

Impact of cancer on cryopreserved sperm quality and fertility: A cohort study

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Abstract

Background: Sperm quality at cancer diagnosis is often compromised by the disease and any given gonadotoxic treatment will further diminish fertility.

Objectives: Here, we aim to analyze the cryopreserved sperm quality according to the cancer types as well as the fertility outcomes.

Methods: Our study included all cancer patients who cryopreserved sperm over 20 years at Erasme Hospital Brussels (from 1999 to 2019). First sperm samples from 111 hematologic, 104 testicular, 19 prostate, 28 gastrointestinal, and 16 neurological cancer patients were compared.

Results: Oligozoospermia was observed in 30% of the samples, including 19.33% with severe oligozoospermia (<5 million/ml). Our results showed a significant reduction in sperm concentration among testicular cancer ($p < 0.01$). No significant differences in progressive motility, sperm volume, and number of frozen straws were observed. Significant correlations were found between sperm concentration and cancer type ($p < 0.01$) as well as patients' age ($p < 0.01$). Twenty-eight cancer survivors returned for using their cryopreserved sperm (9.33%), fertilization rate was 60.5% and implantation rate was 29.6%. There was no correlation between sperm concentration and fertility outcomes.

Conclusion: Our results confirm the negative impact of cancer on sperm quality without affecting assisted reproductive technology (ART) success rate, which is utterly important as a male reproductive health perspective. All cancer patients should be counselled and offered fertility preservation options as a gold standard.

KEYWORDS

ART, cancer, fertility preservation, semen quality

Abbreviations: ANOVA, analysis of variance; ART, assisted reproductive technology; CPA, cryoprotective agents; DFI, DNA fragmentation index; ET, embryo transfer; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; SPSS, statistical package for the social sciences; STATA, statistical software for data science; WHO, World Health Organization.

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1 | INTRODUCTION

Cancer has affected 18.1 million people worldwide in 2018, leading to around 9.6 million deaths.¹ In Belgium, cancer incidence is increasing with more than 70,000 new cases in 2018, among which 42,593 were male patients.^{2,3}

The most common cancers in men in reproductive age are testicular neoplasia, hematologic malignancies (including leukemia, Hodgkin and non-Hodgkin lymphoma), colorectal cancers, and brain tumors.^{2,4,5}

Treatments such as chemotherapy and radiotherapy have well-known gonadotoxic effects depending on the type of drugs as well as the doses and localization of the radiation.^{2,6} The cancer itself and the treatment may both impair male fertility by affecting sperm DNA and spermatogenesis, leading to temporary or permanent azoospermia.⁷⁻⁹ Moreover, evolution of the disease and response to treatment may be unpredictable and it is not excluded that a patient will eventually benefit from a second-line gonadotoxic treatment not initially planned.¹⁰

Since 2018, the cryopreservation of semen is covered by the insurances up to 45 years of age in Belgium for oncological indications including solid tumors, hematopoietic or lymph node malignancies, testicular neoplasia (with or without adjuvant treatments), and all indications of hematopoietic stem cell transplantation. The sperm straws are stored for a renewable period of 10 years, unless otherwise requested by the patient himself.

Nowadays, the number of cancer survivors is increasing through the development of sensitive screening tools to detect early stage cancers and of new targeted cancer therapies.^{6,11} Hence, in a society where both women and men become parents later in life,¹² an increasing number of cancer patients do not have children or do not yet complete their family projects at the time of diagnosis. Therefore, the possibility of sperm banking before starting their potentially gonadotoxic therapies is crucial for their future quality of life as it offers them the opportunity to have children after remission.^{2,4-6} This procedure is highly recommended by guidelines and considered as a gold standard to preserve fertility in adults and adolescents.^{13,14}

Previous studies showed sperm quality impairment before the gonadotoxic treatment due to cancer itself,¹⁰ focusing mainly on the testicular cancers and hematologic malignancies.^{9,11} Few authors evaluated the fertility outcomes,¹⁵⁻¹⁷ emphasizing the importance of the use of frozen sperm for male cancer patients.

