International Journal of Reproduction, Contraception, Obstetrics and Gynecology
*Mansi R et al. Int J Reprod Contracept Obstet Gynecol. 2025 Nov;14(11):4066-4071*
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20253568

**Review Article**

# Preservation of fertility in men with cancer

**Ramani Mansi[1], Anjali Rajan[1], Barry Cooper Hynniewta[2], Faridha Jane R. M. Momin[3]***

[1]Department of Clinical Embryology, Yenepoya University, Mangalore, Karnataka, India
[2]Department of Clinical Embryology, MOMSOON Fertility and IVF Center, Bangalore, Karnataka, India
[3]Department of Oncology, Shillong Civil Hospital, Shillong, Meghalaya, India

**Received:** 28 June 2025
**Revised:** 18 August 2025
**Accepted:** 19 August 2025

***Correspondence:**
Dr. Faridha Jane R. M. Momin,
E-mail: barrycooperhynniewta@gmail.com



## ABSTRACT

Fertility preservation in males is acknowledging a developing recognition as essential in treatment planning for cancer. Many currently available cancer therapies including chemotherapy, radiation and novel immunotherapy can affect sperm production, testicular function and reproductive potential. Although sperm cryopreservation is the gold standard for patients, considering post pubertal patients, experimental approaches to preserve fertility including cryopreservation of testicular tissue as an option for prepubertal boys, are in development. Whilst we do not currently lack options, several barriers prevent patients from timely access to fertility counselling, primarily a lack of awareness at their diagnosis or timely education of specific services. Early access to fertility preservation services as part of oncology health care can improve reproductive outcome and enhance long-term quality of life for survivors. Changes in our current practices will require better communication, collaboration, and a focus on improving patient access to fertility preservation options.

**Keywords:** Male fertility preservation, Cancer therapy, Sperm cryopreservation, Onco-fertility, Counselling

## INTRODUCTION

Advances in oncological treatments have significantly improved survival rates of male cancer patients. Nevertheless, many treatments pose a serious risk of infertility, especially in young men and boys who have yet to have families. The gonadotoxic effects of cancer treatment are well-known, and permanent infertility can occur without determined actions. As survival becomes more normal, quality of life issues, including fertility potential, are being identified by more oncologists as part of overall cancer care.[1,2]

Cancer in men is different in South Asia, both by type and place. Common cancers in men include lip/oral cavity, lung, oesophagus, stomach, and colorectal, with variation across countries.[3,4] Prognosis differs depending on cancer type and stage. Lung and oesophageal cancers often present in advanced stages, contributing to poor survival outcomes, while lip/oral cavity and colorectal cancers have better prognoses when detected early. These variations reflect disparities in healthcare access and awareness, emphasizing the need for tailored early detection strategies.[5]

Fertility preservation has been identified as an important aspect of oncofertility for men. For adult men, sperm cryopreservation prior to cancer treatment is the standard and most effective method. It is safe, widely used, with high post-thaw motility and fertilization potential. In a 10-year monocentric cohort study, three out of four cryopreserved sperm samples were eventually used for reproduction, confirming its relevance in ART.[6] Although effective, sperm cryopreservation remains underutilized due to lack of knowledge among patients and oncology teams, inaccessibility of services, time constraints before treatment, and psychological burden related to diagnosis.[7]

In prepubertal boys, conventional sperm cryopreservation is not feasible as there are no mature spermatozoa. Testicular tissue cryopreservation and *in vitro*

spermatogenesis are experimental approaches under study but without clinical translation yet.[8,9] Studies show spermatogonial stem cells (SSCs) in testicular tissue may be reactivated post-treatment or matured ex vivo, but ethical, technical, and safety issues prevent routine clinical use. Furthermore, fertility preservation discussions should occur as soon as cancer is diagnosed. However, in many studies, discussions were delayed or absent.[10]

Most malignancies and regimens have different fertility risks. Alkylating agents and testicular radiation are highly gonadotoxic, whereas other agents have mild and transient effects. Risk stratification models help individualize fertility preservation approaches. In adults, techniques such as testicular shielding during radiation, testosterone use alongside alkylating agents, and gonadotropin-releasing hormone analogs have been studied; however, preservation of fertility potential remains debated.[11] Fertility loss can have strong emotional and psychological effects. While awareness is growing, gaps remain, especially in resource-limited contexts.[12]

