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Organ Sparing Surgery in Testicular Cancer

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Abstract: Testicular cancer is the most common cancer amongst young adult men. The gold standard of treatment for a testicular tumor is a radical orchidectomy, where the testis and spermatic cord are removed, however up to 50% of testicular pathology is benign and these patients are being overtreated. Organ-sparing surgery can be an alternative for patients with small, indeterminate testicular lesions and normal tumor markers. It can also be considered as an option for patients with tumors in a solitary testis, or where bilateral tumors are present. Combined with frozen section examination, tumors can safely be removed, and any residual disease identified intraoperatively. Organ-sparing surgery has safe oncological outcomes, with low recurrence rates on follow up data. It also provides a beneficial effect on the fertility and the hormonal profile of these patients. As these patients have a >95% survival rate, providing a high quality of life should be prioritized.

Keywords: guidelines for organ-sparing surgery of testicular cancer; organ-sparing surgery in testicular cancer; partial orchidectomy; risk factors for testicular cancer; testicular sparing surgery

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INTRODUCTION

Testicular cancer is the most common cancer amongst young adult men (1), though overall in the population, it is a relatively rare cancer. The incidence has however been increasing over the past 40 years, affecting mostly the Caucasian population in Western countries (1). The majority of testicular cancers are germ cell tumors, either seminomas or non-seminomatous subtypes, and other benign and malignant tumors also exist. Testicular cancer is commonly associated with cryptorchidism, or maldescent of the testes, which carries a two-to-four-fold increase in the risk of developing a malignancy (2). Other risk factors include previous testicular tumor, high levels of maternal estrogen in utero, advanced maternal age, the presence of carcinoma in situ (2) or a testicular tumor in a first degree relative (3). Tumors are diagnosed with an ultrasound scan, which is easily available and quick to perform. With improving imaging modalities, ultrasound scans can detect smaller lesions within the testes including those which are impalpable, with a pick-up rate up to 7.4% in lesions of 10–15mm (4). Contrast-enhanced ultrasound has also improved the characterization of small testicular masses (5), though it is unable to definitively identify whether a lesion is benign with a standalone test. Tumor markers (alpha fetoprotein, human chorionic gonadotrophin, and lactate dehydrogenase) are used alongside imaging to aid the diagnosis of testicular tumors. They also guide disease management after surgery, and are used for cancer surveillance, as elevated tumor markers levels post-surgery are indicative of residual, metastatic disease, even if it is not evident on imaging (6).

The current gold standard of treatment for a testicular tumor is a radical orchidectomy, where the spermatic cord and testis is removed to the level of the internal inguinal ring. However, 10- 50% of testicular histology is benign (3, 6), therefore radical surgery may be overtreatment for these patients, especially those with small testicular masses. Radical orchidectomy can result in subfertility, necessitate lifelong androgen replacement therapy, and have a severe psychological impact on these young patients. Organ sparing surgery (OSS) has been well practiced in urology, most notably in renal cancer patients with partial nephrectomies. The first OSS for testicular cancer was performed by Seppelt in 1982, in a patient with a testicular tumor who had previously undergone a radical orchidectomy (7). Unfortunately, the testes had to be removed six weeks later due to infection, but no residual cancer was present in the specimen (7) which proved OSS was feasible. In 1984, Richie performed OSS in a patient with bilateral testicular tumors, in a procedure he called ‘unorthodox’, and the patient was disease-free at 2.5 year follow up (8). Since then, OSS has been considered an option for testicular tumors to preserve testicular endocrine and exocrine functions (3). However, there is no clear consensus on which patients are eligible for this surgery, though recommendations do exist in many urological guidelines. Specific patient and tumor factors influence whether OSS can be considered for a particular individual. Aside from patient factors, consideration also needs to be given to where this surgery is performed as surgeons require sufficient operative experience and need appropriate availability of additional intraoperative diagnostic tools to perform a partial orchidectomy. Patients with testicular cancer have >95% five-year survival rate (6), so the long-term morbidity implications of radical surgery need to be considered; however, this needs to be in balance with providing safe oncological outcomes. The surgical management of testicular cancer should reflect the longevity of these survivors and

should consider the impact on quality of life, potential effects of the hormonal profile of the testes, and the impact on fertility. This chapter describes which patients are eligible for OSS, summarizes the current testicular cancer guidelines, explains the surgical technique of a partial orchidectomy, presents the outcomes of OSS, and finally provides key take home messages for urologists.

