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Cancer: impact on male fertility

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ABBREVIATIONS

BSTC - Bone and soft tissue cancer

CNSC - Central nervous system cancer

DC - Digestive cancer

HC - Haematological cancer

HL - Hodgkin’s lymphoma

L - Lymphoma

NHL - non-Hodgkin’s lymphoma

OC - Other types of cancer

SD - Standard deviation

TC - Testicular cancer

WHO - World Health Organization

ABSTRACT

Infertility is a common problem among cancer survivors mostly due to treatment toxicity. Consequently, cryopreservation represents, for some men, the only possible way to conceive biological children. The main aim of this study is to understand the impact of the oncologic diseases themselves in male fertility through the examination of semen parameters at the time of sperm cryopreservation upon diagnosis and prior to the beginning of treatments. The second aim is to compare the results among the different groups.

In a retrospective design we analysed sperm samples of 202 men collected at the time of cancer diagnosis. Sperm parameters were compared among several groups of oncological diseases. Semen parameters were defined using World Health Organization (WHO) 2020 reference values.

Testicular cancer and lymphomas were found to be the most common diagnosis. At the time of fertility assessment patients had a median age of 29.7 years. Sperm concentration was significantly lower in patients with testicular cancer when compared with patients with haematological cancer. No other significant differences in fertility were found between the groups. Sperm parameters were separately compared between Hodgkin's and non-Hodgkin's lymphomas and no significant differences were found. Among the 202 patients, 85 (42.1%) had normal sperm parameters, 15 (7.4%) exhibited azoospermia and the remaining 102 (50.5%) showed oligozoospermia, asthenozoospermia and/or teratozoospermia. Digestive cancer and central nervous system cancer were the only groups with no azoospermic patients and also the groups exhibiting higher rates of normozoospermia. On the contrary, the group of other types of cancer showed the highest percentages of azoospermia and dyspermia.

Sperm banking is the best and, in some cases, the only option to allow cancer survivors to achieve their parental ambitions. Even with a considerable percentage of men presenting sperm impairment at the time of diagnosis, cryopreservation is possible for most patients, therefore it should be offered to all men facing an oncologic diagnosis, early and before the beginning of treatments, to assure their best chance to have biological children.

Keywords: male infertility, cryopreservation, fertility preservation, neoplasms, semen analyses

RESUMO

A infertilidade é um problema comum após a cura de uma doença oncológica, em particular devido à toxicidade dos tratamentos. Deste modo, a criopreservação representa, para alguns homens, a única possibilidade de vir a ter filhos biológicos. O objetivo principal deste estudo é perceber o impacto das doenças oncológicas propriamente ditas na fertilidade masculina através da análise dos parâmetros do espermograma realizado aquando do diagnóstico e antes do início de tratamentos. O segundo objetivo do estudo é comparar os resultados entre os diferentes grupos de cancros.

Foram analisados, num estudo retrospetivo, os parâmetros espermáticos de 202 homens referenciados para preservação da fertilidade aquando do diagnóstico oncológico. Os espermogramas foram comparados entre diferentes grupos de doenças oncológicas. A qualidade espermática foi definida com recurso aos valores de referência apresentados pela WHO 2020.

Os diagnósticos mais frequentemente identificados foram tumores testiculares e linfomas. Na altura da análise espermática a idade média era de 29,7 anos. Verificou-se uma concentração espermática significativamente mais baixa em doentes com tumores testiculares do que em doentes com neoplasias hematológicas. Não se registaram outras diferenças significativas na fertilidade entre os diferentes grupos. Os parâmetros espermáticos foram avaliados separadamente entre doentes com linfoma de Hodgkin e linfoma não-Hogdkin não tendo sido observadas diferenças significativas entre os dois grupos. Entre os 202 homens, 85 (42,1%) apresentaram parâmetros espermáticos normais, 15 (7,4%) eram azoospérmicos e os restantes 102 (50,5%) mostraram diminuição da qualidade espermática. Os grupos de cancros digestivos e de cancros do sistema nervoso central exibiram as maiores percentagens de normozoospermia e foram os únicos sem doentes azoospérmicos. Pelo contrário, as maiores percentagens de azoospermia e de dispermia foram encontradas no grupo dos outros tipos de cancro.

A criopreservação de espermatozoides é a melhor e, em alguns casos, a única opção que permite a sobreviventes de cancro concretizar os seus planos de parentalidade. Mesmo quando há diminuição da qualidade espermática na altura do diagnóstico, a criopreservação é geralmente viável, portanto deve ser oferecida atempadamente a todos os homens que se deparem com um diagnóstico oncológico e antes do início dos tratamentos de modo a assegurar a sua melhor hipótese de vir a ter filhos biológicos.

