Review Article

Contemporary and future insights into fertility preservation in male cancer patients

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Abstract: In recent years, survival rates of cancer patients have increased, resulting in a shift of focus from quantity to quality of life. A key aspect of quality of life is fertility potential; patients suffering from iatrogenic infertility often become depressed. Since many cancer therapies—chemotherapy, radiotherapy and/or surgery—and even cancer itself have detrimental effects on the male reproductive system, it is important to preserve fertility before any treatment commences. Currently, the only reliable method of male fertility preservation is sperm banking. For patients who are unable to provide semen samples by the conventional method of masturbation, there are other techniques such as electroejaculation, microsurgical epididymal sperm aspiration and testicular sperm extraction that can be employed. Unfortunately, it is presently impossible to preserve the fertility potential of pre-pubertal patients. Due to the increasing numbers of adolescent cancer patients surviving treatment, extensive research is being conducted into several possible methods such as testicular tissue cryopreservation, xenografting, *in vitro* gamete maturation and even the creation of artificial gametes. However, in spite of its ease, safety, convenience and many accompanying benefits, sperm banking remains underutilized in cancer patients. There are several barriers involved such as the lack of information and the urgency to begin treatment, but various measures can be put in place to overcome these barriers so that sperm banking can be more widely utilized.

Keywords: Cancer; male infertility; sperm banking; fertility preservation

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Introduction

Advances in anti-cancer therapies and supportive care have led to increased survival rates in cancer patients (1,2), with 5-year survival rates surpassing 70% in children and adolescents (3). This has resulted in a shift of focus from merely lengthening the patient's lifespan to improving his quality of life (4,5). Fertility preservation is deemed an important aspect of post-treatment quality of life (6,7), especially since anti-cancer therapies are known to have gonadotoxic side effects (1,3). Approximately 15% to 30% of male cancer survivors lose their reproductive potential after treatment (2,6), causing much distress and unhappiness (8-10). Moreover, among those who recover, sperm parameters are likely to be reduced, thus having a negative impact on future fertility (3,11).

The World Health Organization (WHO) defines infertility as "the inability of a sexually active couple (at least three times per month), not using contraception, to achieve pregnancy within one year" (12). Since there is hitherto no cure for infertility, the only way to preserve male fertility is by sperm banking before treatment (4,5). Sperm banking involves sperm retrieval, usually by masturbation, and cryopreservation of the semen sample. Subsequently, the sample can be thawed and used in various assisted reproductive technologies (ART) to achieve pregnancy. Not only is sperm banking non-invasive and safe, but it has also been reported to be very effective (13). This option should therefore be offered to all patients before treatment commences because it is very difficult, if not impossible, to predict who will be rendered permanently sterile post-

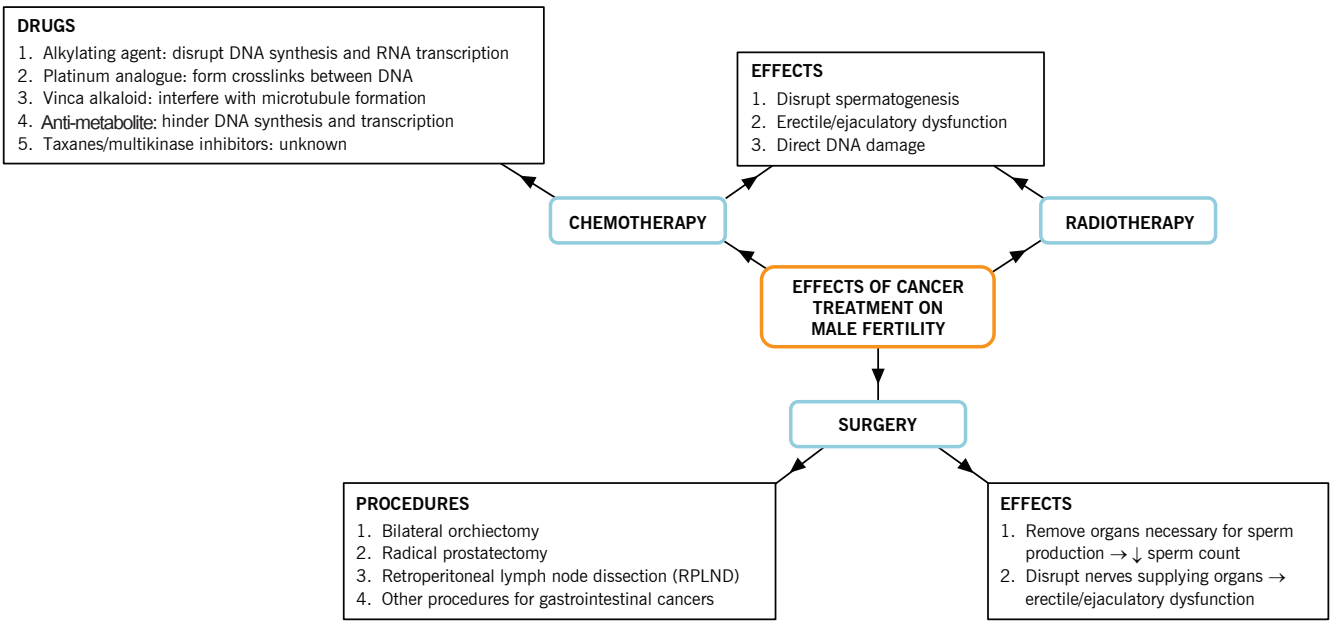

Figure 1 Effects of the three main modalities of cancer treatment on the male reproductive potential.

treatment (14,15). In fact, only 20% to 50% of patients regain their fertility within three years after treatment (16). At present, indications for sperm banking include, but are not limited to, couples who are physically separated (10,17), men with high-risk occupations (18,19), men about to undergo vasectomy (18,20) or potentially gonadotoxic therapies (17,20), sperm donation (21,22), and men with reproductive problems such as anejaculation, severe oligozoospermia and obstructive azoospermia (17,18).

