Review Article

Oncofertility in sarcoma patients

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Abstract: Treatment for sarcoma can significantly decrease fertility, both due to the irradiation of gonads, and the impact of chemotherapy on gametogenesis. Infertility in cancer survivors causes significant regret and decreased quality of life in their adulthood. As this cancer mainly affects children and young adults, fertility preservation is an essential part of survivorship care, however it remains one of the least implemented services in adolescent and young adult cancer patients. Success of fertility preservation is highly dependent on the referral prior to oncologic treatment. Early patient counseling with possible consult with oncofertility specialists should be offered to every oncologic patient in reproductive age or younger. There are several options available and in continuous evolution for fertility preservation. Cryopreservation of sperm and oocytes constitutes nowadays the standard of care, and should be offered to all patients. Other methods currently under development will potentially bring in the future reliable options for fertility preservation in a wider range of patients, such as those in pre-pubertal age at the time of diagnosis, or with an insufficient sperm count for semen banking. These include testicular sperm extraction (TESE), autologous ovarian tissue transplant, and in vitro maturation of gametes. Novel therapies such as molecular-targeted agents offer a safer toxicity profile regarding fertility, but further research is required to evaluate their impact on the long term, both alone and in combination therapies. Difficulties to access fertility preservation and its costs remain a significant impediment for many patients in need. Warranting access to all sarcoma patients should be a priority in all healthcare professionals involved in their care.

Keywords: Sarcoma; oncofertility; fertility preservation

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Incidence of adolescent and young adult cancer has been rising over the last decades, and it is expected to continue to do so during the next. There are 640,000 cancer survivors aged 15 to 39 years old at this present moment in the USA (1). The improvement in treatment options and curation rates contributes to this increase in number, as overall survival rates currently range from an 85% in stage I to 10–20%, with great variation depending on the specific type of cancer (2). These encouraging results have some downsides: the side effects of the oncologic treatments, which constitute the reason behind the increasing attention paid to the patient care during survivorship. In this present review we will address the risk of infertility in sarcoma survivors that results from their treatment: the surgery, radiotherapy and/or chemotherapy they require for curation, can have a significant impact on spermatogenesis in males, or cause premature ovarian failure in females (3,4).

The term "oncofertility" was first used in 2006. It refers to the field of research and clinical care that responds to the specific needs of cancer patients regarding their present or future desire for reproduction (5). However, even before the term was coined, patient advocates were first calling for improvements in the field of fertility more than 15 years ago. The American Society of Clinical Oncology (ASCO) published the first guidelines recommending fertility preservation in 2006, and updated them in

2013 (6). The field of oncofertility aims to bring together oncologists and reproduction specialists, with the common goal of developing more and better reproductive options, and making clinically accessible to every patient the most appropriate one for him or her.

In a survey in a cohort of cancer patients without children, 75% revealed they would like to have them in the future (7). Oncofertility constitutes a real need for adolescent and young adult cancer patients. As most would not have yet started their own families, infertility carries for them significant distress on the long-term: infertility due to cancer and its treatment was linked to experiencing grief and a decrease in quality of life as late as 10 years after diagnosis (8,9). On the other hand, a study on female patients diagnosed with cancer on reproductive age showed that those who received counseling from a fertility specialist scored higher in standardized questionnaires validated to evaluate quality of life and satisfaction with life, and had lower scores on the questions quantifying long-term standing feelings of regret (10).

As aforementioned, the benefits of counseling cancer patients on the risk of infertility and the options oncofertility may offer for them are well documented, and the National Comprehensive Cancer Network practices guidelines on adolescent and young adult oncology acknowledge its relevance and encourages this practice. However, these same guidelines state that despite the known impact of infertility on quality of life, the practice of fertility preservation is far from widespread amongst oncologic patients, being its prescription and implementation in adolescent and young adult patients in the lowest rates of all oncologic services (11). The patterns evidenced studying the attitudes and practices regarding fertility preservation are characterized by an evident contrast between the knowledge and beliefs on the issue, and the actual clinical practice: 86% of medical oncologists think pubertal patients should be offered fertility preservation before their cancer treatment, but only 47% actually do so on half or more of their clinical encounters. Specifically regarding sperm banking, 92% of oncologists think this service should be offered to pubertal patients, but it is the 72% of them who actually do it half or more of the times. Seventy-three percent agree that pubertal cancer patients should be referred to fertility preservation specialists even if that option becomes available after they already have received oncologic treatment, but only 30% of them who makes the referral half or more of the times. About half of them never use the ASCO recommendations on fertility preservation, 80% uses them half or less of the times, and less than 10% do so on all their clinical encounters (12). Probably because fertility preservation is often more technically complex in female patients, studies show how this under-referral for fertility preservation is significantly more pronounced in women: in a study sample of 810 cancer survivors diagnosed from 2003 to 2007, 80% of the males discussed at some point with their provider the impact of their treatment on fertility in front of 48% of females. The option of undergoing fertility preservation was discussed with 68% of male patients and 14% of females, and while 54% of men used fertility preservation, only 2% of women did so (13).

