



Collaborative Review – Testis Cancer

Organ-Sparing Surgery for Adult Testicular Tumours: A Systematic Review of the Literature

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Abstract

Context: According to current guidelines, radical orchidectomy is the standard treatment for testis tumours of malignant and unknown origin. Testis-sparing surgery (TSS) has recently been proposed as an alternative option in selected cases.

Objective: Our aim was to analyse the cumulative evidence for TSS in the treatment of adult malignant tumours of different histology, including notes on operative technique, indications, complications, and oncologic and functional outcome.

Evidence acquisition: A systematic literature search of the Medline/PubMed database for full-length papers reporting on TSS for adult malignant tumours was performed up to September 2009. Bibliographies of retrieved articles and review articles were also examined. Only those articles with complete data on operative technique, complications, and oncologic or functional outcome were selected. Furthermore, published abstracts at major urologic meetings in the last decade (1999–2009) and guidelines on testis cancer from major oncologic and urologic medical associations were searched and evaluated.

Evidence synthesis: No randomised controlled trials have compared TSS and radical orchidectomy; only retrospective outcome studies and case reports on TSS are available. In patients with small malignant germ cell tumours arising in both or in solitary testes, TSS coupled with local adjuvant radiotherapy ensures good oncologic control and is associated with a preserved endocrine function in most cases. In patients with small Leydig cell tumours, TSS can also be performed with elective indications (healthy contralateral testes), provided that pathology fails to reveal aggressive features. Finally, TSS is an option for patients with small ultrasound-detected, nonpalpable tumours even with elective indications because the incidence of benign definitive histology is high at approximately 80%. The overall complication rate is low (<6%). Data on exocrine and endocrine gonadal function, male body image, and health-related quality of life after TSS are still immature.

Conclusions: TSS can be safely adopted for the treatment of carefully selected cases of tumours of different histology. Prospective multicentre studies are warranted to further qualify TSS as a treatment option to be recommended as an alternative to radical orchidectomy and to explore the perceived functional advantages of testis preservation.

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1. Introduction

Radical orchidectomy is currently considered the standard treatment for testis tumours of malignant or unknown origin [1,2]. In the last 2 decades, however, due to the improvement in oncologic outcome and growing attention devoted to functional issues of cancer survivorship, the management of testis tumours has started to evolve in favour of conservative surgery, mirroring the current trend of organ preservation in the treatment of several other cancers [3].

Until the late 1980s, urologic surgeons followed the axiom that testes harbouring any suspicious mass had to be removed, based on the historically reported very low (<1%) prevalence of benign testis tumours and the belief that intraoperative biopsies in the presence of malignancy would invariably induce tumour seeding [4,5]. Conversely, in the recent past, a higher proportion of histologically proven benign testis tumours has become apparent [6,7] and frozen section examination (FSE) has achieved higher diagnostic accuracy, thus obviating the need for an immediate radical orchidectomy [8,9]. Furthermore, the widespread use of high-frequency ultrasonography has led to a marked increase in the number of incidentally detected and small testis tumours, most of which have been shown to be benign [10]. Finally, there is growing awareness of the potential advantages of testis preservation over traditional extirpative surgery in terms of health-related quality-of-life issues, namely preservation of fertility, preservation of endocrine function thereby avoiding the risk of late-onset hypogonadism, and preservation of male body image [11]. The question has therefore emerged whether or not the entire testis needs to be sacrificed without exception in every case of a known or suspected malignancy.

The objective of the present review is to analyse systematically the cumulative evidence for testis-sparing surgery (TSS) as a treatment option for adult malignant tumours of different histology, including critical notes on operative technique, indications, complications, and oncologic and functional outcome.

2. Evidence acquisition

A systematic literature search using the Medline/PubMed database for full-length papers and including both medical subject heading and free text protocols was performed up to September 30, 2009. Entry terms were *testi* sparing OR preserving surgery, hemiorchiectomy, partial orchidectomy, and testi* lesion OR mass OR neoplasm OR tumour OR germ cell cancer OR germ cell tumour OR seminoma* OR non seminoma* OR teratoma OR intraepithelial neoplasia OR carcinoma in situ OR gonadal stromal tumour OR sex cord tumour OR Leydig cell tumour OR Sertoli cell tumour OR cyst* in conjunction with *organ sparing surgery OR organ preserving surgery OR conservative surgery OR enucleation OR excision OR resection OR biopsy*. Search limitations were title/abstract, humans, male, and all adults.

