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ORIGINAL ARTICLE

Male Infertility

Sperm banking before gonadotoxic treatment: is it worth the effort?

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We aimed to compare the sperm quality in different cancer types and benign diseases before gonadotoxic treatment, and assess the usage rate of cryopreserved sperm for assisted reproductive treatment (ART). This retrospective study was conducted at two university clinics between January 2008 and July 2018. A total of 545 patients suffering from cancer or benign diseases were included in the study. The pretreatment sperm analyses were based on the World Health Organization (WHO) guidelines. Patients with testicular malignancy (TM) showed a significantly lower sperm count (median [interquartile range]: 18.7 × 10^6 [5.3 × 10^6–43.0 × 10^6] ml^{-1}; *P* = 0.03) as well as total sperm count (42.4 × 10^6 [13.3 × 10^6–108.5 × 10^6] per ejaculate; *P* = 0.007) compared to other malignant and benign diseases. In addition, patients with nonseminomatous TM showed the lowest sperm count (14.3 × 10^6 [6.0 × 10^6–29.9 × 10^6] ml^{-1}, *vs* seminomas: 16.5 × 10^6 [4.6 × 10^6–20.3 × 10^6] ml^{-1}; *P* = 0.001). With reference to the WHO 2010 guidelines, approximately 48.0% of the patients with TM and 23.0% with hematological malignancies (HM) had oligozoospermia. During the observation period, only 29 patients (5.3%) used their frozen sperms for 48 ART cycles, resulting in 15 clinical pregnancies and 10 live births. The sperm quality varies with the type of underlying disease, with TM and HM patients showing the lowest sperm counts. Due to the observed low usage rate of cryopreserved sperm, further patient interviews and sperm analyses should be included in the routine oncologic protocols to avoid unnecessary storage expenses. However, sperm banking is worth the effort as it provides hope for men who cannot reproduce naturally after gonadotoxic treatment.

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INTRODUCTION

Gonadotoxic treatment regimens such as chemotherapy, radiotherapy, and surgery cause spermatogenic damages, leading to transient or permanent male infertility.[1] The extent of gonadal damage caused by chemotherapy depends on the toxicity of the chemotherapeutic agent used, the dosage, and the duration of the exposure.[2] It has been reported that 76% of male cancer patients receiving gonadotoxic medications desire to have children.[3] However, the possibility of fatherhood in long-term survivors with testicular cancer is decreased by approximately 30%, when compared to age-matched men in whom it is estimated to be around 50%.[4,5] Successful pregnancy after the end of testicular tumor therapy is achieved after 6–7 years.[6,7] Although the recovery of spermatogenesis can take up to 12 years after chemotherapy, it reportedly depends strongly on the drug administered. In men receiving cyclophosphamide, a median recovery time of 31 months was reported.[6] Furthermore, fertility decreases significantly, when the treatment regimen includes radiotherapy.[7] With the consistent improvement in the survival rates for both adolescents and men with cancer,[8,9] sperm banking is being recommended more frequently to ensure future fertility.[10]

Increasing evidence suggests that the sperm quality of patients with certain cancer types is already affected before the initiation of gonadotoxic therapy. Thus, among other factors, the type of malignancy significantly affects the quality of sperms. Local displacement effects in the intratesticular hormonal milieu/environment and the balance are responsible for spermatogenesis defects,[11,12] particularly in patients with testicular malignancy (TM) and Hodgkin's disease (HD).[13,14] Azoospermia was observed in 3% of HD patients at the time of diagnosis, and this proportion increased significantly up to 14% in testicular cancer.[15,16]

The judicature in Austria as well as in other European countries is considering offering cryopreservation of sperm or intraoperatively obtained testicular tissues to men with TM undergoing ablative surgery and/or subsequent gonadotoxic therapy. This approach has been supported by various national and international guidelines.[17]

As cryopreserved sperm can be potentially stored for decades, it enables men suffering from permanent infertility after gonadotoxic therapy to father children.[18] However, the usage rate of cryopreserved sperm for assisted reproductive treatment (ART) in cancer patients is reported to be as low as 3%–10%.[2,19,20] A greater amount of it is destroyed mostly due to the patient's death, spontaneously conceived pregnancy, regained fertility, or the lack of a desire to father children.[2] In a study by Muller *et al.*,[2] 34% of cryopreserved sperm was destroyed upon the patients' request without being used for ART. In another

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study by Meseguer *et al*.,[21] only 8.6% of the cryopreserved sperm was disposed due to spontaneous pregnancy (55%), recovery of normal sperm quality (27%), and death (18%).

