CONTEMPORARY ROLE OF TESTIS SPARING SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

Testis-sparing surgery (TSS) represents a therapeutic choice for testicular cancer (TC). However, international guidelines are very cautious about the use of the testis-sparing technique, namely due to the lack of certain indications and long-term oncological outcomes. The aim of this systematic-review is to illustrate current trends of what may today be the uses of organ-sparing surgery in TC, to evaluate the relationship between the organ-sparing safety and oncological features such as definitive histology, tumour size, and post-surgery oncological outcomes. This analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. An electronic search of the Medline and Embase was undertaken until September 2014. The search was limited to English-Language articles. Current indications of TSS are synchronous bilateral testicular tumours, metachronous contralateral tumours, or tumour in a solitary testis with normal preoperative testosterone levels. Moreover, histological characteristics should not be taken into account when performing a TSS approach. TSS outcomes for germ cell tumours are encouraging and we reported high rates of disease-free survival and a few cases of patients receiving neoadjuvant chemotherapy or radiotherapy. In light of the examined, TSS could be considered a viable alternative to radical surgery of the testis but it should be performed in specialised centres with competence.

Keywords: Testicular cancer, testis sparing surgery, risk factors, germ cell tumour, orchiectomy.

INTRODUCTION

Today, testicular cancer (TC) is one of the most important challenges in urology. The reasons must primarily be due to the increasing incidence of neoplasia in Caucasian patients, as reported by the statistics of the Surveillance, Epidemiology, and End Results in the USA.[1] To confirm this trend Huyghe et al.[2] showed that TC incidence is increasing throughout Europe, although there was no difference between European countries. For instance, the present incidence rate is 0.8/100,000 in Portugal and 15.4/100,000 in Denmark. Common risk factors, according to the European Association of Urology (EAU) guidelines 2014, are identified in the history of cryptorchidism or undescended testis (testicular dysgenesis syndrome), Klinefelter's syndrome, familial history of testicular tumours among first-grade relatives (father/brothers), the presence of a contralateral tumour or testicular intraepithelial neoplasia (TIN), and infertility.[3-7] Other risk factors has been also recently introduced, such as tallness[8,9] and the use of pesticides such as the p,p'-dichlorodiphenyldichloroethylene, primary metabolite of dichlorodiphenyltrichloroethane,[10] but these associations should be further confirmed Another controversy is represented by the choice of the surgical approach. EAU guidelines identify radical orchiectomy as the gold standard treatment for TC when a 'suspicious testicular mass' is found. In recent years, a new concept of surgery has emerged, the minimally invasive surgery (MIS), and not only in the urological field. To this regard, the organ-sparing surgery (OSS) represents a therapeutic

choice. However, EAU guidelines are very cautious about the use of the testis-sparing technique, due to the lack of certain indications and long-term oncological outcomes.

It is with this in mind that some reports have raised doubts about this surgical approach. The main skepticisms on this topic precisely regard the heterogeneous histological features of TCs and the lack of appropriate diagnostic techniques that can distinguish and characterise them. Furthermore, matched-paired analyses and randomised studies, comparing testis sparing versus orchiectomy, are lacking; all these controversies limit the evaluation of current data. The aim of this systematic review is to illustrate current trends of what may today be the uses of OSS in TC, to evaluate the relationship between the organ-sparing safety and oncological features such as definitive histology, tumour size, and post-surgery oncological outcomes.

MATERIAL AND METHODS

This analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[11] An electronic search of the Medline and Embase was undertaken until September 2014. The search was limited to English-Language articles. The search terms included: "testis cancer", "testis sparing surgery", "risk factor", "cancer specific survival", "disease recurrence", "predictors", and "outcomes". Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. References of the included papers were hand searched in order to identify other potential relevant studies. Studies were reviewed by two independent reviewers (G.I.R. and G.R.); differences in opinion were discussed in consultation with the last author (G.M.) (Table 1). Figure 1 shows the flowchart of included studies.

