Role of testis-sparing surgery in the conservative management of small testicular masses: Oncological and functional perspectives


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KEYWORDS
Testicular neoplasms; Small testicular masses; Radical orchietomy; Testis-sparing surgery; Oncological outcomes; Functional outcomes

Abstract
Introduction: Radical orchietomy (RO) is still considered the standard of care for malignant germ cell tumours, which represent the vast majority of the palpable testicular masses. In those patients diagnosed with small testicular masses (STMs), testis-sparing surgery (TSS) could be an alternative treatment to RO. The aim of this updated review is to evaluate the current indications for TSS, and discuss the oncological and functional results of patients who had undergone organ-sparing surgery for STMs.

Evidence acquisition: A non-systematic review of the Literature using the Medline database has been performed, including a free-text protocol using the terms "testis-sparing surgery", "testicular sparing surgery", "partial orchietomy" "testis tumour", "sex cord tumour", and "testis function". Other significant studies cited in the reference lists of the selected papers were also evaluated.

Evidence synthesis: No randomized controlled trials comparing TSS with radical orchietomy have been reported yet. In those patients with normal contra-lateral testis, the use of TSS is still controversial. In selected cases of gonadal masses <2 cm, TSS seems to be a safe and feasible treatment option. Frozen section examination allows us to discriminate between benign and malignant neoplasms during TSS. Intermediate and long-term follow-up results showed no significant risk of local and distant recurrences in the main series reported in the literature.

Conclusions: TSS is an effective treatment for STMs in selected patients, limiting the unnecessary surgical over-treatments, without compromising the oncological and functional outcomes. Further studies are needed in order to confirm the oncological safety.

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Introduction

Testicular cancer accounts for about 5% of all urological tumours, with an estimated incidence of 3–10 new cases occurring per 100,000 males/year in Western countries.1 Radical orchiectomy (RO) is still the standard of care for solid, palpable, symptomatic testicular masses,2 which demonstrated to be malignant in the vast majority of cases at the definitive histological examination. However, a radical surgical management could be considerably disabling in those patients with bilateral testicular malignancies or congenital monorchidism, in which a definitive treatment by RO is associated with androgen deficit and infertility, and the detrimental functional effects have been widely documented.3 Substantial late-appearing endocrine and reproductive consequences have been described even at long-term follow-up after unilateral orchiectomy,4,5 with the subsequent emotional and physical related side-effects. The widespread use of ultrasonography has led to an increasing number of incidentally detected small testicular masses (STMs), defined as non-palpable, <25 mm diameter intra-scrotal masses.6 In those cases, considering that most of the STMs proved to be benign,7 and bearing in mind the negative endocrine and exocrine consequences related to the loss of testicular parenchyma,6,9 a radical orchiectomy could represent an overtreatment. Therefore, the 2011 EAU Guidelines consider organ-sparing surgery as an alternative to radical orchiectomy, but only in those patients with synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a lesion in solitary testis with normal preoperative testosterone levels, provided that tumour volume is <30% of testicular volume and surgical rules are respected.2 The aim of this updated review is to evaluate and reaffirm the current indications for testis-sparing surgery (TSS), and discuss the oncological and functional results of patients who had undergone organ-sparing surgery for small testicular masses.

Evidence acquisition

We performed a nonsystematic review of literature using the Medline database, including a free-text protocol using the terms “testis-sparing surgery”, “testicular sparing surgery”, “partial orchiectomy”, “testis tumor”, “sex cord tumor” and “testis function” across the title and abstract fields of the records, using these limits: English language; humans; male; adults. Three Authors (M.B., E.B. and G.G.) reviewed separately all the retrieved abstracts and selected the papers reporting data about organ-sparing surgery for testicular or sex cord neoplasms. In a second step analysis we carefully examined the full-length articles, and any discrepancy has been resolved by open discussion. Other significant studies cited in the reference lists of the
selected papers were also evaluated, basing on the quality and the strength of the manuscript.

