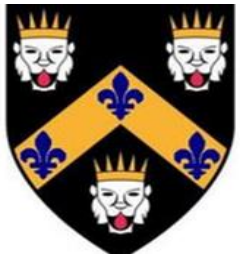
Fertility Preservation in Men

Majid Shabbir

Consultant Urologist
Lead for Andrology, Male Infertility
& Genito-urethral Reconstruction

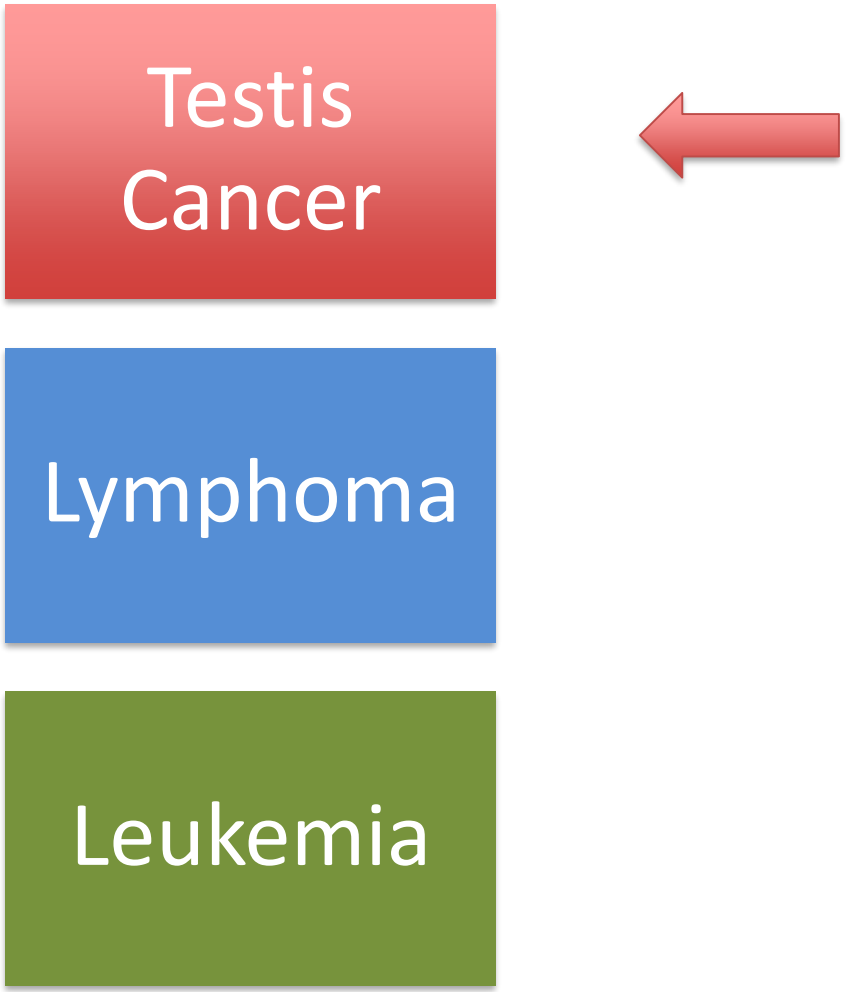
Guy's and St Thomas' Hospital
London



Concepts

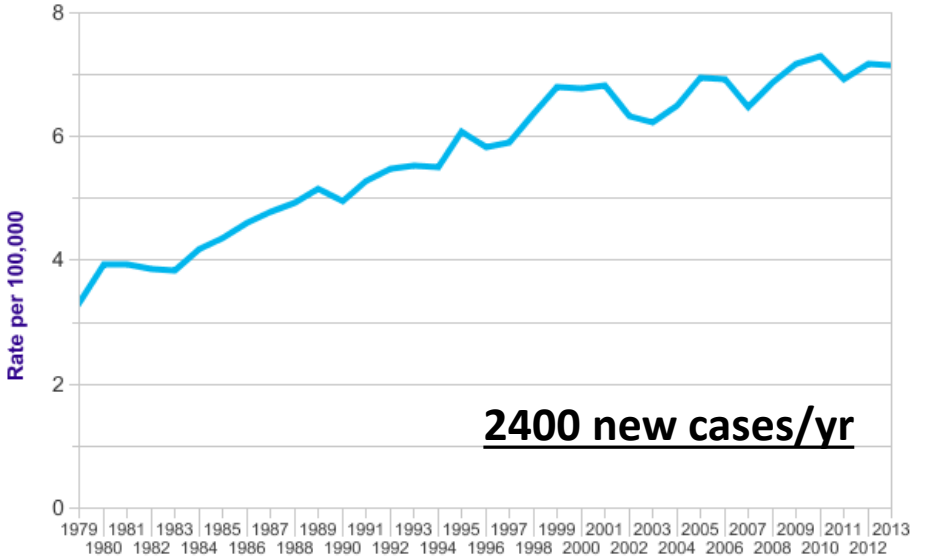
- Improved survival rates among young cancer patients
  - Early detection
  - More effective treatments
- Improved focus on survivorship
  - Return to normal life after cancer
  - Managing impact of the disease and its treatment on fertility

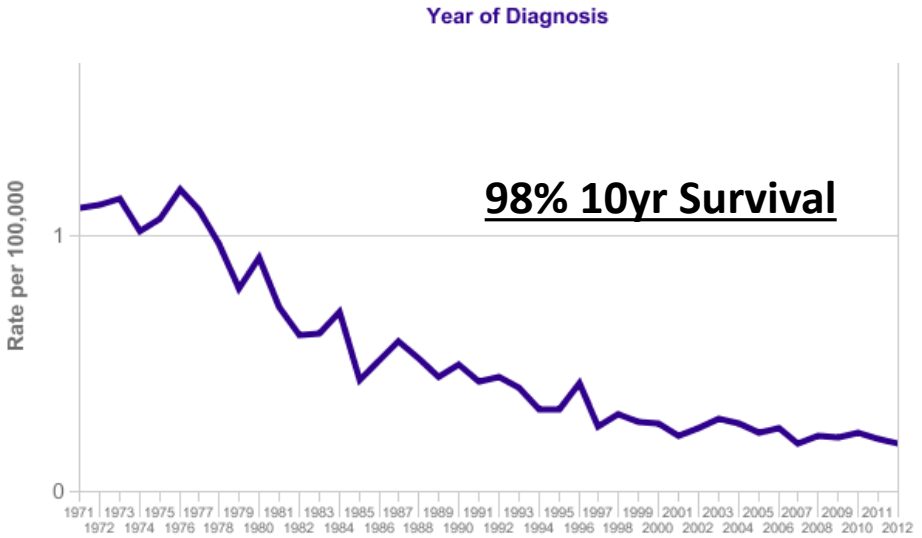
Common cancers in young men



TESTICULAR CANCER IS THE MOST COMMON CANCER IN MALES 15–35 YEARS OLD.