In this review, we will discuss the effect of cancer and its treatment on male fertility, explain how and when sperm banking should take place, and explore current and future alternative strategies that can be employed should sperm be unobtainable due to the inability to masturbate or in cases of azoospermic and pre-pubertal patients. In addition, we will also elaborate on the benefits of sperm banking and possible barriers that may exist, resulting in the low utilization of sperm banking despite its effectiveness (23,24).

Effect of cancer and its treatment on male fertility

Cancer treatment involves cytotoxic chemotherapy, radiotherapy or radical surgical procedures (19,25), and these have the potential to affect one's reproductive capacity by impairing spermatogenesis, damaging sperm DNA, and/or causing erectile or ejaculatory dysfunction (3,26). An outline of these effects can be seen in *Figure 1*. The presence of cancer itself can also impair fertility, and this will be elaborated upon in the following section. Iatrogenic infertility caused by anti-cancer treatment can be temporary or permanent and differs in severity between patients (4). A myriad of factors—pre-existing defects, endocrine disturbances, type of cancer, and dosage and duration of treatment—contribute to the patient's likelihood of regaining fertility (27,28), making it practically impossible to predict who will be severely affected (11,29). Some patients may regain fertility in a few months' time while others may take several years, but usually with suboptimal sperm quality (16,30). To date, the most gonadotoxic regimen is the combination of intensive chemotherapy and total body irradiation in bone marrow transplantation procedures (25).

Cancer

The presence of cancer may affect a patient's fertility potential via different possible mechanisms even before any gonadotoxic treatment is given, and this is summarized in *Table 1* (16,36). Men with testicular cancer and Hodgkin's lymphoma are known to have impaired spermatogenesis and are likely to be oligozoospermic or azoospermic at the time of cancer diagnosis (29). It is also interesting to note that testicular cancer seems to affect the quantity, rather than the quality, of sperm produced (4). A study conducted

Table 1 Possible mechanisms by which common cancers in the male could impair fertility

Type of cancer	Effect on male fertility	Possible mechanism
Testicular cancer	↓ Sperm quantity > quality (4) ↓ Sperm DNA integrity and compaction (31)	Pre-existing defect due to flawed development of testes (32,33)
Hodgkin's lymphoma	↓ Sperm quantity and quality (29) ↓ Sperm DNA integrity and compaction (31)	Secrete β-human chorionic gonadotrophin (34)
Testicular germ cell tumours (TGCTs)	↓ Spermatogenesis (35)	Secrete β-human chorionic gonadotrophin (35)
Other tumours	Prevent proper sperm function (35)	Production of antisperm antibodies that bind to sperm (35)

by O'Flaherty *et al.* showed that sperm DNA integrity and compaction were compromised in patients with testicular cancer and Hodgkin's lymphoma before chemotherapy (31). Although the exact mechanism by which cancer affects semen quality is not known (19), it is likely that pre-existing defects due to flawed development of the testes could contribute to testicular cancer (32,33), while abnormal cytokine secretion in the presence of cancer could result in Hodgkin's lymphoma (34).

Cancer can also affect spermatogenesis via autoimmune, endocrine or systemic effects (5,17). For instance, testicular germ cell tumours (TGCTs) secrete β-human chorionic gonadotrophins, which depress spermatogenesis, while other tumours spur the production of antisperm antibodies, which could bind to sperm and prevent proper sperm function (35). Moreover, it has been established that the emotional stress experienced by patients who receive a diagnosis of cancer impairs spermatogenesis (5,30). It is therefore evident that cancer itself, prior to any treatment, can affect male fertility.

Chemotherapy

Chemotherapy regimens target proliferating cancer cells and thus, exert their effects on rapidly dividing spermatogonia as well (10,37). These drugs penetrate the blood-testes barrier and interrupt spermatogonial differentiation, hence hindering spermatogenesis (5) and causing oligozoospermia or azoospermia (38,39). Spermatogonial stem cells (SSCs) in the germinal epithelium, though comparatively less active, are also susceptible to permanent damage at higher doses (35,40). More mature germ cells such as spermatocytes and spermatids are less sensitive to chemotherapy because they have stopped dividing, and hence, the effects are only temporary. This may be the reason why some sperm can be found immediately after chemotherapy but gradually decrease in numbers over time (4). Due to their low proliferation rates, Leydig cells are relatively resistant to chemotherapy (35,36). However, there has been some evidence of damage to Leydig cells—increased luteinizing hormone (LH) levels with normal to low testosterone levels (41). In addition to disrupting spermatogenesis, cytotoxic chemotherapy may also contribute to erectile or ejaculatory dysfunction (42) or directly damage sperm DNA (10), resulting in the transmission of defective DNA and abnormal chromosomes to offspring (43).