The aim of this study was to assess the sperm quality in patients suffering from cancer or benign diseases, before the initiation of gonadotoxic therapy as well as the utilization of cryopreserved sperm after the end of therapy. We assumed that the sperm quality may already be reduced in cancer patients before any therapy initiation. Furthermore, costs of sperm banking are generally not covered by public or private insurance in several countries across Europe, and therefore, counseling strategies are urgently needed.

PATIENTS AND METHODS

Study population

This retrospective study included all patients who had their sperm samples cryopreserved between January 1, 2008, and July 1, 2018, at the Department of Gynecological Endocrinology and Reproductive Medicine, Medical University Innsbruck (Innsbruck, Austria) or the Department of Urology and Andrology, University Hospital of Salzburg (Salzburg, Austria). Sperm cryopreservation was performed immediately after the diagnosis of malignant or benign testicular diseases that required surgery or, potentially, gonadotoxic treatment. Men who had not completed their family planning before any treatment with a potential for negative impact on male fertility were referred for this procedure by urologists, hemato-oncologists, or other collaborators. Medical history as well as the sociodemographic parameters and laboratory data were obtained (*i.e*., age, body mass index [BMI], smoking behavior, and the levels of thyroid-stimulating hormone [TSH], follicle-stimulating hormone [FSH], and luteinizing hormone [LH]). Malignant diseases were classified according to the international guidelines, such as Ann Arbor staging (for hematological malignancies) or Union Internationale Contre le Cancer stadium (UICC, for testicular malignancies).

Sperm analysis and cryopreservation

Sperm samples were obtained by masturbation-induced ejaculation before commencing gonadotoxic treatment. The time of ejaculation abstinence was recorded with the recommendation of an interval of at least 2–3 days. However, for urgent cases, sperm storage was performed regardless of the abstinence. Men with low total sperm counts were advised to provide one or more additional samples, again with an optimal abstinence time of 2–3 days to obtain sufficient numbers of sperms for cryopreservation. Normozoospermia was defined for all samples in accordance with the 2010 World Health Organization (WHO) criteria (sperm concentration $\geq 15 \times 10^6$ ml^{-1}, progressive motility ≥32%, and ≥4% normal morphology).[22]

The sperm samples were processed after liquefaction, according to the methods specified in the WHO laboratory manual for examination and processing of human sperms.[22] The sperm count was calculated using a single-use counting chamber (CellVision Semen Analysis Slide CV 1020-102 10 micron, Heerhugowaard, The Netherlands), according to the manufacturer's protocol. In brief, 5 μl of liquefied sperm sample was loaded onto the counting chamber and at least five random squares were counted. The total count in the five squares was equal to the count of sperm per ml. In cases of low sperm numbers, more squares were counted until a total number of 200 sperm cells were reached. For the calculation of the sperm count per milliliter, the number obtained was divided by the number of squares counted and multiplied by five. Motility was calculated by analyzing at least 200 sperm cells in the same counting chamber, according to the WHO criteria (progressive motility, nonprogressive motility, and no movement). As progressively moving sperm cells were found in all samples, no viability staining was performed. Morphology was analyzed by preparing smear slides according to the manufacturer's protocol (RAL Diagnostics, Martillac, France). The morphology was assessed at ×1000 magnification (Leica CME, Wetzlar, Germany).

Sperm selection on PureSperm® gradients was accomplished in all patients, according to the manufacturer's instructions (Nidacon International AB, Gothenburg, Sweden). The processed sperm was diluted 1:1 with a cryoprotectant (Freezing Medium TYB, Irvine Scientific, Santa Ana, CA, USA). Each cryostraw (high security sperm straw 0.3 ml, Cryo Bio System, L'Aigle, France) was filled with 0.3 ml of sperm-cryoprotectant solution and then sealed. Subsequently, the straws were incubated for 10 min at 4°C and thereafter frozen in graduated vapor-phase nitrogen tanks for over 30 min before being transferred to larger vapor-phase nitrogen tanks for storage at −196°C.