Palavras-chave: infertilidade masculina, criopreservação, preservação da fertilidade, neoplasias, análise do sémen

INTRODUCTION

The estimate incidence and mortality rates for 25 major cancers across 40 European countries for the year of 2020 showed 4 million new cases of cancer, among which, in EU-27, 1.4 million occurred in men. Cancer incidence increases with age had been estimated that 60% of new diagnosis would occur in people aged 65 years or older, 34% in people aged between 45 and 64 years old and 7% in people younger than 45 years old, being the estimation of deaths in this last group of 3%.[1] In the United States of America (USA) in 2024 it is estimated that 9620 children (aged 0 to 14 years) and 5290 adolescents (aged 15 to 19 years) will have a cancer diagnosis.[2]

In older men, the most common oncological diagnosis are prostate cancer, lung cancer and colorectal cancer. In the group of men under 45 years of age, testicular cancer, skin melanoma, brain and other central nervous system cancers, leukemia and non-Hodgkin's lymphoma are the most frequent oncological diagnosis, being specifically brain and other nervous system tumours the most common in adolescents and leukemia the most common in children.[1,2]

Improvements in diagnosis and treatment of oncologic diseases in the last decades were responsible for increasing life expectancy, being both prostate cancer and testicular cancer among the four main cancers with the highest survival rates. In the USA the 5-year relative survival rate for all cancers combined from the mid-1970s to 2019 has increased from 49% to 69% and concretely among children and adolescents it improved from 58% to 85% and from 68% to 87% respectively. Mortality for leukemia decreased substantially in both children and adolescents, with the achievement of acute lymphocytic leukemia presenting now remission rates of 90-100% in children.[2]

Whilst the assessment of prevalence of temporary and permanent infertility in cancer survivors has not yet been well established, it is known that cancer treatments can lead to sexual dysfunction and often cause spermatogenesis impairment leading to infertility. Long-term azoospermia is expected to affect 1% to 42% men with testicular cancer undergoing orchiectomy and chemotherapy, 0% to 82% of men who received chemotherapy for Hodgkin's lymphoma, 19% to 55% of men who received chemotherapy for leukemia and 12% to 41% of prepubertal boys who underwent chemotherapy and/or radiotherapy for cancer.[3] Yumura *et al.* (2022) estimate infertility affects 15% to 30% of male cancer survivors and shows the possibility of fertility recover and the time to achieve it depends on the type of drug, regimen and dose being the chance to recover decreased and the time to recover enhanced as the number of cycles and doses raise.[4] The extent

of male infertility after cancer is also highlighted by Kitlinski *et al.* (2023), which reveal that cancer survivors were significantly more likely to achieve fatherhood through assisted reproductive technologies than men without history of cancer, particularly using donated sperm.[5] Therefore, there is an increasing number of cancer survivors facing infertility while wanting to pursue parenting aspirations.[6] Although there are several options to achieve it, a significant number of patients admit a preference for biological children. Consequently, when addressing the quality of life after cancer in younger patients, infertility stands as a significant issue.[7]

In this line, children, adolescents, and young adults facing cancer diagnosis can benefit from fertility preservation options, which must be addressed with the patients and/or their parents, in the case of young children. This must be discussed early after diagnosis and during staging and treatment planning, since preservation must occur preferentially before the beginning of treatments given its negative impact in future fertility.[8]

To preform sperm cryopreservation in postpubertal males with cancer, semen can usually be easily collected by masturbation. However, this is not possible for some men, in particular young teenagers, and in such cases other options such as the use of phosphodiesterase type 5 inhibitors, vibratory stimulation and electroejaculation can be presented. For men, who cannot ejaculate even with this options, who cannot provide sufficient sperm to freeze by ejaculation or who have obstructive azoospermia, surgical sperm extraction can be considered. For prepubertal boys the only possibility for fertility preservation is through testicular tissue cryopreservation which is still considered experimental.[9]

Besides treatment gonadotoxicity, some oncologic diseases itself also have a negative impact in male fertility. That was confirmed in studies that analysed sperm at the time of fertility preservation, even before treatment was initiated.[10–12] Therefore, several studies have been conducted to establish correlations between infertility and oncologic diseases. Patients with testicular cancer and Hodgkin's lymphomas had reduced sperm quality before treatment. It has been showed that at diagnosis in testicular cancer there was 50% of oligospermia and 10% of azoospermia.[6] However, some results are controversial, and research is still limited in particular when dealing with less common cancer diagnosis.[13,14]

In this study, we intend to evaluate the impact of oncologic diseases on male fertility, through the evaluation of the spermogram and the correlation of its results with the oncologic diagnosis.

METHODS

A retrospective study was conducted after collection data on 538 male patients who were referred to perform fertility preservation with sperm cryopreservation following an oncologic diagnosis between 2013 and 2023 in Reproductive Medicine Unit, Centro Hospitalar e Universitário de Coimbra. Clinical data including age at the time of sperm analysis, oncologic diagnosis, underwent cancer therapies, previous infertility history, previous oncologic diagnosis and spermogram data was obtained anonymously from electronic medical records. Cancer stages were not available in most cases so they were not collected for this study. Oncologic diagnosis and semen analysis was not gathered for 318 patients. Among the 220 patients, 15 fulfilled exclusion criteria, 10 due to previous oncologic treatments and 5 due to documentation of previous infertility being considered not eligible and thereby excluded from the study.