## REPRODUCTIVE COUNSELING

Fertility preservation has become an increasingly important aspect of cancer care for males, especially adolescents and young adults (AYAs) who may not yet have started families. Timely reproductive counseling allows patients to be educated, informed, and empowered to make decisions about fertility preservation prior to starting treatment. However, studies suggest delivery of this counseling may vary markedly and often fail to meet emotional and informational needs.[13]

Adolescents and parents may not always share the same perspective on fertility, which may result in confusion or inaction regarding options such as sperm banking. Quinn et al emphasized the importance of tools that bring both perspectives together during counseling.[14] Similarly, Nahata et al noted that many families face the emotional challenges of a cancer diagnosis, making time-sensitive fertility decisions stressful.[15]

Although clinical guidelines support early and comprehensive fertility counseling, uptake in practice remains inconsistent. Structured counseling given before treatment can improve outcomes and provide access to options such as sperm cryopreservation.[16] However, many patients feel unsupported and report that counseling often omits psychological, educational, and logistical elements.[17] Even when discussions occur, patients may feel overwhelmed and unable to consider long-term consequences. The quality of counseling impacts preservation decisions, satisfaction, and emotional well-being.[18]

## CHEMOTHERAPY

Chemotherapy is an essential cancer treatment, using cytotoxic drugs to kill fast-dividing cells through processes like cell cycle arrest, apoptosis, and DNA replication inhibition. Agents are grouped by their mechanism: alkylating agents (alkylate DNA), antimetabolites (inhibit nucleotides), and agents like vinca alkaloids and taxanes (target mitotic spindle).[13] Recently, topoisomerase I inhibitors such as irinotecan and topotecan have been introduced, stabilizing the DNA-topoisomerase I complex, causing double-strand DNA breaks and cell death.[14,15] Irinotecan, a pro-drug converted to SN-38, is effective in colorectal and lung cancers but limited by toxicities like neutropenia and diarrhea.[16,17]

Chemotherapy can cure cancers like testicular tumors and lymphomas but is limited by a narrow therapeutic window and individual differences in drug metabolism.[18,19] Effectiveness relies on the tumor's ability to undergo apoptosis, regulated by proteins including p53 and Bcl-2.[20,21]

## TESTICULAR EFFECTS

Testicular cancer is the most common malignancy in men aged 20-44, with high cure rates from cisplatin-based chemotherapy.[22] Despite excellent survival, treatment often damages germ cells, Sertoli and Leydig cells, and crosses the blood-testis barrier, leading to azoospermia or oligospermia.[23] Damage increases with higher cisplatin doses, with >850 mg linked to reduced paternity and higher hypogonadism risk.[24,25]

Spermatogenesis recovery varies; some remain azoospermic for years, and ~25% remain so after 3 years.[26] DNA damage can persist even with normal counts, lowering fertility and increasing miscarriage risk.[27] Fertility rates fall significantly post-treatment, especially with combined radiotherapy.[28]

Testosterone deficiency may occur, causing infertility and symptoms of androgen loss.[29] Less than thirty percent of eligible patients will cryopreserve sperm prior to initiating chemotherapy, and of stored samples, less than 10% will be used for future assisted reproduction.[30] Few patients bank sperm before chemotherapy, yet when used, cryopreserved samples achieve fatherhood in ~50% of cases.[31] Barriers include lack of counseling, cost, urgency, and psychological distress.[32] Patients routinely overestimate their chances of spontaneously recovering fertility, and they typically miscalculate the likelihood of developing azoospermia, particularly when undergoing multi-agent combination chemotherapy.[33] For azoospermic men, surgical sperm retrieval or hormonal rehabilitation may restore fertility.[34,35]

## EFFECTS ON SPERM

Chemotherapy has a large effect on male fertility; this is accomplished primarily through the impairment of spermatogenesis. The most common outcome is azoospermia, which can develop 8-12 weeks after the start

of treatment, coinciding with the depletion of differentiating spermatogonia.[36]