Two authors (GG and KPD) reviewed the abstracts of the retrieved records and selected only those pertinent to the objectives of the present review. All authors carefully

examined the corresponding full-length articles, and they hand-searched and retrieved additional referenced papers. Only those articles reporting complete data with clinical relevance for the present review (ie, description of the operative technique, data on both FSE and definitive pathology, complications, and oncologic or functional outcome data) were considered for analysis. In the case of two or more papers reporting on the same updated series, only the most recent one was selected. Review articles were also analysed.

In addition, published abstracts at the meetings of the American Society of Clinical Oncology (ASCO), American Urological Association (AUA), European Association of Urology (EAU), European Society for Sexual Medicine, International Society for Sexual Medicine, and Société Internationale d'Urologie in the last decade (1999–2009) were hand searched, critically examined, and considered for the present review only if not followed by the full-length publication in a peer-review journal and if of outstanding clinical significance.

Recent unpublished data of major interest were also included. Finally, the most recent guidelines and consensus reports on the management of testis cancer released by the ASCO, AUA, EAU, and National Comprehensive Cancer Network (NCCN) were located on the corresponding official Web sites and critically reviewed.

Levels of evidence of the Oxford Centre for Evidence-Based Medicine were used to rank the papers [12]. We adopted the 2004 World Health Organisation pathologic classification of testis tumours to present and discuss the results of our search [13].

3. Evidence synthesis

The search generated 97 full-length papers and 2 congress abstracts. From the retrieved material, 68 relevant full-length papers and 2 congress abstracts were selected for final analysis. Two personal communications were also included. There are no randomised controlled trials comparing TSS and radical orchidectomy; only case reports and retrospective outcome studies on TSS are available (maximum level of evidence 2c).

3.1. Operative technique

The operative technique was concisely described for the first time in 1986 by Stoll et al [14], who used high-frequency ultrasound as a guide to enucleate a nonpalpable Leydig cell tumour. The technique evolved in the early 1990s in Europe with the pioneering work of the German researchers Weissbach [15] and Heidenreich et al [5], and it further improved until 2002 when Hopps and Goldstein [16] codified the procedure introducing the use of a magnification system, with the aim of improving the localisation and the complete and safe excision of small nonpalpable tumours. It was lastly refined by Hallak et al [17], who reported on the microsurgical technique of enucleation coupled with microdissection for sperm extraction in azoospermic patients with nonpalpable masses.

All of the surgical steps summarised in this paper have never been validated in prospective randomised trials and largely rely on the traditional principles established by Chevassu in 1906 [4], with only some recent modifications (level of evidence 4).

As a rule, the testis is delivered through a standard inguinal incision in preparation for radical orchidectomy. The spermatic cord is isolated and suspended, and spermatic vessels are occluded with a tourniquet or a rubber-shod clamp while leaving the vas deferens untouched. Some experts in referral centres have abandoned ischaemia with the intent of maximally preserving vascularisation and thereby gonadal function [18].

The testis is then exteriorised from the same access and placed in a separate operative field, generally consisting of a folded towel resting on the ipsilateral upper thigh, to avoid

potential spillage and wound contamination in case a malignant tumour is encountered. The gubernaculum testis is either clamped or sectioned. Some authors recommend carrying the procedure with cold ischaemia [17,19]; others deem it unnecessary or even dangerous [18]. When cooling is performed, the testis is immersed in an ice slush solution for 10 min after cord clamping and then kept in the same environment throughout the procedure. A temperature probe inserted in the testis ensures that the temperature is kept between 15 °C and 19 °C. The tunica vaginalis is opened and the testis inspected. An operating microscope, providing $\times 6$ –25 magnification, or magnifying optical loops may be used to aid identifying and subsequently avoiding the blood vessels subjacent to the tunica albuginea [16,18]. The mass is localised by intraoperative ultrasound, and a small-calibre needle may be placed adjacent to it for