Sperm quality was defined according to 2020 World Health Organization (WHO) reference values, which are: semen volume more than 1.4 mL, sperm concentration more than 16 x 10^6/mL, progressive motility more than 30% and for morphology more than 4%. According to WHO criteria,[15] the sperm analysis were divided into three groups: normal, azoospermia and dyspermia. Following that, among the patients with dyspermia was counted how many had sperm concentration, progressive motility and normal forms values below normal and were labelled respectively as oligozoospermic, asthenozoospermic and teratozoospermic, the patients who presented two or the three conditions were included in more than one group. Finally, the sperm analysis were classified into 10 categories: normal, azoospermia, cryptozoospermia, oligozoospermia, asthenozoospermia, teratozoospermia, asthenoteratozoospermia, oligoasthenozoospermia, oligoteratozoospermia and oligoasthenoteratozoospermia.

The statistical analysis was performed in IBM SPSS Statistics Version 29.0.

Quantitative variables are expressed as mean, standard deviation and maximum and minimum and compared among the multiple groups of different diagnosis using a one-way analysis of variance (ANOVA). Post-hoc Tukey tests were used for multiple comparisons. Qualitative variables are displayed as numbers and percentage. The rates of semen parameter abnormalities of each diagnosis group were compared using the Chi-square test.

A P value <0.05 was considered as statistically significant.

The study involved anonymous data extraction from electronic medical records and was submitted for approval by the local ethics committee of Centro Hospitalar e Universitário de Coimbra.

RESULTS

CANCER TYPES

A total of 202 men were included in this study. The most common diagnosis was testicular cancer (TC), present in 85 (42.1%) patients. Lymphoma (L) was diagnosed in 65 (32.2%) patients of which 41 had Hodgkin´s lymphoma, 21 non-Hodgkin's lymphoma and for the remaining 3 the type was not specified. Twelve (5.9%) men had other haematological cancer (HC), specifically 10 had leukemia (5 with acute lymphocytic leukemia, 4 with acute myeloid leukemia and 1 was unspecified) and 2 multiple myeloma. Digestive cancer (DC) was diagnosed in 11 (5.4%) patients, 7 with colorectal adenocarcinoma, 2 with anal carcinoma, 1 with duodenal adenocarcinoma and 1 with gastric carcinoma. Central nervous system cancer (CNSC) was composed by 9 (4.5%) patients, including 3 central nervous system germ cell tumours, 2 astrocytomas, 1 glioblastoma, 1 neurocytoma and 1 unspecified cerebral tumour. Bone and soft tissue cancer (BSTC) was present in 8 (4.0%) divided in the following way, 4 Ewing sarcomas, 2 osteosarcomas, 1 sarcoma and 1 schwannoma. Other types of cancer (OC) were diagnosed in 12 (5.9%) patients and included 2 patients with retroperitoneal tumours, 2 with prostate cancer, 2 with melanoma, 1 patient with both lung and spine tumours and 1 patient each with mediastinal germ cell, parathyroid, bladder, skin and lung cancer (Figure 1).

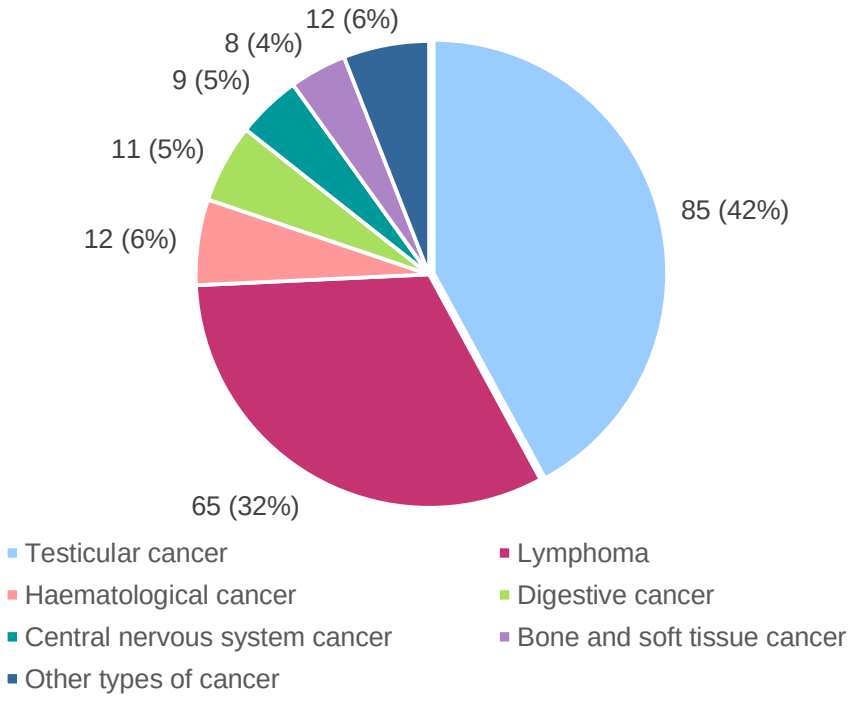

Figure 1. Types of cancer in oncological patients who cryopreserved sperm. Number of cases and percentage (%).