RESULTS

Indication

Current indications of testis-sparing surgery (TSS) are synchronous bilateral testicular tumours, metachronous contralateral tumours, or tumour in a solitary testis with normal preoperative testosterone levels. However, organ preserving surgery can be performed when the tumour volume is <30% of the testicular volume, and surgical rules are respected. The need for such strict regulations suggests that TSS is still not a safe technique as opposed to an extremely definitive surgery such as orchiectomy. On the other hand, orchiectomy itself could be considered as an overtreatment of neoplastic disease in selected cases. Regarding international guidelines on TC, European urologists still refer to the EAU guidelines.[12] The latest update in TC has inserted a new section on OSS, confirming the need for support for this minimally invasive surgical approach. It also reported that some histological features for which a minimally invasive surgical approach is more suitable are Leydig cell or Sertoli cell tumours. Patients with gynaecomastia, or hormonal disorders, or typical imaging such as calcifications, or small circumscribed tumours may be suspected for Leydig cell or Sertoli cell tumours. However, a TSS is recommended in every small intraparenchymal lesion with the purpose of obtaining a histological diagnosis. The testis-sparing approach must be performed only if testicular parenchyma (TP) is sufficient for endocrine and also exocrine (in stromal tumours) functions.

Currently, the American Urological Association guidelines do not seem to agree on the choice for a MIS in TC, and therefore define it as 'controversial'. Indications given by the American Society are similar to those of the EAU: available for mass <2 cm, for simultaneous bilateral tumours, in solitary testicle with normal serum testosterone levels, biopsy performed on adjacent parenchyma (for the possibility of intratubular germ cell neoplasia presentation in 80% of cases), and eventually treatment with 20 Gy radiotherapy in the remaining TP. The National Comprehensive Cancer Network guidelines did not take into consideration TSS. Regarding the TSS technique, the ability to operate on a frozen section during the procedure appears to be of great interest. Subik et al.[13] performed frozen section in a series of 45 patients with testicular masses and found that 36 of 43 patients (83.7%) demonstrated the oncological feasibility of this technique. The utilisation of the frozen section has also been confirmed in a study by Steiner et al.[14] which performed 32 testis-sparing procedures using an initial frozen section from each sidewall and from the bottom of the tumour bed, from August 1994 to May 2002. They moved the subsequent frozen section into the adjacent parenchymal, in case of TIN in the initial frozen section. In this way they identified the presence of 10 TIN on 11 germ cell tumours (GCTs) and proceeded with appropriate treatment (i.e. radiotherapy). Another challenge of TSS seems

to be the preservation of fertility. The choice of a MIS (saving the normal TP) is obviously indicated when one would ensure the best exocrine function directed to procreation.

As reported by the EAU Guidelines, the infertility rate after OSS significantly increases in patients receiving adjuvant radiation therapy. For this reason it raises the possibility of delaying the radiological treatment or carrying out any sperm preservation after procreation. Focussing on this, Hallak et al.[15] conducted a study of five patients with TC associated with azoospermia, and treated with TSS and contemporary microdissection for excision of the best tubules in order to select them and perform cryopreservation: in 80% of patients it was seen that the extraction procedure for all patients and the levels of serum testosterone were maintained in the normal range after one year of follow-up. The question of radiotherapy therefore seems controversial in the literature: on one hand it is necessary for the control of localised disease with the simultaneous presence of TIN, on the other it is deleterious for the reproductive and endocrine functions of the testis. So what is the best approach for adjuvant radiation therapy? It seems evident that a dose of 20 Gy radiation represents a concentration sufficient to eradicate the carcinoma *in situ* (CIS), if present.[16,17] The EAU Guidelines to this regard, however, conceived the possibility of delaying radiation therapy for all those patients who wish to have a child, obviously paying them a rigorous follow-up with ultrasonography of the residual TP.[17]

Histological Features

A careful analysis of the literature confirmed that there are no limitations, in terms of histological features, for TSS. Likewise GCTs stromal tumours can be treated with MIS. Concerning GCTs, the European Germ Cell Cancer Consensus Group indicated that testis-sparing is a viable alternative for small tumour volume but it must be performed only in specialised centres that can manage technique-related complications.[18] In a report on 27 patients treated with TSS, the average size of the tumour mass detected by ultrasound was 11 mm (range 6-27 mm). Although three of these patients had a multifocal carcinoma and seven had an associated CIS, no local occurrence occurred after 5.7 years of follow-up.[19] Focus on the presence of TIN and multifocality in GCTs has been investigated in the literature.[20]

