Fertility issue in cancer survivors

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Introduction

- Although chemotherapy and radiation therapy for malignancies are highly effective, gonadotoxic side effects may severely impair fertility in agent- and dose-dependent manners → temporary or permanent gonadal toxicity.

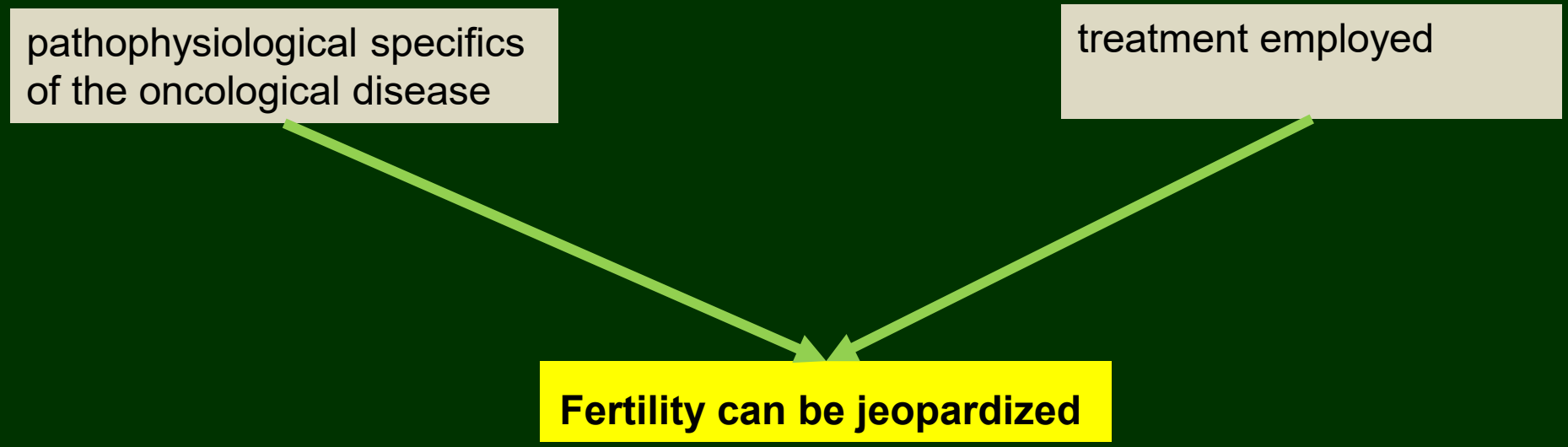
- The resumption of spermatogenesis after therapies is unpredictable
- Spermatogenesis in long-term cancer survivors: persistent azoospermia or severe oligozoospermia in up to 24% of cases.

Effect of cancer treatment on testes & spermatogenesis

- Cancer incidence: ½ men will develop an oncological disease at some point in his life, from which 4% will be under 35 years of age.
- A traditional approach to anticancer treatment: elimination of the cancer tissue itself

- ✓ Increasing efficiency and safety goes hand in hand with the rise of long-term survival rate of young adults who underwent this therapy.
- ✓ 5-year survival rate in patients under 15 years old undergoing anticancer therapy is 75 %.
- ✓ In patients between 15–44 years of age, this rate is estimated at 66 %.

Fertility maintenance in cancer patients should belong to the list of issues of major importance before, during and after the cancer treatment



Anticancer treatment is potentially harmful

- Anticancer treatment is potentially harmful not only to testes directly, but also to H-P-G axis, which controls the function of the male gonads.

- Germinal epithelium of the testes is highly susceptible to harmful effects of chemotherapy.

