

# Sperm Cryopreservation for Newly Diagnosed Cancer Patients in South of China: A 12-Year Retrospective Study in 1034 Patients

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## Research Article

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## Abstract

**Background:** Sperm cryopreservation is an effective method to fertility preservation for cancer patients before anti-cancer treatments. However, there were very few data on fertility preservation for the large number of cancer patients in South China.

**Objectives:** To understand the fertility preservation status of newly diagnosed male cancer patients in South China.

**Methods:** A retrospective cohort study was evaluated in 1034 cancer patients performed sperm cryopreservation in the human sperm bank of Guangdong Province in China between the years 2010 and 2021. The data were collected from medical records and analysed including demographics, cancer information, semen examination, and cryopreservation.

**Results:** Of these 1034 cases, 302 had reproductive system tumors, mainly testicular cancers (99.0%), and 732 found non-reproductive system tumors, including lymphoma (33.1%), gastrointestinal cancer (16.3%), nasopharyngeal carcinoma (15.7%), leukemia (7.7%), sarcoma (3.6%) and others (23.6%). The number of cancer patients with sperm cryopreservation had been increasing since the last 12 years. The patients with reproductive system tumors had significantly lower sperm concentration, pre-freezing progressive motility, and post-thawing progressive motility than those with non-reproductive system tumors ( $p < 0.001$ ). Significant differences were observed on sperm parameters mentioned above and normal sperm morphology between the patients undergone anticancer surgery before sperm cryopreservation and those without surgery ( $p < 0.05$ ).

**Conclusions:** This study provides valuable data derived from the geographical area for the understanding of its fertility preservation status, which demonstrates that reproductive system tumors greatly harmed the sperm quality of the patients prior to anti-cancer treatments and reflects more cancer patients would have strong willingness to undergo fertility preservation in South China.

## Background

Human sperm bank is a professional institution providing male fertility preservation, especially for tumor patients in need. With the development of assisted reproductive techniques (ART) and freezing technology of human sperm bank, males with poor sperm quality may also have sperm cryopreservation, which is a blessing for male cancer patients, most of whom are faced with poor semen quality [1]. In recent years, the incidence rate of cancers in reproductive age has been growing, meanwhile, the 5-year survival rate of patients with advances in anticancer therapy is also rising [2]. For cases with successful anti-cancer and without child-bearing, most of them have reproductive needs during their prolonged life [3]. Unfortunately, the patients have to face the declining fertility due to the negative effects of cancers and treatments [4, 5]. Nearly one-third of patients suffered long-term infertility after the chemotherapy and radiation treatments [6]. Although clinicians have noticed the gonadal toxicity of anti-cancer treatment in cancer therapy, sperm cryopreservation is still the gold standard for maintaining male fertility after tumor patients survive [7]. In human sperm banks worldwide, there have been many investigations to deal with fertility preservation for cancer patients [8, 9]. Impaired semen quality was observed on newly diagnosed patients of many types of cancer including testicular, leukemia/lymphoma, gastrointestinal tract, brain, head and neck, lung, prostate, bone/soft tissue and others.

Since China's first human sperm bank was established in 1980s, there have been 27 human sperm banks with official approval. Self-sperm cryopreservation has been carried out in most human sperm banks in China. The only human sperm bank in Guangdong Province provides the maximum number of sperm cryopreservation for the tumor patients, which accounts for more than 60% of the nationwide number of tumor sperm deposits. Guangdong province is located in South China, being one of the provinces with a large permanent resident population in China. At the same time, the region of human sperm bank in Guangdong Province is also one of the most economically developed regions in China. Malignant tumors in Guangdong Province have distinctive characteristics, where the incidence rate of nasopharyngeal carcinoma and liver cancer related to infection is the highest in the world. Compared with other cities in China, the incidence rate of colorectal cancer, nasopharyngeal carcinoma, ovarian cancer, breast cancer, prostate cancer, lymphoma and leukemia in Guangzhou city is relatively high, and they are among the top five in the 31 city cancer registration areas in China.