In this study, we aim to address these questions in a large cohort who cryopreserved sperm over a two-decade period. The characteristics of the sperm were compared according to the type of cancer with the objective to further evaluate the correlation between the type of cancer and sperm quality. Other potential confounding factors such as smoking, alcohol consumption, andrology history, and the age of the patient at diagnosis were also considered. Fertility outcomes were analyzed as a secondary objective.

2 | MATERIALS AND METHODS

2.1 | Study design

This monocentric retrospective study was conducted in Brussels, at the CUB-Erasme Hospital, Université Libre de Bruxelles. All data were collected from electronic medical records. The study was approved by the Erasme Ethical Committee (P2019/397).

The patients included in the study were male cancer patients, who performed sperm cryopreservation procedures for fertility preservation at the time of diagnosis.

Information regarding the type of cancer, sperm analysis parameters, smoking or alcohol consumption, andrology history, age, treatment already received, and history of assisted reproductive technology (ART) were collected from the medical reports. Oncological diseases were classified into different categories: hematologic malignancies (including leukemia and lymphoma), testicular, prostate, colorectal, brain, and other less common cancer types.

2.2 | Data extraction

A total of 2558 patients banked sperm between January 1st, 1999, and June 30th, 2019, among them 2193 were excluded as the indication was not oncological. The remaining 365 cancer patients were screened and 65 of them were excluded due to the procedure being not feasible ($n = 19$), a gonadotoxic treatment given before the procedure ($n = 20$), a previous neoplasia ($n = 7$), a relapse ($n = 4$), an ART before cancer ($n = 1$), and due to lack of information ($n = 14$). Finally, a total of 300 patients were eligible for analysis (Figure 1).

A standardized protocol was used in Erasme Andrology Lab for sperm freezing including liquefaction, semen analysis, sperm dilution with cryoprotective agents (CPA), balancing and cooling, slow freezing method in liquid nitrogen.

2.3 | Statistical analysis

All the analyses were carried out on STATA 15 software and SPSS (version 27). Continuous data with parametric distribution are presented as mean \pm SD and analyzed with the analysis of variance (ANOVA) and Turkey test. Continuous data with nonparametric distribution are presented as the median and interquartile range (IQR) and analyzed with the Kruskal-Wallis and Wilcoxon-Mann-Whiney tests. Categorical data are described by number of cases, including numerator, denominator, and percentages, and analyzed with the Fisher exact test. Regression analyses were analyzed by univariate regression analysis. A p value < 0.05 threshold was defined as statistically significant for all statistical tests.