PATIENTS' AGE

At the time of sperm cryopreservation, the patients had a mean age of 29.7 ± 8.5 [12-56] years old. The highest mean age was found in the group of other types of cancer (38,33 years), followed by digestive cancer (37.91 years), in third place testicular cancer (29.92 years), then with similar values followed lymphomas, central nervous system cancer and other haematological cancers (respectively, 27.89 years, 27.78 years and 27.55 years) and finally the younger group was bone and soft tissue cancer (22.71 years). Patients with digestive cancer were significantly older than patients with testicular cancer ($p = 0.032$), lymphoma ($p = 0.003$), haematological cancer ($p = 0.040$) and bone and soft tissue cancer ($p = 0.002$). Also in all groups, except digestive cancer, the mean age was significantly lower than in the other types of cancer group ($p = 0.013$, $p < 0.001$ $p = 0.022$ $p = 0.045$ and $p = 0.001$ comparing with, respectively, testicular cancer, lymphomas, other haematological cancers, central nervous system cancer and bone and soft tissue cancer) (Figure 2).

Comparing lymphomas separately non-Hodgkin's lymphoma presents a mean age of 31.14 years old not being statistically significant comparing to any other diagnosis, while patients with Hodgkin's lymphoma have a mean age of 26.29 years old being significantly younger than patients with digestive cancer ($p < 0.01$) and comparing to patients in the group of other cancers ($p < 0.01$).

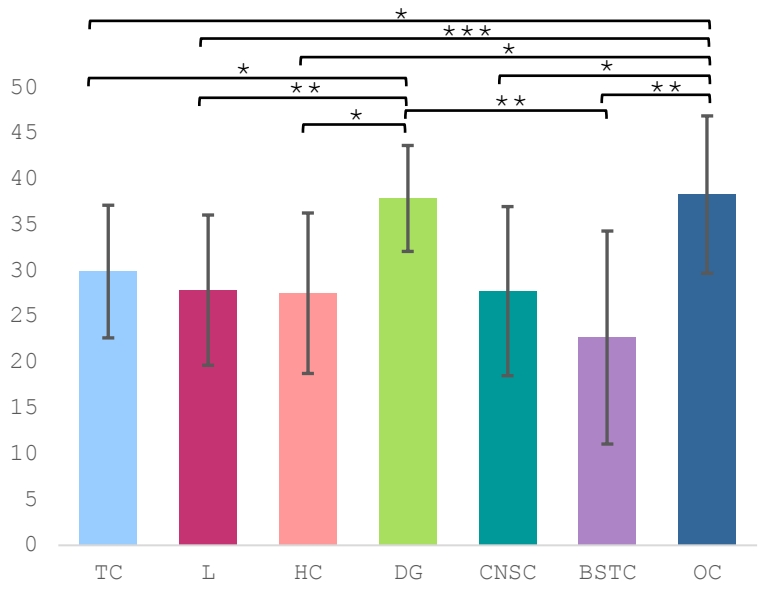

Figure 2. Patients' age at time of sperm cryopreservation. Data are presented as mean and standard deviation bars. Statistical significance between groups is represented by *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$. TC = Testicular cancer; L = Lymphoma; HC = Haematological cancer; DC = Digestive cancer; CNSC = Central nervous system cancer; BSTC = Bone and soft tissue cancer; OC = Other types of cancer.

SEMEN ANALYSIS

Mean semen volume, sperm concentration, sperm progressive motility and sperm normal forms were respectively 3.42mL, 43.40 x 10^6/mL, 40.71% and 3.81% (Table 1).

Table 1. Mean values of semen parameters.

Semen parameter	Mean ± SD
Semen volume (mL)	3.42 ± 5.10
Sperm concentration (10^6/mL)	43.40 ± 47.10
Progressive motility (%)	40.71 ± 20.53
Normal forms (%)	3.81 ± 1.53

SD = Standard deviation.

The semen parameters according to cancer group are shown in Table 2. Although the mean volume and concentration values were within the WHO 2020 parameters for all groups, the mean value of progressive motility was bellow the reference (<30%) in group of other types of cancer and the mean values of normal forms were also under the reference value (<4%) in all diagnosis, except for digestive cancer.

Table 2. Semen characteristics according to oncologic diagnosis.