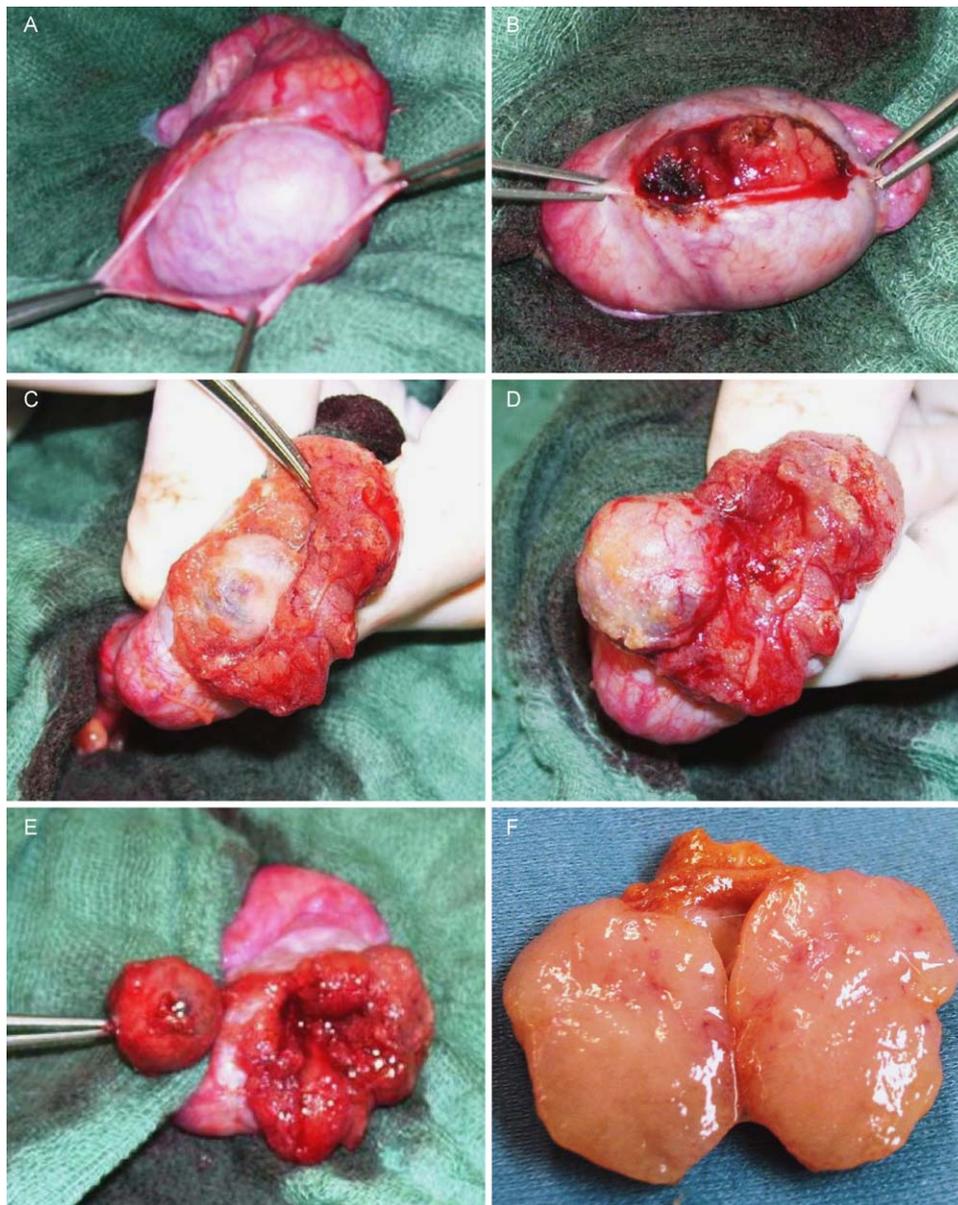


Fig. 1 – The critical steps of the operative technique. (A) Incision of tunica vaginalis. (B) Incision of tunica albuginea just above the tumour. (C) The adjacent testicular parenchyma is gently peeled away from the tumour, which exhibits a typical pseudocapsule. (D) The tumour is completely exposed. (E) The tumour is completely excised. (F) The tumour is split into two halves; one is sent for frozen section examination, the other for definitive pathology.