**Evidence synthesis**

**Indications for testis-sparing surgery, operative technique and role of frozen section examination (FSE)**

In those patients with normal contralateral testis and with no imperative indications, the use of TSS as conservative treatment of testicular malignancies is still controversial. According to the German Cancer Study Group, TSS can be offered only in selected patients with malignant tumour in solitary testis or bilateral tumour with a diameter of the lesion <2 cm and no invasion of the Rete Testis, with normal preoperative LH serum levels. In these cases, the enucleation of the mass must be accompanied by multiple biopsies of the surrounding tissue and adjacent radiotherapy must be considered for seminomas. Moreover, the 2011 update of the EAU Guidelines consider organ-sparing surgery as an alternative surgical management only in those patients with synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a lesion in patients with solitary testis and normal preoperative testosterone levels, but provided that tumour volume is <30% of testicular volume and surgical rules are respected. Testis-sparing surgery has already been described for the treatment of benign tumours. The use of intraoperative ultrasound (US) and frozen section analysis (FSE) can allow the operator to know with certainty the benign nature of the testicular mass with extremely low possibility of recurrence. Concerning the threshold diameter, several studies demonstrated that in case of non-palpable, asymptomatic masses with diameter <2 cm, TSS can be the best management, because in these cases the prevalence of benign histology is approximately 80%, similarly to that observed for small renal masses. Stol and collaborators firstly described the operative technique of TSS in 1986, by performing the enucleation of a non-palpable Leydig cell tumour with intraoperative US. More recently, Hallak and collaborators introduced the use of operating microscope, which allows the surgeon to perform a precise microscopic dissection of the tumour and the sperm extraction in case of azospermia. Testis-sparing surgery could represent a quite challenging procedure, especially when considering the need for optimal oncologic control and functional recovery, as widely discussed for other urological procedures. An accurate perioperative staging by radiological or nuclear medicine imaging studies is generally not recommended, in contrast with other urological malignant diseases. The operative technique for TSS starts with the exploration of the testis through an inguinal access, in order to be able to convert the operation to RO if necessary. In order to prevent dissemination or seeding of the neoplasm, the spermatic cord is isolated and clamped by a tourniquet; the clamping time should be minimized in order to reduce the warm ischaemia time; some authors proposed to enucleate the tumour without clamping the spermatic cord, with the aim to preserve the vascularization of the testis. Thereafter, the testis is exteriorized thought the same inguinal access and located in a separate operative field to avoid contamination or dissemination of the neoplasm in case of malignant tumour. The mass is usually identified by straight palpation of the testis or with intra-operative ultrasonography (US), usually guided by a needle. The use of cold ischaemia is still controversial, and some authors consider this approach even harmful. After the complete enucleation of the testicular mass, with or without a rim of a normal-appearing parenchyma, frozen section examination (FSE) is generally performed. Multiples biopsies of the surrounding tissue should be performed after the enucleation. The vascular clamp should be removed at the end of tumour excision, thus limiting the potential damage of the healthy testicular parenchyma. In case of negative FSE findings, the procedure is completed with a suture of the albuginea and the allocation of the testis in its original position; conversely, in case of positive FSE findings, a traditional radical orchiectomy is performed. After testis-sparing surgery, the rate of post-operative complications is quite low, in contrast with other urological procedures. After an initial scepticism about the reliability of a precise analysis, FSE has gained increasing credibility among the scientific community, thanks to the standardization of processes of handling and processing of the specimens. A non-conclusive diagnosis at FSE seems to be very rare. The experience of a pathologist represents the main limit of FSE. Therefore, frozen section specimens should be evaluated by a dedicated uro-pathologist with wide experience in this field.