Statistics

Analysis of variance (ANOVA) was performed for normally distributed raw data, which was presented as mean ± standard deviation (s.d.). For nonnormal data distribution, the differences between the individual parameters of the groups were analyzed using the Kruskal–Wallis test and presented as median (interquartile range [IQR]). To prevent alpha-error accumulation, Bonferroni correction was applied for multiple comparisons. The Spearman's rank correlation analysis was used to identify correlations between different parameters. A significance level of $\alpha = 0.05$ was assumed for all statistical evaluations. The statistical analysis was conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical approval

The Human Investigation Review Board of the Medical University Innsbruck (EK1261/201) as well as the Human Investigation Review Board of University Hospital of Salzburg (EK1066/2020) approved the study. Both Human Investigation Review Boards stated that due to the retrospective study design, no informed consent was required.

RESULTS

Demographic data

Table 1 presents a summary of the demographic data and sperm parameters. At the time of cryopreservation, the mean age of the patients was 28.7 years and the mean BMI was 24.4 kg m^{-2}. Twelve patients already had a child at time of sperm cryopreservation.

Study population

TM (n = 254, 46.6%) and hematological malignancies (HM; n = 156, 28.6%) were the most common diagnoses, with both being present in more than two-thirds of the study population. Benign diseases were diagnosed in 11.7% (n = 64) of the patients, including benign testicular tumors (n = 26, 40.6%), autoimmune diseases (n = 34, 53.1%), and benign hematological diseases (n = 4, 6.3%). Among the testicular diseases, seminomas (n = 116, 45.7%) and nonseminomatous germ cell tumors (NSGCT; n = 138, 54.3%) showed a similar distribution. Over one-third of the patients with hematological diseases suffered from HD (n = 71, 45.5%), around one-fourth of them had non-Hodgkin's lymphoma (NHL; n = 38, 24.3%), and one-fifth had acute lymphocytic leukemia (ALL; n = 28, 17.9%). Solid tumors (n = 42) and sarcomas (n = 29) were less common, accounting for only 7.7% and 5.3%, respectively. An even lesser number of patients had acute myeloid leukemia (AML; n = 9, 1.7%) and other diseases (n = 10, 1.8%).

Sperm parameters

The sperm parameters are provided in **Table 1**. The sperm quality indices varied between different cancer types with TM, demonstrating a significantly reduced sperm count and total sperm count ($P = 0.03$), when compared to other malignant and benign diseases. Among the testicular cancer cases, NSGCT had the lowest sperm count ($P = 0.001$, compared to seminomas). When the WHO 2010 reference values for human sperm characteristics were applied, oligozoospermia was observed in up to 48.0% of the patients with TM and in only 23.0% of patients with HM (**Figure 1**). The mean duration of abstinence in all patients was 4.5 (s.d.: 3.8) days and did not differ significantly between the groups.

UICC stadium, Ann Arbor stadium, BMI, and the levels of TSH, FSH, and LH

A two-tailed correlation analysis of 97 patients suffering from lymphoma did not show any association between the Ann Arbor stage (I, II, III, and IV) and the sperm parameters (**Table 2**). Furthermore, the sperm parameters were not affected by the (early/advanced) stage of the disease. The sperm test results based on the UICC stage of 164 TM patients revealed no association between the UICC stage (I, II, III, and IV) and sperm parameters (**Table 3**). No statistical significant correlation between the TSH values or BMI and the sperm parameters in the study was noted. The mean FSH and LH values were 6.2 IU ml^{-1} and 4.5 U l^{-1}, respectively, which were within the in-house laboratory reference range.

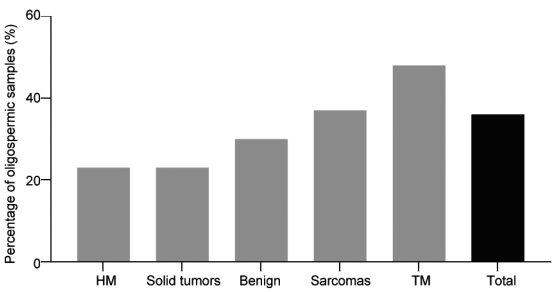

Figure 1: Percentage of oligospermic samples (WHO 2010) by cancer type. A total of 545 patients were included. Percentages of patients with oligospermia (<15 million per ml) by patient group are shown. HM: hematological malignancies; TM: testicular malignancies; WHO: World Health Organization.