Table 1 – Individual case reports reporting the use of testis-sparing surgery for the management of germ cell tumours

First author	Year	Patients, n	Age, yr	Indication	Diagnosis	Adjuvant RT (dose)	Local recurrence	Treatment of recurrence	Sperm count (10 ⁶ /ml)		Paternity		Testosterone level (ng/ml)		Testosterone supplement post	Sexual function post	Follow-up, mo [†]
									Pre	Post	Pre	Post	Pre	Post			
Sobeh [29]	1994	1	26	Metachronous	Seminoma, no TIN	No	Yes	Radical orchidectomy	50	28	NR	Yes	NR	NR	No	NR	42
Mearini [30]	1996	1	27	Synchronous	Nonseminoma, no TIN	No*	No	–	0.7	3	NR	NR	10.9	3.9	No	Normal libido	50
Kazem [31]	1999	2	44	Metachronous	Seminoma, no TIN	Yes (20 Gy)	No	–	NR	0	NR	No	2.85	1.7	No	Normal virility	24
			36	Synchronous	Seminoma, TIN	Yes (19.8 Gy)	No	–	NR	0	NR	No	5.09	2.7	No	Normal virility	24
Kirkali [32]	2001	1	34	Metachronous	Seminoma, no TIN	No	No	–	NR	NR	Yes	NR	Normal	Normal	No	NR	50
Demir [33]	2004	1	32	Synchronous	Seminoma, no TIN	Yes (19.8 Gy)	No	–	NR	NR	No	NA	Normal	Normal	No	NR	30
Hentrich [34]	2005	3	33	Metachronous	Seminoma	Yes (20 Gy)	No	–	NR	NR	NR	NR	NR	NR	Yes	NR	73
			31	Metachronous	Seminoma	Yes (20 Gy)	No	–	NR	NR	NR	NR	NR	NR	NR	Yes	NR
Hughes [35]	2006	1	20	Solitary testis	Nonseminoma, no TIN	No	No	–	NR	0	No	No	NR	NR	No	Normal	93
			NR	Metachronous	Seminoma, TIN	No	Yes	Testis-sparing surgery, RT	NR	NR	NR	NR	NR	NR	NR	No	Normal
Hallak [17]	2009	1	NR	Metachronous	Seminoma, TIN	Yes (18 Gy)	No	–	0	0	No	No	Normal	Normal	No	NR	36
Canda [37]	2009	1	43	Metachronous	Nonseminoma, no TIN	No	No	–	NR	0	No	No	2.05	1.58	No	Normal	6

NA = not attempted; NR = not reported; RT = radiation therapy to the testis; TIN = testicular intraepithelial neoplasia.
* Chemotherapy (clinical stage IIB).
† Until local recurrence, if any.

stereotactic enucleation [16,17]. The tunica albuginea overlying the tumour is incised and the mass visualised by gently displacing the parenchyma. The tumour is enucleated with or without a rim of normal-appearing parenchyma and is then submitted for FSE. Postexcision ultrasound can be used to control for the complete removal of the mass. If pathologic findings are benign, the testis and wound are irrigated with sterile water, the spermatic vessels are declamped, and, once complete haemostasis is achieved, the tunica albuginea is closed with running absorbable suture. If FSE reveals malignancy, but radical orchidectomy is not performed, some authors advise obtaining multiple biopsies of the remaining parenchyma to rule out concomitant distant foci of malignancy or testicular intraepithelial neoplasia (TIN) on permanent histology [20]. Technical notes on specimen handling for FSE have been thoroughly discussed elsewhere [21]. Fig. 1 shows the most critical steps of the surgical technique.

FSE during TSS is gaining an increasingly prominent role. Despite initial concern due to potential sampling error and insufficient quality of the frozen section preparation [8], FSE has recently been demonstrated to be a highly reliable method to characterise testis tumours. Tokuc et al [8] and Elert et al [9] found that FSE was able to identify all malignant and benign testis tumours among 26 and 354 cases, respectively. Likewise, Leroy et al [22] reported a sensitivity of 81% for benign and 100% for malignant tumours in 15 patients, and Connolly et al [23] a 94.2% positive predictive value and a 92.6% negative predictive value for malignancy in 80 patients. Among malignant tumours, an approximately 10% failure to differentiate seminomatous from nonseminomatous tumours and vice versa has been documented [9], but this weakness has no major impact on the type of surgical procedure to be performed. Furthermore, inconclusive diagnosis on FSE has only rarely been observed [9].