In the present study, the fertility preservation status of newly diagnosed male cancer patients were carried out to investigate in South China. The data was collected to focus on those men with cancers implementing a formalized institutional fertility preservation program in the only and large human sperm bank of Guangdong Province, China. This study would enrich the research data of tumor fertility preservation worldwide as an important data of Chinese cancer patients in South China.

## Materials And Methods

### Patients

Medical records of all patients with cancer who attempted sperm banking at the human sperm bank of Guangdong Province from January 1, 2010 to December 31, 2021 were reviewed. The cancer patients who cryopreserved samples after microsurgical sperm extraction were excluded. The following information was extracted from the records: age, marital status (married or not married), fertility status (giving birth or not giving birth), cryopreservation status (cryopreserved or not cryopreserved), cancer type and surgical resection or other anti-cancer treatment, if known, reasons for failure to bank (including failure to extract a sample, and poor quality semen sample without active spermatozoa), pre- and post-thaw sperm counts and motility, normal sperm morphology, recovery rate. An informed consent was sign by each patient for sperm cryopreservation form. The study was approved by the reproductive ethics committee of Guangdong Reproductive Hospital.

### **Semen samples and tests**

All the specimens were collected by masturbation. Two-seven days of sexual abstinence was recommended, however, about 15% of the specimens had abstinence beyond 2-7 days.

The samples were tested after they were fully liquefied in a 37 °C water bath for 20 minutes. Routine manual semen analysis was performed on each sample before and after cryopreservation according to the guidelines on semen analysis in the World Health Organization (WHO) manual [10], as described in the previous study [11]. Kruger's strict criteria were used for the evaluation of sperm morphology.

### **Sperm cryopreservation**

Cryopreservation of sperm was performed with commercial cryoprotectant (Origio, Denmark, NO:1067). Samples were placed in liquid nitrogen vapors at about 10 cm above the level of liquid nitrogen (-80°C) for 8-10 minutes to allow initial slow rate freezing and then immediately plunged in liquid nitrogen [12]. Thawing was performed by placing the cryogenic vial exposed to air for 1 minute and then immediately placed in an incubator containing 37°C water until all ice crystals had disappeared.

### **Object grouping**

The cryopreserved samples were divided into two groups according to the pathological report and the location of tumor: reproductive system tumor group and non-reproductive system tumor group. The malignant tumors located in the reproductive system, such as seminoma, mixed germ cell tumor, germ cell tumor and embryonic cancer, etc., were classified into the reproductive system tumor group, while the malignant tumors in other system were classified into non-reproductive system tumors group, including lymphoma, leukemia, nasopharyngeal carcinoma, thyroid cancer, gastric cancer, sarcoma and so on. Seminoma accounts for about 70% in the reproductive system tumor group.

### **Quality control**

As described in previous study, the quality control was well done for all the procedure of semen tests [11]. The semen analysis in this study was performed by the same group of 6 technicians in laboratory of the human sperm bank. Internal and external quality controls were routinely conducted for semen analysis. There was no difference among the technicians. Monthly mean values of routine semen parameters were well monitored in the laboratory.

### **Statistical analysis**

Continuous outcomes including sperm characteristics are expressed as median and range if there was a non-normal distribution. They were analyzed by using the Kruskal-Wallis test. Dichotomous outcomes, expressed as ratio, were compared by using Chi-square test. In all cases, all p-values were two-sided and  $p < 0.05$  was considered statistically significant. All the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 19.0, Chicago).

## **Results**

### **Population studied**

A total of 1034 newly diagnosed cancer patients had been carried out to attend their fertility preservation between January 2010 and December 2021. During contemporaneous period, other 160 patients failed to cryopreserve their semen samples. Of these, 8 failed to extract a semen sample by masturbation, 25 suffered azoospermia after the anti-cancer therapy and 127 were excluded for extremely poor sperm quality. Of 1034 cases with successful sperm cryopreservation, 302 were included in the reproductive system tumor group, with testicular tumor (99.0%), epididymal tumor (0.3%), penile cancer (0.7%) (Fig. 1), and 732 in the non-reproductive system tumor group, with lymphoma

(33.1%), gastrointestinal cancer (16.3%), nasopharyngeal carcinoma (15.7%), leukemia (7.7%), sarcoma (3.6%), thyroid carcinoma (2.5%), lung cancer (2.5%), liver cancer (2.0%), other (15.0%), and unspecified (1.6%) (Fig. 2). The 'other' group was composed of mediastinal, bladder, brain, skin, renal, urachal, and urethral carcinomas, primitive neuroectodermal tumor, neuroendodermal tumor, chondroma, a chest teratoma, and others.