The severity of damage depends most importantly on the type and total dosage of drug used, as well as the patient's age (5,42,44). As expected, a higher cumulative dose of drugs given over a longer time period will result in more extensive damage (8). Alkylating agents, such as cyclophosphamide, procarbazine and chlorambucil (45), are the most gonadotoxic drugs because they interfere with DNA synthesis and RNA transcription, thus causing new mutations that may lead to apoptosis (46). Cisplatin, a platinum analogue, is also equally harmful as it causes crosslinks to form between DNA (23,46). Whereas vinca alkaloids interfere with microtubule formation thereby preventing mitosis from occurring, anti-metabolites hinder DNA synthesis and transcription (46). Furthermore, different combinations of drugs are usually given simultaneously in chemotherapeutic regimens, thus making it more challenging to predict their additive effects on reproductive function (27,47). Unfortunately, the effect of newer drugs like the taxanes and multikinase inhibitors are still unknown (19,46), although there have been indications that when used as an adjuvant, taxanes may enable cyclophosphamide to become more toxic (25).

To combat this problem, less gonadotoxic alternatives or lower doses of drugs are used whenever possible (5,48). Also, since chemotherapy targets rapidly proliferating cells, it has been proposed that hormonal manipulation such that the hypothalamus-pituitary-gonadal (HPG) axis is suppressed may cause spermatogenesis to slow down or even

stop, hence protecting spermatogonia from the cytotoxic effects of chemotherapeutic drugs (16,49). In studies conducted on rats by Cespedes *et al.* and Kangasniemi *et al.*, the administration of flutamide and a luteinizing hormone releasing hormone (LHRH) agonist successfully prevented chemotherapy from damaging the germinal epithelium (50,51). However, both Johnson *et al.* and Fosså *et al.* had earlier found that the results could not be produced in humans (49,52). As such, hormonal manipulation is not clinically recommended for patients (53).

Radiotherapy

As in chemotherapy, the rapidly dividing cells in the germinal epithelium of the testes are most susceptible to damage and can be permanently destroyed by irradiation (17,48). Radiation doses as low as 0.1-1.2 Gray (Gy) can damage spermatogonia morphologically, hence preventing spermatogenesis from occurring (19,25,37). This can be caused by direct DNA damage or by disturbing the HPG axis (19,35). Exposure to 2 to 3 Gy permanently damages spermatocytes (46), giving rise to azoospermia (19), while doses exceeding 4 Gy generally affect the spermatids and cause an even longer period of azoospermia (5,46). Again, the Leydig cells are more resistant to radiotherapy (48,54) and are only affected by doses above 15 Gy (19,25). In addition, radiation may also play a role in causing erectile dysfunction (39).

The extent of damage depends on various factors such as the total dose, radiation source, field of treatment, and whether it is fractionated (37,54). A higher dose of radiation not only causes more damage, but also increases the time needed for recovery, if at all (5). Radiation damage occurs when radiotherapy is used directly on the testes in testicular cancer (35,36) but is more commonly caused by scatter radiation from radiotherapy directed at the lower abdominal and pelvic regions (38,55). Although lead shields are always used to protect the testes, some scatter radiation is inevitable and can often be extremely gonadotoxic (16,37). Hormonal manipulation via administration of gonadotrophin releasing hormone (GnRH) agonists was used to decrease the rate of spermatogenesis and to reduce the gonadotoxic effects of radiotherapy without success (56).

Surgery

Cancer surgery may decrease the patient's fertility potential if the organs necessary for reproduction need to be removed or the nerves supplying these organs are disrupted (42). In both cases, sperm counts decrease and erectile or ejaculatory dysfunction occurs (10,29). Bilateral orchiectomy in patients with testicular cancer will result in permanent azoospermia (38,55), whereas radical prostatectomy in patients with prostate cancer can lead to erectile dysfunction (38,39). Retroperitoneal lymph node dissection (RPLND) in testicular cancer patients may damage the autonomic pelvic plexus (4,46), causing retrograde ejaculation or anejaculation (55,57). However, nerve-sparing RPLND can be successfully carried out with the maintenance of normal ejaculatory function post-surgery (23). Other surgical procedures for gastrointestinal cancers in the lower abdomen and perineal regions may also damage nerves and affect ejaculation, resulting in infertility (4).

Process of sperm banking

The entire process of sperm banking is complex and involves many steps from the initial cancer diagnosis to semen collection, sperm cryopreservation and eventually, the use of ART to hopefully result in a pregnancy. This is illustrated in *Figure 2* and will be further elaborated on in the following sections.

Sperm retrieval

The first step of sperm banking involves collecting semen samples from patients by self-stimulation and masturbation (35,54). Not only is ejaculated sperm of the best quality, but masturbation is also inexpensive and safe (46). However, men must understand that masturbation cannot be carried out with lubrication, and that the entire ejaculate has to be collected in the sterile specimen cups provided (19). This is because the first part of the ejaculate usually contains the most sperm (30,35). Should the patient wish to masturbate in the privacy of his home, he must be instructed to keep the specimen at body temperature and bring it to the laboratory within the next hour (35). After collection, the samples will be left to liquefy at room temperature (22,30,58).