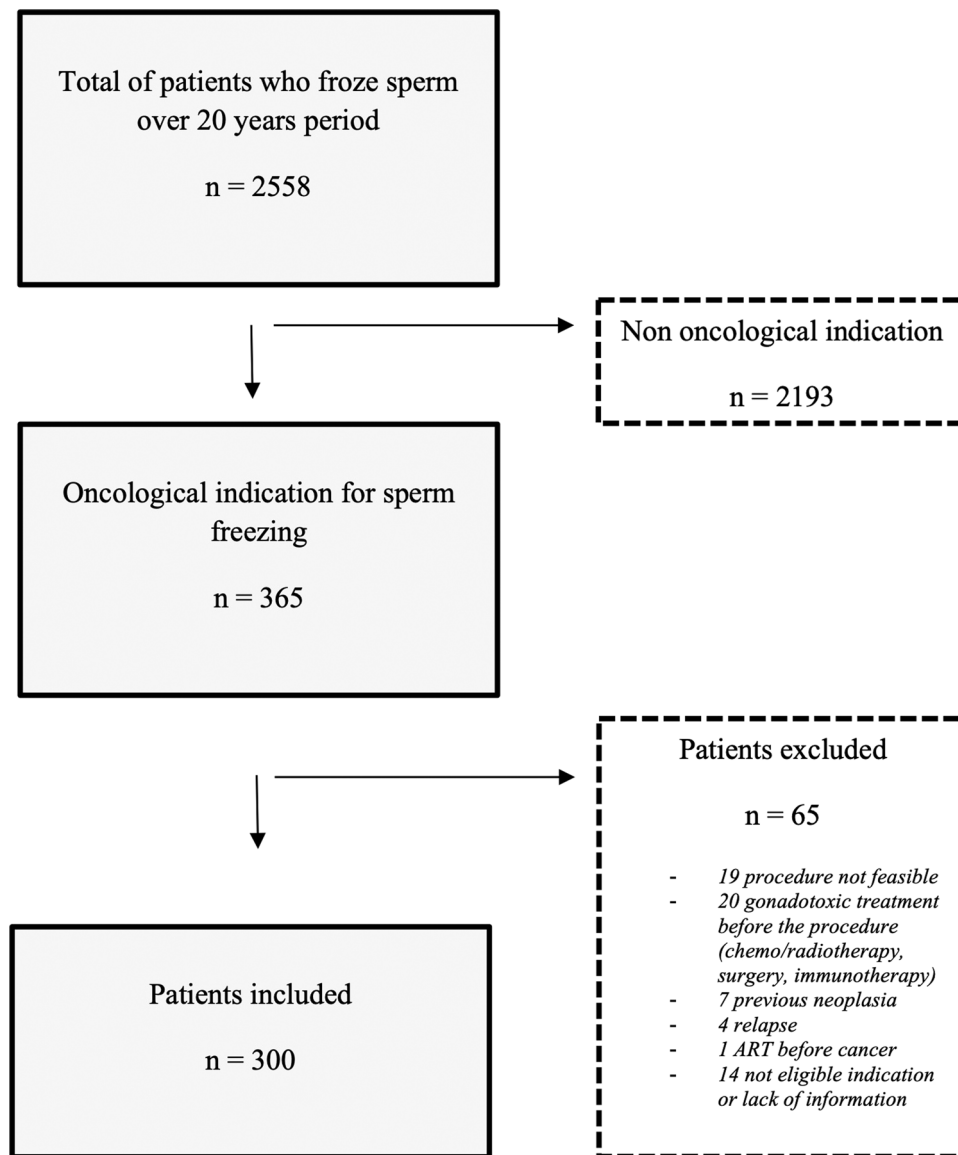


FIGURE 1 Flowchart of patients who came for sperm freezing at Erasme Hospital between January 1st, 1999, and June 30th, 2019.

3 | RESULTS

3.1 | Study population

The main neoplasia found were hematologic malignancies (37%) and testicular cancers (34.7%). The median age of the patient at the time of the diagnosis was 29 years (IQR 23–37), with patients diagnosed with prostate cancer being the oldest (Table 1).

No significant differences in tobacco and alcohol consumption, andrology history, and pre-cancer paternity were observed between the categories (Table 1). Twenty-one percent of the patients had at least one child at the time of the diagnosis, however, the information was missing for one-third of the patients (121 patients).

3.2 | Sperm parameters

Sperm concentration was significantly lower in patients with testicular cancer compared to the other cancer groups (hematologic, prostate, and colorectal neoplasia). No statistical differences were observed between the studied groups for the volume of the ejaculate, the sperm progressive motility, and the number of frozen straws per sample. Regression analysis also confirmed a lower semen concentration in the testicular cancer group compared to the hematologic malignancies group (Table 2).

Based on the WHO 2010 criteria, more than 30% of the collected samples are considered as oligo-astheno-terozoospermia, including 58 patients (19.33%) with severe oligospermia (<5 million/ml). Among them, half had testicular neoplasia (Figure 2). No statistical differences of sperm parameters were observed between Hodgkin lymphoma,

TABLE 1 Characteristics of the population according to the type of neoplasia: H, T, P, GI, N, and O