PATIENT ELIGIBILITY

There is a lack of consensus regarding which patients are eligible to be considered for OSS. Testicular tumors may be malignant or benign in nature; however, it is only possible to determine this for certain with histology once the tumor has been removed. Percutaneous testicular biopsies are not routinely performed due to the risk of cancer seeding as a result of scrotal violation (9). Palpable tumors have been shown to be malignant in up to 90% of cases (10). If there is a confirmed malignant germ cell tumor present, in almost all cases, the adjacent tissue will contain carcinoma in situ (CIS) (10), also known as tubular intraepithelial neoplasia. CIS is a precursor to testicular cancer, which has 70% risk of transforming to a testicular tumor within 7 years (11). Patients should therefore only undergo OSS for a malignant germ cell tumor in specific circumstances. These patients should be recommended low dose adjuvant radiotherapy, close surveillance, or radical orchidectomy if CIS is present (11). Radiotherapy and a radical orchidectomy will affect any potential of fatherhood, so if the patient wants to preserve fertility, this can be delayed, but close observation with ultrasound is mandatory (11). Epidermoid tumors, which are a subtype of germ cell tumors, are benign and are not surrounded by CIS (12) and therefore, OSS is safe option for these patients.

There has been increased detection of impalpable, small testicular masses in recent years due to advancements in imaging, which are predominantly benign (80%) (10), with Leydig cell tumors being the most common (13). A multicenter randomized controlled trial from France collated all cases of Leydig cell tumors between 1986–2014 and randomized 56 patients to radical orchidectomy or OSS. They found no difference in disease free survival between groups, demonstrating that OSS is a viable option for these patients (14). As well as tumor factors, there are also patient factors that need to be taken into account. For patients to be considered for OSS, they need to have normal preoperative testosterone levels and the tumor volume needs to be less than 30% of the testis (10), so that a sufficient amount of the testicular parenchyma can be preserved for endocrine and exocrine function for the surgery to be beneficial.

The major urological committees, including the American, European, and Canadian associations, have all produced guidelines for testicular cancer and these include recommendations for patient selection for OSS. A summary of these guidelines is shown in Table 1.

American Urology Association guidelines for OSS

The American guidelines do not recommend OSS for a suspected malignant tumor. They specify strict criteria for which OSS may be considered, these include: a mass <2cm, indeterminate findings on ultrasound, negative tumor markers

TABLE 1 **Summary of patient eligibility criteria for organ-sparing surgery for testicular cancer according to Urological Association Guidelines (European, American, and Canadian)**

Patient factors	Tumor factors
Normal levels of testosterone pre-operatively	Size <2cm
Solitary testes	Bilateral synchronous tumor
	Indeterminate findings on ultrasound
	Normal tumor markers

(alpha fetoprotein and human chorionic gonadotrophin), solitary testis, or bilateral synchronous tumors. If OSS is used, they state that patients should be informed of: a higher risk of local recurrence, strict monitoring with ultrasound and clinical examination, the need for radiotherapy to reduce the risk of local recurrence, the impact of radiotherapy on sperm and testosterone production and the risk of testicular atrophy, altered fertility and potential need for testosterone therapy (15). It is also recommended that when the tumor is removed, multiple biopsies of the surrounding tissue should be taken for histology with an experienced pathologist (15) to assess the presence of residual disease.

European Association of Urology guidelines for OSS

The European Association of Urology guidelines state that testicular sparing surgery is an acceptable treatment option in patients with suspected benign tumors, or indeterminate masses with negative tumor markers. They maintain that a radical orchidectomy is the gold standard of care in patients with a likely malignant testicular tumor. However, testicular sparing surgery can be considered in patients with synchronous bilateral tumors or tumors in a solitary testis, but it should only be offered in combination with frozen section examination. Patients should be aware that limited data exists on the safety of OSS oncologically, and local recurrence rates are up to 26% (16). Patients should also be informed of the risks of requiring radiotherapy should the histology show evidence of CIS. They also state that OSS should only be carried out in experienced centers (11).