ART treatment

The mean paternal age at the time of sperm usage was 36.4 years, resulting in a mean storage time of 7.7 years. Only 29 patients (5.3%) used their cryopreserved sperm for ART at the Department of Gynecological Endocrinology and Reproductive Medicine in Innsbruck or Salzburg. A total of 29 patients received 48 cycles of intracytoplasmic sperm injection (ICSI), resulting in 15 clinical pregnancies and 10 live births. Interestingly, out of these 29 patients, only three patients, who later fathered a child with the cryopreserved sperm, had impaired sperm parameters (decreased count and/or low number of sperms with normal morphology) at the time of cryopreservation. Seven out of the 29 patients already had a child at time of sperm cryopreservation.

DISCUSSION

In the present study, impaired sperm quality was recorded in cancer patients even before the initiation of the gonadotoxic regimen. Patients with TM showed the lowest sperm concentration and total sperm count values. Among testicular tumors, NSGCT showed poorer sperm quality compared to seminomas and benign testicular diseases. Interestingly, no association was noted between the Ann Arbor or UICC stages (I, II, III, and IV) and sperm parameters in lymphoma or TM patients. There was also no correlation between the BMI and TSH values and the sperm parameters.

Although the pathophysiology of spermatogenesis impairment in cancer patients is not fully understood, several mechanisms have been proposed for TM. Local displacement effects and alterations in the systemic or intratesticular hormone balance are conceivable mechanisms.[11,12] Skakkebaek and Jørgensen[23] also described TM as being a part of the variable testicular dysgenesis syndrome, implicating an altered embryonic development of the male gonads due to the environmental factors.

Different types of testicular tumors can have different effects on the surrounding gonadal tissues.[24] A low sperm count in NSGCT patients during the diagnostic workup should prompt urologists to refer patients for sperm banking as soon as possible to ensure that sufficient amount of sperm is available for cryopreservation.

Table 1: Summary of sperm test results by patient group (according to WHO 2010)

Parameter	*TM (n=254)*	*HM (n=156)*	*Benign diseases (n=64)*	*Solid tumors (n=42)*	*Sarcoma (n=29)*	*P*
Age (year), mean±s.d.	28.8±7.7	28.2±7.6	28.8±7.2	28.5±8.5	30.3±8.7	0.737
BMI (kg m^{-2}), mean±s.d.	24.6±3.8	24.1±4.2	24.7±3.9	23.5±5.5	22.8±4.6	0.088
pH, median (IQR)	7.6 (7.5–7.8)	7.6 (7.5–7.8)	7.6 (7.4–7.7)	7.7 (7.5–7.9)	7.6 (7.4–7.8)	0.189
Semen volume (ml), median (IQR)	2.6 (2.0–3.8)	2.5 (1.8–3.8)	2.8 (2.0–4.0)	3.0 (1.6–4.1)	2.3 (1.0–3.5)	0.409
Sperm concentration ($\times 10^6$ ml^{-1}), median (IQR)	18.7[ab] (5.3–43.0)	28.4[a] (11.0–55.4)	29.5[b] (1.6–58.9)	22.4 (7.6–42.5)	24.9 (7.7–45.3)	0.032 0.014[a] 0.011[b]
Total sperm count (million per sample), median (IQR)	42.4[b] (13.3–108.5)	65.5 (29.9–148.8)	74.9[b] (32.1–169.7)	54.0 (26.9–131.2)	31.3 (10.1–127.7)	0.007 0.024[b]
Round cells (million per ml), median (IQR)	0.8 (0.4–2.0)	0.8 (0.4–3.0)	1.0 (0.1–3.5)	0.8 (0.2–1.4)	0.8 (0.3–1.9)	0.581
Progressive motility (%), median (IQR)	51.0 (39.0–60.0)	47.0 (33.8–56.3)	48.0 (31.3–60.5)	47.5 (33.8–57.5)	48.5 (33.5–57.7)	0.230
Motility A (%), median (IQR)	10.0 (2.0–22.0)	10.0 (4.0–0.8)	10.0 (5.0–27.8)	9.0 (1.3–15.5)	13.5 (3.0–26.8)	0.720
Motility B (%), median (IQR)	32.0 (21.0–44.0)	31.5 (20.0–45.0)	27.0 (17.5–40.0)	35.5 (22.3–46.0)	32.0 (24.0–42.8)	0.193
Motility C (%), median (IQR)	10.0 (7.0–15.0)	10.0 (6.0–14.0)	10.0 (5.0–13.0)	11.0 (7.25–15.8)	10.0 (7.25–14.5)	0.088
Motility D (%), median (IQR)	38.0 (30.0–48.0)	40.0 (30.0–54.8)	44.5 (30.0–52.0)	36.5 (31.0–48.5)	41.5 (28.0–56.3)	0.270
Normal morphology (%), median (IQR)	10.0 (7.0–15.0)	12.0 (8.0–18.0)	14.0 (6.0–19.0)	12.0 (8.0–19.0)	14.0 (8.0–16.0)	0.289

