

Original Article

Low utilization of fertility preservation among Chinese male cancer patients

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Abstract: Advances in cancer treatment have led to improved long-term survival and fertility is often an important aspiration for these patients. This study aimed to provide information regarding fertility preservation, which has been under-reported outside of Europe and the USA, for male cancer patients in China, a country with a high population and a low income. After screening the retrieved data, a total of nine articles from seven sperm banks in mainland China, one assisted reproductive technology unit in Hong Kong and one Andrology Department in Taiwan were included. Frozen semen storage is the only method used for fertility preservation for men in China. Testicular tissue cryopreservation and spermatogonial stem cell cryopreservation have not been used in clinics in China. Until November 4, 2017, there were only 835 male cancer patients who had undergone frozen semen storage. Recently, the number of male cancer patients referred for sperm cryopreservation has progressively increased. Of the 734 patients reported to have pathological cancer, over 1/3 had testicular tumors (263/734; 35.8%). Only four articles have reported the number of patients with cryopreserved semen, and only 5.9% (26/440) of these patients utilized assisted reproductive technology. However, only four achieved successful live births. Unfortunately, only a few male cancer patients realize the necessity of fertility preservation, and these services are highly underutilized.

Keywords: Cancer, fertility preservation, male, frozen semen storage, sperm cryopreservation

Introduction

Cancer is a major public health problem worldwide [1]. Traditionally, cancer treatments have focused on efficacy and safety. With advances in cancer treatments, the number of men who are long-term survivors of cancer, especially those who developed cancer as adolescents, is growing [2]. Therefore, the focus of treatment is increasingly shifting toward quality of life, and fertility is a very important part of that. Infertility is a common adverse effect of cancer treatment. The use of gonadotropic chemotherapeutic agents such as alkylating agents and addition of radiation for cancer treatment significantly increased the risk of gonadal dysfunction [3]. Additionally, spermatogonia are susceptible to radiation and chemotherapeutic toxicity [4]. Therefore, preservation of reproductive potential has become a very important

quality of life issue for cancer survivors: many clinical guidelines propose the important role in fertility. Prevention of fertility loss due to cancer treatment as well as non-malignant causes has been gaining importance over the past few decades. However, very few patients know this and little has been published regarding this in China, a country with high population or low income. Not only should the Chinese physician improve this, but also the entire world should keep a close watch on the situation. Therefore, a retrospective review of fertility preservation for male cancer patients in China was performed to explore the current situation.

Materials and methods

The review was restricted to published research articles that reported fertility preservation for male cancer patients in China. PubMed, Web of

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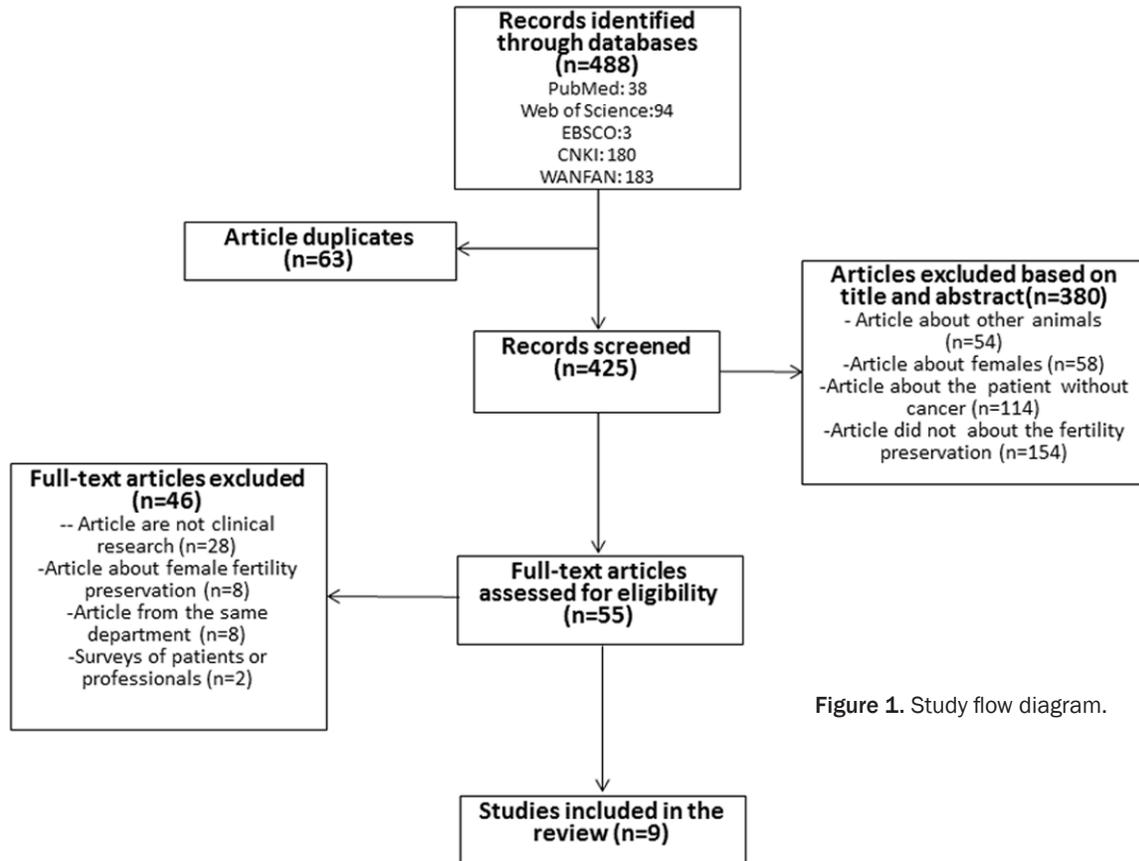