Men are usually encouraged to bank three samples with at least 48 hours of sexual abstinence between samples for maximal concentration of healthy sperm (14,19). However, patients with low sperm concentrations or poorer sperm parameters may be asked to provide more samples in order to pool a sufficient number of sperm for cryopreservation (5,35). In some cases, men who are unable to produce more than one sample due to urgency of treatment or health

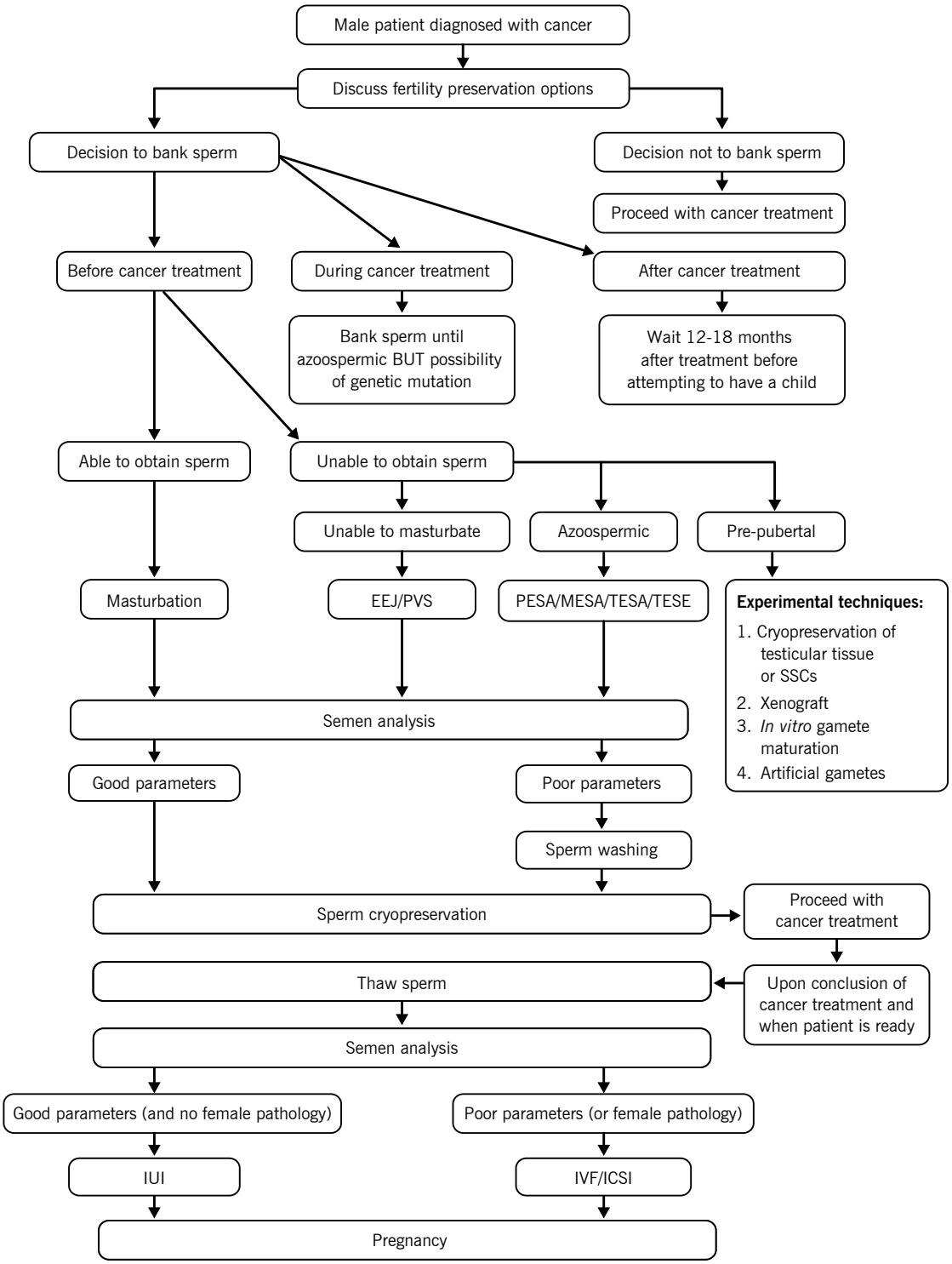

Figure 2 Algorithm showing the process of sperm banking from initial diagnosis of cancer to possible methods of sperm collection, followed by sperm cryopreservation and thawing, and depending on the sperm parameters obtained, its use in suitable assisted reproduction techniques. EEJ, electro-ejaculation; PVS, penile vibrostimulation; PESA, percutaneous epididymal sperm aspiration; MESA, microsurgical epididymal sperm aspiration; TESA, testicular sperm aspiration; TESE, testicular sperm extraction; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination.

reasons should still bank their sperm as more advanced techniques are now available that enable a single motile sperm to fertilize an egg (14,55). Finally, for patients who are unable to masturbate or produce viable sperm, other alternative options of sperm retrieval are available, and this will be expanded upon later.

Cryopreservation

After liquefaction and before cryopreservation, the semen samples are analysed and the colour, viscosity, and semen parameters such as sperm count, motility and morphology are recorded (4,22,55). In the event that a sample has poor sperm characteristics, the sample can be enhanced via sperm washing procedures like swim-up or density gradient centrifugation (35,46). Swim-up involves centrifuging the sample and adding culture medium on the top—only motile sperm will be able to swim up into the media. On the other hand, density gradient centrifugation involves centrifuging the semen sample on top of a density gradient, allowing only the motile sperm to move in the direction of the sedimentation gradient and thus forming a pellet at the bottom (10). Both these techniques will allow only healthy, motile sperm to be selected from the seminal plasma and other cellular debris, hence improving the sample's quality and concentration (10,35,46).