Characteristics	Population	H	T	P	GI	N	O	p Value
Patients, n (%)	300 (100)	111 (37)	104 (34.67)	19 (6.33)	28 (9.33)	16 (5.33)	22 (7.33)	
Age, years (median, IQR)	29 (23–37)	28 (22–35.5)	27 (23–31.25)	50 (46.5–54)	36 (26.65–38)	27 (20–34.75)	37 (24.5–45.75)	<0.01 ^a
Tobacco, n (%)								0.564 ^b
Smoker	91 (30.33)	33 (29.73)	36 (34.62)	6 (31.58)	4 (14.29)	4 (25.00)	8 (36.36)	
Nonsmoker	165 (55.00)	61 (54.95)	55 (52.88)	11 (57.89)	18 (64.29)	11 (68.75)	9 (40.91)	
Unknown	44 (14.67)	17 (15.32)	13 (12.50)	2 (10.53)	6 (21.43)	1 (6.25)	5 (22.73)	
Alcohol consumption, n (%)								0.535 ^b
Yes, daily	22 (7.33)	7 (6.31)	7 (6.73)	5 (26.32)	2 (7.14)	1 (6.25)	0 (0.00)	
Yes, occasionally	55 (18.33)	20 (18.02)	25 (24.04)	2 (10.53)	3 (10.71)	2 (12.50)	3 (13.64)	
Yes, unknown frequency	4 (1.33)	2 (1.80)	2 (1.92)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
No	175 (58.33)	65 (58.56)	57 (54.81)	10 (52.63)	17 (60.71)	12 (75.00)	14 (63.64)	
Unknown	44 (14.67)	17 (15.32)	13 (12.50)	2 (10.53)	6 (21.43)	1 (6.25)	5 (22.73)	
Andrological history, n (%)								0.672 ^b
Yes	27 (9.00)	11 (9.10)	11 (10.58)	1 (5.26)	0 (0.00)	1 (6.25)	3 (13.64)	
No	142 (47.33)	52 (46.85)	48 (46.15)	7 (36.84)	15 (53.57)	9 (56.25)	11 (50.00)	
Unknown	131 (43.67)	48 (43.24)	45 (43.27)	11 (57.89)	13 (46.43)	6 (37.5)	8 (36.36)	
Proven fertility, n (%)								0.266 ^b
Yes	64 (21.33)	21 (18.92)	20 (19.23)	5 (26.32)	7 (25.00)	3 (18.75)	8 (36.36)	
No	115 (38.33)	43 (38.74)	49 (47.12)	4 (21.05)	9 (32.14)	3 (18.75)	7 (31.82)	
Unknown	121 (40.33)	47 (42.34)	35 (33.65)	10 (52.63)	12 (42.86)	10 (62.50)	7 (31.82)	

Note: Variables are presented by median surrounded IQRs or n and percentage (%). p Value considered significant when <0.05.

Abbreviations: GI, gastrointestinal; H, hematologic; IQR, interquartile interval; N, neurological; O, others include 3 teratoma, 1 penile cancer, 1 tongue cancer, 2 osteosarcoma, 4 multiple myeloma, 1 bladder cancer, 4 lung cancers, 6 head and neck cancers; P, prostate; T, testicular.

^aKruskal–Wallis.

^bFisher's exact test without the unknown.

non-Hodgkin lymphoma, and leukemia patients with hematologic malignancies (Supporting Information).

3.3 | Fertility outcomes

Over 20 years, 28 patients returned for using their frozen sperm after a median of 4.25 years. A total of 85 ART cycles were performed including 38 intrauterine insemination (IUI), 1 in vitro fertilization (IVF), and 46 intracytoplasmic sperm injection (ICSI) cycles. A total of 91 embryos were transferred: 52 were fresh embryo transfer (ET) and 39 were frozen ET. The overall fertilization rate (FR) and implantation rate (IR) reached 60.5% and 29.6%, respectively.

The characteristics of the cohort including maternal age, sperm parameters, indications, and fertility outcomes are provided in Table 3 and Supporting Information. No correlation was observed between sperm concentration and pregnancy success. No significant differences in the sperm parameters were observed between the sperm of patients who achieved pregnancy and those who failed.