	TC (n=85)	L (n=65)	HC (n=15)	DC (n=11)	CNSC (n=9)	BSTC (n=8)	OC (n=12)	p-value
Semen volume (ml)	3.91 ± 7.11	3.51 ± 3.61	2.46 ±1.05	1.71 ± 0.79	3.00 ± 1.20	2.10 ± 1.24	2.86 ± 1.21	0.819
Sperm concentration (10^6/ml)	32.23 ± 31.40*	50.17 ± 47.67	82.33 ± 97.72 *	35.80 ± 27.08	64.75 ± 46.19	28.30 ± 35.21	44.36 ± 58.29	0.009
Progressive motility (%)	45.30 ± 20.38	37.46 ± 21.31	35.30 ± 17.26	43.82 ± 21.26	41.63 ± 12.77	36.20 ± 22.79	28.00 ± 17.81	0.148
Normal forms (%)	3.89 ± 1.62	3.86 ± 1.73	4.00 ± 1.27	4.00 ± 0.67	3.57 ± 1.27	3.25 ± 0.96	3.13 ± 1.13	0.845

Values are presented as mean ± standard deviation. *Represents statistical significance between groups ($p < 0.05$). TC = Testicular cancer; L = Lymphoma; HC = Haematological cancer; DC = Digestive cancer; CNSC = Central nervous system cancer; BSTC = Bone and soft tissue cancer; OC = Other types of cancer.

Sperm concentration was significantly lower in patients with testicular cancer (32.23 x 10^6/mL ± 31.40 [0.00-150.00 x 10^6/mL]) than in patients with haematological cancer (82.33 x 10^6/mL ± 97.72 [0.00-350.00 x 10^6/mL]) (p=0.009). There were not found significantly differences in concentration between the other groups.

The other variables of sperm quality as volume, progressive motility and normal forms were not significantly different between any group of diagnosis (p = 0.819, p = 0.148, p = 0.845 respectively).

These comparisons were repeated considering Hodgkin's lymphoma and non-Hodgkin's lymphoma separately and again no new significant differences were found between the groups, including between HL and NHL. Semen characteristics found in Hodgkin's lymphoma and non-Hodgkin's lymphoma are displayed in Table 3.

Table 3. Semen characteristics in Hodgkin's lymphoma and non-Hodgkin's lymphoma.

	HL (n=41)	**NHL (n=21)**
Semen volume (ml)	4.21 ± 4.26	2.34 ± 1.61
Sperm concentration (10^6/ml)	47.70 ± 31.496	56.80 ± 70.16
Progressive motility (%)	35.85 ± 21.05	40.55 ± 22.68
Normal forms (%)	3.75 ± 1.24	4.36 ± 2.73

Values are presented as mean ± standard deviation. HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma.

Using the values of semen parameters described above, sperm samples were classified and patients were first divided into three groups: normal, azoospermia and dyspermia. Within the last group was counted how many had oligozoospermia, asthenozoospermia and teratozoospermia.

The results showed 85 patients (42.1%) with normozoospermia and 15 (7.4%) with azoospermia (Figure 3). The remaining 102 men were dyspermic: 50 (24.8%) presented oligoszoospermia, 55 (27.2%) asthenozoospermia and 50 (24.8%) teratozoospermia (Table 4).

The group of other types of cancer registered the lowest percentage of normozoospermia (16.7%) and central nervous system cancer followed by digestive cancer exhibited the highest (55.6% and 54.5% respectively), the last two groups were also the only where there were no patients suffering from azoospermia. The other types of cancer group had the highest percentage of azoospermia (25.0%), asthenozoospermia (41.7%) and teratozoospermia (33.3%) having in the latter the same percentage as the central nervous system cancer. The highest rate of oligozoospermia was found in bone and soft tissue cancer (50%).

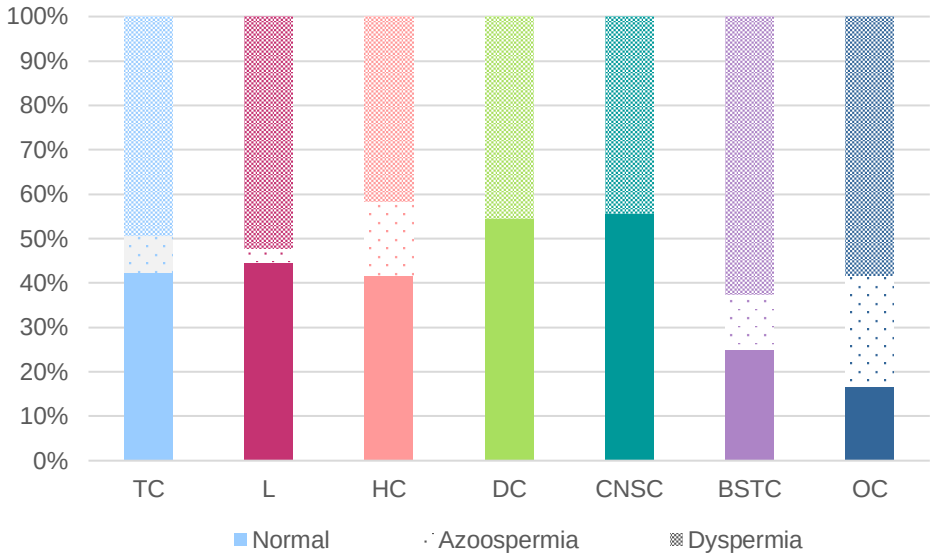

Figure 3. Percentage of patients presenting normal sperm counts, azoospermia and dyspermia. TC = Testicular cancer; L = Lymphoma; HC = Haematological cancer; DC = Digestive cancer; CNSC = Central nervous system cancer; BSTC = Bone and soft tissue cancer; OC = Other types of cancer.