These strengths notwithstanding, some controversy remains among experts on the real usefulness of FSE during TSS in cases of germ cell tumours (GCTs) [1,2]. The main concern relates to the fact that the reported high accuracy for FSE may be limited to only a few high-volume referral centres where experienced dedicated pathologists are available. Due to the rarity of testis tumours, confidence about the histopathologic evaluation of testicular specimens is perceptibly inferior in community hospitals. This potential pitfall needs to be addressed in further studies. Additionally, when considering non-GCTs cases, a formal diagnosis of benign versus malignant form can hardly be made unambiguously on FSE in all cases.

3.2. Indications and oncologic outcome

3.2.1. Germ cell tumours

The increasing incidence of early-stage malignant GCTs of the testis [24] and the constantly improving high survival rates of the affected patients are fuelling interest towards conservative treatment options [3]. Accordingly, TSS is gaining increasing acceptance in the urologic community. In one study, the introduction of routine ultrasonography in

the follow-up of patients treated with radical orchidectomy for malignant GCTs led to the detection of significantly smaller tumours in the contralateral testis, thereby resulting in a significantly higher rate of TSS [25].

Seppelt is credited with the first TSS ever performed for a malignancy [26]. The case, which dates back to 1982, concerned the management of a metachronous contralateral seminoma after radical orchidectomy, but the preserved testis had to be removed due to an infection 6 wk postoperatively. No tumour was found in the remaining parenchyma; thus this report should be regarded as the first *feasibility* study of TSS. The second description of TSS for a malignant tumour was reported 2 yr later by Richie [27], who concurrently performed a radical orchidectomy and hemiorchiectomy of the contralateral testis in a man with bilateral seminoma. After adjuvant radiotherapy to the remaining testis, the patient remained free of disease at the 2.5-yr follow-up. This approach was labelled as “unorthodox” by the author himself, but it stimulated the research of subsequent investigators.

Since then, in fact, two series [19,28] and several individual case reports [29–37] (Table 1) on TSS for GCTs have appeared in the literature, all of them concerning imperative indications (ie, synchronous bilateral tumours, metachronous contralateral tumours, or tumours in solitary testes). No single case of elective (ie, with healthy contralateral testes) enucleation of malignant GCTs has been reported so far.

The German Testicular Cancer Study Group compiled the largest case series [19] and presented the updated results in 2006 [38]. A total of 101 men with seminomatous and nonseminomatous bilateral tumours or tumours in solitary testes and a tumour volume <75% of the testis volume were treated with TSS at eight centres. Mean tumour size was 15 mm (range: 5–30 mm). During surgery, multiple biopsies of the surgical bed were taken to disclose concomitant foci of TIN, and local adjuvant radiotherapy with an 18-Gy dose was offered to all patients with TIN. A total of 85 patients had TIN, and 80 underwent local radiotherapy. After a mean follow-up of 80 mo, cancer-specific survival was excellent (100 of 101) with a low local recurrence rate (6 of 101). Of note, local recurrence developed in four patients who refused adjuvant radiotherapy.

In the second largest series, Steiner et al [28] reported on 11 patients treated with TSS for malignant GCTs. Mean tumour size was approximately 17 mm. Local adjuvant radiotherapy with a 18-Gy dose was offered to all patients who had concomitant TIN detected on multiple tumour bed biopsy. A total of 10 patients had TIN, and 8 underwent local radiotherapy. After a mean follow-up of approximately 60 mo, all patients were alive with no evidence of disease, and the only case of local recurrence occurred in a patient who had refused adjuvant radiotherapy.

