The effects of cancer treatment on male infertility

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Disclosure statement

"I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content"

This lecture includes

- Spermatogenetic recovery after low and high dose exposures
- What factors contribute to impaired spermatogenesis?
- Effect of follow-up time for spermatogenetic recovery

International Harmonisation Group / PCSF-WP6, Male Gonadotoxicity Guidelines Group

Skinner et al. Lancet Oncol 2017; 18: e75–90

Cancer therapy

Impact of chemotherapy and irradiation on testicular function depends on

- Type of drug used
- Dosage
- Fractionation schedule for radiation
- Age at treatment, only Leydig cell function
  - no evidence that age at exposure is associated with susceptibility to spermatotoxicity
- Time since treatment (slow recovery)
- genetic variation

Effects of high dose cancer therapy in testis

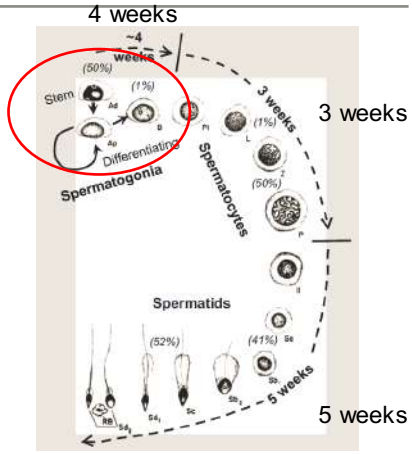
- Spermatogenesis is stem cell driven system
- Toxic insult with HIGH INTENSITY
  - Depletes spermatogonial stem cell pool

  → Permanent spermatogenetic failure = azoospermia
- Toxic insult with NEARLY STERILIZING INTENSITY
  - Surviving spermatogonial stem cells begin to proliferate and repopulate the tubules

  → Recovery follows, but takes time!

Recovery at different stages of spermatogenesis

- Even moderate gonadotoxic doses produce azoospermia that lasts longer than the 12 weeks
- Recovery is delayed for months or decades if gonadotoxic therapy kills stem cells



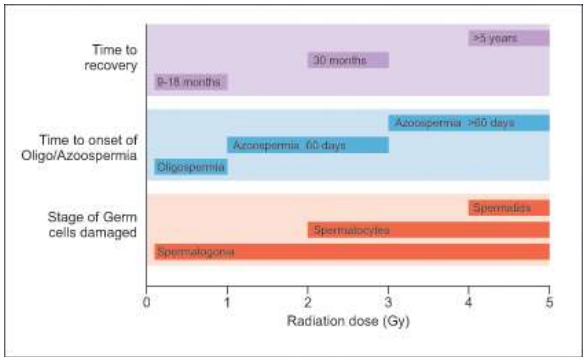
Meistrich. Fertil Steril 2013;100:1180-6

Recovery of spermatogenesis depends on the dose of irradiation

≥0,1 Gy
The differentiating spermatogonia are killed → short term cessation of spermatogenesis

2–3 Gy
Kills also SSCs → long term azoospermia.

>6 Gy
Able to deplete the SSCs pool →permanent/long term infertility



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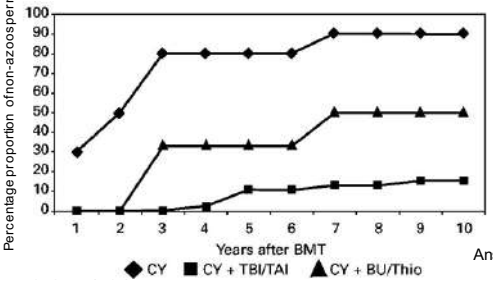
Mitchell et al. Male Hypogonadism: Basic, Clinical and therapeutic Principles

Spermatogenetic recovery after hematopoietic stem cell transplantation in adults

Recovery of spermatogenesis after allogeneic HSCT is predicted by
- younger age (<25 years)
- a non–total body irradiation (TBI) -based conditioning regimen
- no treatment for the underlying malignancy before HSCT
- no chronic graft-versus-host disease Rovó et al. Blood 2006:108:1100-1105



Cyclophosphamide	90%
Cyclophosphamide + busulphan or thiotepa	50%
Cyclophosphamide +TBI	17%

