Submitted: 14 November, 2024 Accepted: 09 January, 2025 Published: 30 June, 2025 DOI:10.22514/j.androl.2025.023

ORIGINAL RESEARCH

REV INT ANDROL
Revista Internacional de Andrología

Revisiting sperm cryopreservation timing in testicular cancer patients: pre- versus post-orchiectomy in the era of assisted reproductive technology

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Abstract

Background: This study aims to evaluate the clinical importance of the timing of sperm cryopreservation in patients diagnosed with testicular cancer who did not receive adjuvant therapy. **Methods**: We conducted a retrospective analysis of medical records from patients who underwent orchiectomy and sperm cryopreservation due to testicular tumors between 2013 and 2023. Patients with a normal contralateral testis were included. Participants were divided into two groups based on the timing of sperm cryopreservation. Group I comprised patients whose sperm was frozen before orchiectomy, while Group II comprised those whose sperm was frozen after orchiectomy. The groups were compared regarding age, tumor characteristics, serum tumor markers and sperm parameters. **Results**: A total of 160 patients met the inclusion criteria and had complete data, with 33 (20.6%) in Group I and 127 (79.4%) in Group II. Group I had a significantly higher prevalence of multiple tumors, while Group II had larger tumor diameters. Sperm concentration and total sperm count were higher in Group I. **Conclusions**: Sperm cryopreservation before orchiectomy is recommended for testicular cancer patients. Our findings particularly highlight the negative effects of orchiectomy on sperm motility. However, considering advancements in assisted reproductive technologies such as intracytoplasmic sperm injection, the timing of sperm cryopreservation—whether performed before or after orchiectomy—may not result in significant clinical changes in patient management.

Keywords

Testicular cancer; Orchiectomy; Fertility preservation; Sperm cryopreservation; Infertility

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Revisando el momento de la criopreservación de esperma en pacientes con cáncer testicular: antes versus después de la orquiectomía en la era de la tecnología de reproducción asistida

Resumen

Antecedentes: Este estudio tiene como objetivo evaluar la importancia clínica del momento de la criopreservación de esperma en pacientes diagnosticados con cáncer testicular que no recibieron terapia adyuvante. **Métodos**: Realizamos un análisis retrospectivo de los registros médicos de pacientes que se sometieron a orquiectomía y criopreservación de esperma debido a tumores testiculares entre 2013 y 2023. Se incluyeron pacientes con un testículo contralateral normal. Los participantes se dividieron en dos grupos según el momento de la criopreservación de esperma. El Grupo I comprendió a los pacientes cuyo esperma se congeló antes de la orquiectomía, mientras que el Grupo II comprendió a aquellos cuyo esperma se congeló después de la orquiectomía. Se compararon los grupos en relación con la edad, las características del tumor, los marcadores tumorales en suero y los parámetros del esperma. **Resultados**: Un total de 160 pacientes cumplieron con los criterios de inclusión y tenían datos completos, con 33 (20.6%) en el Grupo I y 127 (79.4%) en el Grupo II. El Grupo I presentó una prevalencia significativamente mayor de tumores múltiples, mientras que el Grupo II tuvo tumores de mayor diámetro. La concentración de esperma y el recuento total de esperma fueron más altos en el Grupo I. **Conclusións**: Se recomienda la criopreservación de esperma antes de la orquiectomía para los pacientes con cáncer testicular. Nuestros hallazgos destacan especialmente los efectos negativos de la orquiectomía sobre la motilidad espermática. Sin embargo, teniendo en cuenta los avances en tecnologías de reproducción asistida, como la inyección intracito plasmática de esperma, el momento de la criopreservación de esperma, ya sea antes o después de la orquiectomía, puede no tener implicaciones clínicas significativas en la gestión del paciente.