A rate of multifocality of up to 63% has been reported[13] in tumours with a size of up to 20 mm. Furthermore, multifocality could be a finding in testicular GCT cases and in those with seminomatous histology, as reported by a recent study. Anyway, the significance of this finding is not well understood.[21] However, the high percentage of multifocal tumour presence is inconsistent with the number of tumour relapses reported in the literature or with the histological tumour type, regardless of administration of adjuvant therapy following TSS. In contrast with these observations, we have recently reported a much smaller percentage of tumour multifocality. In 140 analysed tumours with a size <4 cm, the percentage of multifocality was around 26%. This pathological feature of testicular GCT did not correlate with the histological subtype, in particular seminomatous histology, as previously described,[21] neither with other adverse clinical and pathological variables. Based on these considerations and because they are different to other urological tumours, such as bladder or kidney cancer, the presence of multifocality in TC should not be considered as an adverse pathological feature at the time of orchiectomy, together with all of the others.

The presence of TIN must be also established whenever TSS is performed. The rate of TIN has been reported as ranging from 72-98%, but a recent perspective has attributed the presence of TIN in TP as adjacent to a GCT. TIN is found in 4.9% of patients with tumours on the contralateral testicles. To this regard, we have retrospectively reported data on 126 patients affected by testis cancer (76 seminomatous and 50 non-seminomatous) and treated with orchiectomy. We showed that the prevalence of multifocal TC and TIN decreased in the presence of a smaller main mass (1 cm) and increased when the index mass tumour diameter is >1.1 cm.[22] Based on these considerations, tumour volume and focality should be considered before performing a TSS.

In the literature, TSS is also described for other histological types of GCTs, such as teratoma, although pertaining to paediatric urology. Shukla et al.[23] have revised their own data from 1976-2002 and reported 77 pediatric testicular tumours: 43 were GCTs. They reported 13 testis-sparing procedures, including 8 teratomas and epidermoid cysts, with 5 confirming, as final consideration, the OSS as a safe technique with good cancer control. Furthermore, the focus of TSS has also been reported for leydigomas.

Table 1: Characteristics of included studies.

Year	Authors	Country	Number of Cases	Number Treated with TSS	Mean Size Tumour mass US D_{max} (range)	Histological Findings (% on TSS procedures)	Outcome after TSS
2014	Favilla et al.[22]	Italy	126	nv	19.4 mm (6-50 mm)	Seminomatous: 76 (60.31%) Nonseminomatous: 50 (39.69%)	nv
2014	Leonhartsberger et al.[31]	Austria	65	33 in 30	14.8 mm (2-30 mm)	Stromal cell tumour: 19 (57.57%) Metachronous bilateral: GCT: 6 (18.18%) Bilateral Synchronous: Seminoma: 2 (6.06%) Benign lesions: 6 (18.18%)	- Disease-free survival: 100%
2014	Favilla et al.[22]	Italy	254	nv	35 mm (5–120 mm)	Seminomatous: 148 (58.26%) Nonseminomatous: 106 (41.74%)	nv
2014	Bojanic et al.[32]	Serbia	44	26	>20 mm	Seminoma: 16 (61.53%) Nonseminoma: 9 (34.61%) Leydigoma: 1 (3.84%)	- Local recurrence: 7 (26.92%) - Radical orchiectomy: 5 (19.23%) - Overall survival: 100%
2013	Bozzini et al.[25]	Italy	22	22	11.4 mm (5-31 mm)	Leydig cell tumour: 20 (90.90%) Non-malignant stromal: Tumour: 1 (4.54%) B cell lymphoma: 1 (4.54%)	- Local recurrence or distant: 0 (0%) - Disease-free survival: 100%
2010	Lawrentschuk et al.[19]	Canada	30	27	Benign 10 mm (5–28 mm) Malignant 11 mm (6–27mm)	Benign Seminoma: 8 (36.3%) Nonseminomatous GCT: 2 (7.4%) Malignant Seminoma: 11 (40.7%) Nonseminomatous GCT: 3 (13.6%) Mixed: 1 (4.54%) Teratoma: 2 (7.4%)	- No perioperative complications - Observation in 12 of 17 cases (70.59%) - Local recurrence: 2 (11.76%) - Retroperitoneal lymph node dissection: 1 (5.88%)
2009	Suardi et al.[24]	Italy	610	28	13.3 mm	Leydig cell tumour: 28 (100%)	- Patient died from the disease during the follow-up: 0 (0%) - Local or distant recurrence: 0 (0%)
2004	Shukla et al.[23]	USA	77	13	nv	Mature teratomas: 8 (61.53%) Epidermoid cysts: 5 (38.47%)	- No recurrence, testicular atrophy or persistent orchialgia.