The significant variation between opinions and actual application to practice regarding fertility preservation may respond to several reasons. From our own experience, it is mainly caused by practical difficulties to access this service in some institutions; and because in this clinical context of numerous acute health issues and focus on survival, it is sometimes relegated as a non-priority element of the patients' healthcare. As an emerging field, sometimes misconceptions of the actual process also contribute to this phenomenon, i.e., fertility preservation is time consuming and may unacceptably delay the care for urgent acute issues and life-saving treatment; pediatric patients are often too young to benefit from sperm or oocyte cryopreservation and thus do not need a referral to an oncofertility specialist, as neither do those patients undergoing a fertility-sparing chemotherapy protocol.

Sarcoma of soft tissues is the third more common cancer in children and young adults. It presents in a great variety of different histologic types, and can arise in any body location. Rhabdomyosarcoma is the most frequent type and accounts for almost half of the total cases (14). Sarcoma represents a 20% of the overall cancers of childhood, a 10% of the total cancers affecting adolescents and young adults, and the 7% of the overall cancer total in the USA population (15). The more common locations where sarcoma arises include tights, pelvis and retroperitoneum (14). This places the reproductive organs on a significant risk of being involved in the radiation field or scatter region during radiotherapy treatment. Radiation therapy modalities developed more recently, like intensity modulated radiation therapy, provide a more precise irradiation of the target region and better clinical outcomes, but cause a low-dose irradiation of larger areas (16). Such low doses are sometimes enough to impact fertility: 2 Gy of cumulative irradiation to the testicles are enough to affect gametogenesis in males. Additionally, pelvic radiotherapy can affect erectile function

in men. Treatment options for erectile dysfunction are numerous, ranging from pharmacologic oral or injectable treatment, to vacuum devices or surgically implanted penile prosthesis (17).

In females, the threshold of radiation dose with a toxic effect on the ovaries decreases with age (18), a phenomenon likely due to the natural decrease of the ovarian follicle reserve over time. For instance, an accumulated dose of 6 Gy places a significant risk of ovarian failure when administered to an adult, while doses up to 15 Gy are usually safe in the pediatric population. Although irradiation to CNS is uncommon in treatment of sarcoma, osteosarcomas can arise in bones of skull and jaw, and the most common location of chondrosarcomas, a subtype which represent a little less than one third of sarcomas, is in the spine. The location of this tumors makes them particularly challenging surgically, thus they need radiation in almost all cases. The required dose is a mean of 60 Gy for most chondromas, and up to 80 Gy to reach appropriate local control in chordomas of the skull base (19). Due to suppression of gonadotropin secretion by the hypothalamus-hypophysis axis, 40 Gy of irradiation to the central nervous system place more than an 80% risk of amenorrhea, and a 30–70% risk in radiotherapy doses equal to or higher than 25 Gy. In men, it may also suppress hormonal secretion from the pituitary gland, and cause the need for supplemental hormones like FSH and/or testosterone (20,21).

Systemic chemotherapy is often required in the treatment of high grade sarcomas, and it constitutes the main treatment for certain specific types of sarcoma such as Ewing's sarcoma and rhabdomyosarcoma. The main chemotherapy group known to decrease fertility in both male and female patients is the one constituted by alkylating agents (22): it is well documented how they inhibit spermatogenesis, causing long term azoospermia in men on a dose-dependent effect (23,24). Regardless of the efforts made to administer doses below the toxicity threshold, most current protocols include them in combination regimens. In this setting, toxicity of alkylating agents is additive and not yet fully determined (25). Other agents such as taxols and dacarbazine are considered safer, and usually causing azoospermia only temporarily. Their toxicity is however also additive when they are used with alkylating drugs in combination regimens (26).