TCANCER.ORG

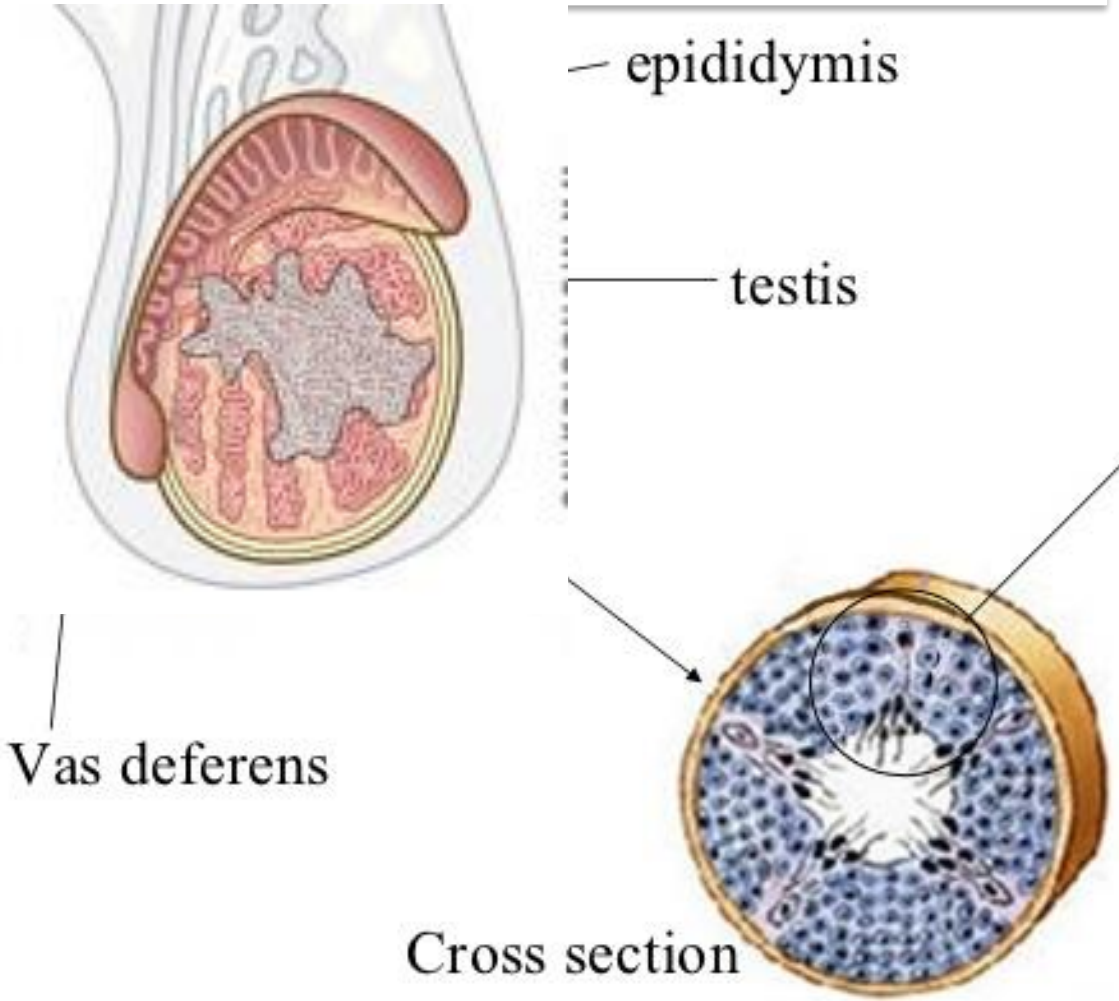


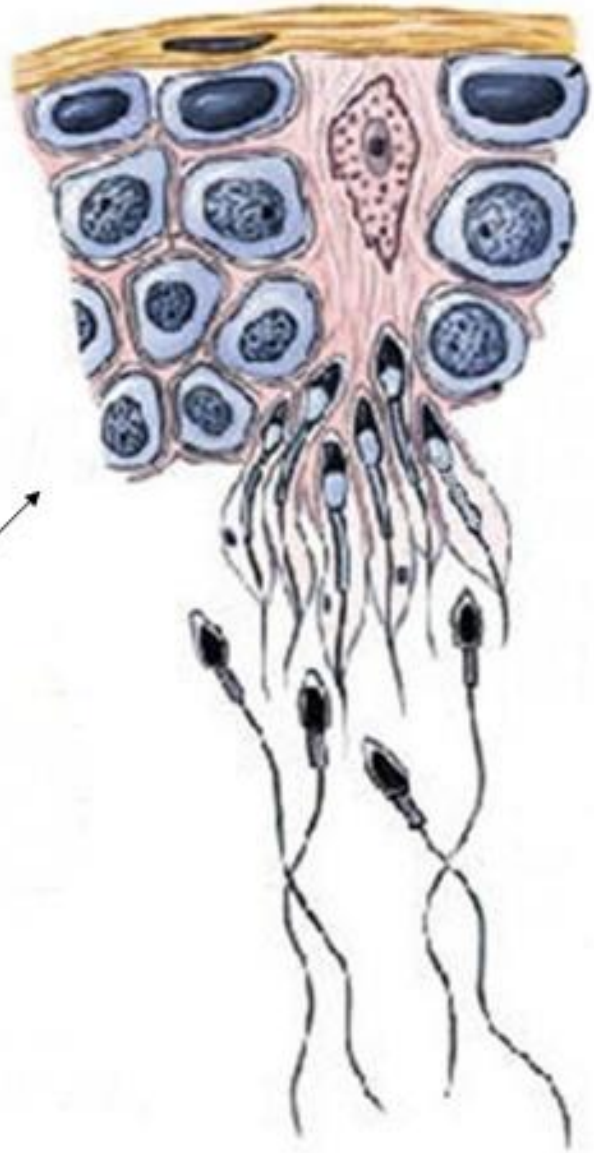


Testicular Cancer (C62): 1979-2013

CANCER RESEARCH UK

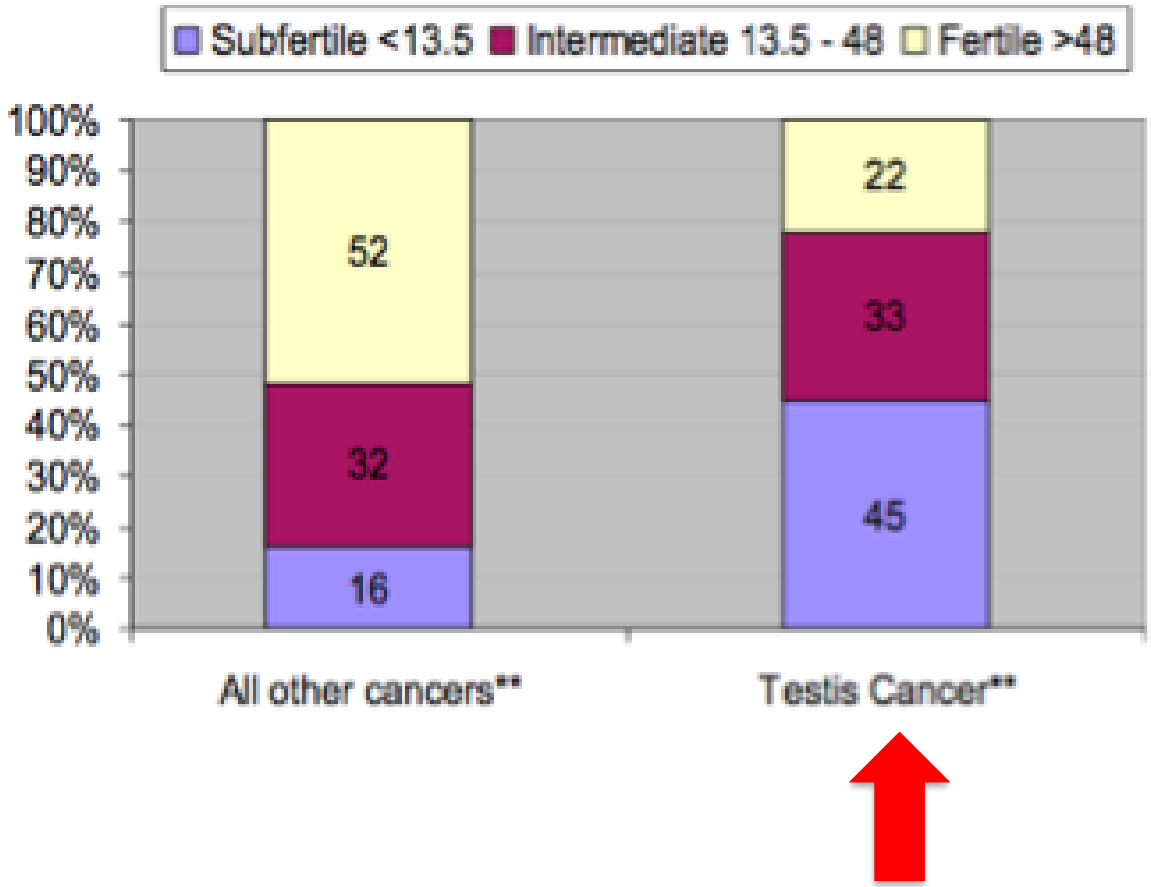
Testis: Spermatogenesis





Pretreatment semen parameters in men with cancer

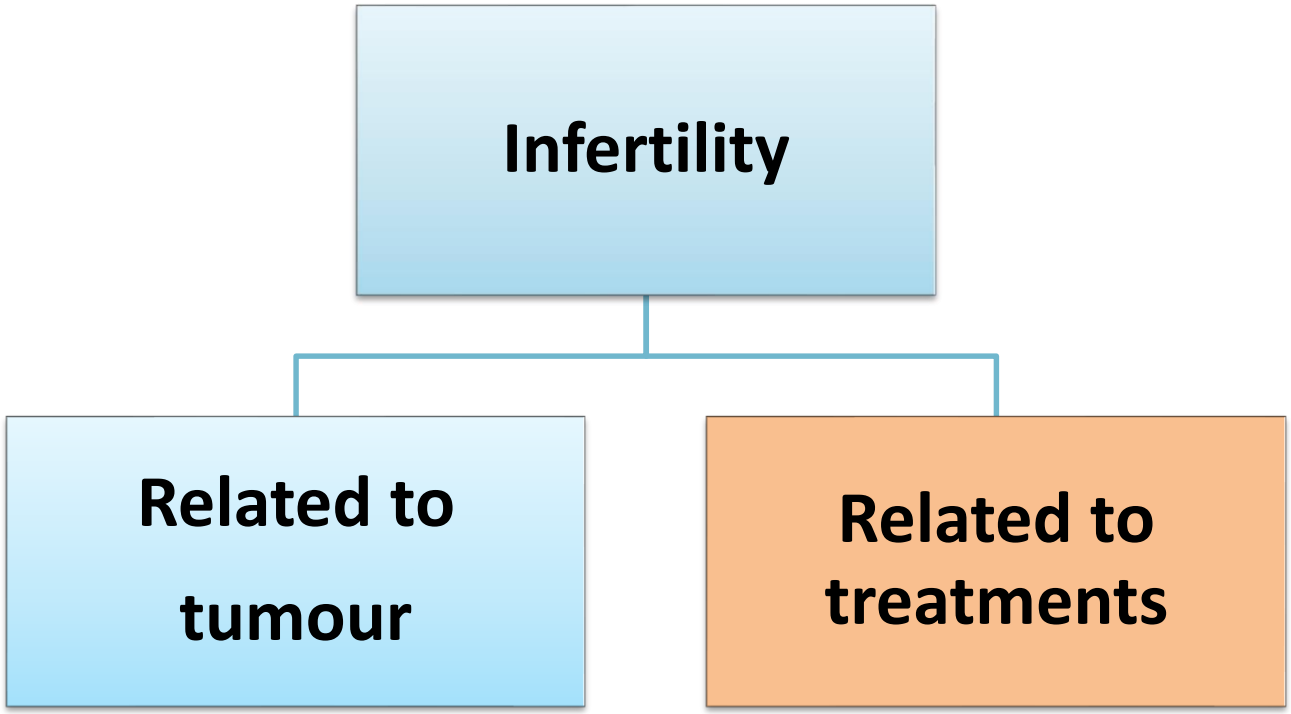
Williams DH et al J Urol 2009 181, 736-740,



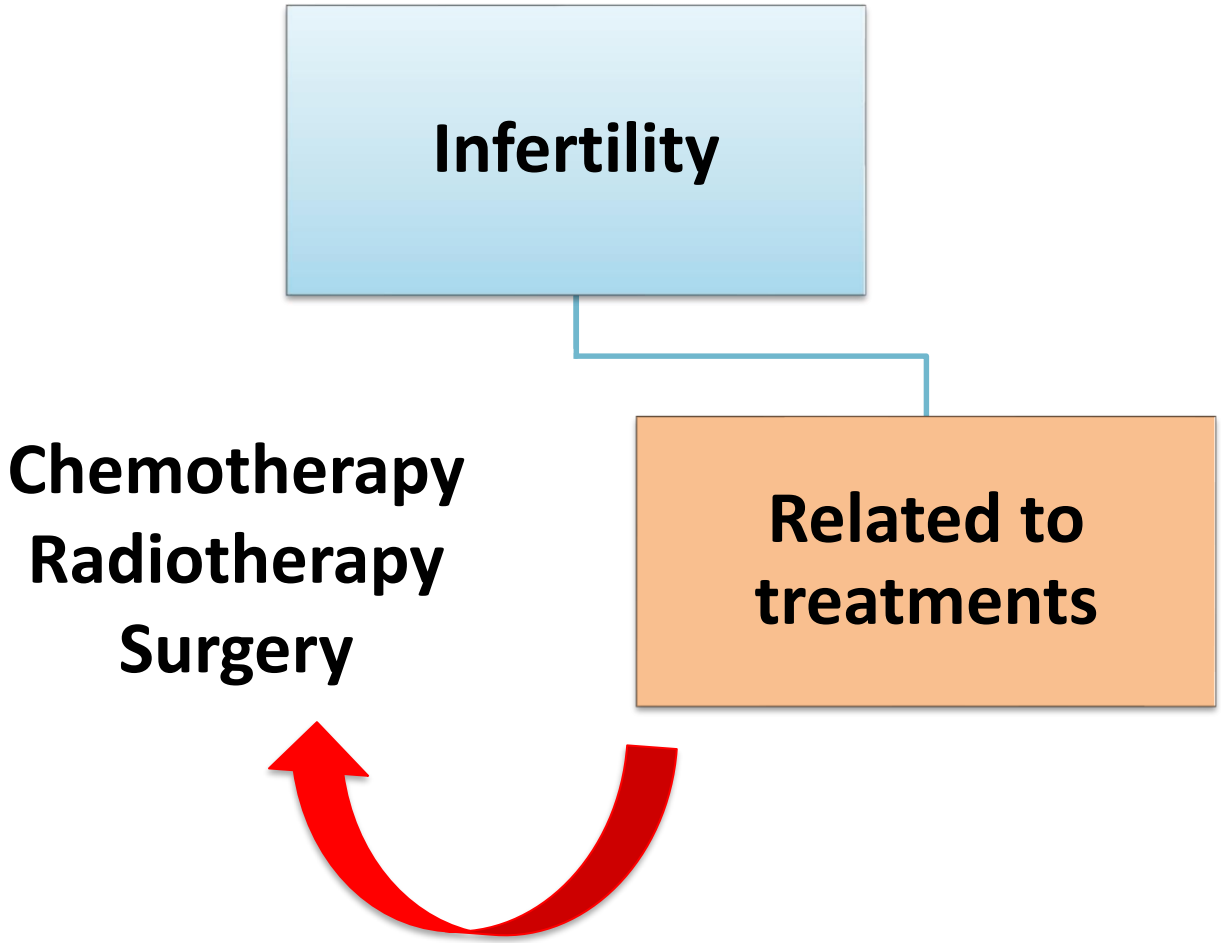
≈ 50% subfertility at presentation

≈ 10% azoospermic at presentation

Infertility & Testis Cancer (TC): Why does it occur?



Infertility & Testis Cancer (TC): Why does it occur?



Effect of Chemotherapy

- Targets rapidly dividing cells
- Effect Dependent on type of agent and dose
  - **Alkylating agents most harmful**
- Testis cancer
  - Carboplatin less toxic than cisplatin
  - Cisplatin: dose-dependent germ cell damage and impaired testosterone metabolism

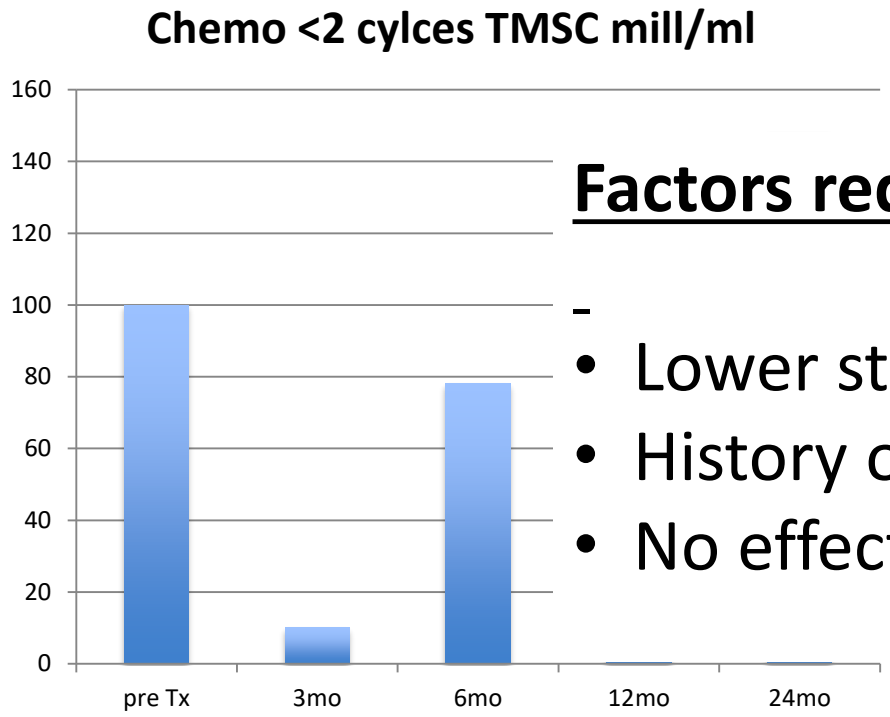
Table 1 The risk of chemotherapy for impairment of spermatogenesis (adapted from Wallace WH *et al*. Lancet oncology 2005; 209–218)[3]