Leydig cell, testosterone production

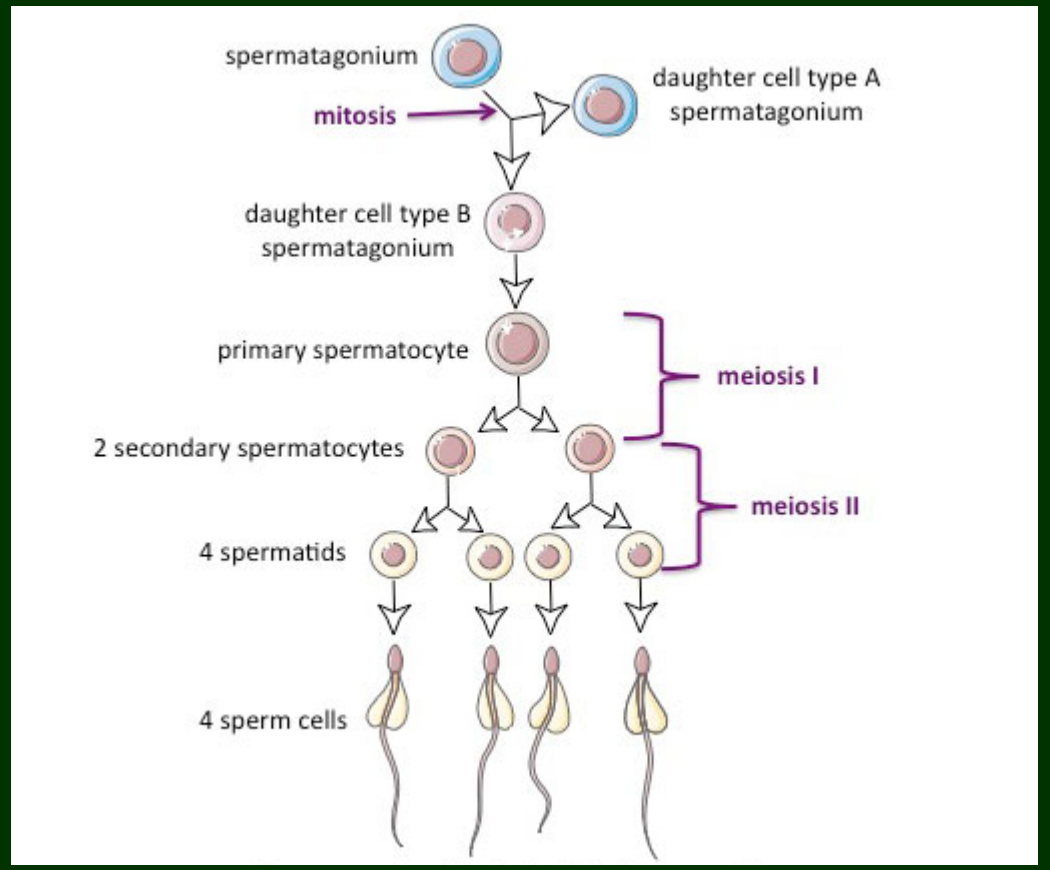
- Production of testosterone by Leydig cells usually remains unaffected, so secondary sex characteristics develop normally.