As mentioned earlier, irradiation of pelvis or abdomen in female sarcoma patients decreases the ovarian follicle reserve. There is some degree of risk of infertility at any dose of radiation, which increases with the dose of exposure (22). Chemotherapy also impacts female fertility, as alkylating agents such as ifosfamide, commonly used in the treatment of sarcoma, have been associated to a high risk of amenorrhea and infertility (27).

This risk of infertility associated to the treatment for sarcoma must be disclosed to all patients, as it is essential information for them to make informed healthcare choices. If they have any interest in undergoing fertility preservation, or they wish to have some more information before making that choice, a referral to a fertility specialist must be done immediately. The consult should take place before initiation of treatment, as this will greatly increase the procedure's chance of success (6).

Oncofertility is in constant progress, and evolves to develop new fertility preservation options. Undergoing sperm banking before starting oncologic treatment is the most efficient and validated fertility preservation method for male patients, and it is easily accessible and available in more than 95% of the patients (28). When the referral is done before the start of treatment with systemic chemotherapy, in the vast majority of the cases viable sperm suitable for cryopreservation can be obtained by masturbation. Other options are available for those patients not able or willing to masturbate, including e.g., penile vibrostimulation and electro-ejaculation. In some rare cases where all these methods fail to provide semen containing sperm, testicular sperm extraction (TESE) is a surgical, more invasive but highly effective technique: microdissection TESE (microTESE) allows to directly examine the testicular parenchyma to identify the larger, more opaque seminal tubules where spermatogenesis is most advanced. Presence of viable sperm must be assessed in all samples by semen analysis, or direct microscopic examination of tissue (29). If it is absent in ejaculate, sperm can also be extracted with a testicular biopsy. This option can be a useful resource for sexually immature patient, as can be used for testicular sperm banking, a method still undergoing experimental development. Cryopreservation of testicular tissue for its transplant and growth *in vivo* is another potential option for pre-pubertal men, as long as they have normal testicular architecture. It has led to successful births in mice, but not in humans so far. Spermatogonial stem cells matured *in vitro* also can produce mature haploid spermatozoa to use with intracytoplasmic sperm injection (ICSI), a technique very successful for fertilization (30).

Conception will also require ICSI when the sperm is obtained from the testicle, of if there are very few sperm in the ejaculate. This is often the case in patients referred for

infertility after chemotherapy, whom often present non-obstructive azoospermia. TESE can be successful even after exposure to alkylating agents, but the success rate is a modest 20% in these cases (31). Some patients never recover spermatogenesis after chemotherapy, and will require sperm from a donor to achieve a pregnancy.

As mentioned, age is critically important in the case of female patients. Ovarian follicle reserve naturally decreases over time, and is additionally impacted by treatment of sarcoma. Again, it is essential to discuss the significant risk of infertility before starting the treatment, as well as informing the patient of the different fertility preservation options available to her (32). Again in this case, fertility treatments are significantly less successful for patients referred after having received cancer treatment, and they will often require oocytes from donors, or undergo a surrogate pregnancy (6).

Cryopreservation of embryos and oocytes are currently the most common fertility preservation options for women. Embryo cryopreservation is still the most successful and validated method, but it is complex and challenging at a practical level: it requires sperm from the partner or a donor, which might not be readily available to all patients, and it is rather unrealistic in very young or minor females (6). In such cases, cryopreservation of oocytes provides the best, more practical alternative. It is a more novel method but nowadays validated and no longer considered experimental. Accompanied with adequate counseling, current recommendations agree that it should be offered and recommended to all women undergoing cancer treatment with a potential risk of infertility, with a level B of evidence in such recommendation. It however presents a few downsides. Mainly, it only possible in post-pubertal women, and it consists in a fairly complex process requiring injection of FSH for retrieval of oocytes (33). The use of FSH and the need for frequent monitoring represent somehow inconveniences of the process. Additionally, FSH ovarian stimulation raises additional concerns regarding the theoretical risk of excessive estrogen levels and its associated complications: e.g., thrombosis, breast cancer and ovarian hyperstimulation syndrome. To evaluate the risk of breast cancer, an extensive metanalysis of smaller studies (34) and a cohort of 9,892 women followed up for a mean of 30 years (35) have been conducted. They both concluded that the use of gonadotropins to perform IVF is not associated with an increased risk of breast cancer (28). Regarding ovarian hyperstimulation syndrome, this was a severe complication seen with earlier ovarian stimulation protocols using HCG, especially in young patients with extensive ovarian reserve. More recent protocols have discarded the use of HCG and substituted it for FSH, significantly decreasing the time of exposure to estrogens, and therefore the risk of ovarian hyperstimulation (36) and the additional delay in cancer treatment that it carried (37). However, there still might be some rare situations requiring special measures regarding hyperestrogenism, such in females with thrombophilic syndromes, which may include use of anti-coagulants or transfusions (38).