Palabras Clave

Cáncer testicular; Orquiectomía; Preservación de la fertilidad; Criopreservación de esperma; Infertilidad

1. Introduction

Testicular cancer is the most common malignancy diagnosed in adolescent and young adult men between ages 15 and 40 years [1]. Although the overall 5-year survival is over 95%, fertility remains a significant morbidity in this patient group. Fertility problems may be due to the disease itself or may occur due to the treatment of the disease [2, 3]. The exact mechanism by which testicular tumors affect fertility at diagnosis remains unclear, though testicular dysgenesis syndrome, tumor size, anti-sperm antibody development, and the paracrine and autocrine effects of elevated tumor markers may contribute. Additionally, orchiectomy, necessary for diagnosis and initial treatment, along with subsequent therapies like chemotherapy, radiotherapy, retroperitoneal lymph node dissection or multimodal regimens based on histological subtype and staging, may cause both temporary and permanent fertility damage [3]. Although sperm cryopreservation is recommended for patients with testicular tumors and fertility concerns before orchiectomy, this is not always possible in daily practice. A significant portion of patients apply after orchiectomy and before adjuvant treatment. The main reason for this situation appears to be the insufficient information provided to patients regarding the preservation of fertility.

This study seeks to assess the significance of the timing of sperm cryopreservation in patients diagnosed with testicular cancer who did not receive adjuvant therapy.

2. Materials and methods

2.1 Patients

We retrospectively evaluated the medical records of patients who underwent unilateral orchiectomy and sperm cryopreservation due to testicular tumor between 2013 and 2023. Patients whose contralateral testicle was confirmed to be normal by physical examination imaging were included in the study. History of chemotherapy and/or pelvic radiotherapy was considered as exclusion criteria.

2.2 Clinical evaluation

All patients underwent a comprehensive assessment, including a detailed medical history and a thorough physical examination. Semen samples were obtained using audio-visual stimulation in a dedicated room within our embryology laboratory. Seminal parameters were interpreted in accordance with the criteria outlined by the World Health Organization (WHO) [4]. After evaluation, ejaculate samples were cryopreserved using the rapid freezing method [5] by experienced and senior embryology staff. Alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) levels at the time of diagnosis were documented, with AFP and bHCG considered for their potential paracrine and autocrine effects on spermiogenesis, while LDH was recorded to assess tumor burden. Additionally, tumor numbers, the largest tumor diameters, and contralateral testis were assessed through scrotal color Doppler ultrasonography.

2.3 Data interpretation

To assess the significance of sperm cryopreservation timing, participants were stratified into two groups based on the timing of sperm freezing. Group I comprised patients whose sperm

was cryopreserved before orchiectomy, while Group II comprised patients whose sperm was cryopreserved after orchiectomy. The groups were compared based on age, tumor side, tumor number, multiplicity (the presence of more than one tumor in one testicle) and diameter, tumor histopathological type, serum levels of AFP, bHCG and LDH, as well as ejaculate volume, total sperm count (TSC), sperm concentration, sperm motility and total motile sperm count (TMSC).

2.4 Statistical analysis

Kolmogorov-Smirnov test or Shapiro-Wilk test was used to determine whether the distributions of continuous variables were normal. Continuous variables were defined as mean ± standard deviation if they were normal, and as median if continuous variables were not normal. Continuous variables were compared according to whether they were parametric or non-parametric, using Student's *t* test or Mann-Whitney U test, respectively. The categorical variables between the groups were analyzed by using the Chi square test or Fisher's Exact test. Statistical significance was considered when the *p*-value was < 0.05. Statistical analysis was performed using Statistical Package for the Social Science (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The number of patients meeting the study's inclusion criteria and having complete data was 160. The median age of the patients was 26.6 ± 5.2 years (range, 17–40). In 70 (43.8%) patients, the tumor was located on the left side, while in 90 (56.2%) patients it was located on the right side. While Group I consisted of 33 (20.6%) patients, there were 127 (79.4%) patients in Group II. The characteristics of patients and tumors, semen parameters and the results of the statistical analysis are presented in Table 1.

All parameters of both groups were evaluated. The number of tumors in the testis undergoing orchiectomy was more than one in only 10 cases, and the number of tumors and multiplicity were significantly higher in Group I. Tumor diameter was significantly higher in Group II. Sperm concentration and TSC were statistically significantly higher in Group I.

The overall incidence of azoospermia was 2.5%. When we evaluated the groups within themselves, this rate was 2.4% (1/33 patients) for Group I and 3% (3/127 patients) for Group II. There was no statistically significant difference between the groups (Table 1).

All patients had germ cell tumors, except 2 patients with Leydig cell tumors in Group II. There was no difference histopathologically between the groups.