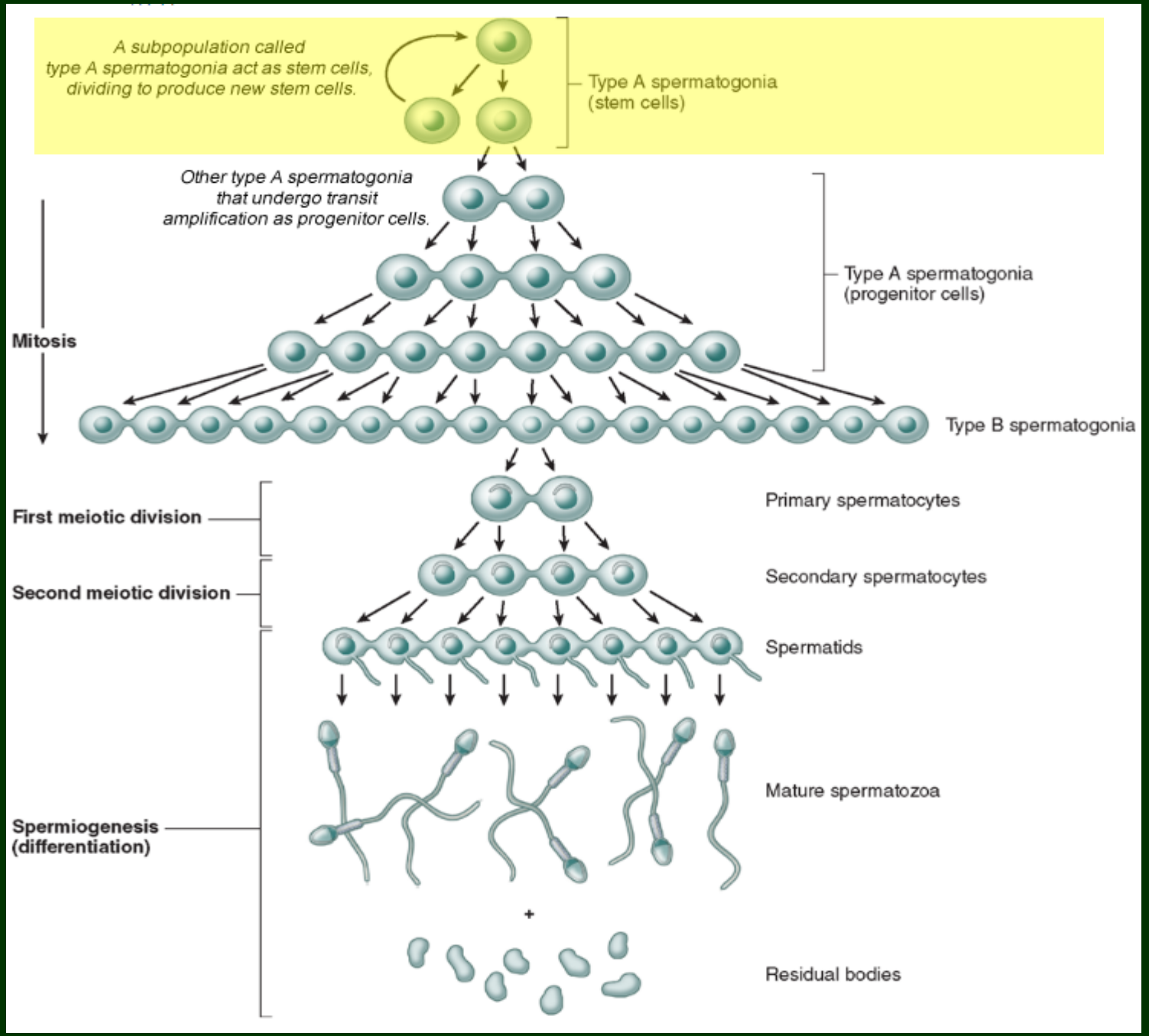
- Nevertheless, when gonadotoxic effect of chemotherapy is evaluated from the perspective of cumulative dose, Leydig cells are no longer able to tolerate this detrimental burden, so their dysfunction is presumably inevitable.

Spermatogenesis

- Spermatogenesis may still continue over several years if the spermatogonial cell population is not completely depleted.

- If a population of these germ stem cells remains after cancer treatment, the regeneration of spermatozoa may continue for years.




A subpopulation called type A spermatogonia act as stem cells, dividing to produce new stem cells.
Type A spermatogonia (stem cells)
Other type A spermatogonia that undergo transit amplification as progenitor cells.
Type A spermatogonia (progenitor cells)
Mitosis
Type B spermatogonia
First meiotic division
Primary spermatocytes
Second meiotic division
Secondary spermatocytes
Spermatids
Mature spermatozoa
Spermiogenesis (differentiation)
Residual bodies

Radiation

- **Testis is one of the most radiosensitive organs.**
- Radiation doses of 0.1–1.2 Gy can disrupt spermatogenesis.
- Higher than 4 Gy cause a permanent azoospermia.
- Sertoli cells are more resistant than spermatogonia.
- Dysfunction of Leydig cells is not detectable, until the radiation exposure reaches 20 Gy in prepubertal patients and 30 Gy in men after sexual maturity.

Gonadal damage caused by radiotherapy

- It depends on the gonadal **dosage** and how radiation is delivered.
- Damage may be caused during direct irradiation of the testis or, more commonly, from scattered radiation during treatment directed at adjacent tissues.
- Sperm production may be diminished even if the testes are shielded.

- Patients with **leukemic infiltration of the testes** usually undergo the radiation therapy with doses of **24 Gy**, resulting in a **permanent azoospermia** (direct radiation exposure of the testes).

Total body irradiation

- Total body irradiation (at least 7.5 Gy) is the main etiological factor of azoospermia in patients after ***hematopoietic stem cell transplantation***.

- 81% azoospermia vs 1% normal sperm count after total body irradiation: *from large retrospective cohort study –* ***European Group for Blood and Marrow Transplantation***

Chemotherapy

- **Most chemotherapeutic drugs** are considered to be toxic to the **gonads**, particularly **alkylating medications**.