Anserini et al. Bone Marrow Transplantation 2002;30:447-451

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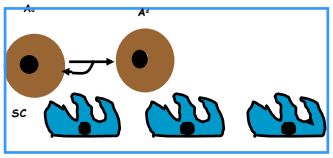
Male fertility after allo HSCT

- Pregnancy rates for partners of male patients after allogeneic transplantation in EBMT database is <2%
  - for SAA patients 5.3%, acute leukemia 0.8%
- No fertility data on reduced-intensity conditioning protocols
- No fertility data for pediatric HSCT recipenents
- An increased incidence of prematurity and low birth weight (LBW) among the single spontaneous pregnancies fathered by HSCT survivors

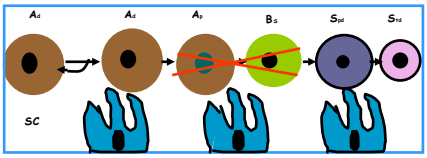
Socié et al Blood 2003 101: 3373-3385

Effects of low dose cancer therapy in child and adult testis

Child

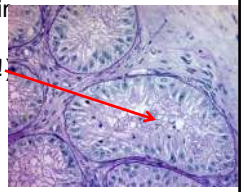


Adult



Adult
- Differentiating spermatogonia are killed
- Spermatocytes and spermatids survive and continue their maturation into sperm but are not replaced by new cells

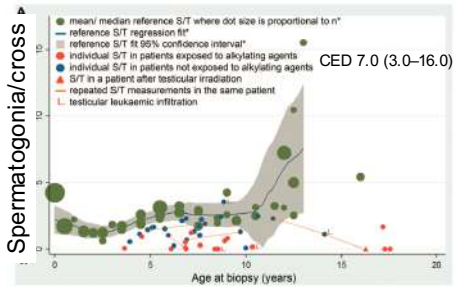
→ some sperm production 4-10w (do not cryopreserve!)
→ short term loss of sperm production and recovery

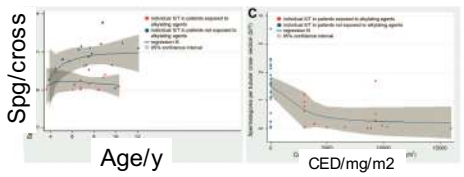


Child
- No morphological effects

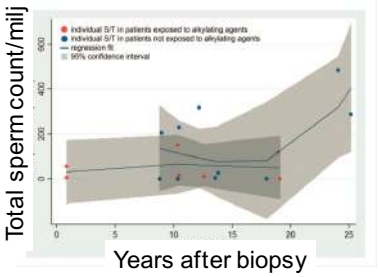
Conventional leukemia therapy and acute depletion of the spermatogonia

Median age at testicular biopsy 5 (1-16) years, n= 37





Spermatogonial quatity in testicular samples at the end of leukemia therapy



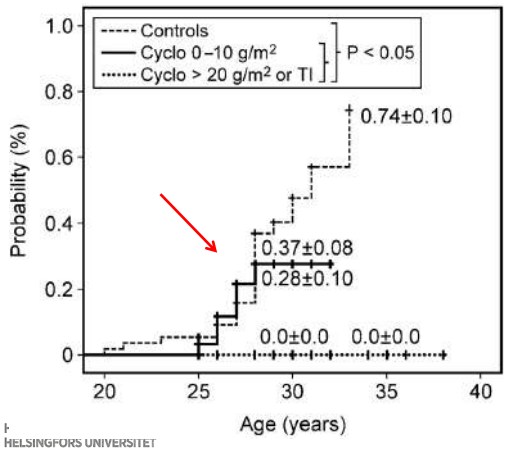
No difference in total sperm count after a follow-up period of 9-19 years between non-alkylating vs alkylating therapy

Poganitsch-Korhonen et al Leukemia 2017;31:1460-1463.

Cumulative rate of first fathered child by age of men

Childhood acute leukemia

Follow up 20y (range11-30), n=50



Leukemia therapy with 0-10 g/m^2 cyclophosphamide does not affect early male fertility

No fertility after Cyclophosphamide>20g/m^2

Jahnukainen et al. Fertil Steril 2011;96:837-42

Sperm quality after spermatogenetic recovery

- The recovery is almost always progressive, and significant declines in sperm counts are rarely observed (Cave! CNS irradiation)
- Many recover to normospermic levels
- When the human testis contains <3–4 million sperm, sperm do not survive epididymal transit and do not reach the ejaculate
- It is possible that some sperm are produced in the testis. Recovery may be patchy.
- Spermatozoa can be retrieved from the testes by microdissection testicular sperm extraction (TESE)

What factors contribute to impaired spermatogenesis?

