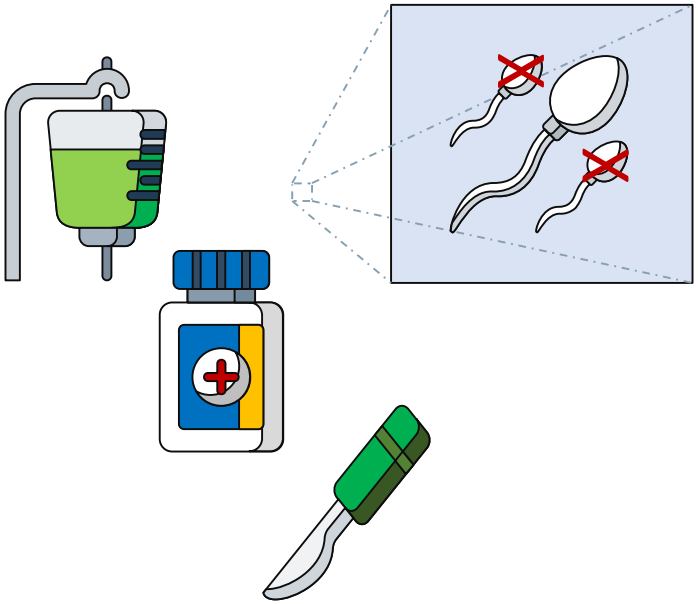
Gilbert, Kirven, et al. "Fertility preservation for men with testicular cancer: Is sperm cryopreservation cost effective in the era of assisted reproductive technology?." *Urologic Oncology: Seminars and Original Investigations*. Vol. 36. No. 3. Elsevier, 2018.

Fertility



- Reproductive toxicities of testicular cancer treatment
  - CUA, AUA, American Society of Clinical Oncology (ASCO), and American Society for Reproductive Medicine (ASRM)
    - All have clinical guidelines recommending fertility counseling and preservation to all patients requiring testicular cancer treatment
    - *not always adhered to.*
  - Radical Inguinal Orchiectomy results in:
    - reduced [sperm], sperm count,
    - elevated FSH / LH, no change in testosterone
    - associated c/ lifelong androgen replacement, infertility, emotional distress
    - even with an apparently normal contralateral testis, results in:
      - semen parameter impairments (85% of pts), an additional 9% developing azoospermia after unilateral orchiectomy
      - *NCCN guideline: can perform cryopreservation before OR after radical orchiectomy*

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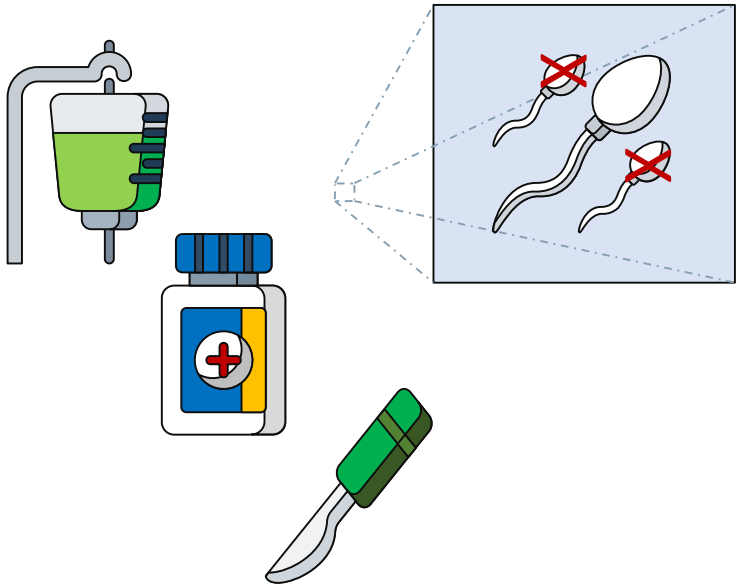
Fertility

- Reproductive toxicities of testicular cancer treatment
  - Chemotherapy
    - well-recognized gonatotoxic effects
    - effects vary greatly depending on dosing, combo regimens, and tx duration
    - identifying which patients are most vulnerable to long-term sequela of chemotherapy is challenging
      - We lack vigorous data including follow-up semen analyses and fertility rates related to various combinations of drug regimens
    - Common combo: bleomycin, etoposide, and cisplatin (BEP)
  - Platinum-based agents (i.e. cisplatin / carboplatin)
    - intermediate risk for permanent azoospermia
    - MOA: formation of DNA cross-linking
    - Meta-analysis of testicular Ca pts with normal pre-tx [sperm] showed (Lampe et al., 1997):
      - 48% and 80% recovered spermatogenesis by 2 and 5 years
      - those exposed to carboplatin fared better than cisplatin