Cryoprotectant is then added to the sample to prevent the formation of ice crystals—inside or outside the cell—during cryopreservation (46). This is because cryoprotectants contain glycerol (and egg yolk), which helps reduce salt levels, decreases osmotic stress, and ultimately maintains the integrity of the sperm cell membrane (22). After equilibration, small aliquots of the mixture are frozen in separate vials for ease of thawing (16,25). Usually, an aliquot is frozen separately, then thawed and analysed again the following day. This 'test-thaw' will give a good indication of the quality of that particular semen sample after cryopreservation (4,22,35).

There are two methods for conducting cryopreservation—slow or controlled freezing and vitrification. With slow freezing, the most conventional and commonly used method, freezing medium is slowly added to the sample, which allows dehydration to occur during cooling (10). The vials are immersed in –20 ℃ for 15 to 30 minutes, then in –79 ℃ for another 15 to 30 minutes, and finally dipped into liquid nitrogen and stored at –196 ℃ until they are needed (10,30). These steps can be done manually or in a programmable freezer (10,35). Despite the effectiveness of this method, slow freezing takes up to 1.5 hours and exact protocols differ between labs (22,35).

In contrast, vials are quickly plunged into liquid nitrogen with vitrification (21), and this decreases the protocol time to five minutes (22). Vitrification completely avoids freezing, and consequently the formation of ice crystals, by causing the sample to form an amorphous solid state. However, vitrification is still a novel procedure and is not part of standard clinical practice (10,35).

In the process of cryopreservation, it is inevitable that sperm parameters will be drastically affected, especially that of motility (21,22). It is not uncommon to see a decrease in motility of 25% to 75% after thawing, and the acrosome structure and sperm nuclei may also be damaged (40,44). Furthermore, sperm concentration will be reduced due to dilution with the cryoprotectant (20). As such, in order to attempt a pregnancy, the vials may have to be pooled together to obtain enough viable sperm (5). Nevertheless, semen samples can be stored for up to 50 years in liquid nitrogen with no further damage incurred (59).

Use of sperm in assisted reproductive technologies (ART)

There are three main techniques used to achieve a pregnancy with thawed sperm—intrauterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). The decision to use a particular technique depends on the number and quality of thawed sperm available, female factors and individual preferences (19,35,40).

IUI is only used when the number of viable sperm post-thaw exceeds five million and the woman has at least one normal fallopian tube (35,60). In this procedure, a thin catheter is used to introduce the semen sample into the woman's uterus (55). Two inseminations—one given two days prior to ovulation and the other on the day of ovulation itself—are necessary to increase chances of fertilization because sperm can only survive for 48 hours in the female (30). In some cases where ovarian stimulation is also employed, a few IUI cycles are sufficient to achieve pregnancy in 15% to 30% of women (60).

On the other hand, IVF and ICSI are more rigorous techniques that are used when sperm count and/or quality is too low, both of which are commonly seen in cancer patients (3,25), or when the woman has some abnormality in her reproductive tract (38). In both IVF and ICSI, oocytes are removed from the woman and fertilized *ex vivo* in the laboratory (47). The fertilized egg is allowed to develop

into an embryo, which is then returned to the uterus to be implanted (55). In IVF, all motile sperm in the sample are added to the same petri dish as the oocyte in the hopes that fertilization will occur, but ICSI is more complicated (55). ICSI only requires a single viable sperm which will be directly injected into the oocyte (35,60). This circumvents the need for sperm to be of good quality and hence, patients are still encouraged to bank sperm even if there is a very small number of good quality sperm in the sample (9,20,26). In fact, this novel technique can also be employed to enable less mature sperm retrieved from the epididymis or testes to be of reproductive use (60). A study conducted by Chung *et al.* revealed that 75% of patients, including one with only a few motile spermatozoa, who attempted to father a child post-treatment were successful, thus lending credence to the feasibility of ART with cryopreserved sperm (61).

When sperm banking should occur

According to the American Society of Clinical Oncology (ASCO) [2006], "fertility preservation should be considered as early as possible during treatment planning" (6,62). Ideally, sperm banking should be completed before any potentially gonadotoxic treatment—chemotherapy, radiotherapy or surgery—commences (14,30,63). Patients who start on low-dose treatments should also be advised to bank sperm in case stronger treatment is indicated before their testes are able to fully recover from the initial milder gonadotoxic therapy (7,8). A study conducted by Ginsberg *et al.* reported that 60% of patients who banked sperm after treatment began were azoospermic (64). This highlights how susceptible the testes are to gonadotoxic treatments—even a single low dose of therapy can severely affect spermatogenesis (19,42). Moreover, providing semen samples before treatment also ensures that sperm DNA already affected by the cancer is not further damaged by therapy (5,20).

If treatment has already begun, patients can still bank their sperm until they become azoospermic (4,14). Although chemotherapy is capable of causing gene mutations, it is not known whether gonadotoxic treatments have any detrimental effect on existing sperm (11). However, animal studies have shown that young produced when the male is undergoing gonadotoxic therapy tend to have many genetic mutations (14). As a precautionary measure, preimplantation genetic diagnosis (PGD) is recommended when reproduction is attempted with sperm obtained during treatment (11). Therefore, it is safer to bank sperm before initiation of gonadotoxic therapy.

In cases where treatment has ended, patients are advised to wait 12 to 18 months before banking sperm or attempting to father a child (19,35,65). This is due to the fact that increased genetic and chromosomal abnormalities have been reported to last up to 18 months post-treatment (14,19,35).