TSS: testis-sparing surgery; GCT: germ cell tumours; nv: not valuable; US: ultrasound.

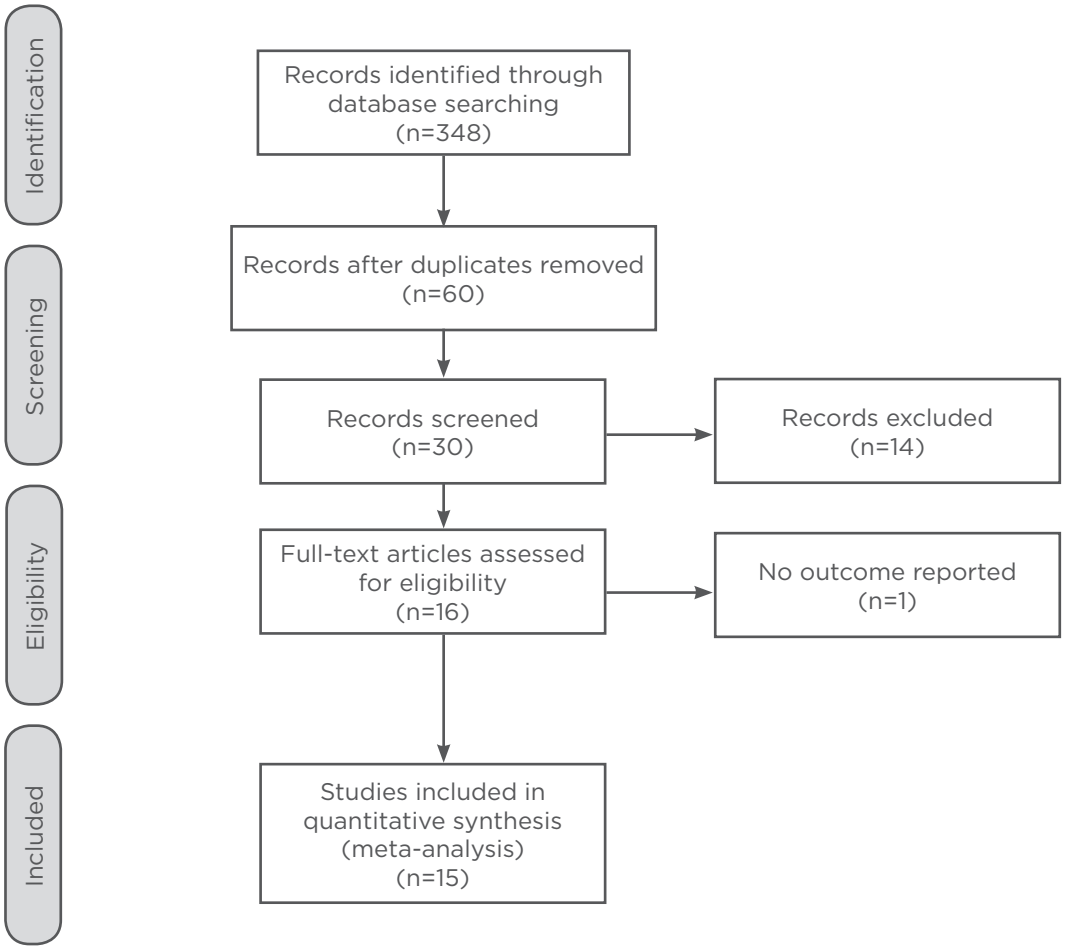

Figure 1: Flow diagram of included studies.

In a single-centre case series TSS was performed in 29 patients with Leydig cell tumour and after 4.6 years of follow-up, no patients had disease relapse.[24] Similarly, a multicentre retrospective clinical study of Bozzini et al.[25] evaluated 22 patients with Leydig cell tumour treated with a conservative technique. The author examined the results after a mean follow-up of 180 months and emphasises the importance of an 'early diagnosis' of leydigomas, suggesting, in these situations, 'a minimally invasive approach' as the 'gold-standard treatment'.

Sertoli cell tumours may be also treated with TSS. However, limited evidence is available for a conservative surgical approach. In most cases, this evidence is based on case reports.[26,27] To the best of our knowledge, literature data such as systematic reviews or meta-analyses are lacking, probably due the rarity of their presentation. Another rare type of tumour stromal cells that can be applied in this technique are tumours of the granulosa: for this extremely rare histotype, there is a case report of a 6-month-old baby affected by bilateral juvenile granulosa cell tumour, treated with conservative surgery.[28] Based on these considerations, histological characteristics should not be taken into account when performing a TSS. However, further studies are warranted in order to better investigate these results.