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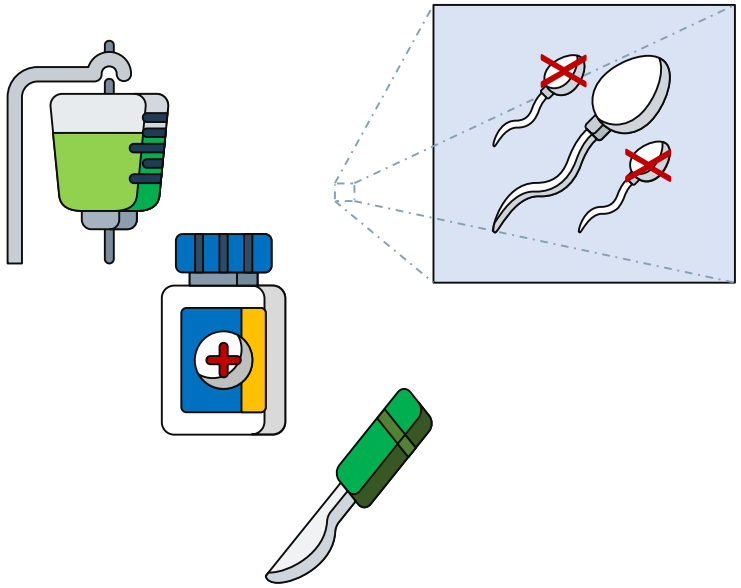
Lampe, H., et al. "Fertility after chemotherapy for testicular germ cell cancers." Journal of Clinical Oncology 15.1 (1997): 239-245.

Fertility

- Reproductive toxicities of testicular cancer treatment
  - Chemotherapy – BEP (Bujan et al., 2013)
    - looked at 129 patients who received BEP for testicular Ca
    - < 3 cycles: spermatogenesis returned 12 mo post tx
    - 3+ cycles or Rads: spermatogenesis returned @ 24 mo post tx
  - Chemotherapy Timeline – expedited radical orchiectomy? (Emmanuel et al., 2021)
    - Many pts forgo fertility preservation in order to expedite radical orchiectomy, with the perceived benefit of improving oncological outcomes
    - EAU recommends orchiectomy within 24h, but may be delayed up to 72h, evidence guiding this is limited
    - explored whether delayed tx to allow for fertility assessment/preservation negatively impacted oncological outcomes
    - Inclusion: studies comparing delayed vs expedited orchiectomy with at least one oncological outcome
    - *Zero studies met criteria*, most explore delays of 30—100d
    - Moody et al. (2019) showed fertility preservation usually requires 1 week to arrange and perform



Reference:

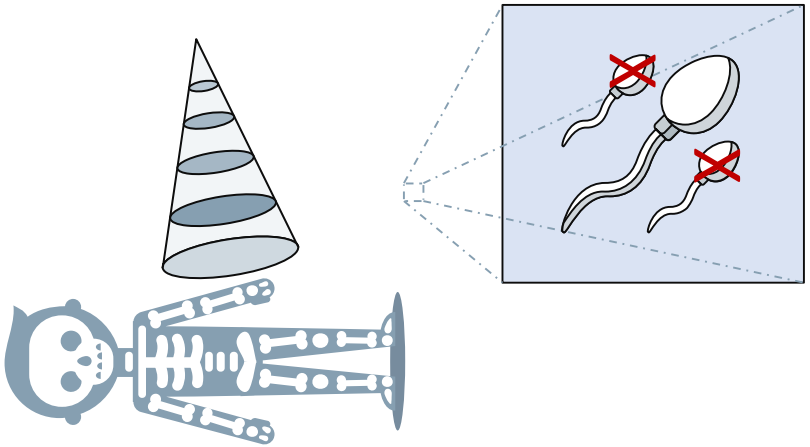
Bujan, Louis, et al. "Impact of chemotherapy and radiotherapy for testicular germ cell tumors on spermatogenesis and sperm DNA: a multicenter prospective study from the CECOS network." Fertility and sterility 100.3 (2013): 673-680.

Emmanuel, Anthony, et al. "Expedited Radical Orchidectomy for Testicular Cancer: Compromising Fertility Outcomes Without Oncological Benefit?." European urology 80.6 (2021): 766-767.

Moody JA, Ahmed K, Yap T, Minhas S, Shabbir M. Fertility manage- ment in testicular in testicular cancer: the need to establish a standardised and evidence-based patient-centric pathway. BJU Int 2019;123:160–72.