Several groups have attempted to develop a method to prevent the loss of ovarian reserve due to oncologic treatment. It is based on maintaining fertility by temporary ovarian suppression with GnRH analogues. This principle is somehow controversial, but relies on the concept that "quiet" or less active follicles thanks to GnRH analogues, are less likely to be destroyed by chemotherapy. Some studies showed a higher chance to resume menses and ovulate after chemotherapy in those patients treated with GnRH agonists, by adding goserelin to their chemotherapy regimen. However, this approach has only been tried so far for breast cancer patients, and fertility data is still not available (39).

Preimplantation genetic diagnosis is nowadays an experimental method still undergoing validation trials, but there are a substantial number of successful cases reported worldwide. Its incorporation to screening of genetic cancer may eventually constitute an added benefit to the use of cryopreserved oocytes or embryos. This might be highly relevant in the context of sarcomas, as they can be the result of hereditary syndromes. Li-Fraumeni syndrome, Retinoblastoma and neurofibromatosis constitute the most well-known examples, but more recent research is showing germline mutations in up to 27% of sarcoma patients, suggesting germline testing for all patients with sarcoma might be warranted in the future (40).

Retrieval of immature eggs and their *in vitro* maturation is also still under experimental development, but constitutes a faster technique that requires little or none gonadotropin stimulation. Thus, it would further diminish the risks associated with the retrieval process: shorter stimulation time has advantages including less exposure to hyperestrogenism, and therefore lower risk of ovarian hyper-stimulation syndrome, lower total cost and duration of retrieval process. Further research is still needed to increase the success rate of this method that has not yet led to human births, and assess its long-term safety (41). Last but not least, the complete cycle of ovulation for egg

retrieval can take up to 4 weeks, placing a big concern on how fertility preservation can delay oncologic treatment in female patients. But more recently developed techniques, like natural cycle stimulation, are already available and can speed egg retrieval to take less than 2 weeks. In fact, in a cohort of cancer patients evaluated for treatment delay relative to fertility preservation, those referred for fertility preservation actually started treatment sooner than their peers (42).

Fertility preservation options for pre-pubertal patients are still experimental, but many have proved successful in preliminary trials. Cryopreservation and autologous transplant of gonadal tissue are promising techniques (6). Ovarian tissue banking is the only option in prepubertal girls, and has already led to more than 40 successful pregnancies worldwide. It consists in the surgical removal of ovarian tissue, and its autologous transplantation after completion of oncologic treatment. Additional advantages of this method include that it does not require ovarian stimulation or the intervention of a male partner, and the delay in start of oncologic treatment is minimal (43).

Regardless of the fertility preservation method of choice, the treatment for cancer may carry significant systemic toxicity. Therefore, the health of the cancer survivor will have to be thoroughly assessed prior to the use of cryopreserved oocytes or embryos. Consultation with a specialist in maternal-fetal medicine is recommended for that aim. If the survivor suffers sequelae of the toxicity that make pregnancy impossible or contraindicated, surrogacy may be a feasible option.

The future of oncofertility still presents challenges for the many different professionals involved. These include divulgation and education of health providers on the new and constantly evolving preservation options to offer to their patients; and evaluating the more recent oncologic treatments to determine how they impact patient's fertility; amongst many others. Regarding particularly the new chemotherapy agents that have shown to improve survival in sarcoma patients, evidence at the present moment points towards a safer, less toxic profile. These include DNA-binding drugs like trabectedin (44), and molecular-targeted agents like pazopanib and sunitinib, which inhibit angiogenesis through blockage of multiple kinases (45,46); and tyrosin-kinase inhibitors including crizotinib and imatinib (47,48). All these agents have been extensively studied in animal models, and so far generally show significantly less risk of infertility than conventional chemotherapy (49). However, all these agents have been in use for a limited time, and therefore long-term effects in humans are still unknown.