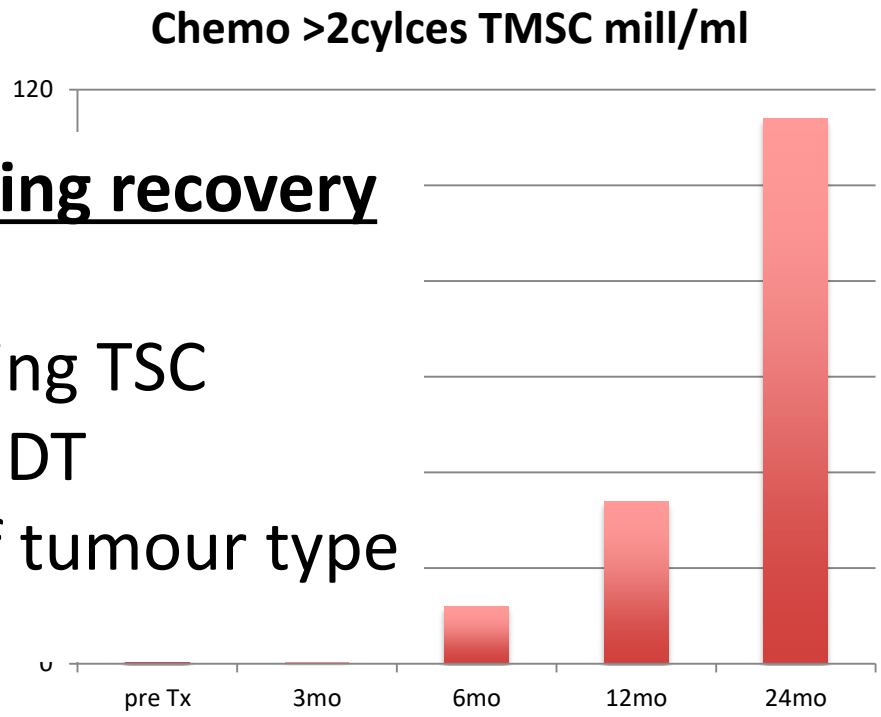
High risk	Medium risk	Low risk
Cyclophosphamide	Cisplatin	Vincristine
Ifosfamide	Carboplatin	Methotrexate
Chlormethine	Doxorubicin	Dactinomycine
Busulfan	BEP	Bleomycin
Melphalan	ABVD	Mercaptopurine
Procarbazine		Vinblastine
Dacarbazine		
Chlorambucil		
MOPP		

ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; BEP, bleomycin, etoposide and cisplatin; MOPP, nitrogen-mustard, oncovin (vincristine), procarbazine and prednison.

Advise contraception for min 6 months post chemotherapy (ESMO guidelines Pecccatori et al 2013)

Effect of BEP Chemotherapy





Factors reducing recovery

-

- Lower starting TSC
- History of UDT
- No effect of tumour type

- Recovery to pre-treatment levels by **12months if BEP ≤ 2**.
- By **24 months if BEP> 2**

(Bujan et al 2013)

Effect of Radiotherapy

Direct: Gonadotrophic

Scatter (pelvic/ abdominal):

Recoverable function

Radiation dose	Effect on fertility
<0.5Gy	Reversible Oligozoospermia
<3Gy	Azoospermia (recovery by 30 months)
<5Gy	Azoospermia (recovery >5yrs)
Fractionated >2.5Gy	Prolonged Azoospermia
16-18 Gy (Tis)	**Permanent Azoospermia >95%**
>20Gy	Leydig cell failure **– irreversible hypogonadism**
Total Body Irradiation	**High risk permanent azoospermia**

Adapted: Trottmann M et al 2007

Effect of Radiotherapy

Direct: Gonadotrophic

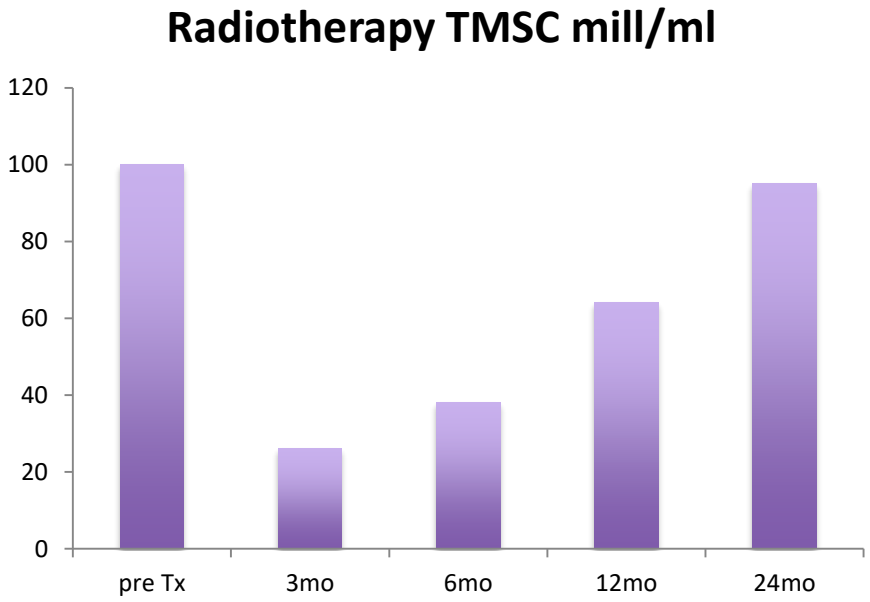
Scatter (pelvic/ abdominal):

Recoverable function

Radiation dose	Effect on fertility
<0.5Gy	Reversible Oligozoospermia
<3Gy	Azoospermia (recovery by 30 months)
<5Gy	Azoospermia (recovery >5yrs)
Fractionated >2.5Gy	Prolonged Azoospermia
16-18 Gy (Tis)	**Permanent Azoospermia >95%**
>20Gy	Leydig cell failure **– irreversible hypogonadism**
Total Body Irradiation	**High risk permanent azoospermia**

Adapted: Trottmann M et al 2007

Effect of Radiotherapy



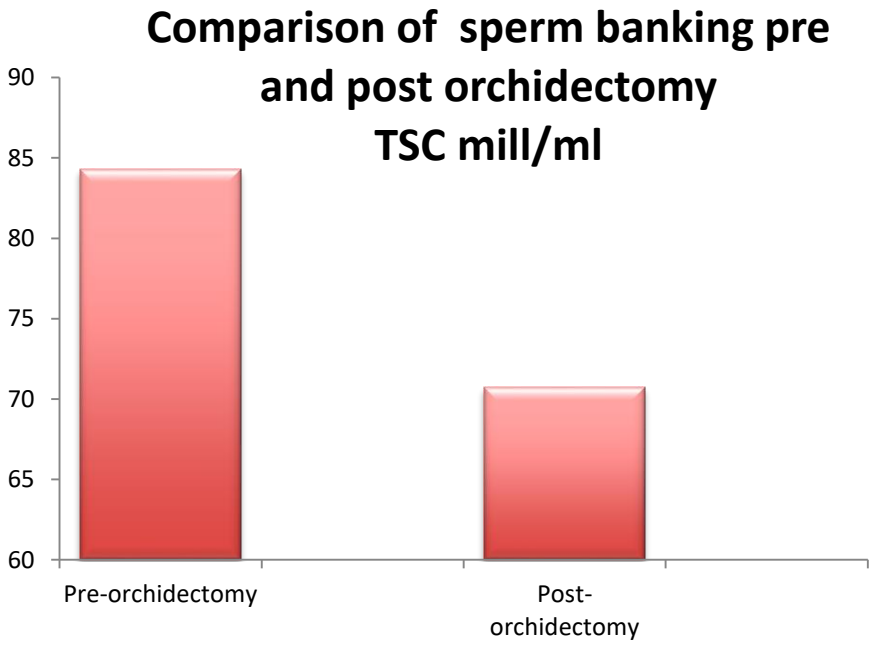
Box 1
Factors that affect recovery of spermatogenesis after radiation

Radiation dose[37]
Adjuvant chemotherapy
Pretreatment total motile sperm count
Age (<26 years old more favorable)
Testicular shielding[37]
Fractionated versus single-dose therapy[38]

- Recovery to pre-treatment levels by **24 months if DXT**

(Bujan et al 2013)

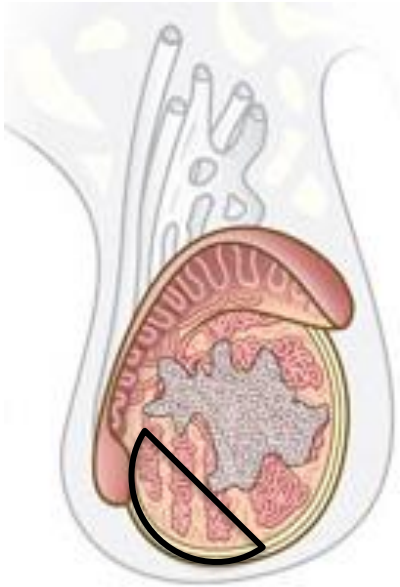
Effect of Orchiectomy



Rives N et al J Urol 2012

- 50% decrease initially post orchiectomy
- 10% with sperm before surgery azoospermic after orchiectomy

Petersen PM et al. J Urol. 1999



Spermatogenesis in Ipsilateral Testis in Testicular Cancer

Study	No of cases	Spermatogenesis
Choy et al 2013	83	62%
Suzuki et al 2015	102	67%
Shoshany et al 2016	214	68%
Moody et al 2018	103	70%

FERTILITY PRESERVATION

Timing: when to tackle issues with fertility

- Fertility furthest thought from the mind when newly diagnosed with cancer
- Best outcome with Fertility Preservation is **before** starting cancer treatment
- NICE 2013- At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed

Impact of Infertility on QoL in Cancer Patients

- Infertility alone associated with Psychological distress, and increased levels of depression
- Superimposed on cancer diagnosis, infertility significantly increases stress on patient and partner
- Planning and discussion of fertility preservation can reduce distress and improve quality of life.

Duffy & Allen Cancer J 2009

"When I was told I had cancer it was a shock, it is terrible news and it changes your world immediately.

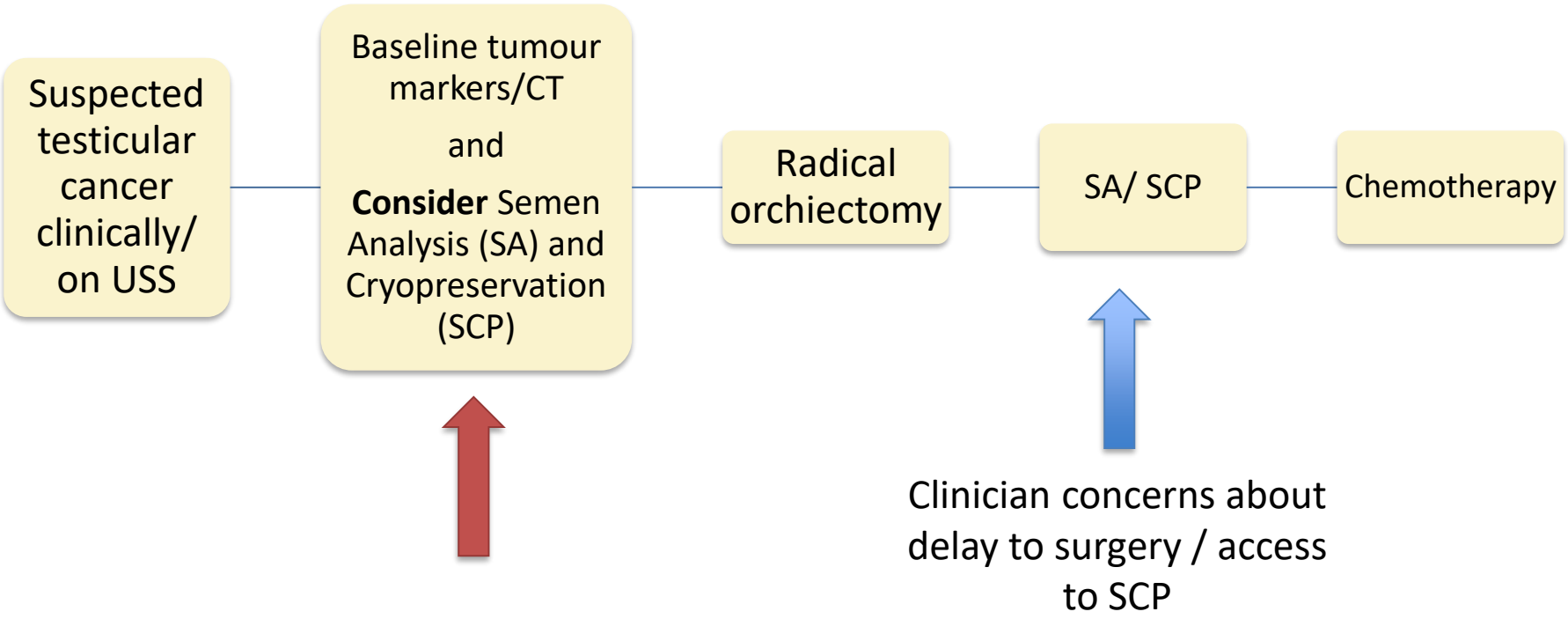
Testicular cancer has a very high survival rate and when I went to the fertility clinic at Guy's Hospital for some tests, the day ended relatively positive.