4 | DISCUSSION

Testicular cancer and hematologic (leukemia and lymphoma) malignancies are the main indications of sperm freezing in our population, which is in line with the literature.^{10,15,18} Overall, more than 30% of patients were oligozoospermic at the time of diagnosis. Almost 20% of them had severe oligozoospermia according to WHO 2010 semen analysis criteria (<5 million/ml), half of whom being testicular cancers.¹⁹

We confirmed that sperm concentration was significantly lower among testicular cancer patients compared to other cancer types (hematologic including both leukemia and lymphoma, prostate, neurological and colorectal cancers). A hypothesis being the direct cancer effect on spermatogenesis impairment and the indirect effect related to endocrine and systemic disturbances.²⁰ It is worth noting that the decline in sperm quality among testicular cancer patients is often associated with local inflammation, a history of cryptorchidism, and/or hypospadias referred as “testicular dysgenesis syndrome.”²¹

TABLE 2 Characteristics of the sperm samples according to the type of neoplasia

Characteristics	H	T	P	GI	N	O	<i>p</i> Value ^a
Volume, ml							
Median (IQR)	2.5 (1.5–3.9)	3 (2–4.1)	2 (1.85–2.45)	3 (2.02–4.25)	2.65 (1.85–3.62)	2.75 (2.02–3.42)	0.175
	(<i>n</i> = 111)	(<i>n</i> = 104)	(<i>n</i> = 19)	(<i>n</i> = 28)	(<i>n</i> = 16)	(<i>n</i> = 22)	
Concentration, million/ml							
Median (IQR)	42 (14.65–84.5)	13.85 (4.75–43.75)	55.55 (21.9–89.5)	48.8 (18.52–116.25)	34.75 (17.32–152)	34.5 (16.5–78.75)	<0.01
	(<i>n</i> = 111)	(<i>n</i> = 104)	(<i>n</i> = 19)	(<i>n</i> = 28)	(<i>n</i> = 16)	(<i>n</i> = 22)	
Progressive motility, ^b %							
Median (IQR)	41 (27.25–52)	51 (38–62.75)	31 (23–60)	43 (25.75–57.25)	28 (16.5–48.5)	32 (22–52.5)	0.637
	(<i>n</i> = 102)	(<i>n</i> = 86)	(<i>n</i> = 17)	(<i>n</i> = 28)	(<i>n</i> = 15)	(<i>n</i> = 19)	
Number of frozen straws, <i>n</i>							
Median (IQR)	8 (3.5–12)	8 (4–12)	6 (4–8)	9 (5–13)	9 (5.75–10.25)	8 (6.25–11)	0.848
	(<i>n</i> = 111)	(<i>n</i> = 104)	(<i>n</i> = 19)	(<i>n</i> = 28)	(<i>n</i> = 16)	(<i>n</i> = 22)	

Note: Variables are presented by median surrounded IQRs and number of straws (*n*).

Abbreviations: GI, gastrointestinal; H, hematologic; IQR, interquartile interval; N, neurological; O, others include 3 teratoma, 1 penile cancer, 1 tongue cancer, 2 osteosarcoma, 4 multiple myeloma, 1 bladder cancer, 4 lung cancers, 6 head and neck cancers; P, prostate; T, testicular.

^a*p* Values are calculated with Kruskal–Wallis's test, significant *p* values < 0.05.

^bInformation is not available for all patients.

A study by Song et al. also showed a statistically significant reduced sperm concentration in testicular cancer patients compared to other neoplasia but 55.6% of the testicular cancer patients had an orchidectomy before sperm cryopreservation.²² In our data extraction, the information regarding orchidectomy was not always available. Usually, sperm cryopreservation was performed before the surgery. Other studies reported a diminished sperm concentration in testicular cancer patients compared to hematologic malignancies,¹¹ or to other cancers without significant changes in motility and volume.^{23,24} A large case–control study in 4480 male patients also showed that human sperm concentration was four-fold lower among testicular cancer (19.6 million/ml) than in the normal population (82.4 million/ml).²⁵ The median concentration of spermatozoa was even lower in our population (13.85 million/ml; IQR 4.75–43).