Data reveal that recovery post-therapy depends strongly on whether spermatogonial stem cells survive cytotoxic insult. Some patients recover sperm production within 12 weeks of stopping treatment; for others, recovery may take several years.[37] Chemotherapy involving alkylating agents or cisplatin/procarbazine regimens can cause irreversible damage, leading to long infertility.[38]

Beyond sperm count reduction, chemotherapy can induce chromosomal abnormalities. Men treated for testicular cancer or Hodgkin lymphoma had significantly increased sperm aneuploidy, with impacts even 24 months post-treatment.[39] Testicular biopsies show germinal aplasia, and FSH elevation indicates germinal epithelial failure.[40] LH increases suggest Sertoli and Leydig cell damage.[41]

Due to possible degenerative effects, sperm cryopreservation prior to chemotherapy is highly recommended as the best chance for biological children, especially for regimens with long-term gonadotoxicity.[42]

## RADIOTHERAPY

About 60-65% of cancer patients receive radiotherapy (RT), either alone or with chemotherapy and surgery.[43] RT delivers ionizing radiation to destroy malignant cells while minimizing injury to normal tissues. Intent may be curative, palliative, or supportive. Effectiveness depends on tumor histology, location, radiosensitivity, and dose delivery accuracy.[43,44] Advances such as 3D-CRT, IMRT, and IGRT have improved tumor control and reduced toxicity.[43,45]

## TESTICULAR EFFECTS

Radiotherapy can lead to severe testicular damage because of the testes high radiosensitivity. Spermatogonial proliferative stem cells are affected at doses as little as 0.1 Gy, leading to impacts on sperm count and quality. Above 2-3 Gy, spermatocytes and spermatids can be affected, and at >6 Gy, there may be a risk of azoospermia. Higher doses (15-20 Gy) can impair Leydig cell testosterone synthesis, leading to increased LH and FSH.[46]

In patients treated for carcinoma-in-situ of the testis, doses of 16-20 Gy achieved remission but caused low testosterone and elevated LH/FSH, indicating permanent Leydig cell damage; some required testosterone therapy even at lower doses.[47] Histology often shows sertoli-cell-only patterns, consistent with complete germ cell loss. Mechanisms include DNA strand breaks, oxidative stress, and apoptotic signaling.[46,48]

## EFFECTS ON SPERM

Radiotherapy damages the germinal epithelium; differentiating spermatogonia are the most radiosensitive. Even 0.2-1.3 Gy can induce azoospermia. In testicular germ cell tumor patients, median time to sperm reappearance was 540 days, with pre-treatment counts reached at ~1250 days; FSH remained elevated long after therapy.[49] Radiotherapy also increases sperm chromosomal anomalies, rising from 0% at baseline to 21% at 36 months post-treatment, associated with higher doses.[50]

Semen quality declines in concentration, motility, and morphology approximately six months after treatment; some remain azoospermic at 24 months. Recovery depends on surviving spermatogonial stem cells and a healthy somatic environment. Doses over 2.5 Gy, especially fractionated, may cause prolonged or permanent azoospermia. TESE may be possible in such cases.[51]

## CANCER SURGERICAL THERAPY

Surgical treatments addressing cancer, especially in the pelvic and retroperitoneal areas, can create significant problems for male fertility. Procedures such as retroperitoneal lymph node dissection (RPLND), done most frequently for testicular cancer, may interrupt nerve pathways important for ejaculation, with retrograde ejaculation or total absence of ejaculation as possibilities.[52] In orchidectomy, particularly where both testes are included or one is under-developed, loss of sperm-producing tissue directly compromises fertility.[53] Additionally, surgery may block sperm passage through the vas deferens or ejaculatory ducts.[54] Conducting surgery that damages brain pathways, such as the hypothalamus or pituitary, could also affect hormone regulation, important for sperm production. Early discussions about fertility preservation and the option of sperm banking should be part of cancer care for men of reproductive age.