**Histological patterns and oncological outcomes of the reported TSS series**

At the best of our knowledge, there are no randomized controlled trials comparing TSS with radical orchiectomy, and only retrospective studies and case reports are currently available in literature. Ninety percent of palpable testicular lesions, or tumour >2 cm, demonstrated to be malignant at the final pathological examination, while small testicular masses proved to be benign in 80% of cases. In detail, the rate of benign findings ranges from 60% to 77% for tumours smaller than 20 mm, and increases up to 80% for lesions under 5 mm. Histological patterns and oncological results of TSS series are reported in Supplementary. In a recent single-institutional study, De Stefani et al. reported 91% of benign lesions in a cohort of 23 patients with STMs treated with TSS. Frozen section examination showed 2 (9%) malignant lesions. The final pathological examination demonstrated typical seminomas in both cases. These two patients underwent RO. A mean follow-up of 35 ± 25 months, all patients were found to be free from disease. In another large series, Steiner et al. reported results of 18 STMs treated with elective TSS in patients with normal contralateral testis. Interestingly, all the lesions were benign at final histologic examination, and no local recurrences had been detected at a mean follow-up of 35.7 months after organ-sparing surgery. In the same series, 12 patients underwent imperative TSS (because of bilateral tumours, local recurrence or a neoplasm in a solitary testis) for 8 seminomas, 2 mixed germ cell tumours 1 mature teratoma and 3 benign lesions. After a mean follow-up of 59.8 months, only one patient (8.3%) diagnosed with seminoma.
and who refused postoperative testicular radiotherapy experienced local recurrence. Carmignani and collaborators, in a recently published series, reported data about TSS (in one patient with imperative indication because of solitary testicle) performed in 7 out of 10 patients (70%) with small non-palpable testicular lesions, with negative intra-operative FSE. Radical orchietomy was performed in the remaining 3 patients after the histological diagnosis of adenomatoid tumour with multifocal abscesses in one case and Leydig cell tumour with positive margins at FSE in the other two cases. Definitive histological analysis confirmed multifocal, diffused Leydig cell tumour. No local recurrence was detected with a mean follow-up of 9 months. More recently, a series of 23 cases of Leydig cell tumour with a median dimension of 11.4 mm has been reported. In detail, TSS was performed in elective fashion in 21 patients; conversely, in 2 cases the conservative management was imperative, because of solitary testis. In 1 patient the frozen section examination revealed a “large B cell Lymphoma”, but patient was conservatively treated with TSS. After a follow-up of 47 months the authors did not report any local recurrence. We recently reported histological and oncological outcomes of 15 consecutive patients treated with surgical exploration with elective TSS for STMs. The final pathological report showed 13 benign lesions (87%) and two malignancies: a pure seminoma in one case and a paratesticular low-grade fibromyxoid liposarcoma in other case. The latter was not detected by FSE as the diagnosis can be the insidious, and RO was performed subsequently after final pathological report. We did not find local recurrence after a median follow-up of 19.6 months. In the reported series by Shilo et al., 16 patients underwent surgical exploration and subsequent elective TSS. Frozen section examination correctly revealed benign findings in all the 11 patients (69%) who underwent TSS. The malignant lesions were described as seminoma in three cases, teratoma in one and embryonal carcinoma in one. These five patients underwent definitive radical orchietomy. After a mean follow-up of 48 months, all patients were alive and free of disease. When planning to perform testis-sparing surgery for malignant small testicular masses, either in imperative or elective cases, additional relevant considerations should be undertaken. Testicular intraepithelial neoplasia (TIN), considered to be a precursor of invasive germinal cell tumours (GCT), is found in testicular tissue adjacent to testicular germ cell tumours in about 90% of cases. Therefore, some authors suggest obtaining multiple biopsies of the normal-appearing testicular parenchyma in order to reveal the presence of TIN, which will inevitably progress to invasive cancer. The largest series concerning TSS for malignant germ cell tumours in patients with bilateral neoplasm or tumour in solitary testes have been shown by the German Testicular Cancer study Group. In this interesting report, 101 patients were conservatively treated for nonseminomatous or seminomatous lesions. Eighty-five (84.1%) patients were diagnosed with concomitant TIN at multiple surrounding biopsies, and adjuvant postoperative radiotherapy (RT) was administered in 80 cases. After a mean follow-up of 80 months, the cancer specific survival was excellent (100/101 patients), and only 6 patients experienced local recurrence. Steiner and collaborators reported on 11 TSS for malignant germ cell tumours at final histological exam. Adjuvant RT was offered to all patients diagnosed with TIN (8 patients). No cancer-related deaths or recurrence were shown at a mean follow-up of 60 months, and local recurrence occurred in one patient who refused adjuvant testicular RT. Considering the high prevalence of TIN in surrounding healthy testicular parenchyma, and according to these reports, adjuvant testicular RT should be offered to all patients undergoing TSS for malignant tumours, even if the risk of damaging the remaining germ cell (with related endocrine and reproductive consequences) remains high. Another aspect that should be considered when performing TSS for small GCT is the risk of tumour multifocality, defined as the presence of cancer cell outside the principal tumour. Indeed, in a recent paper the tumour multifocality has been demonstrated in 33% of patients treated with radical orchietomy for GCT, and higher rate of multiple foci was found in those patients with STMs (<2 cm), especially with seminomatous pattern (63%). In spite of these evidences and the consequent higher risk of oncological failure, the most relevant series of TSS for small GCT show promising results with low incidence of recurrences. A preliminary selection of patients and postoperative testicular irradiation are the best strategies in order to improve the local control of the disease and minimize the risk of local/distant recurrence. The data from these retrospective series or case reports, with medium and long-term follow-up, confirm that the STMs demonstrate to be benign in the majority of cases. Testis-sparing surgery could be a safe and effective conservative option for selected patients, thus avoiding surgical over-treatment, without compromise of the oncological outcomes. The rate of local recurrences after TSS is quite low, especially in those cases in which adequate frozen section analyses have been performed. Careful management must be reserved to patients with small GCT suitable for TSS, in which multiple biopsies of the surrounding healthy testicle and adjuvant postoperative irradiation of the remaining testicle allow to reduce the risk of disease relapse and progression, by destroying foci of TIN or multifocal disease.