"Then I had a phone call from the doctor who said 'you have no sperm' and in a lot of ways that was harder to take than the cancer diagnosis. We knew we wanted to have a family so it was pretty devastating news."

Fertility preservation in Testicular Cancer

- Semen cryopreservation
- Widely available and inexpensive option
- Suitable for all post-pubertal men who are able to give sample
- Ideally before chemotherapy, radiotherapy **or surgery** affecting the male reproductive system

FERTILITY PRESERVATION PATHWAY



FERTILITY PRESERVATION PATHWAY

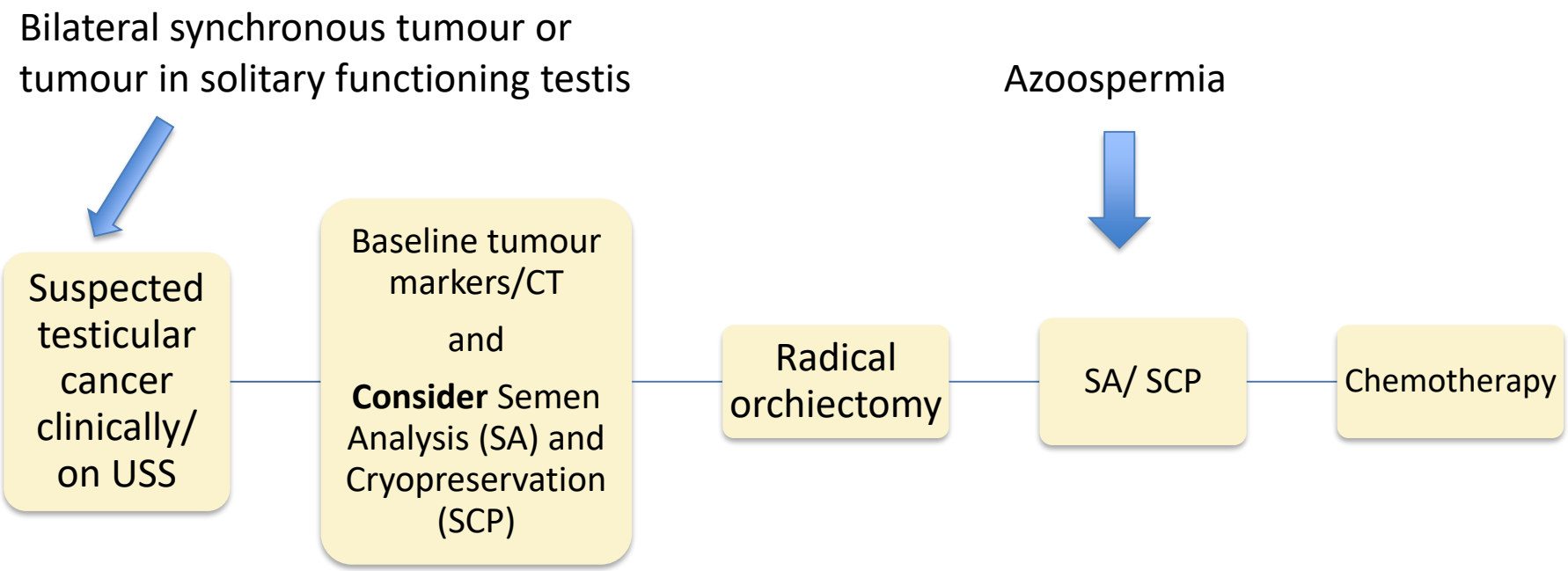
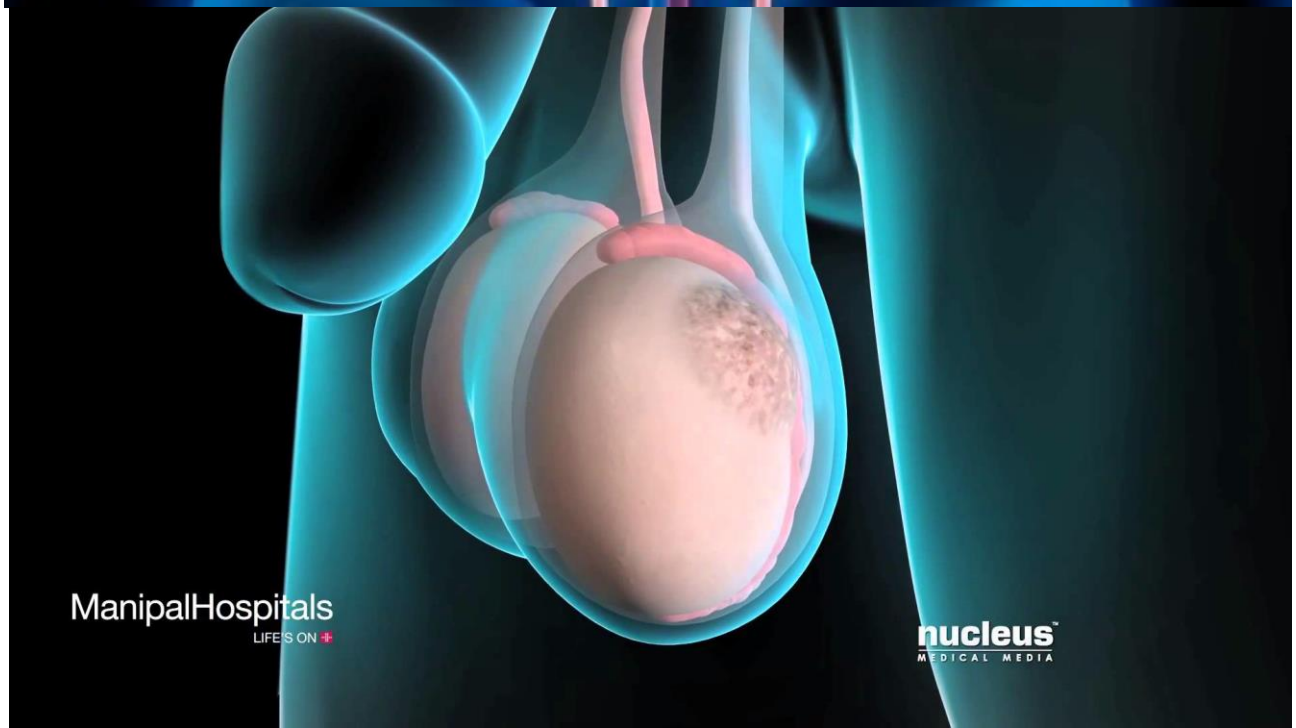


Table 1 – Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	α-Fetoprotein hCG Lactate dehydrogenase	A
Abdominopelvic CT	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or spinal MRI	In the case of symptoms	
Brain scan (CT/MRI)	In the case of symptoms and patients with metastatic disease with multiple lung metastases and/or high β-hCG levels	
Further investigations		
Fertility investigations: Total testosterone Luteinising hormone Follicle-stimulating hormone Semen analysis		B
Sperm banking	Should be offered	A

GR = grade of recommendation; hCG = human chorionic gonadotrophin; CT = computed tomography; MRI = magnetic resonance imaging.

EAU guidelines 2015 – Albers et al


ManipalHospitals
LIFE'S ON
nucleus
MEDICAL MEDIA

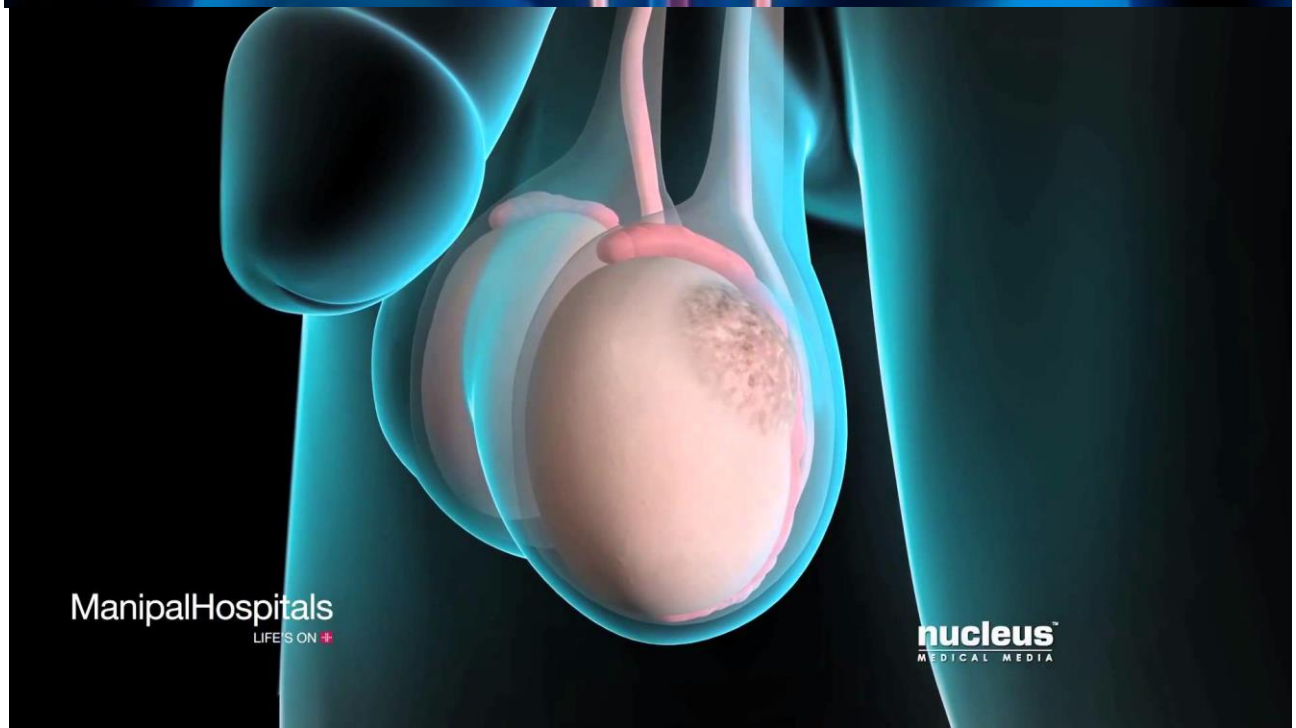

ManipalHospitals
LIFE'S ON
nucleus
MEDICAL MEDIA

Table 1 – Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	α-Fetoprotein	A
	Total testosterone	
	Luteinising hormone	
	Follicle-stimulating hormone	
	Semen analysis	
Sperm banking	Should be offered	A

GR = grade of recommendation; hCG = human chorionic gonadotrophin; CT = computed tomography; MRI = magnetic resonance imaging.