Among hematologic malignancies, we did not observe any significant differences between the subgroups (leukemia, Hodgkin, and non-Hodgkin lymphoma) in terms of sperm parameters. A study by Caponecchia et al. showed a lower sperm concentration in both testicular cancer and Hodgkin lymphoma compared to the native disease-free population.¹¹ A lower concentration and motility were also reported in leukemia patients compared to other cancer types.^{18,22} Finally, a large case–control study reported only 36.7% normospermic samples in leukemia patients.²⁵

For brain neoplasia, similar sperm count and concentration were reported compared to the control population, but with lower motility (30%) and a diminished normal morphology rate.²⁵ For our patients, sperm progressive motility (28%) was similar as previously reported but not significantly different compared to other diseases.

No significant relationship between sperm concentration and habits such as smoking, alcohol consumption, or andrology history were observed in our study. This might be because most of our patients were non-smoker (55%) and did not drink alcohol for 58.3% of them. With regards to alcohol consumption units, this data remains unknown for 14.7% of our patients but we do know that heavy smoking and alcohol abuse are both deleterious for sperm quality.^{26,27} Nevertheless, these parameters should be taken into account in an andrology assessment as they induce oxidative stress and DNA damage.^{28–30}

Age was also considered as an important parameter as a meta-analysis showed a trend of a lower sperm concentration with increasing paternal age, due to endocrine disruptors and accumulated oxidative stresses.³¹ A recent study from 2021, showed a negative correlation between age and sperm volume, motility and morphology; and a positive correlation between DNA fragmentation index and sperm concentration, but results lack information on male cancer history.³² In our study, a significant correlation was found between sperm concentration and cancer type (*p* < 0.01) as well as patients' age (*p* < 0.01) among the testicular group being the lowest and youngest, respectively. Another study by Johnson et al. showed that cancer patients are younger compared to infertile patients (29 vs. 36.4 years old, *p* < 0.001), although they are at higher risk of cryopreservation failure due to azoospermia (5% vs. 1%, *p* = 0.007).¹⁸

Most importantly, we have evaluated the fertility outcomes in our study. In total, 64 patients (21.33%) already had one child before cryopreservation. Although the data were lacking for a third of them, it highlights the importance of referring cancer patients for sperm