The number of tumor patients with sperm cryopreservation had been increasing from 2010 to 2021, and there was the same growth trend in patients with reproductive system tumors and patients with non-reproductive system tumors (Fig. 3). The demographics of the 1034 successfully sperm-cryopreserved cancer patients are listed in Table 1.

Table 1

## 1034 patients' demographics and sperm parameters by tumor location groups

Parameter	All patients	Non-reproductive system tumor group	Reproductive system tumor group	p-Value <sup>a</sup>
Demographics				
age				
<20 years	108(10.4)	80(10.9)	28(9.3)	>0.05 <sup>b</sup>
20-45 years	908(87.8)	636(86.9)	272(90.1)	
>45 years	18(1.7)	16(2.2)	2(0.7)	
marital status				
divorce	16(1.5)	10(1.4)	6(2.0)	<0.001 <sup>b</sup>
not married	665(64.3)	442(60.4)	223(73.8)	
married	353(34.1)	280(38.3)	73(24.2)	
fertility status				
borned	155(15)	114(15.6)	41(13.6)	>0.05 <sup>b</sup>
unborned	879(85)	618(84.4)	261(86.4)	
anticancer surgery				
no	741(71.7)	603(82.4)	138(45.7)	<0.001 <sup>b</sup>
yes	293(28.3)	129(17.6)	164(54.3)	
sperm parameters (range)				
sperm concentration				
azoospermia	9(0.9)	5(0.7)	4(1.4)	<0.001 <sup>b</sup>
<2(10 <sup>6</sup> /ml)	54(5.2)	27(3.7)	27(8.9)	
2-14(10 <sup>6</sup> /ml)	162(15.7)	72(9.8)	90(29.8)	
>=15(10 <sup>6</sup> /ml)	809(78.2)	628(85.8)	181(59.9)	
Median sperm concentration(10 <sup>6</sup> /ml)	46(0-413)	56(0-413)	21(0-169)	<0.001 <sup>c</sup>
Median total number of spermatozoa in the ejaculate (10 <sup>6</sup> )	142.3(0-1551.5)	176.9(0-1551.5)	70(0-627.3)	>0.05 <sup>c</sup>
Median pre-freezing progressive motility (%)	42(0-90)	43(0-90)	40(0-77)	<0.001 <sup>c</sup>
Median pre-freezing motility (%)	47(0-100)	47(0-100)	46(0-81)	>0.05 <sup>c</sup>
Median post-thawing progressive motility (%)	23(0-65)	24(0-64)	20(0-65)	<0.001 <sup>c</sup>
Median post-thawing motility (%)	26(0-60)	28(0-58)	24(0-60)	<0.001 <sup>c</sup>
Median percentage of normal sperm morphology (%)	7.7(0.5-36.5)	7.8(0.5-31.7)	7.1(0.9-36.5)	>0.05 <sup>c</sup>
<sup>a</sup> p<0.05 significant				
<sup>b</sup> Chi-square test was used				
<sup>c</sup> Kruskal Wallis test was used				
<sup>d</sup> A few spermatozoa(0-8 per×200 HPF) can be observed in each visual field of wet preparation				

### Sperm parameters of pre-freezing and post-thawing

Among 1034 newly diagnosed cancer patients with successful sperm cryopreservation, the overall median of sperm concentration was  $46 \times 10^6$ /ml, total number of spermatozoa in the ejaculate was  $142.3 \times 10^6$ , pre-freezing progressive motility was 42%, pre-freezing motility was 47%, and percentage of normal sperm morphology was 7.7%. 21.8% of them had poor sperm quality with sperm concentration lower than  $15 \times 10^6$ /ml (Table 1). The cancer patients had significantly lower sperm concentration, pre-freezing progressive motility, post-thawing progressive motility and post-thawing motility in reproductive system tumor group than those in non-reproductive system tumor group (Table 1). There were no statistical differences of total sperm number in the ejaculates, pre-freezing motility and normal sperm morphology between the two groups.