Paradigm shift

Vital assessment if;

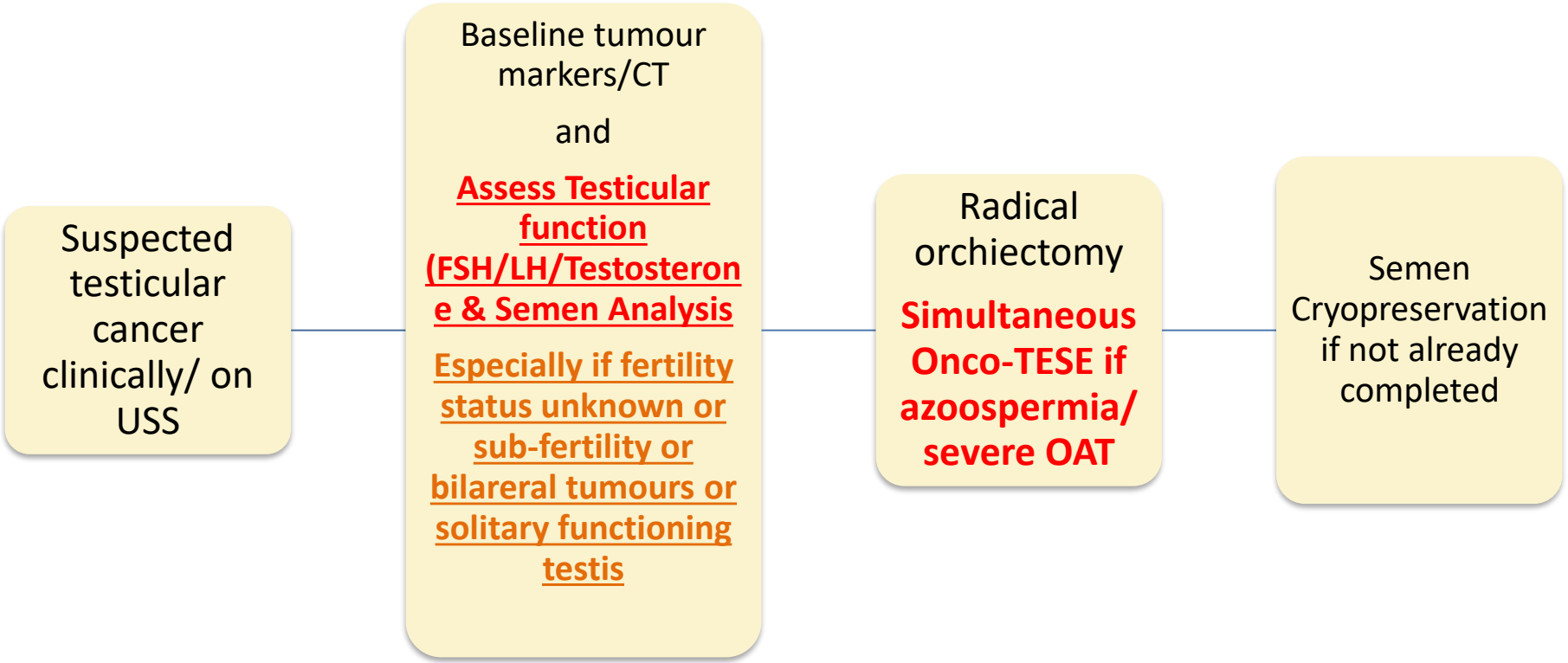
1. unknown fertility status

or 2. history/ risk factors for sub-fertility

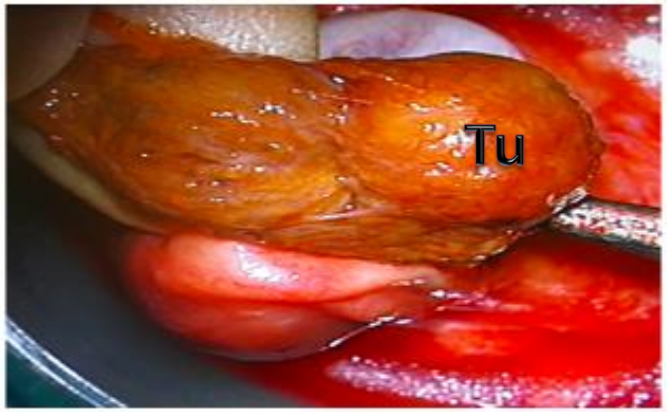
or 3. bilateral tumours/ tumour in solitary functioning testis