Figure 1. Study flow diagram.

Table 1. Main study outcomes

Studies	Regions	Study period	No. of patients with cancer	Diagnosis			Utilization of ART
				TC	L	O	
[6]	Beijing	July 2006-December 2015	137	-	-	-	12
[7]	Guangdong	June 2003-June 2016	288	84	61	143	-
[10]	Shandong	January 2009-December 2015	47	-	-	-	-
[12]	Hunan	February 2004-March 2014	97	53	14	89	2
[9]	Zhejiang	2005-2013	43	22	-	21	-
[11]	Jiangsu	December 2007-December 2014	17	7	-	10	-
[8]	Shanghai	January 1996-December 2010	21	21	-	-	5
[13]	Hong Kong	January 1995-January 2012	110	66	24	44	4
[5]	Taiwan	1995-2004	75	10	19	46	3
Total			835	263	118	353	26

TC, testicular tumor; L, lymphadenoma including Hodgkin's disease and non-Hodgkin's disease; O, other.

Science, EBSCO, and the two Chinese databases (China National Knowledge Infrastructure (CNKI) and WANFAN) were accessed. The literature was searched to identify pertinent studies published from inception until November 4 2017. Key words included the following: "fertility/reproduction preservation/fertility protection", "sperm cryopreservation" OR "testicular

tissue/spermatogonial stem cells cryopreservation", and "cancer/tumor/malignancy/neoplasm". The precise search strategy is shown in Figure 1. Filters were applied for human species and male sex. After eliminating duplicates, the titles and abstract of the works were checked to exclude studies about other animals, female patients, or patients without can-

cer. The reference lists of initially selected and pertinent articles were reviewed to identify further reports that could be included. Selected studies were fully read before final selection. Two authors (Fu and Zhang) independently conducted the search. Inconsistencies were solved by discussion and re-evaluation of discordant selections. If the articles used dates and were performed in the same department, then the newest was included. Final research was performed on December 31, 2017. IBM SPSS Statistics version 22 was used for data entry and analysis. The Chi-square test was used for categorical data and Student's t test was used for continuous variables. $P < 0.05$ was considered statistically significant.

Results

A total of 488 articles were included in the initial literature search. Ultimately, nine articles regarding nine different regions in China were included [5-13]. The main results of the studies are presented in **Table 1**. Sperm cryopreservation is the only approach used for fertility preservation in China. Testicular tissue cryopreservation and spermatogonial stem cell cryopreservation has been proven in animal models, but the two methods have not been clinically applied in China.

At present, there are only 23 human sperm banks in mainland China that are officially approved by the National Health Planning Commission and that have the ability to cryopreserve sperm. Of these human sperm banks, only seven have reported sperm cryopreservation for male cancer patients. These seven are representative of mainland China because they are the first sperm banks approved by the government. The total number of patients who utilized these sperm banks in China was only 835, from one ART unit in the Hong Kong region, or one Andrology Department in Taiwan, which is very small compared to the large population of cancer patients in China. Chang et al. [5] reported that during the study period, a total of 2642 male patients younger than 45 years had a diagnosis of cancer in their hospital, and the total utilization rate of sperm cryopreservation was only 2.9% (75/2642).

The number of male patients referred for sperm cryopreservation has been progressively increasing in the past few years. According to

Song et al. [10], the numbers who used the Shandong sperm bank during 2010, 2011, 2012, 2013, and 2014 were 7, 13, 14, 13, and 18, respectively; however, this number reached 28 in 2015. At our unit [6], the number increased four-fold, from 35 cases in 2012 to 137 cases in 2015. In Hong Kong [13], the number increased 10-fold from 1995 to 2005.