### Effect of the anticancer surgery on semen quality

Significant differences were observed in sperm concentration, pre-progressive motility, post-progressive motility, post-motility and normal sperm morphology between the patients undergone anticancer surgery before sperm cryopreservation and those without surgery (Table 2). For the patients in non-reproductive system tumor group, those performed sperm cryopreservation after anticancer surgery had lower pre-progressive motility than other patients without anticancer surgery, and the similar difference was observed in the post-progressive motility (Table 2).

Table 2  
Effect of the anticancer surgery on sperm quality

Parameter	All patients		p-Value <sup>a</sup>	Non-reproductive system tumor group		p-Value <sup>a</sup>	Reproductive system tumor group		p-Value <sup>a</sup>
	no anticancer surgery (n = 741)	anticancer surgery (n = 293)		no anticancer surgery (n = 603)	anticancer surgery (n = 129)		no anticancer surgery (n = 138)	anticancer surgery (n = 164)	
<b>sperm parameters (range)</b>									
Median sperm concentration( $10^6$ /ml)	51(0-413)	33(0-195)	< 0.05	56(0-413)	49(0-195)	> 0.05	23(0-169)	19(0-104)	> 0.05
Median total number of spermatozoa in the ejaculate( $10^6$ )	157.5(0-1551.5)	104(0-1092)	> 0.05	182.4(0-1551.5)	155.8(0-1092)	> 0.05	70.2(0-627.3)	69.2(0-595.2)	> 0.05
Median pre-freezing progressive motility(%)	43(0-90)	42(0-78)	< 0.05	43(0-90)	42(0-78)	< 0.05	39(0-72)	41(0-77)	> 0.05
Median pre-freezing motility(%)	48(0-100)	46(0-81)	> 0.05	48(0-100)	45(0-79)	> 0.05	44(0-74)	47(0-81)	> 0.05
Median post-thawing progressive motility(%)	24(0-64)	20(0-65)	< 0.05	24(0-64)	22(0-62)	< 0.05	21(0-58)	19(0-65)	> 0.05
Median post-thawing motility(%)	28(0-60)	23.5(0-56)	< 0.05	28(0-58)	25.5(0-55)	> 0.05	25(0-60)	22(0-56)	> 0.05
Median percentage of normal sperm morphology(%)	0.1(0-0.3)	0.1(0-0.4)	< 0.05	0.1(0-0.3)	0.1(0-0.3)	> 0.05	0.1(0-0.3)	0.1(0-0.4)	> 0.05
a p < 0.05 significant									
Kruskal Wallis test was used									

## Discussions

Over the past decades, more and more attention has been paid to the sperm preservation for male cancer patients in China. However, very few studies concerning a large amount of cancer patients was reported on sperm preservation in China up to now except two studies with small samples [13, 14]. The only human sperm bank of Guangdong province is located in Guangzhou, the capital of Guangdong Province,

listed as one of China's mega cities with a permanent resident population near 20 million, one of the three major medical center cities in China, an international trade center and transportation hub in the world. The data of sperm-cryopreserved cancer patients from this sperm bank would well represent the current status of fertility preservation for male cancer patients in South China, concerning propaganda and education on fertility preservation, the willingness of cancer patients to preserve fertility, the economic situation of those patients enough to undertake sperm preservation and the scale of sperm bank.

The current study shows the largest number of cancer patients pursuing sperm cryopreservation before anticancer treatment in South China, consequently offering sound data on semen quality for cancers located in different system. In the human sperm bank of Guangdong Province, there are more and more cancer patients to perform sperm cryopreservation successfully, with the number increasing year by year as the same trend in published literatures [15, 16], and more tumor types are involved. Being two major tumors occurring in childbearing age, testicular cancer and lymphoma are two types of most common tumors for the subjects with sperm preservation before or after anticancer treatments, as identically described in most of studies [17–19]. As a regional tumor with high incidence, nasopharyngeal carcinoma has become the third main reason of sperm storage for those newly diagnosed cancer patients. The data also present that the cancer families in South China have a higher awareness of fertility preservation, regardless of the number or the types of cancer patients with successful sperm cryopreservation.