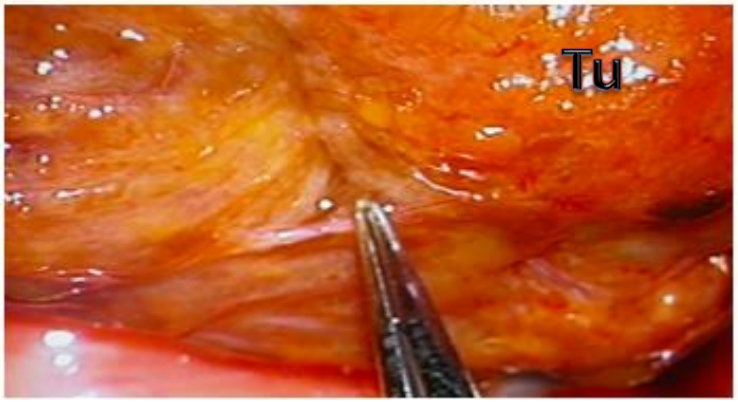
EAU guidelines 2015 – Albers et al

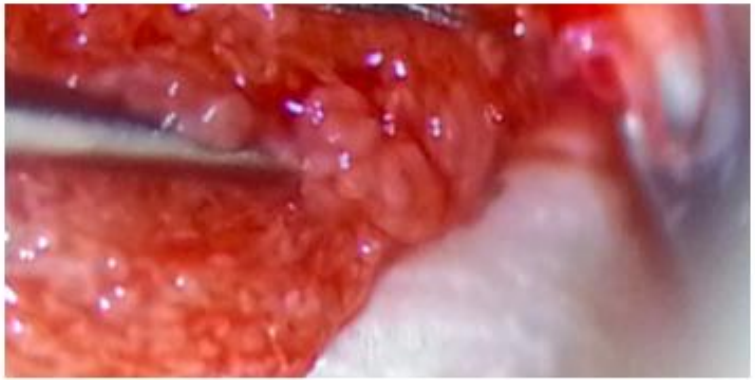
PROPOSED PATHWAY



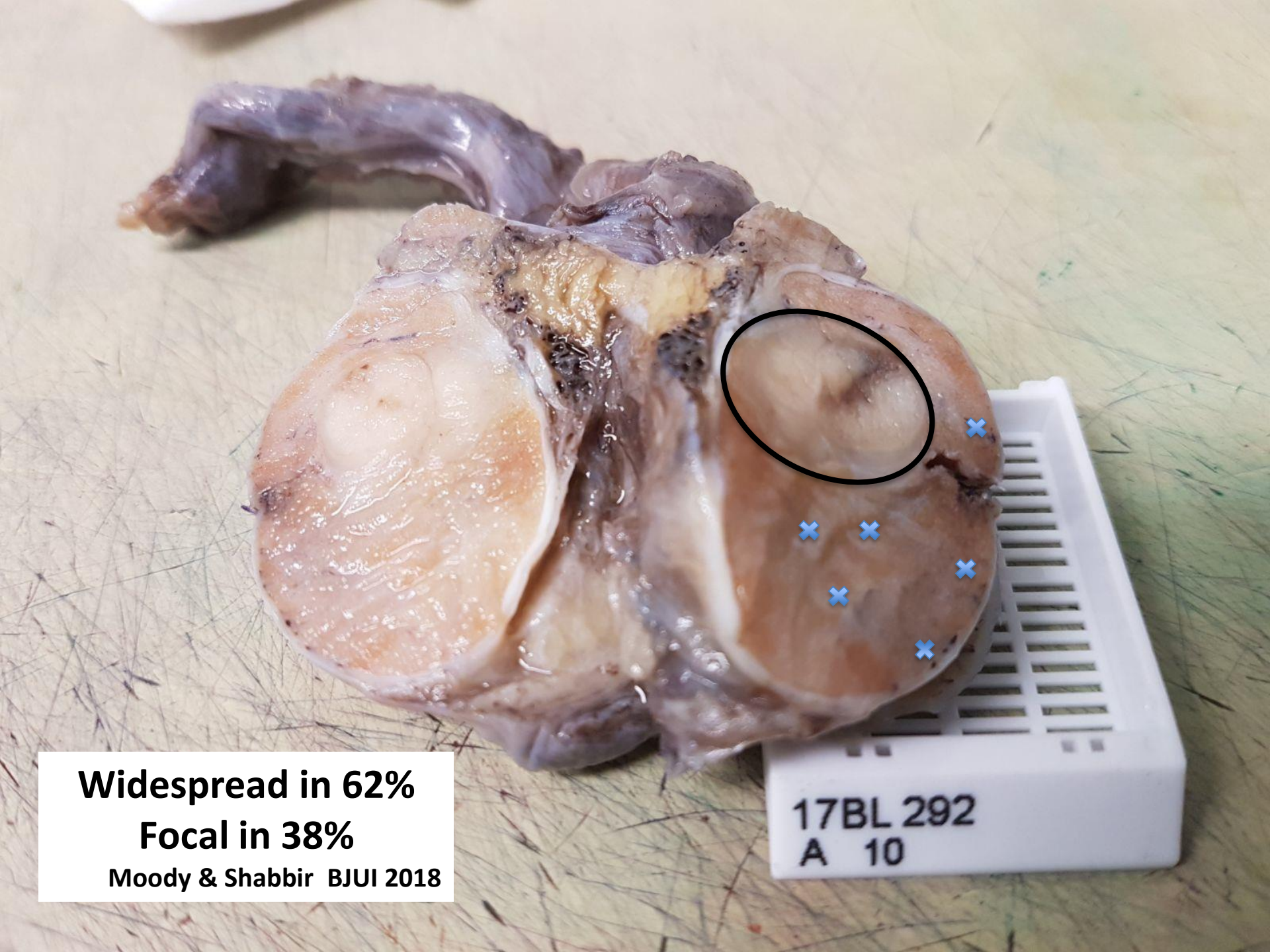
ONCO-MicroTESE



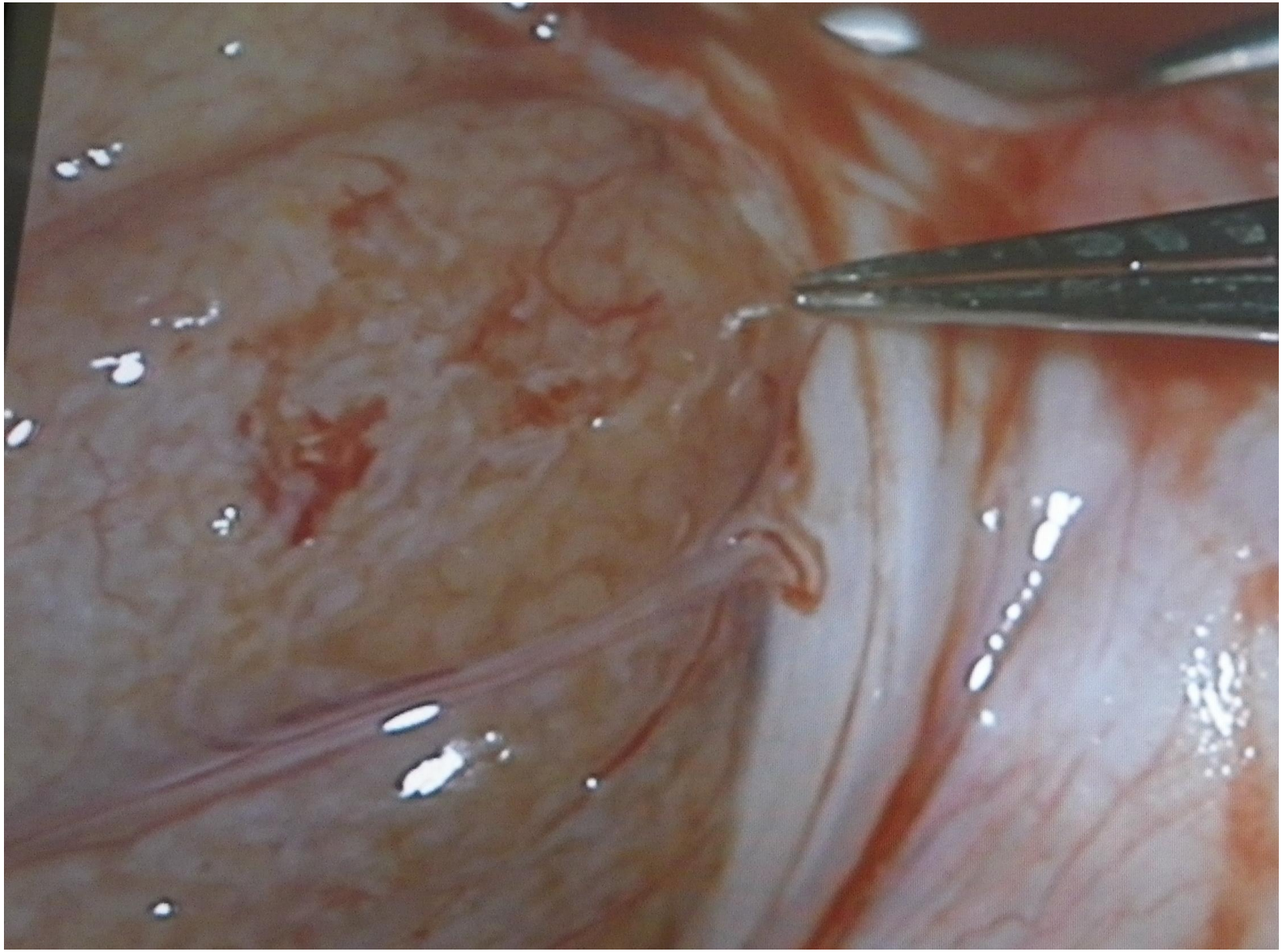


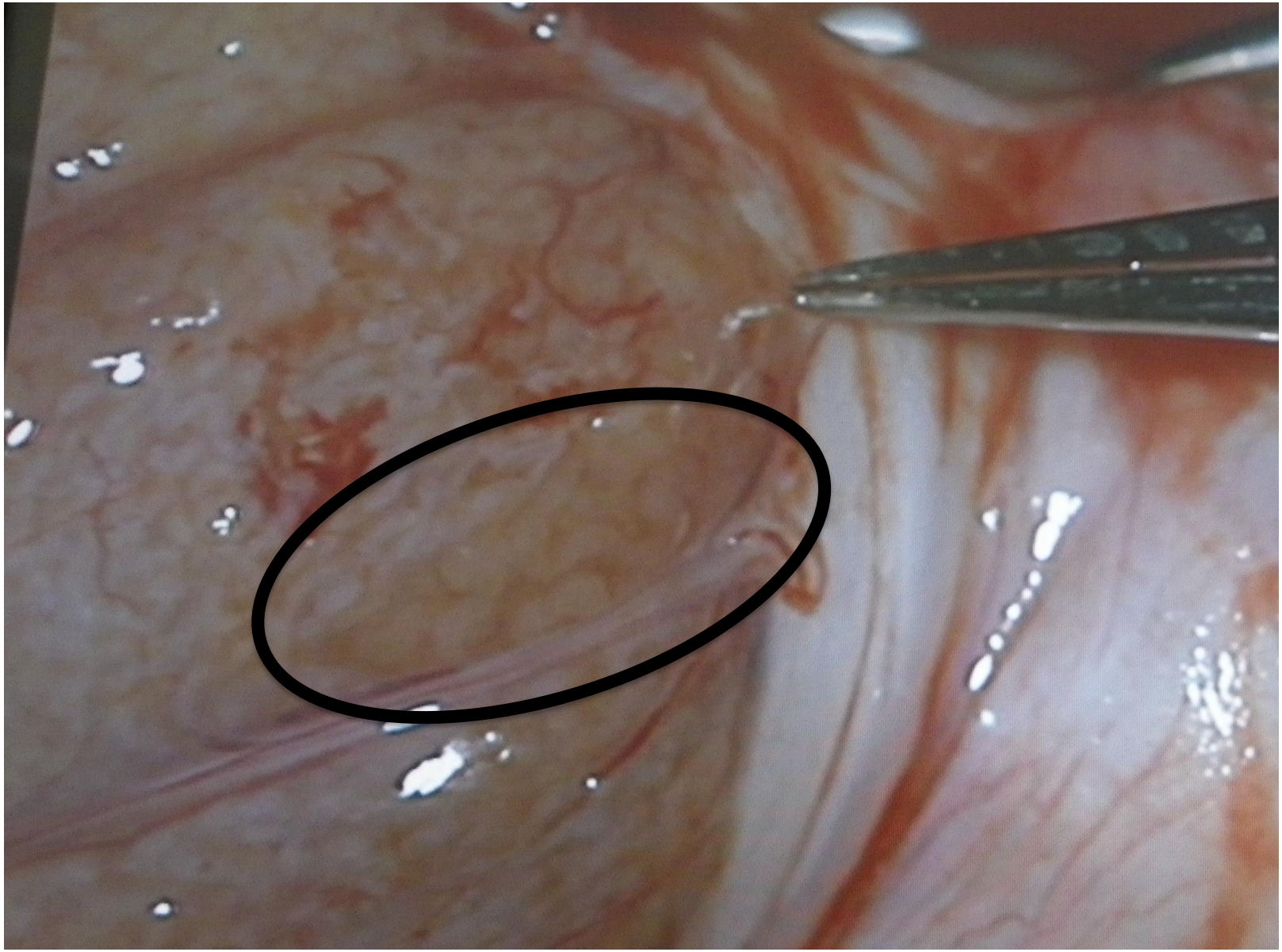


If fails can do micro TESE of contralateral side

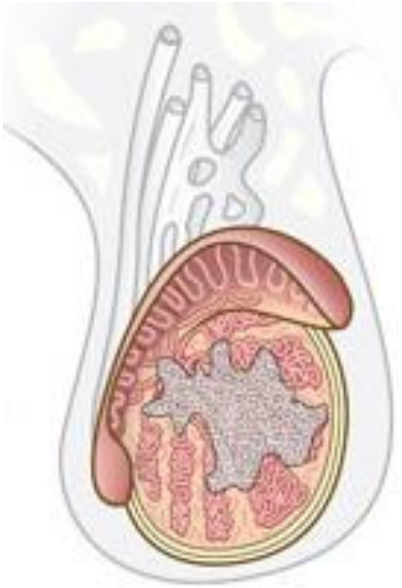


Widespread in 62%
Focal in 38%
Moody & Shabbir BJUI 2018

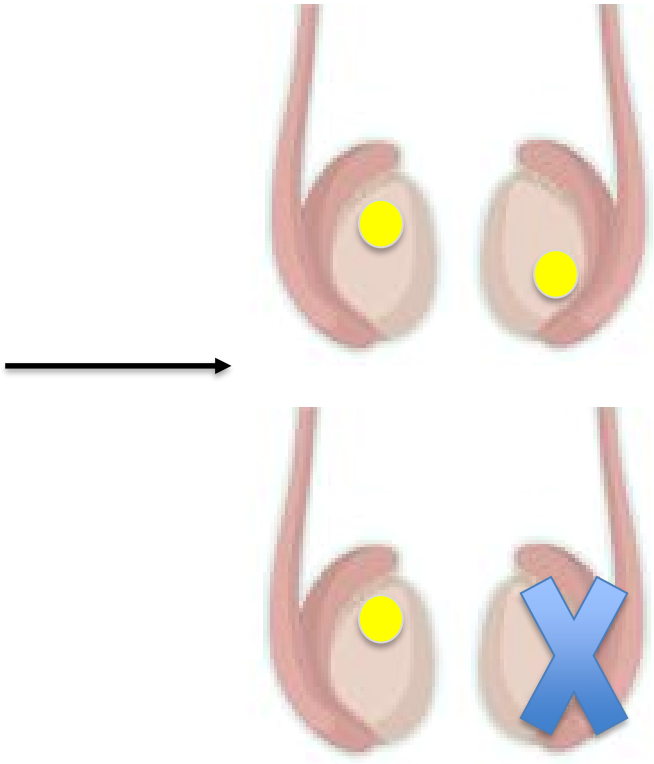




Onco-microTESE @GSTT: RESULTS



TOTAL
65% testes (13/20)
81% patients (13/16)



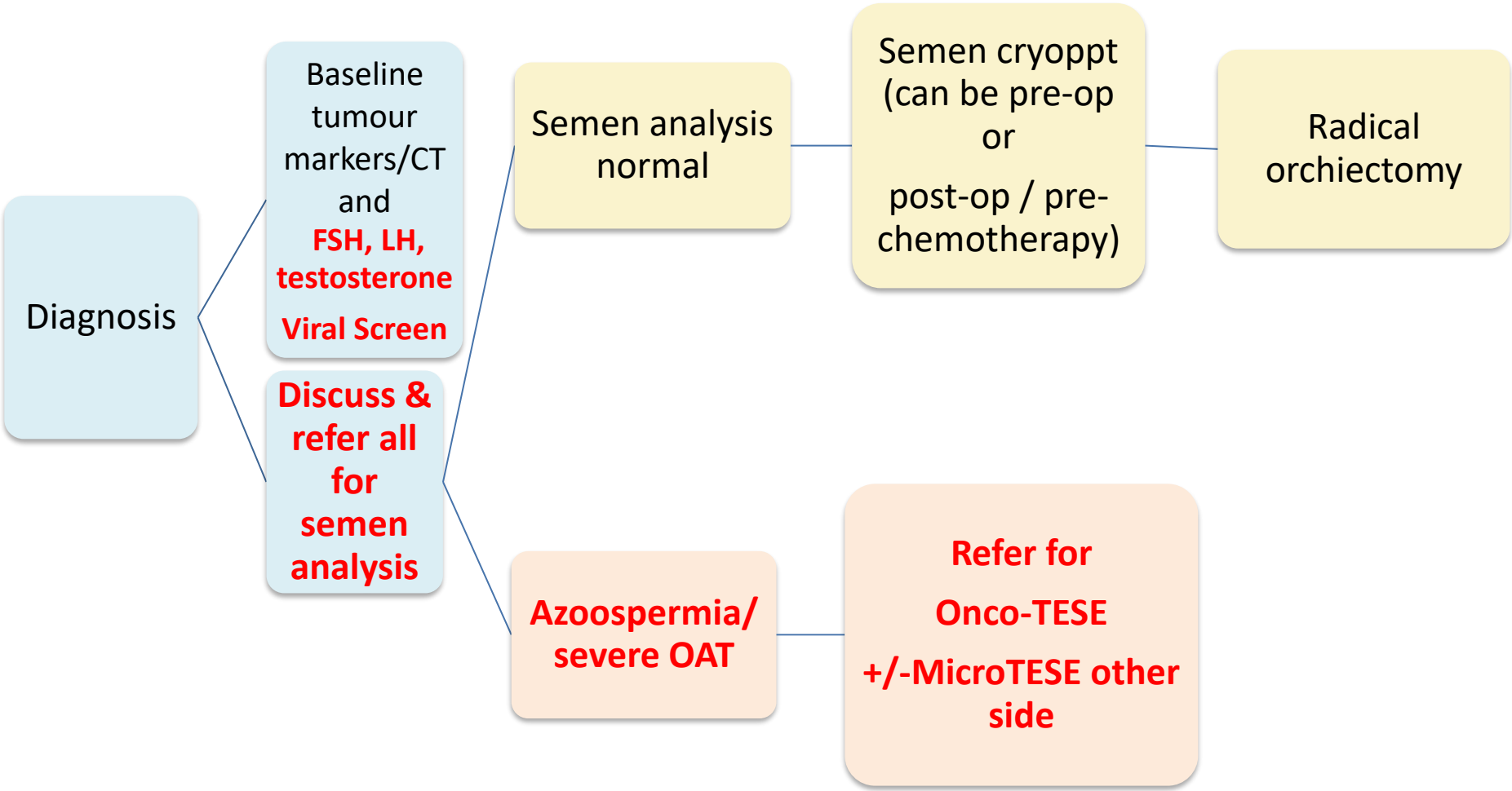
Bilateral Synchronous
100% (4/4)

Metachronous
50% (2/4)

Solitary functioning testis
100% (1/1)

All cases (local/ tertiary) Completed within mean 7 days of referral

RECOMMENDATIONS FOR PRACTICE



Special Considerations

1. Azoospermic after chemotherapy
2. Fertility preservation post TKI/ MCA/ BMT
3. Fertility preservation in paediatric patient

1. SSR post Chemotherapy

Study	No of pts	No of successful SSR (%)	Successful SSR Ca Testis	Mean time since Chemotherapy
Chan et el 2001	17	9 (53%)	67%	16yrs
Damani et al 2002	23	15 (65%)	75%	
Meseguer et al 2003	12	5 (42%)	67%	10.8yrs
Hsiao et al 2011	73	27 ((37%)	86%	18yrs