The median follow-up duration was 54.0 ± 41.7 months (range, 7–168). Throughout the follow-up period, 8 patients in Group I and 25 patients in Group 2 voluntarily consented to the disposal of their cryopreserved sperm ($p = 0.630$). Furthermore, while only 2 patients in Group I opted for the use of their cryopreserved sperm for intracytoplasmic sperm injection (ICSI), this figure increased to 7 patients in Group II ($p = 1.000$).

4. Discussion

Testicular cancer is managed primarily through radical orchiectomy, thereafter dictating treatment selection based on histological subtyping and disease staging. Treatment options encompass active surveillance, chemotherapy, radiotherapy, retroperitoneal lymph node dissection or a multimodal approach [6]. Despite achieving a cure rate in excess of 95%, these interventions may significantly impact patient health and overall quality of life [2]. The demographic predominantly affected by this malignancy often falls within the reproductive age group [7]. Incidence rates peak in the 30–34 age range and 25–29 age range, respectively [8]. Post-treatment infertility remains an important problem in many testicular cancer survivors that has been studied extensively [9]. A considerable proportion of survivors report feeling inadequately informed about the potential impact of treatments on their fertility status. The study by Schover *et al*. [10] showed that merely 60% of male patients undergoing treatment received counseling on fertility consequences before initiating therapy, and within this cohort, only 51% recalled being counseled on sperm cryopreservation.

Sperm cryopreservation has emerged as the primary method of fertility preservation in post-puberty male patients as it is not only the most cost-effective but also the most effective and reliable technique [9]. While there exists a general consensus favoring the undertaking of sperm cryopreservation prior to orchiectomy, a considerable cohort of patients seeks it only in the post-surgery period [11]. This situation may arise not only from the lack of appropriate and/or sufficient information but also from patients' indecision and issues such as azoospermia and ejaculation problems encountered during the sample collection phase for cryopreservation, which contribute to the inadequate and untimely implementation of procedures aimed at preserving fertility [12]. Therefore, numerous institutions continue to routinely perform sperm cryopreservation subsequent to orchiectomy but before chemotherapy [6, 13].

The timing of sperm cryopreservation can lead to two potential issues in clinical practice: the clinically significant disparity between pre- and post-orchiectomy approaches on seminal parameters, and the adverse effects of this disparity on the management of fertility-related concerns. Rives *et al*. [11] reported a significant decrease in total sperm count and sperm concentration during the post-orchiectomy period among patients diagnosed with testicular cancer. In our study, although no discernable differences between the groups concerning total sperm count and sperm concentration, a significant decrease in total motility was observed in the group that cryopreserved sperm after orchidectomy.

After remission, the use of cryopreserved spermatozoa in assisted reproductive treatments depends on the concentration and motility of the sperm recovered after thawing. Despite in some cases intrauterine insemination (IUI) or *in vitro* fertilization (IVF) can be used, due to the special condition, it is advised to use intracytoplasmic sperm injection (ICSI) to enhance fertilization rates, mitigate the risk of failed fertilization, and safeguard against depletion of the finite sperm reservoir [5, 14].

The emergence of azoospermia following orchiectomy in

TABLE 1. Patient and tumor characteristics and sperm parameters.