The cancers located in reproductive system in this study were almost testicular germ cell tumors, a group of heterogeneous cancers occurring in male germ cells, and seminomas and non-seminomas being the main type of them [20, 21]. Previous investigations indicated that the semen quality of testicular cancer patients without any treatment was poorer than that of other types of cancers for the combined influences of such factors as preexisting defects in reproductive cells, part tumor effect, endocrine disorder, autoimmune and systemic effects of cancer itself [22, 23]. The majority of literatures demonstrated that alterations of sperm concentration were observed for testicular cancer patients [18–19, 22, 24–28]. It was reported that significantly poor semen quality was observed in sperm concentration and progressive motility in a retrospective study involving 4480 male cryopreserved patients with several types of cancer and systematic disease in reproductive age [18]. In the present study, the results showed that the patients with tumor in reproductive system had poorer sperm quality, especially in sperm concentration and pre-freezing progressive motility, than those with cancers in non-reproductive systems, which was generally consistent with results in the previous study [18]. The present study observed that 85.8% of patients with cancer in non-reproductive systems were normozoospermic, higher than 59.9% of those with cancer in reproductive system. Similarly, other studies reported that the patients with Hodgkin's disease had better semen quality than those with testicular cancer [29, 30]. The sperm quality of cancer patients was significantly affected by the location and the type of tumors before anti-cancer treatment.

For patients with testicular cancers, reduced semen quality especially in sperm concentration and motility has been attributed to the following possible factors. Histopathological study of testis from testicular cancer patients demonstrated that spermatogenesis in 94% of patients occurred in areas far away from the cancer [31]. However, a previous study showed that testis had less than a 50% opportunity with functional spermatogenesis if more than 50% of the testis was cancer-involved [31]. All of the patients with testicular cancers in those studies were observed a reduced normal spermatogenesis in tissue smears, led by reduced amount of normal testicular tissue to produce sperm accompanied with the cancer directly immersing into the testis [31]. The hypothalamic–pituitary–testicular (HPT) axis is usually affected by testicular seminoma and spermatogenesis is accordingly disturbed, leading to decreased sperm quality or even azoospermia [32, 33]. Previous studies have shown that the levels of such tumor markers as beta-hCG and AFP were increased in patients with testicular cancers, in relation with reduced spermatogenesis and increased testosterone [34, 35]. Furthermore, it is often occurred in cancer patients that the cytokine-mediated inflammatory response of the whole body is usually activated by tumor itself, leading to fever, malnutrition, and stress on the body, even cancer cachexia [36]. Fluctuation of temperature in cancer patients' body and testicular would have further influences in spermatogenesis [37].

The anticancer treatments mainly include surgery, chemotherapy and radiotherapy. It was reported that the cancer therapies such as chemotherapy and radiotherapy for male patients would make direct injury to spermatogenic epithelium and cause oligozoospermia or even azoospermia, during which the reproduction function was deeply damaged [38]. It was noted that surgical treatment would be effective to the fecundity of patients with testicular cancer [39]. Previous study showed that the patients with testicular cancers had no better semen quality just after orchiectomy than before the surgery [40]. Similarly, the present study indicated that the anticancer surgery had a negative effect on semen quality for patients with testicular cancers. But the surgery treatment would lead to reduced semen quality such as sperm concentration, pre-progressive motility, post-progressive motility, post-motility and normal sperm morphology for all sperm cryopreserved patients with cancers in the current study.

The present study has some highlights and limitations. The first highlight is delineated that this study is the first one displaying the results of sperm cryopreservation in the largest number of newly diagnosed cancer patients from China. The second highlight is that the patients were grouped by the cancers' location because cancers located in reproductive system would strongly impair the spermatogenesis and

sperm transport, with the sperm quality directly affected by those cancers themselves. One of the limitations is that as a retrospective study, it has some inevitable and inherent biases in the current study. Secondly, as described in the previous study, we did not collect data of the clinical stage for all cancers and therefore were unable to precisely evaluate the side effects of cancer clinical stages on semen quality [11].