What to do when sperm cannot be obtained

Unable to masturbate

Patients may find it difficult to masturbate due to physical, psychological, cultural or religious reasons (5). Some may be on medications or may feel too ill, stressed or anxious to perform the act (30,42,46) while others may have been brought up in a conservative environment in which masturbation is frowned upon by their culture and/or religion (19,55). Men with ejaculatory dysfunction due to spinal cord injuries, anejaculation or retrograde ejaculation are also unable to produce a semen sample (10,46).

In cases where oral sympathomimetics fail to result in ejaculation (14,19), electro-ejaculation (EEJ), penile vibrostimulation (PVS) or retrieval of sperm from post-coital urine can be carried out to obtain sperm for cryopreservation (27). EEJ is a painful procedure which is performed under general anaesthesia (1,35). A probe is inserted via the anus and placed against the anterior rectal wall. The application of electricity stimulates the prostate gland and seminal vesicles, causing ejaculation (35,42,55). However, EEJ should not be performed when patients are thrombocytopenic or leukopenic as the procedure may give rise to excessive bleeding or infection (4,55). Samples obtained by EEJ usually have a normal concentration but individual sperm are likely to have poor motility, morphology and viability (16,22). These samples are therefore more effectively used in IVF or ICSI rather than IUI (19,35). PVS is simpler and does not require anaesthesia (35). A vibrator is placed against the frenulum of the penis to stimulate the dorsal penile and pudendal nerves and cause ejaculation (35,46). However, this should not be used on boys who have not masturbated previously as it might have psychological side effects. As for patients suffering from retrograde ejaculation, sperm can be obtained from the urine after orgasm (5).

Azoospermia

As mentioned earlier, some patients are azoospermic even

before therapy commences because of the effects of cancer (42). Hence, novel techniques have been developed to extract sperm directly from the testes or the epididymis (5,25). For obstructive azoospermia, percutaneous or microsurgical epididymal sperm aspiration (PESA/MESA) can be carried out to obtain sperm from the epididymis. In cases of non-obstructive azoospermia, testicular sperm aspiration or extraction (TESA/TESE) must be carried out under anaesthesia to extract sperm from the testes (3,5,10).

PESA is the easiest technique because no microsurgical equipment or skill is needed. Under local anaesthesia, a 21-gauge butterfly needle is inserted into the caput epididymis and fluid is drawn up into the attached tube. This procedure is repeated until sufficient fluid is collected. However, due to the lack of visual guidance with a microscope, it is easy to inadvertently puncture blood vessels and cause bleeding (10,46). Alternatively, sperm can be extracted from the epididymis via MESA, and this is the preferred technique for patients with obstructive azoospermia (42,46). In MESA, patients are anaesthetized and the procedure is performed with the aid of an operating microscope. This allows for easy identification and directed insertion of the needle into individual epididymis tubules for aspiration of the fluid into a syringe. Again, this is repeated until sufficient fluid is collected (10,46). The fluid collected via PESA or MESA is then analysed and processed in the lab (10). Sufficiently motile and viable sperm can usually be obtained for ART via MESA (14,46).

In TESA, a needle is inserted into three different locations of the testes (upper, centre and lower segments) and the samples are extracted via negative pressure. The extracted fluid is then analysed for sperm in the lab (10). TESE is the more commonly used option for patients with non-obstructive azoospermia (46). After being cut transversely at its centre and at its upper and lower poles, each testis is then lightly squeezed so that some of the tissue bulges outward. The protruding tissue is excised, transferred into culture media, and sent to the lab to extract sperm cells (10,46). This technique can also be used in cases of testicular cancer where the testes have been removed from the body by orchiectomy (5,66). Sperm obtained from TESE can only be used for ART as only certain sections of the testes will contain sufficiently mature sperm (4,10).

A more recent improvement to TESE is microdissection TESE (mTESE). This technique uses microsurgical equipment to identify larger seminiferous tubules that are more likely to be active in spermatogenesis (10,46). Not only does mTESE minimize the loss of testicular tissue (especially in patients with atrophied testes), but it also prevents the accidental puncture of neighbouring blood vessels (10). Moreover, mTESE has been shown to be more effective than regular TESE, obtaining approximately 18% more healthy, viable sperm from the testes (5).

Pre-pubertal

Another subset of patients from whom sperm cannot be extracted from is pre-pubertal boys, whose reproductive systems have not begun spermatogenesis. There is currently no known method of preserving fertility in such patients, but research into various techniques is being carried out (25,54). These include the cryopreservation of testicular tissue or SSCs, xenografting gonadal tissues, *in vitro* gamete maturation, and the use of artificial gametes (20,25,47). Although results have generally been encouraging, there are still safety, ethical and legal issues that must be addressed before they can be implemented clinically (54).

Cryopreservation of testicular tissue or spermatogonial stem cells (SSCs)

Cryopreservation of testicular tissue or SSCs is the most promising method (5,67). This involves the extraction of testicular tissue, prior to gonadotoxic therapy, to be cryopreserved. When the patient desires to have children, the tissue can be thawed and re-implanted into the patient. Theoretically, SSCs will be recognized by the Sertoli cells and due to their innate ability to self-renew and differentiate, spermatogenesis will resume, restoring gonadal function to the patient (11,37,63). Otherwise, it is expected that by then, advances in technology will find a way to stimulate spermatogenesis from cryopreserved tissue or SSCs (5,35,54).