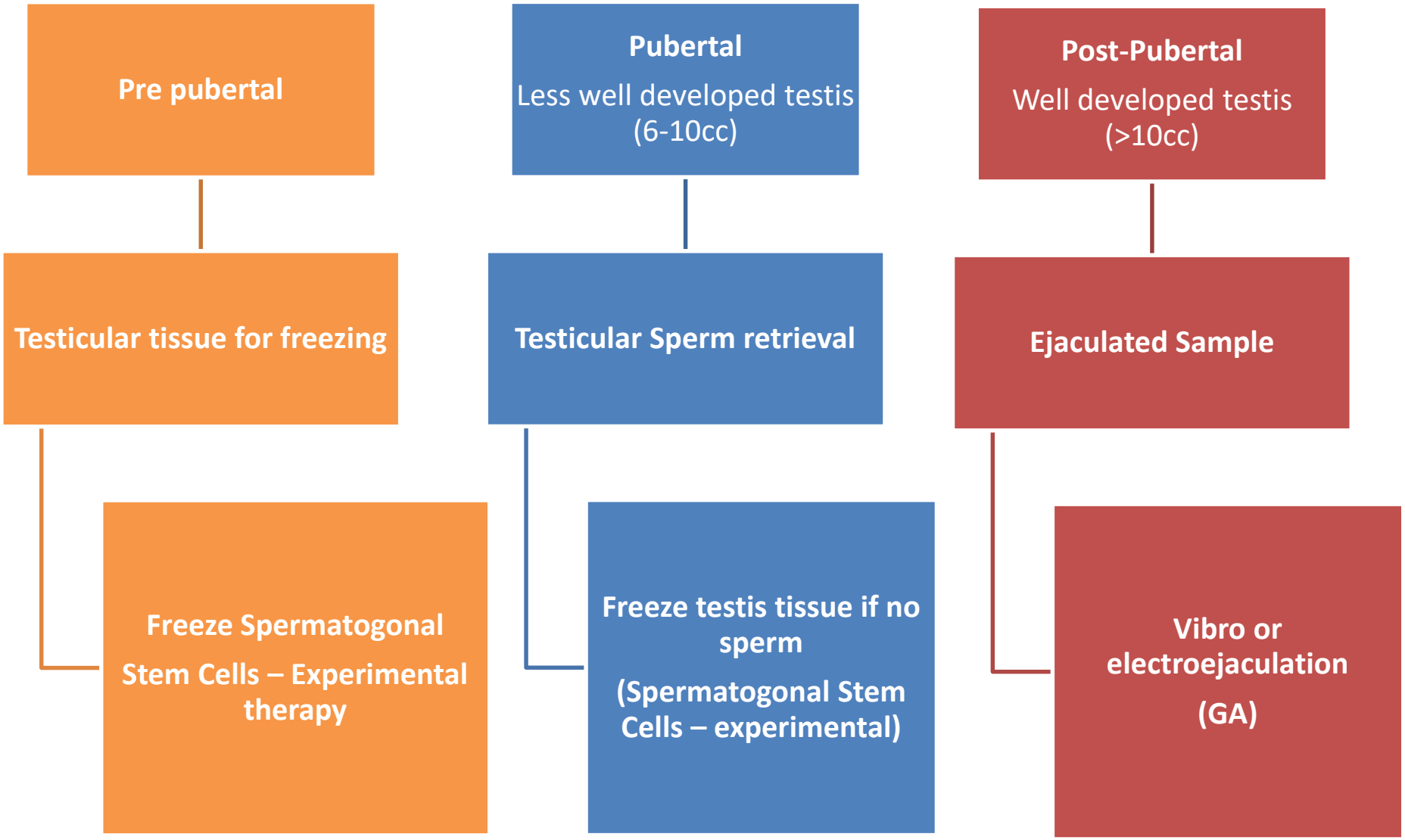
2. Fertility Preservation post TKI/ MCA / BMT

- **Tyrosine kinase inhibitors** (TKI)- all can impair fertility and fetal development. Greater impact on female, likely safe in males (e.g. imatinib for CML). Very limited data on 2nd line and 3rd line TKI's

- **Monoclonal antibodies** (MCA) e.g. rituximab for NHL – use contraception for at least 12months after last dose

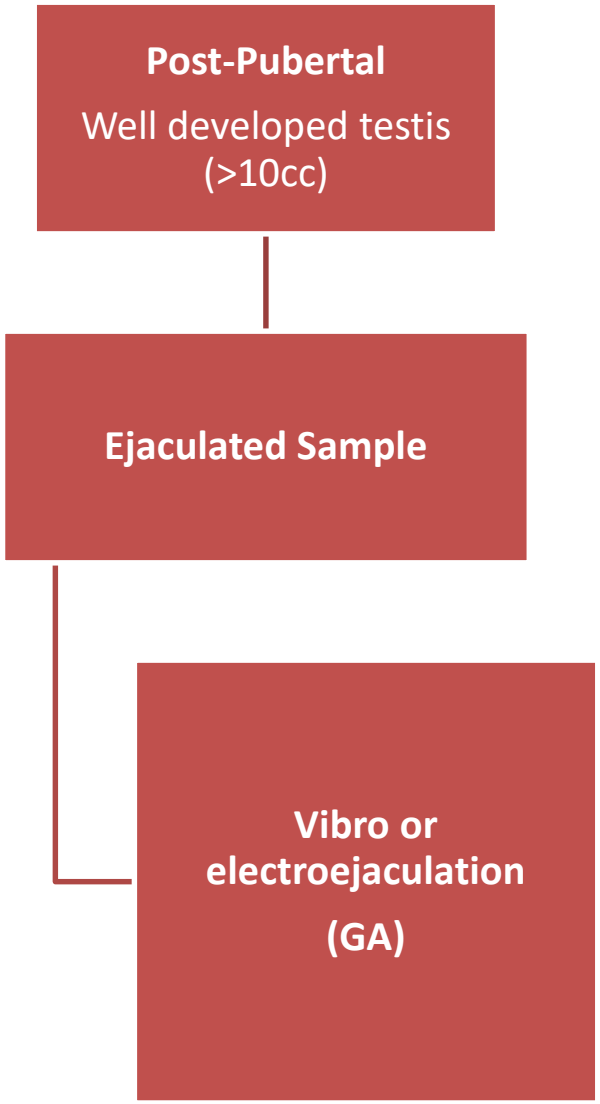
- **Bone marrow transplant** (BMT) high risk of infertility (esp. after TBI) –only 1 in 5 will regain some fertility

3. Fertility preservation in paediatric patient



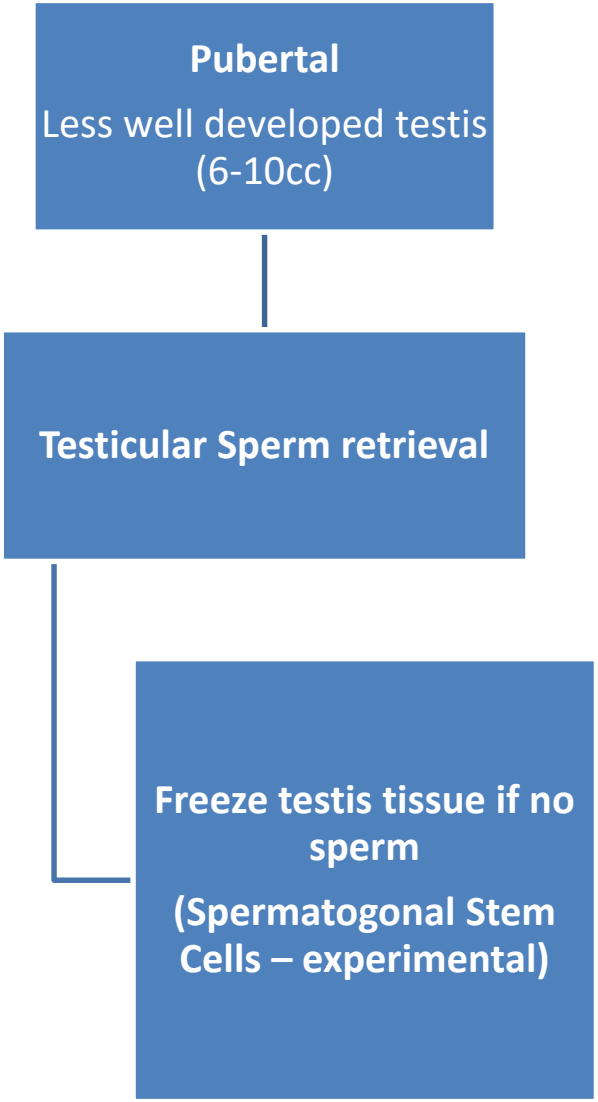
Adapted from Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group 2017

3. Fertility preservation in paediatric patient



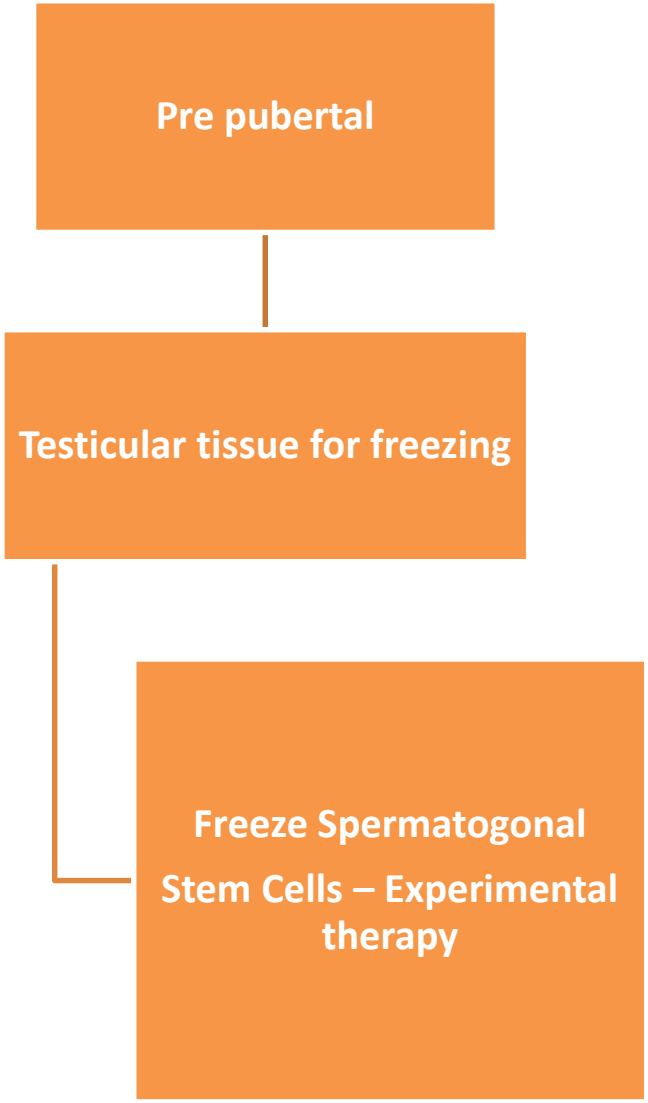
Adapted from Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group 2017

3. Fertility preservation in paediatric patient



Adapted from Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group 2017

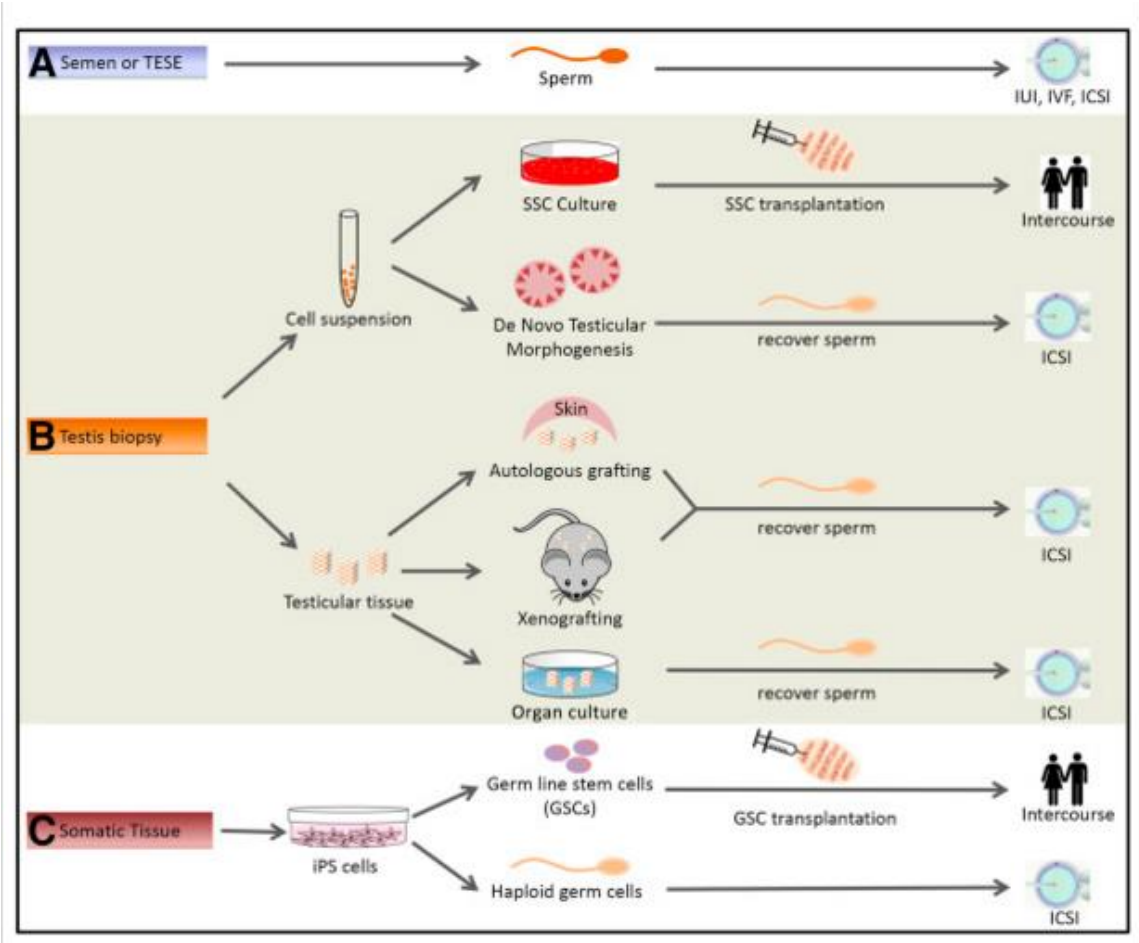
3. Fertility preservation in paediatric patient



Adapted from Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group 2017

Spermatogonial Stem Cells (SSC)

- Procedures used for SSC and testicular tissues preservation far more advanced than methods needed to realize the fertile potential of these cells
- Strategies include
  - Auto-transplantation into testis
  - Growth and maturation of SSCs in vitro
- **Proposed techniques have yet to be proven to be safe for clinical use in humans.**



MEDICAL & BIOTECH

First Baby Monkey Born Using Sperm from Frozen Testicles

Researchers hope that the procedure could be used to restore fertility to human boys undergoing cancer treatment

By Emily Mullin on March 21, 2019

- University of Pittsburgh
- Testicular tissue frozen from 5 pre-pubertal rhesus macaques
- Made sterile by castration.
- At puberty, tissue defrosted and grafted under the scrotum of the same animal from which it was originally taken.