A total of 545 patients were included. Sperm test results are shown by patient group according to WHO 2010 criteria. Motility A: >25 μm s^{-1}, progressive (rapid); Motility B: 5–25 μm s^{-1}, progressive (slow); Motility C: <5 μm s^{-1}, nonprogressive; Motility D: immotile. [a]: TM *vs* HM; [b]: TM *vs* benign diseases. IQR: interquartile range; s.d.: standard deviation; WHO: World Health Organization; HM: hematological malignancies; TM: testicular malignancies; BMI: body mass index

Table 2: Ann Arbor stadium and sperm test results in lymphoma patients

Parameter	*Ann Arbor I (n=15)*	*Ann Arbor II (n=40)*	*Ann Arbor III (n=19)*	*Ann Arbor IV (n=23)*	*P*
Semen volume (ml), median (IQR)	2.2 (1.15–3.7)	2.5 (1.7–4.0)	3.9 (2.0–5.49)	2.0 (1.8–3.2)	0.32
Sperm concentration ($\times 10^6$ ml^{-1}), median (IQR)	28.0 (19.8–38.4)	25.0 (14.0–45.6)	16.0 (4.7–83.2)	28.5 (5.8–42.0)	0.96
Total sperm count (million per sample), median (IQR)	50.7 (14.0–101.5)	56.4 (36.6–149.1)	69.7 (15.3–208.0)	61.0 (14.7–102.0)	0.89
Progressive motility (%), median (IQR)	52.0 (37.0–64.0)	48.5 (31.5–57.0)	50.5 (33.0–65.8)	46.5 (32.8–55.8)	0.68
Normal morphology (%), median (IQR)	15.0 (10.8–23.0)	14.0 (9.0–19.5)	11.0 (7.0–17.0)	12.0 (8.0–20.0)	0.50

A total of 97 lymphoma patients were included. Sperm test results are shown by Ann Arbor stadium, according to WHO 2010 criteria. IQR: interquartile range; WHO: World Health Organization

Table 3: UICC and sperm test results in patients with testicular malignancies

Parameter	*UICC I (n=115)*	*UICC II (n=39)*	*UICC III (n=8)*	*UICC IV (n=2)*	*P*
Semen volume (ml), median (IQR)	2.5 (1.8–3.6)	2.5 (2.0–3.8)	3.3 (2.1–4.7)	2.75 (2.5–no upper limit)	0.582
Sperm concentration ($\times 10^6$ ml^{-1}), median (IQR)	20.4 (5.0–48.0)	21.4 (5.3–55.2)	31.0 (2.0–100.0)	27.5 (1.0–no upper limit)	0.899
Total sperm count (million per sample), median (IQR)	43.0 (10.8–112.8)	49.0 (26.3–154.0)	82.6 (4.1–207.4)	82.3 (2.5–no upper limit)	0.75
Progressive motility (%), median (IQR)	52.5 (44.0–61.0)	52.0 (37.5–57.5)	45.0 (35.5–66.8)	64.0 (55.0–no upper limit)	0.36
Normal morphology (%), median (IQR)	11.0 (7.0–15.0)	10.0 (7.0–15.8)	10.0 (4.0–23.0)	10.0 (8.0–no upper limit)	0.88

A total of 164 patients with testicular malignancies were included. Sperm test results are shown by UICC stadium, according to WHO 2010 criteria. UICC: Union Internationale Contre le Cancer stadium; IQR: interquartile range; WHO: World Health Organization