## IMMUNOTHERAPY

Increased survival among young cancer patients and the expanding use of immune checkpoint inhibitors (ICIs) in early-stage disease, particularly anti-CTLA-4, anti-PD-1, and anti-PD-L1, have raised concerns about possible effects on male fertility. ICIs have shown outstanding success in melanoma and non-small-cell lung cancers, but their gonadotoxicity is not fully understood.[55,56]

Immune-related adverse events from these agents can include endocrine dysfunctions such as hypophysitis and thyroiditis, which may reduce testosterone production and impair spermatogenesis.[55,57] CTLA-4 inhibitors can cause hypophysitis, affecting gonadotropin secretion and testicular function.[57] Use of ipilimumab and atezolizumab in preclinical studies reduced testicular weights and caused ovarian changes in non-human primates, though most subjects were not sexually mature and histopathological sperm assessment was inconsistent.[58,59]

Autoimmune orchitis and inflammatory infiltrates have been reported in patients and animal models.[57] In a clinical

study, 18% of men on ICIs had abnormal semen profiles, including azoospermia and oligoasthenoteratozoospermia; one developed azoospermia after starting therapy, with inflammatory cells in the ejaculate suggestive of subclinical orchitis.[60] Post-mortem studies found testicular atrophy and impaired spermatogenesis in some patients after ICI treatment.[56] Receptor occupation by ICIs can last up to 30 months, suggesting possible long-term or delayed gonadal effects.[55]

Oncology guidelines emphasize informing reproductive-age patients of fertility risks, especially when ICIs are used in neoadjuvant or adjuvant settings.[61]

## FERTILITY PRESERVATION TECHNIQUES IN MALES

Preservation of fertility in males undergoing gonadotoxic interventions is an important aspect of cancer care. Sperm cryopreservation is the most utilized and effective method in postpubertal males, as it is safe, accessible, and suitable for assisted reproductive technologies (IUI/IVF/ICSI).[62] For prepubertal boys, testicular tissue freezing is an experimental strategy, including cryopreserving spermatogonial stem cells (SSCs) with potential for transplant or *in vitro* maturation, though challenges remain.[63]

Sperm cryopreservation involves collecting semen, mixing it with cryoprotective agents, and cooling it to -196°C for storage. Both conventional slow freezing and vitrification are used; vitrification offers faster cooling and may reduce cellular damage. Although some motility and morphology loss occurs after thawing, sperm remain viable for ART.[64]

Live birth rates with cryopreserved sperm are comparable to fresh sperm in ART. Most live births occur via IVF or ICSI, with success reported globally and in Indian fertility centers. Utilization rates remain low, but outcomes are generally positive when used.[65]

## TESTICULAR TISSUE CRYOPRESERVATION

Testicular tissue cryopreservation presents a potential approach to male fertility preservation for those at risk of infertility due to gonadotoxic cancer therapy, especially in the case of prepubertal boys who cannot produce a sperm sample. The cryopreservation of testicular tissue involves the freezing of testicular tissue fragments that contain spermatogonial stem cells to maintain the viability and structural integrity of the tissue. Standardly, slow-freezing protocols are used, with cryoprotectants such as dimethyl sulfoxide or glycerol to limit the damage from ice crystals.[66,67] Although in its infancy in humans, improvements in the ability to mature germ cells *in vitro* and possibly return to sperm production again could be possible someday. Ethical and legal aspects of testicular preservation in children are critical including informed and voluntary parental consent, counselling, and the importance of compliance with safety and regulatory guidelines.[67]

## CONCLUSION

Fertility preservation in male cancer patients is an important but often neglected component of oncologic care. As survival rates rise, quality of life issues, including the ability to become biological fathers, remain a concern. Treatments may impair spermatogenesis and hormonal function. Sperm cryopreservation is the most effective method for post pubertal males, while testicular tissue cryopreservation is being researched for prepubertal boys.

Many patients miss preservation opportunities due to lack of awareness, inaccessibility, psychological hardship, and delayed counseling. Fertility discussions should occur early, preferably at diagnosis, and be part of multidisciplinary cancer care.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Mansi R, Rajan A, Hynniewta BC, Momin FJRM. Preservation of fertility in men with cancer. Int J Reprod Contracept Obstet Gynecol 2025;14:4066-71.