Clinical factor	Group I	Group II	Total	*p* value
Number (%)	33 (20.6)	127 (79.4)	160 (100.0)	
Median age (yr)	27.5 ± 5.3	25.6 ± 5.2	26.6 ± 5.2	0.050
Side (number, %)				
Left	8 (5.0)	62 (38.8)	70 (43.8)	0.006
Right	25 (15.6)	65 (40.6)	90 (56.2)	
Alpha-fetoprotein (μg/L)	11.1 (1.4–4934.5)	26.6 (0.9–52,500.0)	15.9 (0.9–52,500.0)	0.960
Beta-human chorionic gonadotropin (IU/L)	5.6 (0.4–6359.0)	12.3 (0.1–3029.0)	9.6 (0.1–6359.0)	0.911
Lactate dehydrogenase (IU/L)	206.0 (120.0–492.0)	236.5 (152.0–982.0)	220.0 (120.0–982.0)	0.167
Tumor diameter (mm)	35.0 (7.0–65.0)	40.0 (6.0–110.0)	39.0 (6.0–110.0)	0.028
Tumor number	1 (1–5)	1 (1–3)	1 (1–5)	<0.001
Tumor multiplicity (number, %)				
Solitary	26 (16.3)	124 (77.5)	150 (93.8)	0.001
Multiple	7 (4.4)	3 (1.8)	10 (6.2)	
Seminal parameters				
Ejaculate volume (mL)	3.2 (1.5–9.3)	3.0 (0.3–8.5)	3.0 (0.3–9.3)	0.195
Concentration (10^6/mL)	30.0 (0.0–120.0)	16.0 (0.0–144.0)	18.5 (0.0–144.0)	0.039
Total sperm count (10^6)	93.0 (0.0–460.0)	50.9 (0.0–574.0)	60.0 (0.0–574.0)	0.023
Progressive motility (%)	56.0 (0.0–86.0)	56.0 (0.0–85.0)	56.0 (0.0–85.0)	0.529
Total motile sperm count (10^6)	46.3 (0.0–277.2)	23.3 (0.0–327.2)	28.2 (0.0–327.2)	0.091
Seminal diagnosis according to WHO (number)				
Normozoospermia	24 (15.0)	68 (42.5)	92 (57.5)	0.223
Oligozoospermia	6 (3.8)	45 (28.1)	51 (31.9)	
Cryptozoospermia	2 (1.2)	11 (6.9)	13 (8.1)	
Azoospermia	1 (0.7)	3 (1.8)	4 (2.5)	
Histopathology (number)				0.468
Germ cell tumors	33 (20.6)	125 (78.2)	158 (98.8)	0.710
Seminom	8 (5.0)	26 (16.3)	34 (21.3)	
Non-seminom	10 (6.2)	31 (19.4)	41 (25.6)	
Mixt	15 (9.4)	68 (42.5)	83 (51.9)	
Sex cord-stromal tumor	0 (0.0)	2 (1.5)	2 (1.2)	
Leydig cell	0 (0.0)	2 (1.5)	2 (1.5)	

WHO: World Health Organization.

patients with testicular cancer remains a topic of contention. In existing literature, this occurrence has been reported at a rate of 9% among 78 patients [15, 16]. In our cohort of 127 post-orchiectomy patients, this rate stands at 2.4%, mirroring the 3% rate observed in our cohort of 33 patients who underwent sperm cryopreservation prior to orchiectomy. We believe that this finding will contribute significantly to the existing literature on the subject.

Regrettably, the timely utilization of sperm banking remains remarkably low, despite the guidelines set forth by the American Society of Clinical Oncology, the American Academy of Pediatrics, and the European Urology Association [7, 17, 18]. Oncologists and patients frequently fail to prioritize sperm cryopreservation until after the commencement of cancer treatment [19]. During the course of treatment, when the disease reaches a more stable phase, fertility-related concerns may emerge. At this point, failing to provide information supported by medical literature could lead to medicolegal issues.

The primary limitation of our study is its retrospective nature. While it would be appropriate for this study to be prospectively designed to obtain ejaculate samples from each patient before and after orchiectomy, the practical implementation is complicated in this patient cohort due to the patient's immediate request for treatment stemming from high anxiety levels. Furthermore, another limitation lies in the relatively small sample size, particularly in assessing the impact of uti-

lizing cryopreserved sperm on fertility outcomes, as well as the inability to evaluate certain fertility parameters.

5. Conclusions

The recommendation for sperm cryopreservation prior to orchiectomy in cases of testicular cancer still appears to be relevant. Our findings particularly highlight the negative effects of orchiectomy on sperm motility. However, advancements in assisted reproductive techniques, such as intracytoplasmic sperm injection, provide significant contributions to the management of the patient population presenting particularly after orchiectomy.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

CO and MRG—designed and conceptualized the research study. CO, CS and MRG—contributed to acquisition; analysis and interpretation of data. CO, MED, MVK and AE—wrote the draft of manuscript. All authors performed a critical revision of the manuscript and contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee approval was obtained from the Research Ethics Committee of Baskent University (Protocol No: KA 24/105). Participation consent was obtained from all patients prior to the procedure, with explicit agreement for the use of their data in the study.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] McHugh DJ, Gleeson JP, Feldman DR. Testicular cancer in 2023: current status and recent progress. CA: A Cancer Journal for Clinicians. 2024; 74: 167–186.

[2] van der Meer DJ, Karim-Kos HE, Elzevier HW, Dinkelman-Smit M, Kerst JM, Atema V, *et al*. The increasing burden of testicular seminomas and non-seminomas in adolescents and young adults (AYAs): incidence, treatment, disease-specific survival and mortality trends in the Netherlands between 1989 and 2019. ESMO Open. 2024; 9: 102231.