Normal spermatogenesis has been found to resume spontaneously after cytotoxic treatments, depending on the chemotherapeutic agent, dosage used, and the duration of exposure. However, the baseline spermatogenetic capacity before any treatment initiation is crucial.[25] Altered sperm quality may lead to permanent inhibition of male fertility with the risk of infertility being the highest, if azoospermia is already present. Nevertheless, the specific reasons for the inhibition and recovery of spermatogenesis remain unclear.[2] Studies on the toxicity of various chemotherapy regimens enable their stratification into high- and low-risk groups.[26] However, the possibility of harmful effects of using the sperm of men with recovered spermatogenesis following cytotoxic treatment on the progeny should be considered.[27] Sperm cryopreservation remains the first choice for fertility preservation in men with cancer due to its feasibility and high success rate and should be offered to all patients before initiating any potential gonadotoxic therapy.[28,29] In patients who show low sperm quality in test results before therapy initiation (an impaired sperm quality was noted in 62% of the men in our study), timely cryopreservation should be advised. This allows for preservation of multiple samples, thereby increasing the chances of subsequent successful ART treatment. In our study, 211 patients (38.7%) had to provide multiple samples to ensure sufficient amount of sperm for cryopreservation. The live birth rate following ART with cryopreserved sperm is as high as 50% in cancer patients.[30] In a study by van Casteren *et al.*,[30] highest pregnancy rates were achieved with ICSI (30.1%) and comparable to that in noncancer patients. In the present study, 29 patients used the stored sperm for ART, indicating a usage rate of 5.3%, which was in the lower range (5%–10%) of that reported in earlier studies.[19,31,32] This could be due to the patients' age and the short follow-up time after cryopreservation. Moreover, the patients might have achieved spontaneous pregnancies and desired to keep the cryopreserved sperm as they had probably not completed their family planning. However, some patients might have been lost to follow-up due to the retrospective study design.

It was previously assumed that the deleterious effects of gonadotoxic therapy on sperm quality were less pronounced in younger patients due to the immature Sertoli cells and spermatogonia, both of which have low proliferation rates. This assumption has, however, been challenged by recent studies showing impaired sperm quality throughout the reproductive phase. Thus, the cryopreservation of sperm should be encouraged to all men during their reproductive years,[33,34] which presently is being offered to only 50% of the patients with malignancies. Several physicians do not have adequate information regarding fertility preservation methods.[35–37] A survey conducted on 718 oncologists showed that 91% of them considered cryopreservation of sperm as important; however, 48% did not address fertility preservation issues with their patients or did so only in <25% of the patients.[38] Notably, physicians are obligated by law to offer fertility preservation to cancer patients in some European countries. On the other hand, some economists argue that considering the low usage rates, prophylactic sperm banking is unnecessary. However, the availability of fertility preservation option serves as an important psychological support for affected men.[39,40]

The relatively small number of patients within the subgroups is one of the limitations of the present study. Furthermore, the study design lacked a control group of healthy volunteers for comparison due to which it was not possible to extrapolate the sperm test results of the patient groups in terms of regional variability in the general population. Nevertheless, the 2010 WHO criteria enabled us to identify patients with normal sperm parameters.[22]

The storage of sperm for fertility preservation is currently not covered by public or private health insurance in Austria like in several other European countries. To reduce costs and conserve resources, a sperm test should be performed 2–5 years after the end of gonadotoxic therapy, to control spermatogenesis. The disposal of the stored samples should be considered in case oncologic recovery is complete and normozoospermia is regained.

CONCLUSIONS

As sperm cryopreservation and storage are easily available and feasible, it should be offered to all men of reproductive age requiring gonadotoxic treatment. In our opinion, sperm cryopreservation is worth the effort as it allows men suffering from cancer to fulfill their wish to father children subsequent to treatment with cytotoxic drugs. We recommend annual sperm testing but not earlier than two years after completion of gonadotoxic treatment. Furthermore, future efforts focusing improvement of sperm banking techniques are recommended.

AUTHORS CONTRIBUTIONS

KV carried out the conceptualization of the study, methodology, data-curation and validation as well as the writing of the original draft.

ER carried out the conceptualization of the study, data analysis and validation as well as writing of the original draft. GMP participated in the project administration, methodology, reviewing and editing of the manuscript. PT carried out data curation, reviewing and editing of the manuscript. SD carried out data curation. TK performed data curation. WB participated in the methodology of the analysis and data validation. LL participated in reviewing and editing of the manuscript. BT participated in conceptualization and supervision of the project as well as reviewing and editing of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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