## Conclusions

In conclusion, this study provides valuable data derived from the geographical area for understanding of its fertility preservation status. Data of a large number of sperm cryopreserved cancer patients from South China well demonstrated that reproductive system cancers greatly harmed the sperm quality of the patients prior to the anticancer treatments. The present study supports that sperm cryopreservation is a quite reliable choice to preserve their fertilities for the newly diagnosed cancer patients so as to father a child of their own in the future when they would recover from cancers. More and more cancer patients would have strong willingness to undergo fertility preservation in China. More fertility preservation investigations on male malignant tumor patients should be performed in China so as to enrich the fertility preservation data worldwide.

## List Of Abbreviations

ART assisted reproductive techniques

WHO World Health Organization

HPT hypothalamic–pituitary-testicular

## Declarations

### Ethics approval and consent to participate

The study has been approved by the reproductive ethics committee of Guangdong Reproductive Hospital (201911). An informed consent was sign by each patient for sperm cryopreservation form in this study.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. For further information, contact Miss. Wang at wangqiling2006@126.com.

### Competing interests

The authors declare that they have no competing interest.

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### Authors' contributions

Qi-Ling Wang carried out the data analysis, wrote the manuscript and prepared the tables and figures. Gui-Fang Ye, Kai-Xin Zhong, Xin Wu and Wei-Xin Lin verified all data collected. Lulu Luo performed semen tests and sperm cryopreservation. Xin-Zong Zhang designed the study and edited the manuscript. Wei-Jie Zhu designed the study, edited and revised the final manuscript. All authors read and approved the final manuscript.