- **Chemotherapy with alkylating agents**, with or without radiation to sites below the diaphragm, has been associated with a fertility deficit in approximately 60% of men.

- **Duration and permanence of induced azoospermia** depends on the dose of the cytotoxic agent and the additive effects of different agents.

Toxicity to later stage germ cells

- Due to toxicity to later stage germ cells, **10- to 100-fold decreases** in sperm counts may occur **within 1 to 2 months**, while azoospermia generally does not occur until after 2 months.

- Although sperm are produced for several months after the start of cytotoxic therapies, **pregnancy needs to be avoided during this period** because of a higher risk of genetic damage to sperm.

Extent of gonadal damage is largely dependent on the drug type, age of the patient, and amount of the agent

Table 1. Summary of fertility in adult men following treatment with various gonadotoxic drugs

Group	Definite gonadotoxicity	Diagnosis	Effect on spermatogenesis
Alkylating agents	Cyclophosphamide, busulfan, chlorambucil, procarbazine, etc.	HL, NHL, GCT, sarcomas	May induce azoospermia within 90 days
Platinum-based agents	Cisplatin, carboplatin	HL, NHL, GCT, bladder cancer	Spermatogenesis affected, possible chromosomal aberrations
Vinca alkaloids	Vincristine, vinblastine	HL, NHL, leukemia	Spermatogenesis arrested, spermatozoa motility reduced
Antimetabolites	Cytarabine	HL, NHL, leukemia, bladder cancer, colorectal cancer	Spermatogenesis affected, possible chromosomal aberrations
Topoisomerase inhibitors	Etoposide, doxorubicin	HL, NHL, GCT, sarcomas	Cytotoxic with possible chromosomal anomalies

HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, GCT: germ cell tumor.
Adapted from Howell and Shalet (J Natl Cancer Inst Monogr 2005;(34):12-7) [16], and Osterberg et al (Urol Ann 2014;6:13-7) [38].

Alkylating agents are among the most potent germ cell mutagens

- Alkylating agents are among the most potent germ cell mutagens in post-stem cell stages.

- Three alkylating anticancer drugs (*melphalan, mitomycin C, and procarbazine*) have been shown to induce specific locus mutations in spermatogonial stem cells.

Return of spermatogenesis

- A follow-up of 26 male patients with azoospermia after the cessation of cyclophosphamide showed the return of spermatogenesis in 12 patients within 15 to 49 months (mean, 31 months). *by Buchanan JD, Lancet 1975*

- Limited information is currently available on parenthood rates after treatment for Hodgkin disease.
- "***Only 18 out of 101 men*** *who had received chemotherapy, radiotherapy, or both for Hodgkin disease over a* ***21-year period*** *had fathered a child*." *by Swerdlow AJ, Br J Cancer 1996*

Sperm quality in cancer patients and sperm cryopreservation

- Chemotherapy or radiotherapy-induced testicular damage.
- However, negative influence of the testicular cancer itself (before any treatment) on the spermiogram parameters is still controversial.

- Spermiogram is worsened in approximately half of the patients with testicular cancer
  - ✓ Lower sperm concentration, sperm concentration than healthy male
  - ✓ No relationship with cancer stages

MacKenna et al, 2017, Auger et al, 2016

Sperm quality in cancer patients and sperm cryopreservation

- Other types of oncological diseases (*e.g. leukaemia, lymphoma, brain tumour, sarcoma*), can also worsen the **ejaculate quality**.
- Still, the **exact mechanism**, by which the cancer negatively influences the spermatogenesis is **not known**.
- Supposed etiopathogenesis is often linked to 1) congenital abnormalities of the reproductive cells, 2) systemic effect of a tumour, or 3) negative influence of cytokines and hormones produced by the cancer tissue. *by Trottmann et al, 2007*

Sperm cryopreservation

- Global statistics shows that from among men who underwent a treatment due to cancer, approximately **8 %** actually use their **cryopreserved sperm to ART** *(Ferrari et al, 2016).*

- Even though the sperm of cancer patients showed a significantly reduced motility and vitality after thawing, in case of a successful fertilization, **no abnormalities** were observed during the cleavage of the zygote
- in addition, the rate of embryo implantation into the uterine mucosa was also comparable with the control group *(Depalo et al, 2016).*

Záková et al, 2014

- Patients with **testicular cancer** whose sperm cells had been cryopreserved before a treatment will have a good chance to father a child someday.
- **1995 - 2012**; 523 patients (mean age 28.5±6.6 years) with testicular cancer had undergone sperm cryopreservation before a treatment, from which 34 individuals later decided to use these sperm in assisted reproduction.
- This resulted in 16 pregnancies from 46 cycles of artificial fertilization (pregnancy rate was **34.8 %).**
- The average elapsed time from the sperm collection to artificial fertilization was **22.2±14.7** months.