International Guideline Harmonization Group

Risk of long term/permanent infertility is associated with treatment with

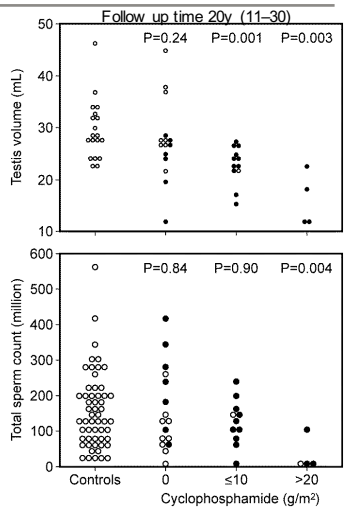
Alkylating agents

- Cyclophosphamide
- Nitrogen mustard
- Procarbazine

Lopez Andreu et al. Pediatr Hematol Oncol. 2000;16:21-30.
van Beek et al. Hum Reprod. 2007;22:3215-3222

→ Sperm concentration decreases with increasing cumulative dose
→ No threshold dose for azoospermia can be identified – genetic variation!

Green et al. Lancet Oncol 2014;15:1215-1223



Jahnukainen et al. Fertil Steril 2011;96:837-42

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What factors contribute to impaired spermatogenesis?

Risk for permanent infertility is associated with **radiotherapy**

- Exposing testes at any dose
- Especially doses >2-3 Gy
- Especially TBI (level C)

Wilhelmsson et al. Pediatr Blood Cancer. 2014;61:1094-1100

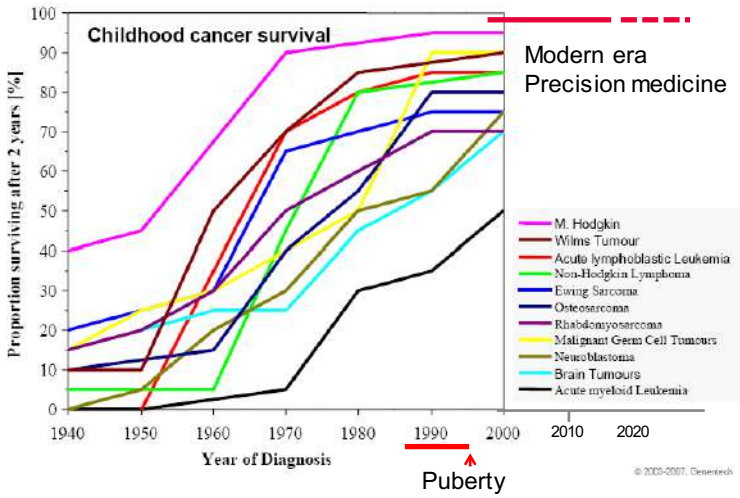
There is no evidence of

- Safe irradiation dose

Gaps in knowledge Impaired Spermatogenesis

- Risks of, and dose thresholds, for impaired spermatogenesis of
  - Radiotherapy exposing the testes, including those treated with TBI
  - Busulfan, chlorambucil, ifosfamide, melphalan and thiotepa
  - Dacarbazine, procarbazine, temozolomide
  - Carboplatin, cisplatin
  - Carmustine, lomustine
- Role of genetic susceptibility in development of impaired spermatogenesis
- Impact of follow up time

Fertility data matures slowly



Modern era
Precision medicine

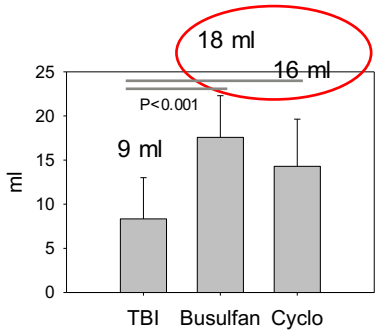
Puberty

Early fertility

Final fertility

Adult testicular volume reflects recovery of spermatogenesis after pediatric HSCT