[3] Hu Y, Fu X, Jiang X, Jiang M, Zheng X, Lu H, *et al*. The experience of fertility concerns in patients with testicular cancer: a qualitative study. Supportive Care in Cancer. 2024; 32: 529.

[4] World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th edn. World Health Organization: Geneva. 2010.

[5] Xie Q, Jiang X, Zhao M, Xie Y, Fan Y, Suo L, *et al*. Effect of freezing and thawing on ejaculated sperm and subsequent pregnancy and neonatal outcomes in IVF. Frontiers in Endocrinology. 2024; 15: 1408662.

[6] Patrikidou A, Cazzaniga W, Berney D, Boormans J, de Angst I, Di Nardo D, *et al*. European association of urology guidelines on testicular cancer: 2023 update. European Urology. 2023; 84: 289–301.

[7] Panner Selvam MK, Agarwal A, Pushparaj PN. A quantitative global proteomics approach to understanding the functional pathways dysregulated in the spermatozoa of asthenozoospermic testicular cancer patients. Andrology. 2019; 7: 454–462.

[8] Zhou X, Zhang Z, Ruan C, Wu Y, Zeng B, Su X, *et al*. Trends in the global, regional, and national burden of testicular cancer from 1990 to 2019: an observational study with 30-year global data. International Journal of Surgery. 2024; 110: 4633–4647.

[9] Davis S, Khizir L, Lichtbroun B, Jang T, Ghodoussipour S, Velez D. Sexual function and fertility preservation in testicular cancer survivors. Journal of Men's Health. 2023; 19: 1–8.

[10] Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. Journal of Clinical Oncology. 2002; 20: 1880–1889.

[11] Rives N, Perdrix A, Hennebicq S, Saïas-Magnan J, Melin M, Berthaut I, *et al*. The semen quality of 1158 men with testicular cancer at the time of cryopreservation: results of the French national CECOS network. Journal of Andrology. 2012; 33: 1394–1401.

[12] Ito K, Ichioka K, Dahal S, Matsui Y, Nakayama T, Hatayama H, *et al*. Barriers for sperm cryopreservation in advanced germ cell tumor patients: a 20-year experience. International Journal of Clinical Oncology. 2020; 25: 906–911.

[13] Moody JA, Ahmed K, Yap T, Minhas S, Shabbir M. Fertility managment in testicular cancer: the need to establish a standardized and evidence-based patient-centric pathway. BJU International. 2019; 123: 160–172.

[14] Li Q, Lan Q, Zhu W, Fan L, Huang C. Fertility preservation in adult male patients with cancer: a systematic review and meta-analysis. Human Reproduction Open. 2024; 2024: hoae006.

[15] Petersen PM, Skakkebaek NE, Rørth M, Giwercman A. Semen quality and reproductive hormones before and after orchiectomy in men with testicular cancer. Journal of Urology. 1999; 161: 822–826.

[16] Liguori G, Trombetta C, Bucci S, Benvenuto S, Amodeo A, Ocello G, *et al*. Semen quality before and after orchiectomy in men with testicular cancer. Archives of Italian Urology and Andrology. 2008; 80: 99–102.

[17] Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, *et al*. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. Journal of Clinical Oncology. 2018; 36: 1994–2001.

[18] Fallat ME, Hutter J; American Academy of Pediatrics Committee on Bioethics; American Academy of Pediatrics Section on Hematology/Oncology; American Academy of Pediatrics Section on Surgery. Preservation of fertility in pediatric and adolescent patients with cancer. Pediatrics. 2008; 121: e1461–e1469.

[19] Ghidei L, Sullivan J, Valero Carrion RJ, Schammel J, Lipshultz L, McKenzie LJ. Current gaps in fertility preservation for men: how can we do better? Journal of Clinical Oncology. 2022; 40: 2524–2529.

How to cite this article: Cevahir Ozer, Mehmet Eflatun Deniz, Cagla Sariturk, Mehmet Vehbi Kayra, Askin Eroglu, Mehmet Resit Goren. Revisiting sperm cryopreservation timing in testicular cancer patients: pre- versus post-orchiectomy in the era of assisted reproductive technology. Revista Internacional de Andrología. 2025; 23(2): 90-94. doi: 10.22514/j.androl.2025.023.