Furthermore, it was found that cryopreservation of testicular tissue instead of SSCs alone is more likely to preserve the natural function of SSCs. This is because freezing the tissue allows for the SSCs' surroundings to be preserved as well, hence maintaining the support system they need for proper functioning (5,46). At present, this method has only been successfully carried out in rodents and its use in humans is still experimental (11,19). In these animal models, spermatogenesis was successfully re-initiated when the SSCs were returned to the animal post-treatment (16).

Despite the advantages of this method, there are certain safety and ethical issues that need further consideration. Firstly, there is a possibility that in the process of returning thawed testicular tissue to the cured patient, malignant cells may be transplanted as well (14,47). To circumvent

this problem, it may be safer to isolate SSCs from the testicular tissue and only transplant those back into the patient (37,42,68). However, as explained above, this will compromise the ability of the SSCs to produce sperm. Alternatively, the SSCs can be allowed to mature *in vitro* and only the mature sperm will be used in ART (14,68). Another ethical issue is that the procedure may be too invasive for young patients who may not be of age to give consent for themselves (5,37).

Xenograft

Testicular tissue extracted from a patient may also be transplanted into a host animal to provide a suitable environment for sperm maturation, after which sperm can be extracted for use in IVF or ICSI (35,47). Nagano *et al.* showed that human SSCs were able to persist and proliferate in mouse testes (69), thus lending support for this method. However, in the use of sperm derived from xenotransplanted SSCs, there is a risk of interspecies transmission of animal DNA, viruses or infections to humans (11,47,54). Therefore, more measures have to be implemented to address these issues before xenotransplantation of gonadal tissue can be considered for clinical use.

In vitro gamete maturation

In vitro maturation (IVM) of SSCs is yet another method that may solve the problem of infertility in pre-pubertal cancer patients. As briefly mentioned above, SSCs extracted from the patient before treatment can be developed into mature sperm cells for IVF or ICSI (46,63). Although this removes the possibility of returning cancer cells to the cured patient, the full intricacies of the support network and environment of the cell culture required for proper maturation are hitherto not understood (37,47). As such, there are concerns about the possibility of improper sperm maturation and subsequent birth defects (5,37).

Artificial gametes

Finally, a newer technique that has been proposed is the creation of artificial gametes (47,70). Geijsen *et al.* showed that mouse embryonic stem cells can be manipulated in the laboratory to produce sperm cells (71). Nayernia *et al.* further demonstrated that these sperm cells could be used to produce live offspring. Unfortunately, the offspring in that study were unhealthy and died young (72). In addition to these safety issues, there are ethical concerns regarding the creation of artificial gametes that result in live births (47).

Benefits of sperm banking

Aside from the obvious benefit that sperm banking will preserve the reproductive potential of the patient after cancer treatment and enable him to have biological children (46,73), there are also many positive psychological and emotional effects that will aid the patient in coping with his cancer diagnosis (13,28).

Firstly, it is known that the loss of fertility is a significant cause of anxiety and distress in many patients, especially for those who have yet to complete their family (5,74). Knowing that they have cryopreserved sperm in case they are rendered infertile by treatment will assuage their worries and reduce their fears of being childless (16,20,38). Not only will this help them to cope better, but they will also have a better quality of life after treatment (15,75,76). Additionally, when a physician discusses sperm banking with a patient, this reinforces the belief in long-term survival and reassures the patient that his diagnosis is not fatal (54,73). With the mindset that they will eventually be cured of cancer, patients and their families will be more optimistic and cooperative in the treatment plan too (25). Moreover, in the midst of all the uncertainties and feelings of helplessness, sperm banking gives patients a sense of achievement and control over their lives (77). Therefore, it can be seen that sperm banking has many psychological and emotional benefits, and this is further supported by the fact that 80% of cancer patients who banked their sperm were happy with their decision (4).

Barriers that prevent sperm banking

Despite the relative ease and reliability of sperm banking as a method of preserving fertility potential and its accompanying benefits, it continues to be underutilized among cancer patients. For example, Babb *et al.* found that only 42 out of 79 patients' banked sperm, and only half of those who banked sperm proceeded to use their samples in ART (78). Furthermore, in a separate study where questionnaires were given to patients undergoing radical prostatectomies, only 20% of them wanted to bank their sperm although 84% of them felt there was a need for sperm cryopreservation to be offered (24). As such, this section will discuss the barriers that exist from the physician's and patient's perspectives as well as more general barriers such as legal issues and the fate of unused sperm.

Physician

One of the reasons that physicians fail to offer the option of sperm banking to patients is lack of time—both during consultation and before treatment begins. During consultation, the oncologist must not only break the news of the cancer diagnosis to the patient, but he must also explain the effects of cancer and the treatment required. With the tight schedule of a busy clinic, physicians have insufficient time to explain and discuss the issue of sperm banking with their patients (79-81). Additionally, there is often a need to start life-saving treatment as soon as possible and hence, physicians are reluctant to advise sperm banking, which will postpone treatment (48,57).

Many physicians also lack knowledge regarding sperm banking and its benefits as well as the facilities that are available for patients. Oncologists may not be aware of the latest developments in fertility techniques and do not have relevant education materials for the patient (9,18). For example, not knowing that only a single motile sperm is required in ICSI may cause physicians to prematurely dismiss a patient's suitability for sperm banking (38,62,82). Physicians also tend to underestimate the importance of fertility and subsequently leave it out of routine discussions with their patients (13,63). Moreover, oncologists are unaware of the nearest and most convenient sperm banking facilities that they can refer their patients to (57,59,83).