Canadian Urology Association guidelines for OSS

The Canadian guidelines are very clear that a radical orchidectomy should be performed for patients with a testicular tumor. They do state that in 'very rare cases', where there is the possibility that the tumor is benign, an excisional biopsy of the tumor can be performed with the use of frozen section. They recommend considering OSS in 'very select patients', who have bilateral synchronous tumors or solitary testis, with normal testosterone levels. If OSS is performed, it should be done by an experienced surgeon and patients should be informed about the risk of requiring radiotherapy should CIS be discovered. Patients should also be counselled on the need for testosterone replacement and the effect on fertility (17).

OSS for malignant germ cell tumors

It can be summarized from the guidelines that the use of OSS in malignant cases should be reserved for patients with bilateral synchronous tumors, or a solitary testis. OSS is therefore not recommended for patients with a ≤2cm likely malignant tumor, with a normal contralateral testis. The largest series to-date of patients who underwent OSS with malignant germ cell tumors is from the German testicular cancer study group. They performed OSS in 101 patients with bilateral tumors, or in a solitary testis. The procedure was performed in eight high-volume centers and the average size of the tumor removed was 15mm (5–30mm). They found concurrent CIS in 84% of the patients, and 79% of these patients underwent radiotherapy, the others underwent surveillance. The main consideration for patients considering OSS is the presence of CIS, which will progress to invasive disease without treatment, hence detailed patient involvement and pre-operative counselling is paramount.

OSS in the pediatric patient

All recommendations mentioned thus far are for the adult population. However, pediatric patients are also at risk of developing testicular tumors, though they are rare, only accounting for 1–2% of all childhood tumors (18). The majority of these are benign, with teratoma being the most common type (19). Teratomas in pre-pubertal boys act in a benign way, unlike in the adult population and are not associated with CIS (20). The most common malignant tumor in the pre-pubertal pediatric patient is a yolk sac tumor, 90% of which will have an elevated alpha fetoprotein level which makes it a very sensitive diagnostic test for these tumors (19). The post-pubertal patients are more likely to have a malignant tumor and therefore OSS is not recommended in this cohort. As with the adult population, the gold standard for treatment is a radical orchidectomy but as the majority of tumors are benign, the implications of testicular removal in such a young patient, who is still developing, should be considered. OSS in the pediatric population is lacking long-term follow-up data, and therefore any divergence from the guidelines should be taken with caution. If OSS is performed for benign tumors, it should be done using intraoperative frozen section as this is proven to correlate well with final histology (19).

SURGICAL PROCEDURE

Testicular sparing surgery has been performed since the 1980s. It was progressively developed until 2002, when Hopps and Goldstein finalized the technique with the addition of intraoperative ultrasound and the use of a microscope to remove non-palpable tumors (21). Tissue diagnosis was confirmed intraoperatively by frozen section (21). The majority of cases reported in the literature are performed macroscopically, with the use of ultrasound for localization of the tumor (13). There is a limited description of the microsurgical technique, for the non-palpable tumors, where a microscope is used to localize the tumor (13). An added benefit of the microsurgical method allows the concurrent extraction of sperm for patients with fertility issues (13). There is no reported comparison of