Table 4. Semen quality according to cancer diagnosis.

	TC (n (%))	L (n (%))	HC (n (%))	DC (n (%))	CNSC (n (%))	BSTC (n (%))	OC (n (%))	Total (n (%))
Normal	36 (42.4)	29 (44.6)	5 (41.7)	6 (54.5)	5 (55.6)	2 (25.0)	2 (16.7)	85 (42.1)
Azoospermia	7 (8.2)	2 (3.1)	2 (16.7)	0 (0.0)	0 (0.0)	1 (12.5)	3 (25.0)	15 (7.4)
Oligozoospermia	24 (28.2)	13 (20.5)	2 (16.7)	2 (18.2)	2 (22.2)	4 (50)	3 (25.0)	50 (24.8)
Asthenozoospermia	17 (20)	23 (35.4)	4 (33.3)	3 (27.3)	1 (11.1)	2 (25.0)	5 (41.7)	55 (27.2)
Teratozoospermia	20 (23.5)	17 (26.2)	2 (16.7)	2 (18.2)	3 (33.3)	2 (25.0)	4 (33.3)	50 (24.8)

Values are displayed as number and percentage (%) of patients. TC = Testicular cancer; L = Lymphoma; HC = Haematological cancer; DC = Digestive cancer; CNSC = Central nervous system cancer; BSTC = Bone and soft tissue cancer; OC = Other types of cancer.

Analysing Hodgkin's lymphoma and non-Hodgkin's lymphoma separately, HL had a lower percentage of patients with normozoospermia (41.5%) comparing to NHL that presented 52.4% of normozoospermia. In both groups there was only one patient with azoospermia, being this percentage higher in NHL (4.8%) than in HL (2.4%). Dyspermia had a higher incidence in HL patients (56.1%) than in NHL (42.8%).

Sperm samples were also classified as normal, azoospermic, cryptozoospermic, oligozoospermic, asthenozoospermic, teratozoospermic, asthenoteratozoospermic, oligoasthenozoospermic, oligoteratozoospermic and oligoasthenoteratozoospermic and compared between the different cancer types noting no significant difference between different diagnoses.

Within the 102 (50.5%) patients with dyspermia, 63 patients revealed single damage: 7 (3.5%) cryptozoospermia, 10 (5.0%) oligozoospermia, 20 (9.9%) asthenozoospermia and 26 (12.9%) teratozoospermia and 39 showed combined damage: 15 (7.4%) oligoasthenozoospermia, 6 (3.0%) asthenoteratozoospermia, 4 (2.0%) oligoteratozoospermia and 14 (6.9%) oligoasthenoteratozoospermia (Table 5).

Despite observing no significant differences, the highest percentage of oligoteratozoospermia and oligozoospermia were detained by testicular cancer patients (2.4% and 10.6% respectively), lymphoma patients registered the highest percentage of oligoasthenozoospermia (10.8%), the other types of cancer group had the highest percentage of asthenoteratozoospermia (8.3%), central nervous system cancer patients the highest percentage of teratozoospermia (22.2%), digestive cancer patients the highest percentage of asthenozoospermia (18.2%) and patients with bone and soft tissue cancer the highest percentage cryptozoospermia (25.0%).

Table 5. Sperm classification among oncologic diagnosis.

	TC	L	HC	DC	CNSC	BSTC	OC	total
Normal	36 (42.4)	29 (44.6)	5 (41.7)	6 (54.5)	5 (55.6)	2 (25.0)	2 (16.7)	85 (42.1)
Azoospermia	7 (8.2)	2 (3.1)	2 (16.7)	0 (0.0)	0 (0.0)	1 (12.5)	3 (25.0)	15 (7.4)
Cryptozoospermia	2 (2.4)	1 (1.5)	0 (0.0)	0 (0.0)	1 (11.1)	2 (25.0)	1 (8.3)	7 (3.5)
Oligozoospermia	9 (10.6)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.0)
Asthenozoospermia	4 (4.7)	9 (13.8)	2 (16.7)	2 (18.2)	0 (0.0)	1 (12.5)	2 (16.7)	20 (9.9)
Teratozoospermia	12 (14.1)	9 (13.8)	1 (8.3)	1 (9.1)	2 (22.2)	0 (0.0)	1 (8.3)	26 (12.9)
Asthenoteratozoospermia	2 (2.4)	3 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	6 (3.0)
Oligoasthenozoospermia	7 (8.2)	7 (10.8)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (7.4)
Oligoteratozoospermia	2 (2.4)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	4 (2.0)
Oligoasthenoteratozoospermia	4 (4.7)	4 (6.2)	1 (8.3)	1 (9.1)	1 (11.1)	1 (12.5)	2 (16.7)	14 (6.9)
Total	85	65	12	11	9	8	12	202