Follow up 13 ± 4.8 y, median age at study 22 ± 6.0 years, n=106



Mean adult testicular size is >15 ml after
- busulfan-based regimes
- cyclophosphamide alone as conditioning

→ suggest very long-term recovery of spermatogenesis after chemotherapy-based regimens

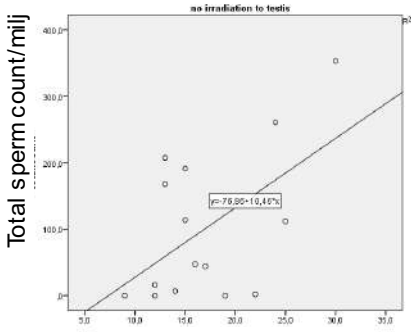
Wilhelmsson et al PBC 2014;61:1094-100.

Spermatogenetic recovery after pediatric HSCT is progressive

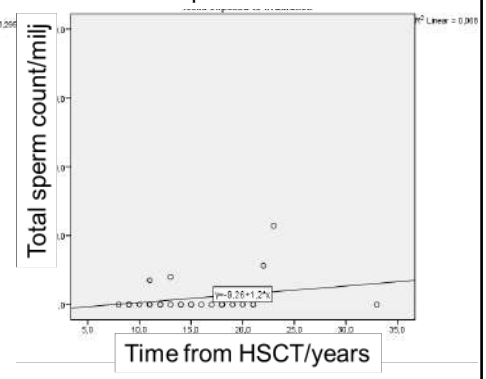
Preliminary HSCT data Helsinki-cohort, n=41 with no testosterone replacement

Follow up 16.1 ± 5.7 y, median age at study 26.1 ± 6.3 years

No irradation to testis

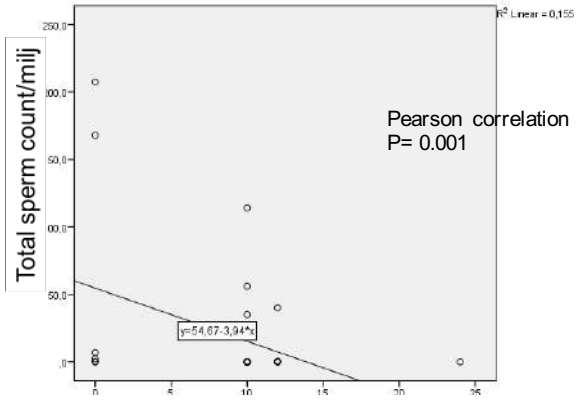


Testis exposed to irradiation



Spermatogenetic recovery depends on cumulative testicular irradiation dose

Preliminary HSCT data Helsinki-cohort, n=41 with no testosterone replacement



Pearson correlation -0.510
P= 0.001

Predictors of total sperm count in multivariate analysis

Preliminary HSCT data Helsinki-cohort, n=41 with no testosterone replacement

Follow up 16.1 ± 5.7 y, median age at study 26.1 ± 6.3 years

Total sperm count	beta	P<
Cum testicular irradiation dose	-0.364	0.013
Time from HSCT	0.346	0.012
Testicular volume	0.344	0.018

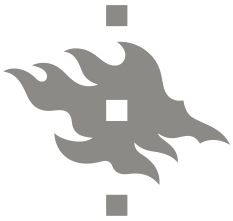
Future challenges for fertility preservation of young boys

- How to councel patients and parents?
- How to offer tissue preservation to right patients?
- What is the right timing for fertility preservation?

Multi-disciplinary teams are required

GROW SPERM

NORDFERTIL
nordic centre for fertility preservation



Karolinska institutet, Stockholm
- Olle Söder
- Jan-Bernd Stukenborg
- Mari Wilhelmsson
- Mi Hou

University of Münster, Germany
- Stefan Schlatt
- Jens Ehmcke

Children´s Hospital, Helsinki
- Anu Vatanen
- Risto Heikkinen
- Outi Mäkitie

Rigshospitalet, Copenhagen, Denmark
- Sidsel Mathiesen
- Klaus Müller
- Anders Juul

Women's and Children's Hospital, Academic Medical Center, Amsterdam
- Ieva Masliukaite,
- Madelon van Welyl
- Ans M.M. van Pelt

Thank you

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