More than one-third of patients had testicular tumors (263/734; 35.8%), whereas two studies including 184 patients did not report the type of malignancy of the enrolled patients. Only five articles [5, 6, 12-14] reported the usage rate of cryopreserved semen. The number of patients who returned to use their cryopreserved sperm for ART was only 26 (5.9%; 26/440). However, only four achieved successful live births.

Discussion

Clinically applied modalities for fertility preservation of male cancer patients include sperm cryopreservation, and cryopreservation of testicular tissue or germ cells. Cryopreservation of semen samples is the main option for male fertility preservation [15]. Before puberty, spermatogenesis is absent and cryopreservation of spermatozoa is not an option. Some Oncofertility Programs collect and freeze testicular stem cells containing spermatogonial stem cells. An increasing number of institutions throughout Europe are now offering fertility preservation to prepubertal boys. Goossens et al. [16] started banking testicular tissue in 2002, and they have stored testicular tissue from 47 boys.

There are limited data available regarding fertility preservation for male cancer patients in China. Only nine studies from seven sperm banks in mainland China were found, one ART unit in Hong Kong and one Andrology Department in Taiwan. Until October 2017, a total of 835 Chinese male cancer patients who had undergone sperm cryopreservation had been reported. The incidence of all cancers was 293.79 per 100,000 for males in 2013 [17]. This suggests under-utilization of these services. In China, before the year 2000, there were only three units that reported providing sperm cryopreservation services for patients. However, due to the efforts of physicians, the number of male patients who have frozen and preserved their semen has been progressively increasing during the past few years. However,

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currently there have been no units that provide testicular tissue or spermatogonial stem cell cryopreservation in China.

For patients to receive proper fertility counseling, not only reproductive physicians but also other health care providers must be educated about fertility preservation options and must have resources readily available to provide this care. Developing fertility preservation programs are a good approach to meeting these needs in China. Johnson and Kroon [18] reported an eight-fold increase in the number of male adolescents and a 90% referral rate for male adolescents receiving fertility counseling before treatment. Furthermore, clinical guidelines have an important role in fertility. However, there are no practice guidelines advocating fertility preservation for men or physicians in China. A survey administered to doctors in Qingdao, China [19], showed that most physicians know that cancer will impair fertility, but only 60.0% of physicians advise their patients to utilize sperm cryopreservation and many of them do not know how to preserve the fertility for their patients. Due to the special relationship between physicians and patients in this country [20], some staff members at the sperm bank do not actively participate in fertility preservation because there are no relevant laws and regulations defining clear responsibilities, and new techniques may increase medical risks and medical problems. Many patients never return to the sperm bank after sperm cryopreservation, and the staff cannot contact them. Because there are no laws regarding how to dispose of samples, and because of the importance of the sperm, most sperm banks have chosen to continue to preserve it, which imposes a financial burden. In addition, in China, all ART services are private services. At our unit, preservation costs approximately CNY 5000 for the first year and CNY 2000 for every year thereafter. This may be a heavy burden for low-income families who already need to pay for cancer treatments.

Only 27 men (7.4%; 27/365) returned to use their cryopreserved sperm for infertility treatments. This usage rate is similar to those reported by other international oncology-infertility centers (2% to 60%), yielding an aggregate value of 8% (95% CI, 8% to 9%) [21]. From an economic perspective, the effectiveness of

sperm banking might be questioned. However, it should be realized that many patients were still young and single at the time of sperm cryopreservation. In addition, many of these patients may still be undergoing surveillance for cancer. Nonetheless, we strongly believe that sperm cryopreservation should be continued for cancer patients because of long-term sterility due to germ cell loss, even if only a few patients return for treatment.

There are several limitations to this study. First, only 9 articles could be found from seven sperm banks in mainland China, one from an ART unit in Hong Kong and one Andrology Department in Taiwan, even though these units are representative of China. Of the 7 sperm banks, they are representative of mainland China for the volume of business and their influence. Second, a detailed account of some characteristics such as age, semen parameters, follow-up period, and efficacy of ART performed with cryopreserved sperm samples could not be done because most researchers in China were not concerned with this topic in the past. Some data were singled out from the articles that included data of fertility preservation for all men, not just cancer patients. Therefore, more attention should be focused on this topic, and specific studies are required to clarify this issue.

The rate of azoospermia after chemotherapy ranges between 0% and 63% [22]. Fertility preservation is very important for male cancer patients, especially adolescents. Unfortunately, only a few patients realize the necessity of fertility preservation. Sperm cryopreservation is the only method of fertility preservation for male cancer patients in China. Collection and freezing of semen are noninvasive procedures that do not require delays in starting treatment and can be proposed to most post-pubertal cancer patients. Advances in fertility preservation techniques using testicular tissue or spermatogonial stem cell cryopreservation and transplantation may be beneficial for prepubertal boys in the future. However, there are no practice guidelines advocating fertility preservation for male cancer patients in China. Therefore, not only andrologists and reproductive physicians but also oncologists and other health care professionals should make an effort to promote fertility preservation for male cancer patients.