Values are presented as number and percentage (%) of patients. TC = Testicular cancer; L = Lymphoma; HC = Haematological cancer; DC = Digestive cancer; CNSC = Central nervous system cancer; BSTC = Bone and soft tissue cancer; OC = Other types of cancer.

DISCUSSION

The proven detrimental impact of oncologic treatments in male fertility requires sperm cryopreservation as the only option to have biologic children for many men. In particular to post-pubertal men is normally a simple and quick procedure allowing it to be easily done before initiating treatments.[16]

Pretreatment impairment of spermatogenesis in cancer patients is not yet completely understood. Some studies claim hypothalamic dysfunction and a generalized inflammatory response can both be responsible for decreased semen parameters as a consequence of the systemic impact of cancer.[17,18] A psychological factor may also be taken into consideration, once the level of excitement during semen collection may influence semen volume so, it is expected that, in patients with a recent cancer diagnosis the psychological condition has a negative influence.[10]

In this study, data from spermograms of cancer patients who, following the oncological diagnosis and before that start of treatments, were referred to fertility preservation in the Reproductive Medicine Unit of Centro Hospitalar e Universitário de Coimbra in a period of 10 years.

Unlike most studies in this topic, we present a larger number of diagnostic groups. Such stratification represents a strength of our study, as it allowed to reduce the variability within each group and allowed the analysis of sperm quality in cancers that are often not evaluated independently.

As expected, based on what is described by most similar studies, testicular cancer was the most frequent diagnosis, present in 42.1% of patients and followed by haematological cancers, specifically, 32.2% with lymphomas and 5.9% with other haematological cancers.[16,19–23] The mean age at cryopreservation was 29.7 years, similar values were found in other studies.[20,22]

The average sperm parameters for volume, concentration and progressive motility were within the normal range for all diagnosis (only in the other types of cancer group the mean progressive motility was lower than the normal). However, the mean values of normal forms were bellow reference values in all groups, except in digestive cancer.

Azoospermia was recorded in 7.4% patients compared with the results obtained by Bizet *et al.* (2012)[22], Crha *et al.* (2009)[19], and Liu *et al.* (2021)[24] who, respectively, reported 30.7%, 9.7% and 6.5 % of patients were azoospermic.

Our results demonstrate more than 50% of patients with normal sperm quality only in digestive cancer (54.5%) and central nervous system cancer (55.6%), which were also the only groups where there were no patients presenting azoospermia. On the contrary, the group of other types of cancer revealed the higher percentage of azoospermia (25%) and the second highest percentage of dyspermia only after bone and soft tissue cancer that had 62.5%.

Our data concerning semen parameters in testicular cancer show that 57.6% of patients are either azoospermic or have impaired semen, which is in line with Auger *et al.* (2016)[10] that report only 50.9% of men with testicular cancer were normozoospermic and with Moody *et al.* (2019)[25] that showed 6-24% of testicular cancer patients were azoospermic and 50% oligozoospermic. In a more recent study Peluso *et al.* (2023)[21] reports 70% of testicular cancer patients had sperm values bellow reference.

However, only sperm concentration in testicular cancer was found significantly lower when compared with haematological malignancies. In many other studies this is also observed, although they also report significant differences between testicular cancer and other diagnosis besides haematological cancer, and also a significant lower concentration,[10,16,22,23,26–28] motility[10,29] and normal morphology[10] besides the lower concentration.

The impact of testicular cancer alone in male fertility is proven by Jacobsen *et al.* (2001) that showed the recovery of 9 patients who presented either oligospermia or azoospermia at the time of diagnosis but, one year after orchiectomy, were normospermic.[30] Mechanisms responsible for semen impairment in testicular cancer prior to treatments are likely to be multifactorial. The direct damage made by the tumour has been proven,[18,31] however it does not explain the effect on spermatogenis in contralateral testis, an observation that points to the systemic impact of testicular cancer in spermatogenesis. Therefore, there are several theories about the systemic effects of testicular cancer. First the possibility of preexisting defects that lead to both cancer and infertility, which implies that semen impairment is not caused by testicular cancer but rather that both cancer and infertility share a cause that is pointed by some authors to be testicular dygenesis syndrome.[10,18,31] Second are the endocrine factors, cancer can be responsible for increased hormones, as beta human chorionic gonadotropic and alpha fetoprotein, that interfere with hypothalamic-pituitary-gonadal axis leading to spermatogenesis impairment.[18,31] Third, testicular cancer is associated with oxidative stress and DNA fragmentation both deleterious to sperm quality.[31] Lastly, the disruption

of blood-testis barrier by testicular cancer allows the development of antisperm antibodies also impacting sperm quality.[18,31]