Providing access to oncofertility care to all oncologic patients still remains the biggest challenge. From the standpoint of its economic cost, it is relevant to note that most insurances still do not cover these services (50), which can be of prohibitive cost for patients paying out of pocket. Optimal care would include counseling on fertility preservation for all sarcoma patients prior to the start of their oncologic treatment. Oncology professionals have an important task making this issue visible, and lobbying for insurance coverage so more patients can afford them (51). Key concepts to make clear in this context include how iatrogenic infertility is a consequence of treatment in no different way as they are hair loss, nausea, vomiting or osteoradionecrosis. The harm is done in a different timing, but this does not make a moral difference. Sperm, oocyte and ovarian tissue cryopreservation are reliable solutions, nowadays validated and no longer considered experimental. And, in other clinical scenarios, procedures social and ethically just as complex are indeed covered by insurances (52). Nowadays, coverage of fertility preservation varies amongst different insurance companies, but many do not cover it, although there is no reasonable explanation to justify this lack. From a logistical point of view, the coordination amongst all the professionals implicated in oncologic care and fertility preservation can place a significant challenge and actually preclude its success. The implementation of a formalized male fertility preservation program at our institution significantly increased overall number and percentage of oncology patients offered fertility preservation consultations. Patients electing to cryopreserve sperm also increased significantly in both number and percentage, not only in sarcoma but across all cancer types. To put in place an effective program, assembling of the team is the first step. This will include obvious members like urologists, reproductive endocrinologists, Hematology and Oncology specialists, and laboratory staff. Less obvious participants include pediatric endocrinologists, urology nurses, oncology inpatient and outpatient nurses, urology phone receptionists, oncology inpatient unit clerks, billing professionals and psychologists. All of these individuals can help with the successful delivery of care, and any of these individuals can potentially disrupt care. An additional strategy that has proved successful in several large institutions to overcome the logistical complications of the process, is the incorporation of the figure of the patient navigator: a professional whose only

job is the counseling and multidisciplinary coordination of the oncologic patients interested in fertility preservation. In other words, to help the patients "navigate" through the fertility preservation process in the midst of their cancer treatment and all the aforementioned professionals necessarily implicated in it (53).

In conclusion, sarcoma treatment places a significant risk on fertility, and 40–100% of patients will experience some form of reproductive dysfunction as consequence of their cancer. Almost all treatments, including surgery, chemotherapy and radiotherapy; have the potential to alter reproductive function, which represents a major quality of life issue. With oncofertility counseling and intervention before treatment, up to 70% of patients can have improved functioning (8). Adult patients have successful and validated options available for fertility preservation, including sperm banking and oocyte cryopreservation. The goal for the healthcare professional in this patient population is to overcome possible biases and prejudices over who might want to use fertility preservation and who might not, so no patient misses the opportunity of this discussion. Pubertal adolescents can most times benefit from the same methods as the adult patients, and are just as well susceptible to the negative, long-term effects of cancer. Their main challenge is developing age and maturity level to make informed choices. Providers will need appropriate educational materials, and to be comfortable delivering the available information to patients. Finally, for the pre-pubertal patient, Technology is still in the process of developing reliable resources for their fertility preservation. Novel methods for preservation and maturation *in vitro* of immature testicular an ovarian tissue, and perhaps autologous transplant of gonadal tissue, offer promising preliminary results and should be discussed as experimental options. The hope is that one day these will be routinely used in clinical practice, and gonadal tissue will serve as a reliable source of sperm and oocytes.

Infertility has a non-negligible psychological impact on patients, and large percentages of cancer survivors wish to become biological parents. Current recommendations by ASCO include, after discussing fertility preservation with all patients if there is a risk of infertility and the appropriate referral to fertility specialist; to evaluate the need for psychosocial consult or intervention. If conventional fertility preservation options are not successful nor indicated, enrollment in clinical trials and registries should be encouraged (6). The entire team in care of sarcoma patients is responsible for the adequate counseling on fertility preservation, and offering the more suitable option for each particular case. An appropriate oncofertility care will largely impact the future quality of life of sarcoma survivors.

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Footnote

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