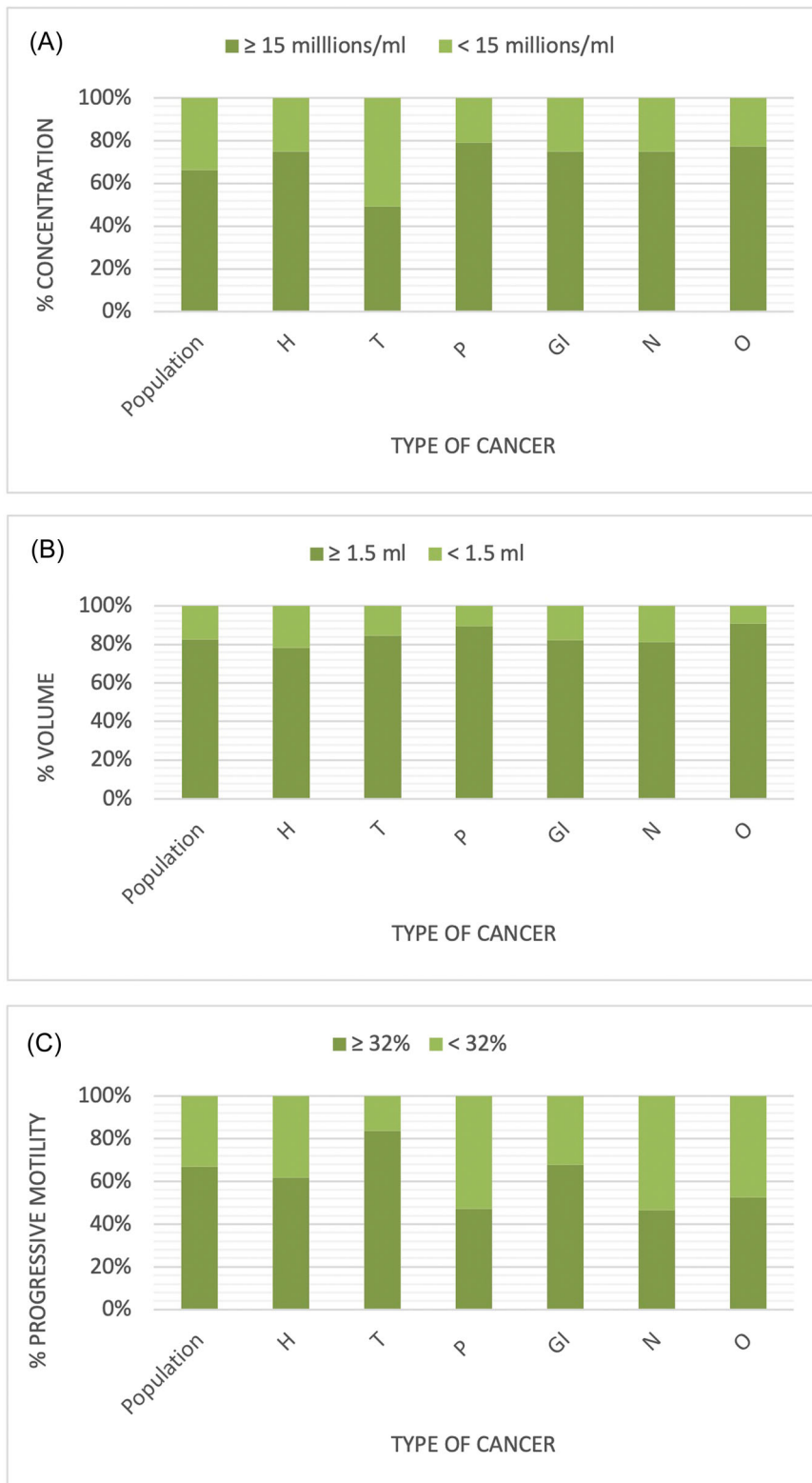


FIGURE 2 Distribution of concentration in millions per ml (A), volume in ml (B), and progressive motility (C) of the studied population and six cancer groups sperm analysis, according to the WHO 2010 reference values.

cryopreservation before any potential gonadotoxic treatment irrespective of their previous fertility history.^{8-10,17}

In our cohort, only 28 patients (9.33%) returned to attempt conception using assisted reproduction technology ART (38 IUI cycles, 1 IVF, and 46 ICSI cycles) after a median time of 4.25 years. This is in line with the literature, with the usage rate varying from

7.5% to 10.3%.^{7,24,33} Among the 38 IUI cycles with frozen-thawed sperm, five patients achieved a pregnancy, and four healthy babies were born. After IUI failure, seven patients went for an ICSI procedure which succeeded in pregnancy and delivery for five of them. With regards to age among cancer survivors who returned for ART, we found a statistically significant difference between the

TABLE 3 Reproductive outcomes of 28 patients stratified by cancer types

Characteristics	Population	H	T	O	<i>p</i> Value ^a
Number of patients, <i>n</i>	28	8	11	9	
Male age, years	35.5 (32.5–45)	33.5 (32.5–44)	33 (31–36)	49 (40–51)	0.004
Female age, years	32.5 (30–36)	33 (30–38)	31 (28–33)	35 (32–37)	0.12
Delay after cancer, years	4.25 (0.16–13.1)	2.76 (0.47–4.98)	6.08 (1.77–13.1)	2.78 (0.16–6.21)	
Type of ART using thawed sperm					
IUI, <i>n</i> cycles	38	16	10	12	
IVF, <i>n</i> cycles	1	0	0	1	
ICSI, <i>n</i> cycles	46	10	26	10	
Number of oocytes					
Inseminated (no. MII)	296	64	161	71	0.40
Fertilized (no. 2 PN)	179	33	103	43	0.29
No. fresh embryo transfer	52	13	28	11	0.43
No. frozen embryo transfer	39	5	20	14	0.53
Fertilization rate (%)	60.47	51.56	63.98	60.56	0.72
Implantation rate (%)	29.61	20.00	36.25	22.50	0.42
Live birth rate (%)	52.20	57.14	64.29	45.71	0.84

Note: Variables are presented by median surrounded IQRs, or *n* and %.