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Disclosure of conflict of interest

None.

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References

- [1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; 67: 7-30.
- [2] Fidler MM, Gupta S, Soerjomataram I, Ferlay J, Steliarova-Foucher E and Bray F. Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study. *Lancet Oncol* 2017; 18: 1579-1589.
- [3] Hudson MM. Reproductive outcomes for survivors of childhood cancer. *Obstet Gynecol* 2010; 116: 1171-1183.
- [4] Katz DJ, Kolon TF, Feldman DR and Mulhall JP. Fertility preservation strategies for male patients with cancer. *Nat Rev Urol* 2013; 10: 463-472.
- [5] Chang HC, Chen SC, Chen J and Hsieh JT. Initial 10-year experience of sperm cryopreservation services for cancer patients. *J Formos Med Assoc* 2006; 105: 1022-1026.
- [6] Fu LL, Zhang KS, Gu YQ. Fertility preservation for male adolescent cancer patients. *Zhonghua Nan Ke Xue* 2017; 23: 262-266.
- [7] Ma CJ, Zhuang JM, Deng SM, Ma T, Tang YJ, Lu LL, Zhang XZ, Hong Y, Tang YG and Wang QL. Reproductive insurance and clinical application of human sperm bank in Guangdong: a retrospective analysis of 13 years. *Guangdong Med J* 2017; 38: 748-750.
- [8] Ping P, Gu BH, Li P, Huang YR and Li Z. Fertility outcome of patients with testicular tumor: before and after treatment. *Asian J Androl* 2014; 16: 107-111.
- [9] Sheng HQ, Zhang XZ and Hong Y. Analysis of the quality of cryopreserved semen from male cancer patients. *Zhonghua Nan Ke Xue* 2015; 21: 44-47.
- [10] Song XH, Wang L, Liu SH, Xiao YH, Tong HY and Han WK. Current situation analysis and countermeasures on autologous sperm preservation in Shandong human sperm bank. *Chinese Journal of Andrology* 2016; 30: 18-22.
- [11] Sun HY, Gu MJ, Sun YY, Liu ZL, Zhang CX, Lin FX and Wang ZJ. Analysis of self sperm preservation in sperm bank. *Jiangsu Medicine Journal* 2015; 41: 2070-2071.
- [12] Xin L, Zhu WB and Fan IQ. The characteristics of male reproductive insurance population in 149 cases. *Zhonghua Nan Ke Xue* 2015; 21: 1146-1147.
- [13] Chung JP, Haines CJ and Kong GW. Sperm cryopreservation for Chinese male cancer patients: a 17-year retrospective analysis in an assisted reproductive unit in Hong Kong. *Hong Kong Med J* 2013; 19: 525-530.
- [14] Perheentupa A, Sadov S, Ronka R, Virtanen HE, Rodprasert W, Vierula M, Jorgensen N, Skakkebaek NE and Toppari J. Semen quality improves marginally during young adulthood: a longitudinal follow-up study. *Hum Reprod* 2016; 31: 502-510.
- [15] Winkler-Crepaz K, Ayuandari S, Ziehr SC, Hofer S and Wildt L. Fertility preservation in cancer survivors. *Minerva Endocrinol* 2015; 40: 105-118.
- [16] Goossens E, Van Saen D and Tournaye H. Spermatogonial stem cell preservation and transplantation: from research to clinic. *Hum Reprod* 2013; 28: 897-907.
- [17] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115-132.
- [18] Johnson RH and Kroon L. Optimizing fertility preservation practices for adolescent and young adult cancer patients. *J Natl Compr Canc Netw* 2013; 11: 71-77.
- [19] Dong G, Yang Z, Wang HQ, Xiu ZC, Wang XS and Wang PT. Investigation and analysis about protection awareness of fertility injury in male cancer patients in Qingdao. *Chinese Journal Reprod Contracep* 2017; 37: 327-329.
- [20] Huang SL and Ding XY. Violence against Chinese health-care workers. *Lancet* 2011; 377: 1747.
- [21] Ferrari S, Paffoni A, Filippi F, Busnelli A, Vegetti W and Somigliana E. Sperm cryopreservation and reproductive outcome in male cancer patients: a systematic review. *Reprod Biomed Online* 2016; 33: 29-38.
- [22] Tomlinson M, Meadows J, Kohut T, Haoula Z, Naeem A, Pooley K and Deb S. Review and follow-up of patients using a regional sperm cryopreservation service: ensuring that resources are targeted to those patients most in need. *Andrology* 2015; 3: 709-716.