- 8-12 months, tissue harvested from graft sites. Viable sperm successfully extracted
- Enough sperm to fertilize 138 eggs
- Only 16 embryos suitable for implantation
- 11 embryo transfers
- 1 pregnancy and subsequent live birth

OPTIMIZING FERTILITY PRESERVATION

- Establishment of National Onco-fertility centres
- Co-localisation of Andrology/ Reproductive medicine unit/ Embryology
- Able to offer
  - Semen cryopreservation
  - Advanced sperm extraction and retrieval (Electro/vibro-ejaculation)
  - MicroTESE
  - Onco-microTESE
  - Drive research into new fertility preservation techniques

Onco-fertility in Men : Take Home Messages

- Important to address fertility from the outset
- Paradigm shift to testing testis function and fertility at first presentation pre-orchiectomy
- Sperm cryopreservstion most effective and cost efficient
- Azoospermic cases who will benefit from onco-TESE
- Onco-TESE can be achieved without delaying cancer treatment and should be made available to all
- If azoospermic after previous chemotherapy, still amenable to SSR with microTESE
- MDT approach to fertility preservation in paediatric patient: Even those who cannot produce sample can still have fertility preserved for the future

Thank you

Email: majed.shabbir@gstt.nhs.uk

Guy's and St Thomas'
NHS Foundation Trust

NHS

Case 1

- 36yr old man
- Testicular cancer - radical orchiectomy and subsequent chemotherapy
- No sperm bank before orchiectomy. Pre-chemo sperm bank - azoopsermia
- Seen 2 yrs post BEP3 cycles - still azoospermic
- FSH 45 Testosterone 10

Case 1

- 36yr old man
- Testicular cancer - radical orchidectomy subsequent chemotherapy
- No sperm bank before orchiectomy. Pre-chemo sperm bank - azoopsermia
- Seen 2 yrs post BEP - still azoospermic
- FSH 45 Testosterone 10

- MicroTese of solitary testis
- Histology SCO
- Successful sperm retrieval
- Currently undergoing IVF/ICSI
- Option would have been for possible OncoTESE at time of orchidectomy

Case 2

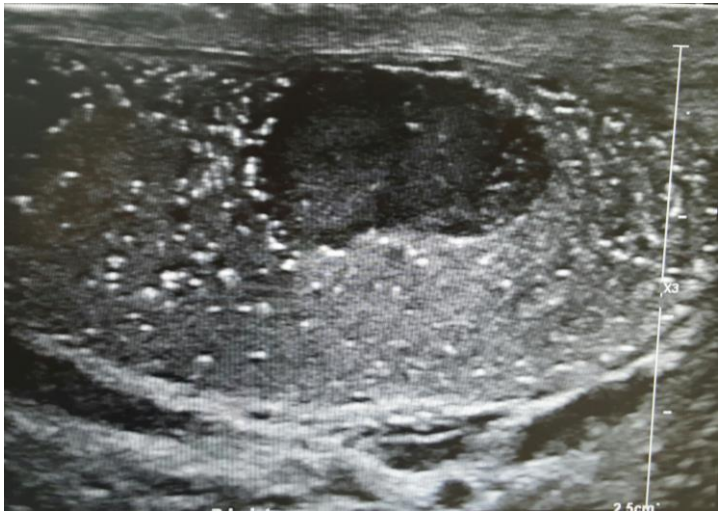
- 33 yr old man
- Large tumour in solitary testis (90%)
- Azoospermia on pre-op sperm bank
- FSH 22 Testosterone 14

Case 2

- 33 yr old man
- Large tumour in solitary testis
- Azoospermia on pre-op sperm bank
- FSH 22 Testosterone 14

- Not suitable for partial given size
- Radical orchidectomy with OncoTESE same time
- Successful retrieval – freeze
- Started onto Testosterone replacement therapy

Case 3



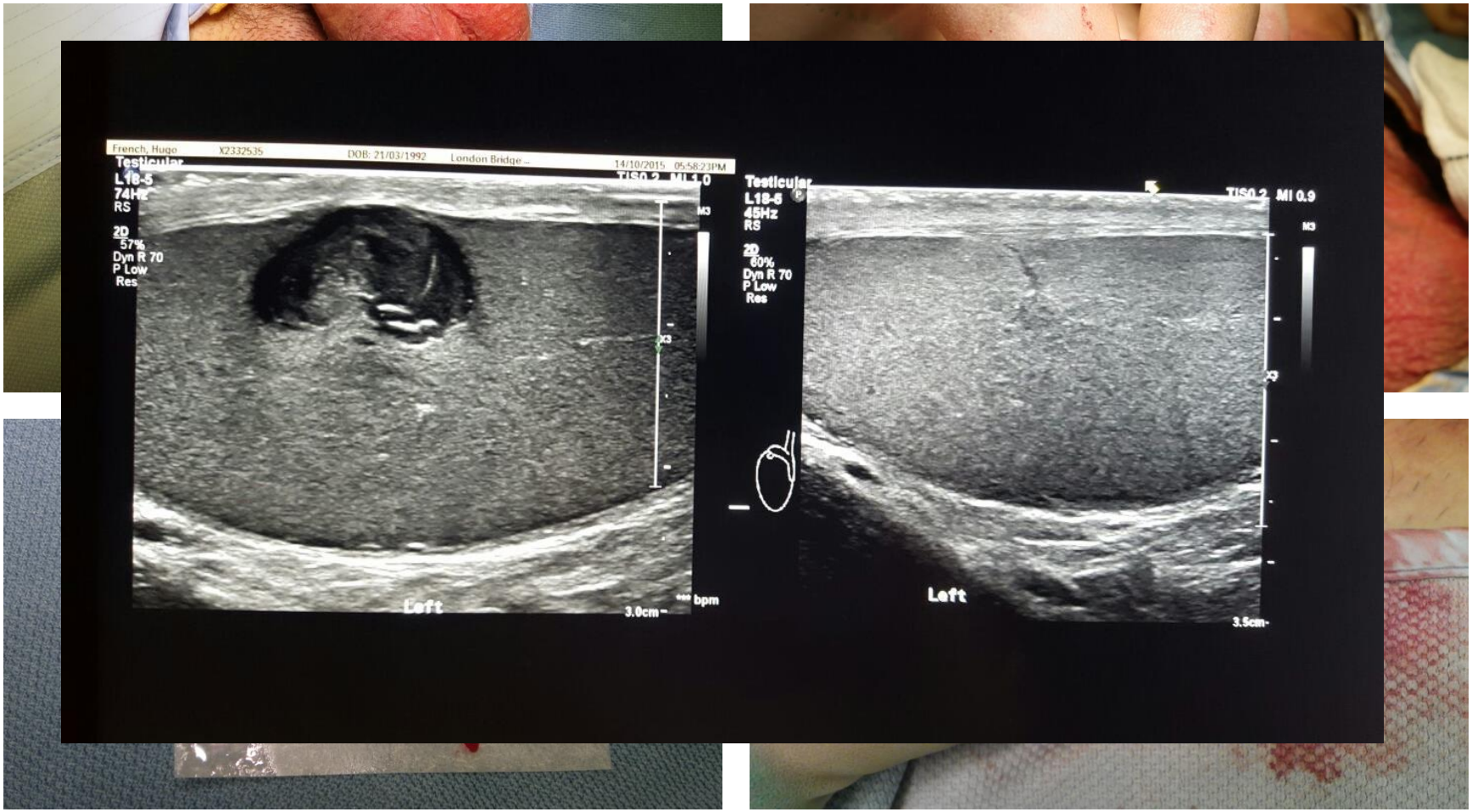
- 27 yr old
- Small atrophic left testis after traumatic injury as teenager
- 1.5cm mass in normal right testis
- Pre-op sperm banking azoospermia
- FSH 13 Testosterone 13

Case 3

- 27 yr old
- Small atrophic left testis post trauma as teenager
- 1.5cm mass in normal right testis
- Pre-op sperm banking azoospermia
- FSH 13 Testosterone 15

- Options:
  - Partial orchiectomy with oncoTESE
  - Radical orchiectomy with oncoTESE
- Complete excision with partial orchiectomy – small seminoma clear margin – no ITGCN
- Successful sperm retrieval – frozen
- Post op testosterone 11 – on close observation

3. Cancer in a solitary functioning testis
Option: Partial Orchiectomy



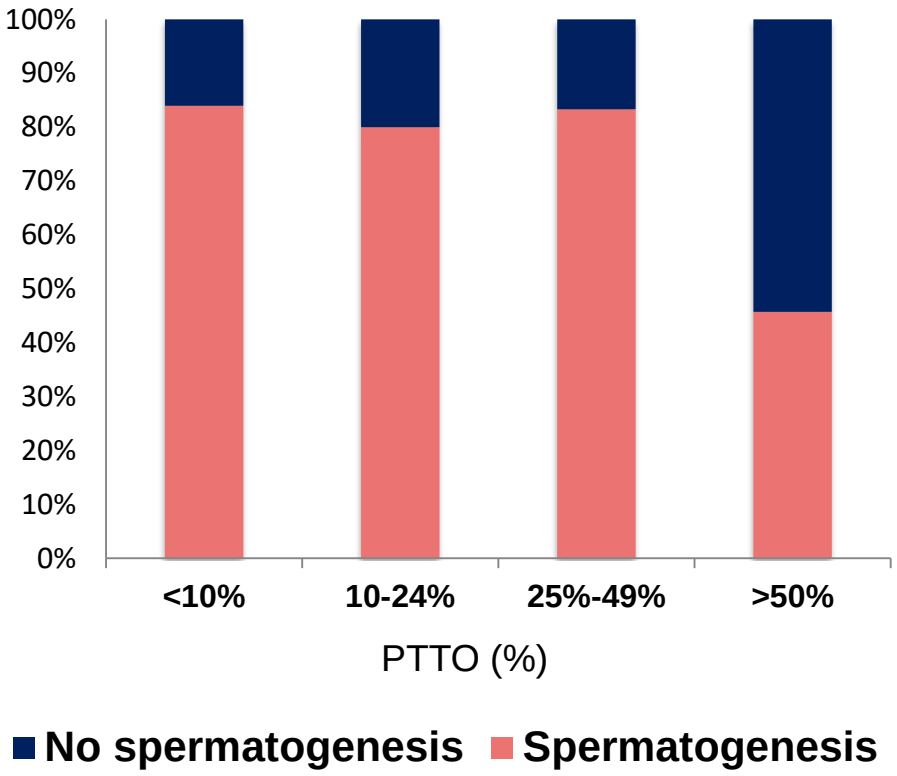
Can we predict spermatogenesis in men with Testis cancer?

Potential predictors

- ~~Type of tumour~~
- ~~TMN stage of tumour~~
- **Size (percentage) of tumour occupying testicle (PTTO)**
- ~~Tumour markers~~
- ~~Presence of testicular microlithiasis (TML)~~

Moody et al BJUI 2018

KEY RESULTS: PTTO



- Men with PTTO were >50% **81%** less likely to have sperm in testicle compared to men PTTO <50%

Moody et al BJUI 2018

RECOMMENDATIONS FOR PRACTICE