Genetic defects or congenital malformations

- Although sperm DNA damage occurs following chemotherapy or radiotherapy, an increase in **genetic defects or congenital malformations was not detected** among children conceived by parents who had previously undergone treatments.

- However, the use of assisted reproductive technologies and micromanipulation techniques may increase this risk *[Arnon J, Hum Reprod Update 2001]*.

Prepubertal boys

- In adolescent males, the most established approach to preserving fertility is the cryopreservation of ejaculated sperm.
- Cryopreserved sperm may be used later for IUI or IVF.

- **However, options are limited to experimental techniques for prepubertal males.**
- Prepubertal testicular tissue banking under an Institutional Review Board-approved protocol is currently available at several institutions.

Future

- **Stem cell therapy** to generate male gametes may represent a promising treatment strategy.
- **Three major stem cell** :
  - ✓ ES cells (embryonic stem cells)
  - ✓ iPS cells (induced pluripotent stem cells)
  - ✓ **SSCs (spermatogenic stem cells)**
- **SSCs** have the ability to self-renew and differentiate into male gametes (ex, mature spermatozoa) in the testis throughout life *(Brinster RL, Science 2002)*
- **Recent studies** showed that spermatogonia, including SSCs, may be induced to differentiate into differentiated male germ cells, eventually resulting in haploid spermatids.

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2015 April 33(1): 8-13
http://dx.doi.org/10.5534/wjmh.2015.33.1.8

Original Article

Semen Analysis in Cancer Patients Referred for Sperm Cryopreservation before Chemotherapy over a 15-Year Period in Korea

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Purpose: This study evaluated the demographics and semen parameters of males with cancer who banked their sperm prior to chemotherapy.

Materials and Methods: This is a retrospective study of 66 cases referred for sperm banking prior to initiation of chemotherapy over a 15-year period (1999～2014). Patients who had previously received cancer treatment including chemotherapy or radiotherapy were not included in this study.

Results: We studied a total of 66 cancer patients referred for cryopreservation of sperm prior to chemotherapy. The mean age of the patients at the time of banking was 32.0±7.9 years (range, 19～58 years). The types of cancer were testicular cancer (31 cases, 47.0%), non-Hodgkin's disease (10 cases, 15.1%), Hodgkin's disease (5 cases, 7.6%), leukemia (8 cases, 12.1%), gastrointestinal malignancy (5 cases, 7.6%), and musculoskeletal malignancy (5 cases, 7.6%). There were significant differences in sperm concentration and viability among the various types of cancer, but no significant difference in semen volume or sperm motility and morphology.

Conclusions: In this study we found that sperm quality could decrease even before chemotherapy. Because chemotherapy can also negatively affect spermatogenesis, sperm cryopreservation prior to treatment should be strongly recommended for cancer patients of reproductive age.

Key Words: Cryopreservation; Drug therapy; Infertility, male; Semen

Table 1. Clinical characteristics of the patients referred for sperm cryopreservation

Characteristic	Value
Age at diagnosis (yr)	32 (19～58)
Interval between diagnosis and referral (mo)	4 (1～18)
Marital status	
Single	48 (72.7)
Married	18 (27.3)
Without children	10 (55.6)
With children	8 (44.4)
Diagnosis	
Testicular cancer	31 (47.0)
Non-Hodgkin's disease	10 (15.1)
Hodgkin's disease	5 (7.6)
Leukemia	8 (12.1)
Gastrointestinal malignancy	5 (7.6)
Musculoskeletal malignancy	5 (7.6)
Other cancer	2 (3.0)

Values are presented as median (range) or number (%).