Another barrier faced by physicians is the sensitivity of the issue. Physicians may feel uncomfortable discussing fertility with their patients, especially with adolescents, and therefore choose to completely avoid the topic (13,45,82). Finally, the last barrier elucidated from interviews and surveys is the perceived high cost of sperm banking. Oncologists tend to overestimate the costs of sperm banking and therefore, knowing a patient's financial situation, may refrain from suggesting the option at all (59,81,83).

Patient

Even if sperm banking is offered, patients may not choose to take the option. The main reason cited is the lack of information (25% of interviewees) that hindered patients from making an informed decision (57,58,79). Even if patients proactively searched the Internet for information, Merrick *et al.* found that resources had incomplete information and were not reader-friendly in terms of design and language (84). As such, patients had insufficient information regarding the effects of cancer on fertility (18) and were equally uninformed about the procedure (45,83).

The next most common reason is patient uncertainty over the desire for biological children (especially for adolescents) (8), or the need for additional children, especially if they have already completed their families (78,79). Moreover, patients may be anxious that offspring produced from cryopreserved sperm will be abnormal, unhealthy, have birth defects, or have a higher risk of cancer (31,47,85).

Additionally, some patients fear that sperm banking will postpone life-saving cancer treatment (8,84,86), while others may feel too ill to provide a sample (6,8) or too stressed to make such a decision (30,38,77). Sperm banking is also often considered too sensitive for discussion, especially with adolescents (8,27,87), and is deemed to be immoral in certain cultures and religions such as the Evangelicals (8,27,75,88). Finally, some patients are unable to afford the cost of sperm banking (18,30,55), which includes freezing, storage, as well as the type of ART and the number of cycles required to achieve pregnancy (66).

General

It has also been found that very few patients return after gonadotoxic treatment to use their cryopreserved sperm in ART procedures. In a study conducted by Girasole *et al.*, only 3 of the 31 patients had used or were intending to use the sperm (23), while in another study by Menon *et al.*, a mere 2.2% of patients used their sperm (81). Tournaye *et al.* established the possible reasons for low utilization—recovery of normal reproductive health (41%), death of patient (37%) and no desire for biological children (7%) (11). Other suggested reasons include the fear that offspring will inherit the disease, uncertainty of their prognoses and the cost of ART (16,25,40). Moreover, some patients refuse to dispose of their sperm even when fertility was regained because they wanted it as backup should there be a relapse (73). With such low utilization rates, sperm banking appears to be a waste of resources, hence physicians and patients may feel it is unnecessary (85).

In cases of patient death, it is also difficult to determine if it is legal and/or ethical for surviving relatives to use sperm posthumously to produce a child (69). For now, this is only allowed if unambiguous consent to do so was given by the patient when he was alive (16,27,55). Moreover, laws regarding sperm cryopreservation differ across countries. For example, the United Kingdom and Canada allow donation and cryopreservation of gametes and embryos for young cancer patients, but more conservative countries like

Switzerland and Italy have outlawed procedures like gamete donation and embryo freezing (47). As such, complex legislations may hinder the process of sperm banking too.

How to overcome these barriers

Not all barriers are insurmountable. Other members of the oncology team, such as nurses can be trained to discuss fertility options with the patients and counsel and support them where needed (59,73). Additionally, appropriate and useful education materials using various platforms such as pamphlets, videos or interactive media can be designed to help patients make decisions about sperm banking (3,74,83). As previously highlighted, the introduction of ICSI eliminates the need for multiple samples of good quality to be collected (11). Hence, the collection of a single semen sample should not delay treatment significantly (57).

Physicians' lack of knowledge regarding fertility issues can be improved by education and training (6,55,82). A simple Internet search will identify the locations of nearby sperm banking facilities (6,59). Alternatively, some sperm banks provide cryopreservation kits that can be returned via post after the semen sample is collected at home. This makes the entire process very convenient and comfortable for the patient (6,19). Furthermore, in order to standardize the level of care provided by all physicians, protocols can be implemented for the discussion of sperm banking with patients (2,82). In fact, ASCO's recently updated guidelines state that all health care providers should be willing to discuss fertility preservation options and "present sperm cryopreservation as the only established fertility preservation method" as other methods are still experimental (53).

Although costs differ among banks, it is projected that the approximate annual cost of storing three ejaculate samples is between $300-$500 (6). A part of it may be covered by insurance, especially if the patient has cancer, and some banks also offer payment plans (6,59). To avoid awkward situations where adolescents are too embarrassed to talk about fertility in front of their parents, separate discussions should be conducted (59,74). Parents should also be advised on how to approach the topic with their children in an appropriate manner (1).

Conclusions and future directions

In conclusion, cancer and its treatment (chemotherapy, radiotherapy and/or surgery) can potentially impair fertility and therefore, it is important to cryopreserve sperm samples before any form of gonadotoxic treatment commences. In cases where sperm cannot be retrieved by the conventional method of masturbation, there are alternative techniques that can be employed such as EEJ, MESA and TESE. With the numerous benefits of sperm banking and its relative ease and convenience, more effort should be put into overcoming the barriers that prevent its utilization so that post-treatment cancer patients can enjoy a better quality of life. Most importantly, there is a need to increase awareness and knowledge of sperm banking among healthcare providers (physicians, nurses and counsellors alike) and the general public as the whole process requires extensive coordination between all parties (89). Also, more research is needed to develop techniques of preserving fertility in adolescent pre-pubertal patients.

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Footnote

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