Concerning haematological cancers multiple previous studies reveal semen parameters impairment.[10,24]

Although with no significant differences, our study shows a higher percentage of normozoospermia in non-Hodgkin's lymphoma (52.4%) than in Hodgkin's lymphoma (41.5%), comparing to the results of Auger *et al.* (2016)[10] that present higher percentages of normozoospermia in both groups and contrary to our study found in Hodgkin's lymphoma higher normozoospermia (65.1%) than in non-Hodgkin's lymphoma (59.5 %).

We found 2.4% of patients with Hodgkin's lymphoma were azoospermic and 56.1% had dyspermia, comparing to Sieniawski (2008)[32] revealing only 20% of patients with Hodgkin's lymphoma had a normal sperm analysis, while 11% were azoospermic and 69% had dyspermia. Paoli *et al.* (2016)[33] exhibited a better result founding 75% of Hodgkin's lymphoma patients normozoospermic prior to treatment.

Acknowledging that in our study the stage is not taken into account, caution is required when comparing results with studies where staging is considered. About azoospermia in Hodgkin's lymphoma patients, we obtained similar values to the ones showed by Van Der Kaaij *et al.* (2009)[17] that described 3% of patients with early stage Hodgkin's Lymphoma were azoospermic.

There were not found significant differences in any semen parameter when comparing Hodgkin's lymphoma with non-Hodgkin's lymphoma, which is in line with the results of Crha *et al.* (2009)[19] who also did not confirm any difference. However, he points that some studies find significantly lower sperm concentration and sperm motility in Hodgkin's lymphoma than in non-Hodgkin's lymphoma. This difference is supported by Adam *et al.* (2021)[29] that found progressive motile sperm count significantly higher among non-Hodgkin's lymphoma patients and Bizet *et al.* (2012)[22] that revealed patients with Hodgkin's lymphoma presented significantly lower sperm concentrations and total sperm counts than patients with other cancers.

Several explanations have been presented to justify decreased semen quality in patients with lymphoma. The presence of B symptoms, in particular fever and night sweats, contribute to poor sperm quality due to hyperthermia,[17] not only for the deleterious effect of elevated scrotal temperature but also for potentially causing germinal epithelium damage and disturbing hypothalamic hypophyseal.[22] Is also considered that systemic

disturbances in the balance between subpopulations of T lymphocytes described in Hodgkin's lymphoma patients may cause semen impairment.[18]

In our study, the group of haematological cancers, excluding lymphomas, showed 13.3% of azoospermia and 46.7% of dyspermia. Even though we found no significant difference to the other diagnosis, and we don't differentiate leukemia from other haematologcial oncologic conditions, this results are in line with other authors who report only 36.9% of men diagnosed with leukemia had normal sperm counts and impairments in both motility and morphology,[10] and authors reporting decreased concentration.[24]

LIMITATIONS

We collected data in a retrospective design making it impossible to fill in missing data which led to several limitations. First, even though we started with a larger number of patients, due to missing data on sperm parameters and diagnosis, the study was performed with a relatively small number of patients. Second, there was a potential lack of information about other previous conditions that could cause infertility. Third, in most patients we did not have access to the possible presence of concomitant symptoms, namely B symptoms that are referred by some authors as particularly important when discussing the impact of lymphomas on male fertility. Fourth, we had access to the stage of the cancer only in very limited number of cases, which is a limitation due to had been verified that advanced-stage disease has a worse impact on semen quality than early stages,[34,35] besides not being able to differentiate between stages is also a barrier when making comparisons with other studies due to some focusing specifically in early stages. Finally, also when comparing results with other studies, we face some difficulties due to different diagnosis groups and by the use of other reference values.

CONCLUSION

Our study suggests that a considerable part of oncologic male patients present a decreased sperm quality even before treatments. Given the knowledge that many treatments can lead to sometimes permanent infertility and, although there are some men who are already azoospermic at the time of diagnosis, fortunately, in the vast majority of cases, sperm banking is feasible even with reduced concentrations and volumes or with motility and morphology parameters also below reference values. Therefore, whenever patients are not azoospermic and thus cryopreservation is possible, it may stand as the only opportunity for these men to have biological children, which is a relevant concern for cancer survivors. Adding to the fact that sperm banking is an easy and quick procedure that does not imply the delay of treatments, the early referral of oncologic patients should be among the priorities of the medical team when addressing a cancer diagnosis and before the beginning of treatments, assuring the best chance to fatherhood of individuals who have not yet completed their reproductive plans.

To achieve a better understanding of the impact of cancer alone in male fertility, further studies are needed to compare the differences between semen parameters in each patient before and after cancer treatment.

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ANNEXES

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2. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

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