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## Figures

### Figure 1

Cancer diagnoses of patients in Reproductive system tumor group

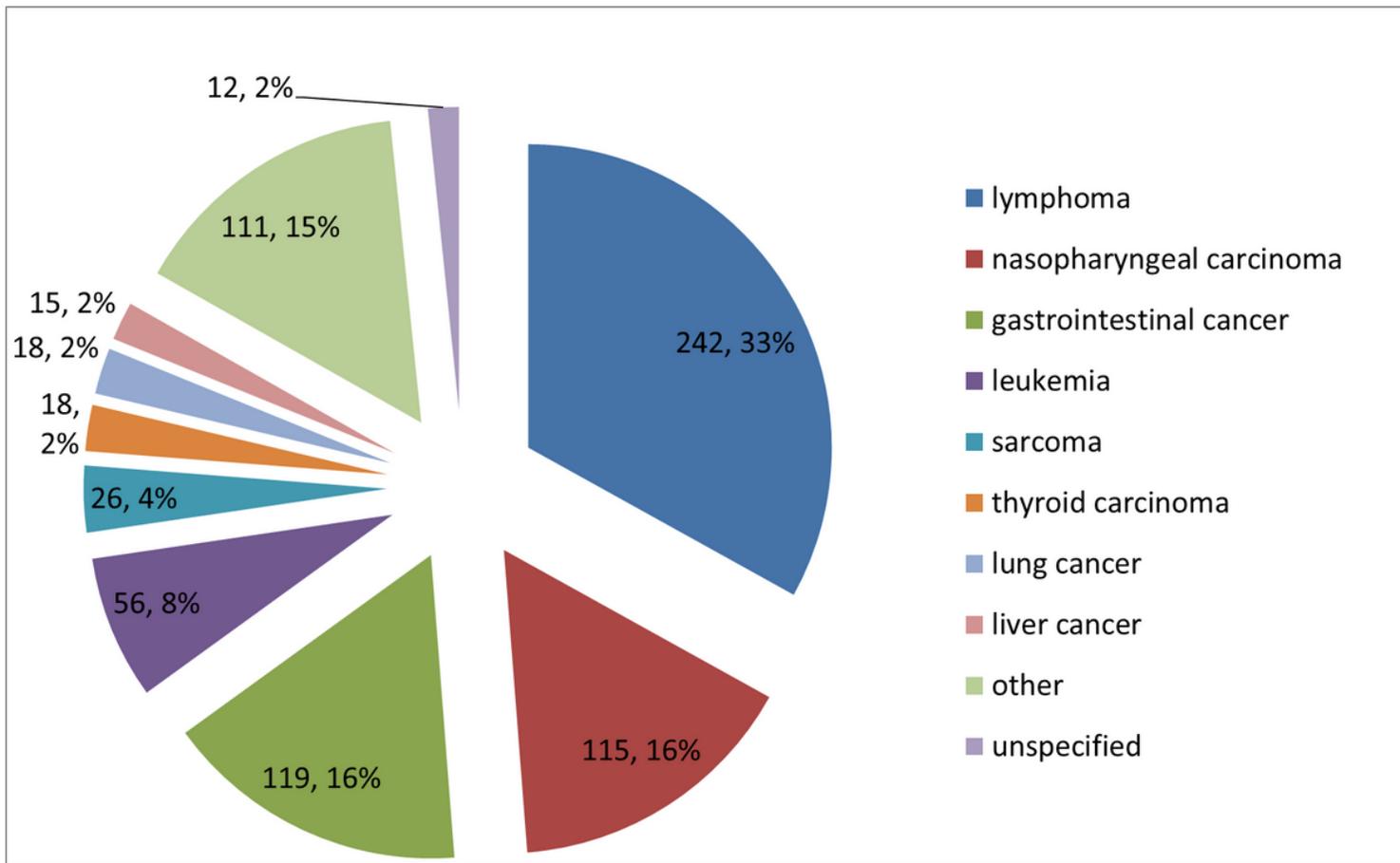


Figure 2

Cancer diagnoses of patients in non-reproductive system tumor group

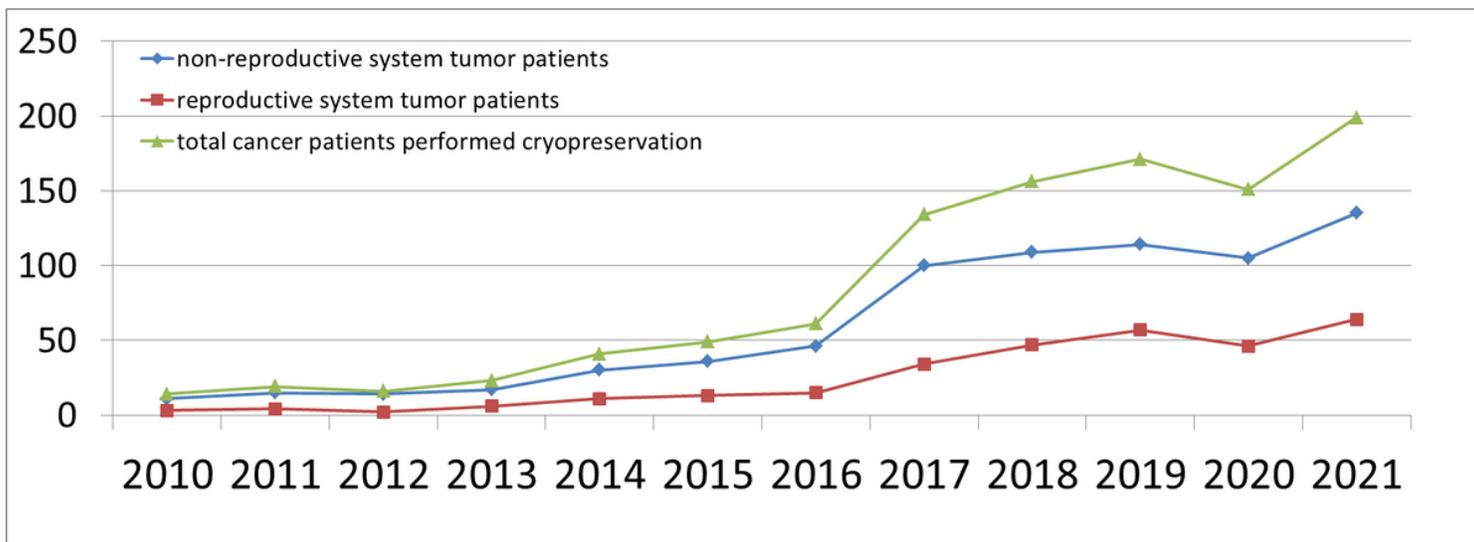


Figure 3

The number of tumor patients with sperm cryopreservation from the year 2010 to 2021