Fertility

- Reproductive toxicities of testicular cancer treatment
  - Radiotherapy
    - pts usually receive gonadal shielding during XRT but are still subject to scatter radiation
    - if shielded appropriately, data suggests scatter radiation dosing is as low as 0.28% of treatment dose
      - Effects are dose related
      - [semen] + morphology can be affected with as low as 0.1 Gy
      - > 4 Gy may cause permanent germ cell damage
      - 16-20 Gy are commonly administered
    - Recovery of spermatogenesis is possible, depending on the dose
      - 1 Gy: 18 mo post XRT
      - 2-3 Gy: 30 mo post XRT
      - 4+ Gy: 5+ years post XRT
    - testicular function may also be disrupted by effects of cranial XRT on HPG axis
    - TRT is required in 15-25% of patients, thus pts should be monitored for adequate testicular androgen production post XRT



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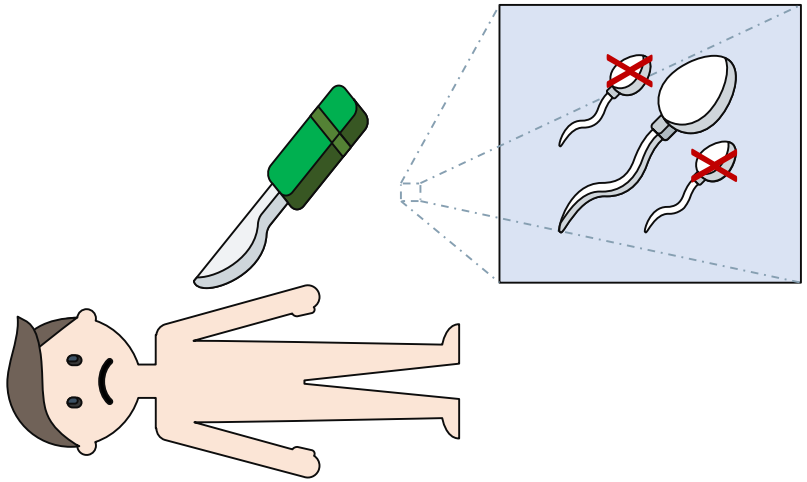
Fertility

- Reproductive toxicities of testicular cancer treatment
  - Retroperitoneal pelvic lymph node dissection (RPLND)
    - performed as primary or salvage treatment
    - risk of injury to RP sympathetic nerves or hypogastric plexus responsible for emission and ejaculation
    - <10% of patients experience significant ejaculatory complications
      - largely to do with nerve sparing technique

- Overall, fertility rates post treatment are high
  (Huddart et al., 2005)
  - Surveillance: 85%
  - chemotherapy: 71%
  - chemotherapy plus radiotherapy: 67%
    - Most experts advocate waiting 6 mo – 2 years prior to attempting to conceive



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Huddart, R. A., et al. "Fertility, gonadal and sexual function in survivors of testicular cancer." British journal of cancer 93.2 (2005): 200-207.

Fertility

- Reproductive toxicities of testicular cancer treatment

Chemotherapy – Role of fertility preservation? Danish study. (Bandak et al., 2022)

- looked at effects of current testicular Ca tx on fertility among:
  1. surveillance
  2. BEP
  3. BEP + retroperitoneal sx
  4. abd radiotherapy
- N = 4846 Ca pts matched c/ 48456 men
- for each patient, 10 men matched on DOB were randomly sampled from the normal population
- Paternity defined as DOB of first child after tx with or without assisted reproductive technology
- 20-year predicted chance of obtaining fatherhood (30yr old man):
  - 39.7% in Ca patients (need for reproductive technologies was higher)
  - 42.5% normal population
  - Pts followed on surveillance program had similar chance of fatherhood as normal population
- Conclusion: chance of obtaining fatherhood post Ca tx substantially higher than previously reported

Reference:
Bandak, Mikkel, et al. "Paternity After Treatment for Testicular Germ Cell Cancer: A Danish Nationwide Population-Based Cohort Study." JNCI: Journal of the National Cancer Institute 114.1 (2022): 149-155.

Summary

- Testicular cancer survivorship includes many long-term sequelae *unique* from other cancers
- All forms of treatment have potential for negatively impacting fertility, and we must ensure each patient has has proper counselling on such prior to treatment
  - *even if this causes short term delay in treatment
- Risk of long-term sequelae varies based on factors such as marital status, age at time of diagnosis, SES, treatments required, and side effects suffered
  - Individual demographics need to be considered
- Barriers to Fertility Preservation need to be discussed and mitigated
  - Awareness
  - Cost
  - Access

Thank You!

- Questions?