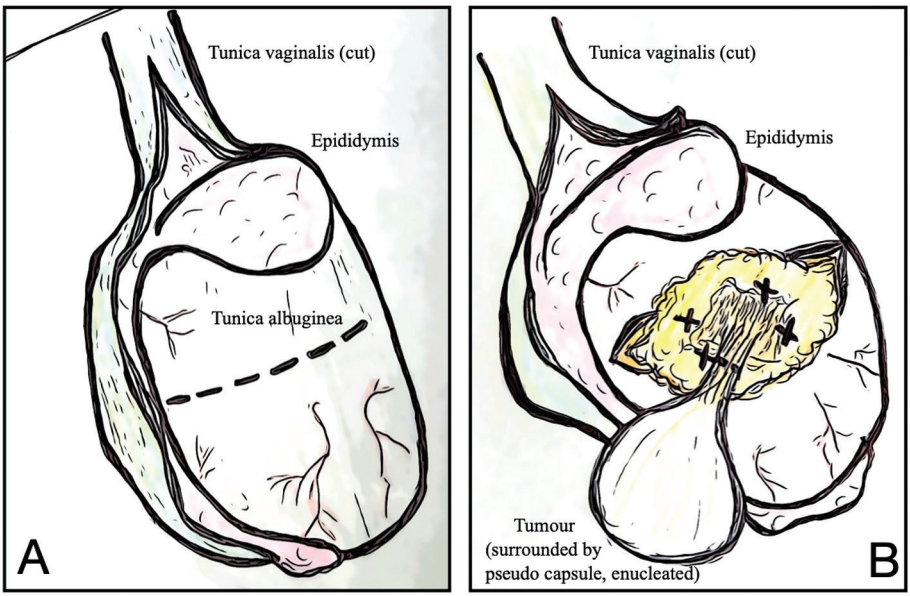
the two techniques and therefore surgeons performing the procedure should choose the technique in which they are most skilled. A recommendation which was imperative in the guidelines, was that partial orchidectomy surgery should only be performed in high volume centers, by experienced surgeons. Urologists should therefore be mindful that it is an option for select patients, even if it is not offered locally and should refer their patients appropriately after multidisciplinary discussion.

Pre-operative assessment

All patients identified with a testicular tumor should have a full work-up alongside the ultrasound scan, which include tumor markers, and a CT scan of the chest, abdomen and pelvis (11). All patients should have a baseline testosterone measurement and if it is normal and the patient is appropriate, they can proceed to OSS (11). All patients should be offered sperm banking prior to OSS, as there is the potential of subfertility following surgery. Patients should be counselled thoroughly before OSS about the risk of residual disease, need for adjuvant therapy if CIS is discovered, the potential limitations of frozen section examination, and the need for close follow up and monitoring (3).

Surgical technique

Partial orchidectomy should be performed through the standard inguinal incision, in the event that a radical procedure would need to be performed and to avoid the involvement of the scrotum (3). There is no clear evidence for cord clamping in a partial orchidectomy and the majority of authors do not advocate this as there may be damage to the testis through by compromising the vascular supply (10). A series of 65 patients in Austria, by Leonhartsberger et al., showed that 'no-clamping' technique had disease-free results at 50-month follow up in all patients (22). The delivered testis should be placed well away from the incision to avoid contamination should the lesion be malignant (9). Some authors advocate the use of cold ischemia with the testes being placed on ice at this time (10); however there is no clear evidence that this is advantageous (22). The main consideration should be for operative time and the excision of the tumor should not take longer than 30 minutes, as there are proven morphology changes to the Sertoli cells after this duration of time (22). The tunica vaginalis should be opened to expose the tunica albuginea and the tumor located if palpable (Figure 1). The tunica albuginea should then be opened over the tumor, in a transverse incision to identify an avascular plane (23). Once exposed, the tumor should separate easily from the normal parenchyma due to the presence of a pseudocapsule covering it; if it is difficult to extract, this can indicate malignant infiltration (24). If the tumor is impalpable, an ultrasound probe or a microscope can be used to identify the lesion and a 2–5mm excision margin should be removed (10). The tumor and additional samples taken from the tumor bed, should be sent for frozen section examination to identify histology, presence of CIS and surgical margin positivity (24). If the histology shows a benign lesion, the incision site in the testis should be irrigated and then the tunica albuginea can be closed with a running suture and the testis replaced in the scrotum (25).



A: Dotted line where incision to be made in tunica albuginea overlying tumour

B: Shows cut tunica albuginea, tumour enucleated. 'X' marks the site for biopsies of tumour base

Figure 1 **Partial orchidectomy surgical technique for excision of tumor.**

Role of frozen section for OSS

Frozen section examination is an integral part of OSS, and if it is unavailable intra-operatively, the surgeon should not perform a partial orchidectomy. When it was initially used, there were concerns about small, insufficient samples providing inaccurate histology results (26), but it has been shown to be a highly reliable method of analyzing testicular tumors. Of note, Elert et al. proved that in a large series of 354 patients with testicular tumors, frozen section was 100% sensitive and 100% specific, meaning all patients with malignant tumors were identified (27). A recent review article of all studies using frozen section in OSS, included 1052 patients, and they showed that <1% of malignant tumors were diagnosed as benign and required a completion orchidectomy at a later date (26). The quoted positive predictive value was 98% (26), meaning that frozen section use intraoperatively is a valuable tool in indeterminate, likely benign testicular lesions, with normal tumor markers. It can be safely used to prevent patients with small, benign tumors having unnecessary radical orchidectomies (28). The main limitation with frozen section is from interpretation of the histology and therefore an experienced urological pathologist with experience in testicular tumors is required.