Table 2. Semen parameters according to type of cancer

Variable	All	Testicular cancer	Non-Hodgkin's lymphoma	Hodgkin's lymphoma	Leukemia	Gastrointestinal malignancy	Musculoskeletal malignancy	Others	p value
Age (yr)	32.0±7.9	33.4±6.0	33.0±7.0	26.6±5.4	28.5±7.2	48.7±12.9	24.0±4.9	32.5±11.4	0.747
Volume (mL)	2.0±1.3	2.6±1.8	1.6±0.3	1.8±0.6	2.1±0.5	1.7±0.3	1.7±0.4	1.9±0.7	0.127
Sperm concentration (million/mL)	42.3±48.6	25.7±18.1	66.3±70.6	35.0±27.8	31.1±19.1	38.3±22.5	56.0±26.1	35.0±30.2	0.033
Sperm motility (grade A+B) (%)	30.2±19.1	31.7±15.2	28.4±19.4	30.0±10.0	28.7±15.4	31.7±25.7	48.6±28.2	42.2±17.9	0.075
Sperm viability (%)	52.4±15.5	42.2±16.8	61.2±13.9	55.7±15.4	51.7±19.1	60.5±18.2	70.4±17.5	49.5±24.5	0.012
Normal morphology of sperm (%)	14.1±10.2	12.7±10.5	15.4±9.5	11.5±7.7	14.2±12.2	15.5±10.5	13.3±11.2	17.5±10.9	0.549

Values are presented as mean±standard deviation. Comparisons between groups were conducted using Kruskal-Wallis tests. p values <0.05 are considered to indicate significance.

PNUH data (2017-2020) 최근 3년간

- **총 67명 (vs 66명 1999-2014)**
- 평균 연령: 27.28세 **(vs 32세 1999-2014)**

Diagnosis	Testis Cancer	21
	Other visceral Cancer	11
	leukemia/lymphoma	28
	others	7

PNUH data (1998-2020)

Clinical characteristics of the patients referred for sperm cryopreservation					
characteristic				Value	
Age at diagnosis (yr)				**36**	**(15-58)**
Interval between diagnosis and referral(mo)				1	(0-44)
Marital Status					
	Single			137	
	Married			21	
		without children		11	
		with children		10	
Diagnosis					
	Testicular cancer			**62**	**(39.2)**
	Non-Hodgkin's disease			20	(12.7)
	Hodgkin's disease			11	(7.0)
	Leukemia			33	(20.9)
	Gastrointestinal malignancy			9	(5.7)
	Musculoskeletal malignancy			10	(6.3)
	Other cancer			13	(8.2)
Total				**158**	(100)

PNUH data (1998-2020)

Semen parameters according to type of cancer									
Valuable	All	**Testicular cancer**	Non-Hodgkin's lymphoma	Hodgkin's lymphoma	Leukemia	Gastrointestinal malignancy	Musculoskeletal malignancy	Other	p value
Age(yr)	27.5±6.7	28.0±6.5	30.2±7.2	24.0±6.5	25.2±5.7	34±4.4	23.4±4.2	28.5±7.5	0.001
Volume(mL)	2.6±1.4	2.7±1.4	2.8±1.4	2.0±1.2	2.6±1.3	2.1±1.0	2.6±1.7	2.8±1.5	0.685
Sperm Concentration (million/mL)	54.9±57.2	**33.0±34.9**	57.5±50.2	88.0±85.6	79.8±69.5	64.5±81.5	66.5±58.7	48.8±35.0	**0.005**
Sperm motility (grade A+B)(%)	35.2±20.4	36.4±19.6	36.9±18.5	40.0±21.8	31.9±21.0	22.7±20.0	50.0±23.7	28.0±17.0	0.074
Sperm viability(%)	57.7±20.8	54.1±28.6	52.8±12.7	69.0±0.0	52.5±2.1	70.0±3.5	79.0±0.0	62.5±9.2	0.596
Normal morphology of sperm(%)	18.2±22.3	11.7±12.5	55±0.0	30.0±0.0	40.0±0.0	14.5±13.0			0.217

요약

- **Sperm cryopreservation** is the only clinical method currently available → **cryopreservation of sperm before treatment needs to be suggested.**
  - Cryopreservation of semen is a safe and effective way of preserving fertility for adolescent and adult males.
  - For adult men with azoospermia, testicular sperm extraction is necessary and is the only option for retrieving sperm.
- However, fertility preservation options for pre-pubertal males are limited.
  - Extensive efforts are being made to improve techniques for testicular tissue or spermatogonial cryopreservation and transplantation and testis xenografting.