Abbreviations: FR, fertilization rate defined as no. oocytes with 2 PN divided by no. MII oocytes injected (for ICSI) or divided by no. COCs inseminated (for IVF); H, hematologic; ICSI, intracytoplasmic sperm injection; IQR, interquartile interval; IVF, in vitro fertilization; IR, implantation rate defined as no. gestational sacs seen on ultrasound divided by no. embryos transferred; IUI, intrauterine insemination; LBR, live birth rate defined as one infant born after 24 weeks of gestation after fresh embryo transfer or after cryopreserved embryo transfer; O, other details: 3 prostate cancer, 2 gastrointestinal cancer, 1 brain cancer, 1 bladder cancer, 1 multiple myeloma, 1 neck cancer; PN, pronuclei stage; T, testicular.

^a*p* Values are calculated with Kruskal–Wallis's Test, significant *p* value < 0.05.

groups for male age, the testicular cancer group being the youngest compared to the other group (*p* = 0.004).

A total of 91 embryos were transferred: 52 were fresh ET and 39 were frozen ET, overall FR was 60.5% and IR was 29.6%. We obtained comparable IR of 36.2% and 20% for testicular cancer and hematologic group respectively as found in the literature.¹⁵ Another study on the clinical outcomes of ART included 34 ICSI and 11 frozen ET reported IR of 22% and 25% for day 3 and day 5 ET.¹⁷

It should be noted that among the patients who failed to conceive, two patients were still under ART treatment, two couples had separated during the ART procedure, one patient refused IVF, one patient changed to another hospital, and one patient had cancer recurrence before being able to have a child.

Finally, a 2021 study compared thawed sperm versus fresh sperm used for IVF/ICSI in cancer patients. The pregnancy rates and live birth rates were similar in the two groups.¹⁶ In our study, we did not observe any correlation between the frozen sperm concentration and fertility outcomes. These results are important to promote sperm cryopreservation before oncological treatment and should be discussed during fertility preservation counselling.

Our limitations are related to the retrospective design of the study, that some data were missing, and for 19 cancer patients their

sperm sample did not enable a freezing procedure (extremely poor sperm sample without enough motile sperm for freezing, and/or azoospermia) but the azoospermic rate was not evaluated in the present study as they were not always identifiable in the patient's selection.

5 | CONCLUSION

Sperm quality at cancer diagnosis is often compromised by the disease and any given gonadotoxic treatment will further diminish fertility. We analyzed sperm quality in a large cancer patients' cohort and included their fertility outcomes. The main findings were the significant reduction in sperm quality in testicular cancer patients, with a significant correlation found between sperm concentration and cancer type as well as patients' age. However, we showed no correlation between sperm concentration and fertility outcomes. Our results further confirm the negative impact of cancer on sperm quality without affecting ART success rate, which is utterly important as a male reproductive health perspective for cancer survivors. All cancer patients should be counselled and offered fertility preservation options as a gold standard.

AUTHOR CONTRIBUTIONS

David Pening: Conceptualization; formal analysis; methodology; writing original draft; writing review and editing. **Marnie Constant:** Conceptualization; data curation; formal analysis; resources; writing original draft. **Manon Bruynbroeck:** Project administration; validation. **Anne Delbaere:** Writing review and editing. **Isabelle Demeestere:** Supervision; writing original draft; writing review and editing. All authors have read and approved the final version of the manuscript. David Pening has full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICTS OF INTEREST

David Pening, Marnie Constant, and Manon Bruynbroeck have no conflicts of interest to declare. Anne Delbaere acted as advisory board and received grants or lecture fees from Merck, Gedeon-Richter, Ferring Pharmaceuticals, and OVVI Diagnostics and travel grants from Merck, Theramex, and Ferring Pharmaceuticals unrelated to the present study. Isabelle Demeestere has acted as a scientific advisory board member and received grant from ROCHE, speaker's fees from Novartis and ROCHE, and travel grants from Theramex and Ferring, outside the submitted work.

DATA AVAILABILITY STATEMENT

The data are available on request from the corresponding author.

TRANSPARENCY STATEMENT

David Pening affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ETHICS STATEMENT

The study was approved by the Erasme Ethical Committee (P2019/397).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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