Complications of OSS

Patients who undergo OSS have different risks and complications from those undergoing a radical orchidectomy. There can be concerns regarding the viability of the

testis after OSS and reported rates of postoperative testicular atrophy can occur in 3–5% of patients (25). This can consequently affect the endocrine function of the testes and account for late onset hypogonadism (25); however, the cases reported in the literature are attributed to poor selection of patients and unfavorable surgical technique (11). There is also some suggestion that handling of the vas deferens can lead to inflammation and chronic obstruction of the vas, which can contribute subfertility (22). In patients where a malignant tumor has been removed, there is a high chance of residual CIS and therefore it is recommended that patients undergo radiotherapy if they wish to preserve the testis. However, the patients should be aware that in a solitary testis, this will result in infertility and patients may choose to postpone their treatment until their family is complete (29). There is also evidence that local radiotherapy can impair Leydig cell function and up to 40% of patient will require exogenous testosterone supplementation, regardless of the radiation dose (29).

OUTCOMES OF ORGAN-SPARING SURGERY

Radical orchidectomy can be regarded as over-treatment of small testicular tumors and therefore OSS should be considered as an alternative for all appropriate patients. Testicular cancer survivors have a long life expectancy and providing a high quality of life for these patients should be prioritized. Testicular tissue preservation can maintain the endocrine function of the testes, so that patients do not require testosterone supplementation, and there are also benefits from a fertility perspective. However, there are concerns regarding the oncological outcomes of this surgery, due to the presence of residual CIS. The data is promising, as survival rates of OSS for testicular cancer are reported in the literature between 80–100%, with the vast majority being 100%, and recurrence rates between 0–15.9% (25). The current literature on this is summarized below, and the take home message for urologists is summarized in Table 2.

TABLE 2 Take home messages for urologists

Organ sparing surgery for testicular cancer

- OSS is not advocated for testicular tumors which are suspected to be malignant, except in patients with a solitary testis or bilateral tumors
- OSS is an option for patients with lesions <2cm with normal tumor markers, and indeterminate findings on ultrasound who wish to preserve testicular tissue
- Partial orchidectomy should be carried out alongside frozen section examination by an experienced surgeon and pathologist
- Patients who undergo OSS should be aware of the need to undergo radiotherapy to prevent disease recurrence should residual CIS be present and of the implications of this on their fertility and hormonal status
- Survival rates of OSS for testicular cancer are reported in the literature between 80–100%, with the vast majority being 100%, and recurrence rates between 0- 15.9%
- Fertility can be altered by the presence of a testicular tumor alone and therefore all patients undergoing OSS should still perform sperm banking preoperatively
- OSS performed for benign lesions does not affect patient's testosterone levels