Functional outcomes after TSS

After unilateral orchietomy the remaining testicle was traditionally considered sufficient to compensate the loss of testicular parenchyma and, therefore, to maintain normal hormonal and reproductive functions. Conversely, more recent studies revealed that even the loss of one testis is significantly associated with important alterations of fertility, long-term exocrine and endocrine deficit and severe sexual and psychosocial implications. Even in the absence of adjuvant therapy, radical orchietomy is associated with a significant decrease in spermatogenesis, potentially evolving in azoosperma in a non-negligible amount of patients. The side effects of radical orchietomy can be partially avoided by the preservation of testicular parenchyma allowed by TSS, that can also be performed in presence of malignant tumour harboured in young, but very selected patients. Indeed, in patients with malignant CGT the gonadal function may be impaired for many reasons, and the preservation of much healthy and functional parenchyma as possible could be an undeniable...
advantage for those patients. In the large series by Heidenreich et al., 84 patients out of 101 treated with TSS for CGT showed normal postoperative testosterone levels. Ten patients developed de novo hypogonadism and received androgen supplementation and 6 suffered for preoperative hypogonadism. In the report by Steiner et al., all patients recovered normal postoperative testosterone levels, except for one, who was treated for a large (30 mm) neoplasm and received adjuvant RT as well. When TSS is performed with the aim of preserving fertility, warm ischaemia time should be lower than 30 min in order to avoid irreversible damages to the gonadal tissues.

Moreover, an increased risk of tubular, interstitial and germ cell damage, with consequent infertility and hypogonadism, has been demonstrated after adjuvant postoperative RT of the remaining testicle. Therefore, a careful counselling should be addressed to the patients, especially in those who desire to father a child.

Conclusions

Testis-sparing approach for small testicular lesions allows preserving as much healthy parenchyma as possible, but should be performed only in selected cases and in experienced centres. The surgical approach is safe and feasible, and optimal results are obtained in case of benign lesions. When performed for small malignant germ cell tumours, TSS should be carefully offered to selected patients, and adjuvant testicular radiotherapy represent the most proper strategy in order to consolidate the local control of the disease, especially in case of concomitant TIN and tumour multifocality. Frozen section examination has a paramount importance in the histological evaluation and the surgical decision-making. Intermediate and long-term follow-up showed no significant risk of local and distant recurrences, and functional outcomes are promising. Testis-sparing surgery should be considered as conservative approach for the management of small testicular masses that turns to be benign at frozen section examination, and could be an alternative, organ-preserving treatment for small malignant lesions in highly selected imperative or elective cases. Further prospective studies or randomized controlled trials are needed in order to confirm the oncological safety and to expand the indications for testis-sparing surgery.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcuro.2014.11.010.

References