Oncological Outcomes After TSS

TSS has now been practiced for more than three decades and data on oncological outcomes are recently emerging.[29] Some parameters related to the TSS, such as MIS, the ability to preserve fertility, and the psychological aspect of the patient are factors of great significance for the urologist. On the other hand, it is clear that several doubts still persist about oncological outcomes following the procedure. Uncertainty about the surgical radicality is also highlighted by the EAU guidelines, which have highlighted the possibility of a neoadjuvantradiotherapy.[12] Due to the rarity of some histological types of testis cancer and (therefore) due to the reduced amount of data available, we will examine the oncological outcome of the two most common types: seminomas and non-seminoma.

Since 1984, a number of studies have been reported in the literature related to TSS; Giannarini et al.[29] have recently reviewed a number of case reports. Heidenreich et al.[30] reported a series of 73 patients treated with TSS and the long-term results, with 98% showing no evidence of disease, normal testosterone values, and 5 spontaneous pregnancies.

Leonhartsberger et al.,[31] from January 2003-October 2010, evaluated the oncological outcomes of 33 patients treated with TSS and followed up for a mean period of 50 months. Of these, 19 presented stromal cells, 6 benign lesions, 6 metachronous bilateral GCT, and 1 synchronous bilateral seminoma. After 50 months of follow-up, no evidence of local or systemic relapse was reported. Similar results were obtained in a retrospective review where 27 patients undergoing OSS were oncologically evaluated: 17 of those patients (63%) had malignant lesions (9 seminoma, 3 teratoma, 1 embryonal, 3 Leydig cell, and 1 CIS) and 10 (37%) had benign lesions. CIS was founded in 53% of patients, including seven with seminoma.[19] Two patients finally underwent radical orchiectomy for local recurrence of CIS; one needed an additional treatment with bleomycin, etoposide, and cisplatin, one case of seminoma was treated with radiotherapy, and only in a patient with an histological finding of teratoma was a retroperitoneal lymph node dissection necessary. The remaining five patients with CIS underwent surveillance. The overall disease free survival was 5.7 years.

In a more recent report, TSS was performed in 24 patients (median follow-up of 51.0 months). Seven patients developed local recurrence, of which five had TIN and were subjected to radical orchiectomy, whereas re-do TSS was done in the remaining two patients. The overall survival of the study group was 100%, and the presence of TIN was associated with worse recurrence-free survival (p=0.031).[32] Fortunately more data on TSS are emerging and confirming that this minimally invasive surgical approach is acceptable both from an oncological point of view, in patients with bilateral testicular GCTs and solitary testicle tumours, and for TP functional preservation.

CONCLUSION

In the last two decades, TSS are improving and many more studies have been published on this topic. Some doubts on TSS could concern indications and long-term oncological outcomes, and their relationship with tumour histology. These limits may be exceeded, but there is a clear need for randomised clinical trials and meta-analysis studies. Despite the current evidences and literature data on this topic, several issues need to be addressed. Firstly, information given by the last EAU Guidelines, should be enriched by a clear cut-off regarding the tumour size (as ultrasonography diameter maximum value). For what concerns the histological subtypes, information, for stromal tumours cells especially, is still lacking. In our opinion, new challenges about diagnostic techniques may offer some contributions in predicting the histological features of small testicular masses, mainly in those with negative alterations of neoplastic markers. Finally, fertility is certainly a main concern of survivors after treatment. In this context a lower level of awareness by the medical team or the patient, with regards to the need to bank sperm or a general knowledge of assisted reproductive techniques, may be present. Furthermore, the occurrence of limited time between diagnosis and treatment, as treatment is usually initiated as soon as possible and poor semen quality leads to immotile sperm after cryopreservation, or failure of ejaculation due to high levels of anxiety or weakness, are the next challenges to overcome.[33] In conclusion, TSS outcomes for GCTs are encouraging and we have reported high rates of disease-free survival and a few cases of patients receiving neoadjuvant chemotherapy or radiotherapy. In light of the all examined, TSS could be considered as a viable alternative to radical surgery of the testis, however, it should be performed in specialised centres with competence.

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