Oncological outcomes

OSS is only recommended for malignant tumors in a solitary testis, or if the patient has bilateral testicular tumors, which is a relatively small patient subset. Therefore, there are only small numbers of patients included in studies who have undergone OSS for a malignant tumor. A meta-analysis in 2020 collated 201 patients with germ cell tumors who had OSS and quoted a local recurrence rate of 7.5% and positive margin rate of 1.4% and concluded that OSS is a safe option in malignant tumors (30). The largest series of patients with germ cell tumors were the 101 patients from the German testicular cancer study group. Their results showed that after a median of 80 months follow up (4- 191 months), 99% of patients were disease free. There were 67 patients who underwent radiation for CIS and two (3%) of patients developed disease recurrence and were successfully salvaged with radical orchidectomy (31). Hiedenreich et al. performed OSS on 73 patients with tumors bilaterally and in a solitary testis, with follow up over a period of 91 months. They found 98.6% of patients had no evidence of disease and one patient died of tumor progression (32). Steiner et al. had a series of 30 patients, 11 of whom had germ cell tumors removed by OSS. Only one of these patients developed disease recurrence, who chose to avoid radiotherapy, and required a radical orchidectomy at a later date (33). All patients were disease free at 46.3 months follow up (31). Bojanic et al. performed 26 OSS on 24 patients with germ cell tumors and found that seven patients developed disease recurrence after an average of 20 months (34). The majority of these patients (71%) underwent radical orchidectomy, however the remaining patients had repeat OSS due to small tumor sizes (5mm and 6mm) and there was a 100% survival rate of all patients (34). However, as mentioned, these studies only include very small patient numbers and there is a lack of evidence on long term follow up of OSS patients with malignant tumors. CIS is shown to recur after several years, but current limited follow up data is only available so longer term follow up will aid in the validation of OSS for these patients.

Fertility outcomes

Fertility should be given careful consideration for testicular cancer patients, as this cohort is the prime age to start having children. It has been noted that for a patient undergoing a radical orchidectomy, there is a significant decrease in spermatogenesis, with some patients being azoospermic after surgery (35). There is likely a genetic association between testicular cancer and impaired spermatogenesis (35) and most men with tumors have abnormal semen analysis preoperatively (13) meaning it is even more vital to preserve as much testicular tissue as possible. There is however limited data available on fertility after OSS (13) and the largest trial to date to record semen parameters after OSS for benign lesions, found no significant decline postoperatively (36). There is no direct comparison of radical surgery and OSS yet conducted and only a small proportion of the current literature reports on postoperative semen parameters. Sexual function can also be altered by body image. In a survey of 234 testicular cancer patients, 96% responded that it was important for self-confidence to have two testes present in the scrotum (37), which OSS can maintain. Preoperative sperm banking should be undertaken in all patients with testicular cancer. If OSS is performed to aid with

fertility, surgeons must be wary of the 30 minute dissection time to preserve Sertoli cell function and postpone radiotherapy if CIS is present, with close monitoring until their family is complete (35).

Hormonal outcomes

Changes in reproductive hormones are well documented after orchidectomy. This should be an important consideration in testicular cancer patients as they are young patients, with long term survival rates. As hypogonadism can cause a decrease in lean muscle mass, poor libido, altered glycemic control and lipid control (38), OSS should be favored where possible. Hormonal changes after OSS are reported in 22 studies to date (13), the largest being the German study group with 101 patients; 9.7% of which had low testosterone levels after 80 months (31). However, most (79%) of these men had radiotherapy and it should be noted that patients who underwent OSS for benign lesions, who do not require additional therapy, did not have any testosterone deficiency (13). Results from the meta-analysis of germ cell tumor patients showed that 2.8% patients had postoperative testicular atrophy and 7.8% patients required testosterone replacement after their OSS (30). An assimilation of case reports showed the majority of OSS patients after 93 months follow up did not require testosterone supplementation and they reported satisfactory sexual function (10). An analysis of hormonal function and bone metabolism in testicular cancer patients found that 19.5% of men who underwent a radical orchidectomy displayed low serum testosterone and 50.6% demonstrated evidence of bone damage (osteopenia and/or osteoporosis) on DEXA scans (39). This again highlights the importance of preserving testicular tissue to maintain normal hormone levels for the patient's long-term health benefit. The cardiovascular health of testicular cancer survivors has also been shown to be negatively impacted and is thought to be due to hormonal alterations of surgery. A study of over 2500 patients over a period of 18 years in the Netherlands, showed that testicular cancer survivors had double the risk of myocardial infarction compared to the general population (40).

CONCLUSION

OSS is a safe option for patients with indeterminate, small testicular lesions and, should also be considered an alternative for patients with bilateral tumors, or tumors in a solitary testis. OSS provides the patient an option in the management of testicular cancer, where radical treatment would leave them infertile and dependent on exogenous testosterone replacement therapy. OSS can be a safe alternative, combined with frozen section and adjuvant treatment with radiotherapy in the presence of CIS, which shows excellent oncological control of testicular cancer.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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