A uniform experience of all reports is that TSS for GCTs does require adjuvant radiotherapy to the remaining testis. Virtually all GCTs are associated with the presence of TIN in the adjacent parenchyma [20,39]. TIN represents the precursor of GCT, and it inevitably progresses to invasive malignancy in the long run [1]. Irradiation does eradicate

Table 2 – Series reporting the use of testis-sparing surgery as an alternative to radical orchidectomy for the management of nonpalpable, ultrasound-detected testis tumours

First author	Year	Patients, <i>n</i>	Tumour size, range, mm	Treatment, No.			Frozen section examination, No.			Final pathology, No.			
				Testis-sparing surgery		Radical orchidectomy	Other	Benign	Malignant	Inconclusive	Benign	Malignant	Not available
				Imperative	Elective								
Buckspan [56]	1989	4	3–6	0	4	0	0	4	0	0	4	0	0
Hopps [16]	2002	4	2–16	1	3	0	0	3	0	1	2	2	0
Carmignani [9]	2003	10	4–16	0	7	3	0	10	0	0	10	0	0
Leroy [22]	2003	15	4–16	0	9	6	0	9	4	2	11	4	0
Sheynkin [57]	2004	9	NR	0	1	7	1*	1	0	0	6	2	1
Carmignani [58]	2004	3	NR	0	3	0	0	3	0	0	3	0	0
Colpi [59]	2005	5	3–5	0	4	1	0	4	1	0	4	1	0
Rolle [60]	2006	7	2–16	0	6	1	0	6	1	0	6	1	0
Assaf [36]	2006	6	4–20	1	1	2	2†	1	1	0	2	2	2
Müller [61]	2006	20	1–5	0	16	4	0	17	3	0	16	4	0
Powell [62]	2006	4	5–6	0	4	0	0	4	0	0	2	2	0
Eifler [63]	2008	19‡	NR		13	0	4‡, 2*	13	0	0	13	0	6
Hallak [17]	2009	5	6.7§	3	2	0	0	NR	NR	NR	4	1	0
Total		111	–	–	–	–	–	–	–	–	83	19	9

NR = not reported.
* Refused surgery or lost to follow-up.
† Active surveillance.
‡ Hypochoic nonpalpable lesions.
§ Mean.

TIN, thus preventing newly arising GCT, but it does also destroy all of the remaining germ cells causing permanent sterility. In contrast to germ cells, Leydig cells seem to be more resistant, yet many patients undergoing local radiotherapy experience some grade of endocrine function impairment. Therefore efforts were made to keep radiation dose as low as possible to preserve the endocrine function. Yet currently, the optimal dose of local radiotherapy remains controversial. Because dose reduction studies failed to prove the efficacy of doses <20 Gy to eradicate TIN [40,41], 20 Gy applied in 10 fractions within 2 wk remains the standard scheme of adjuvant radiotherapy [1].

TSS has also been performed for the treatment of epidermoid cyst, a neoplasm of possible germ cell origin [42]. In contrast to GCTs, epidermoid cysts are never accompanied by TIN; thus local excision is safe with no need for local adjuvant radiotherapy. In a comprehensive literature review, which also included their own experience, Heidenreich et al [43] reported on the use of TSS in >120 patients with epidermoid cysts. After a follow-up of up to 37 yr, not a single patient suffered from local or distant recurrence.

Unlike epidermoid cyst, dermoid cyst and mature teratoma represent true germ cell neoplasms, and the presence of TIN in the accompanying parenchyma must be considered. Nonetheless, local adjuvant radiotherapy does not appear to be mandatory. These tumours are exceedingly rare, and experience with TSS relies on only very few cases reported to date [27,44,45].

3.2.2. Sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours account for 3–5% of all testis tumours, with Leydig cell tumours representing 75–80% of them [46]. Less than 10% of all these tumours follow a malignant course, with metastasising cases mostly confined to older reports [46]. Established histologic criteria are currently used to predict the biologic aggressiveness of these tumours [46]. In contrast to GCTs, Leydig cell tumours may sometimes be suspected preoperatively because of typical heralding symptoms/signs (gynaecomastia, infertility, endocrine abnormalities) or ultrasonographic features [46].

Several studies are available that report on the medium- and long-term outcome of patients treated with TSS for Leydig cell tumours [28,47–53]. The results of the four largest series of men electively treated with TSS were presented by Droupy et al [48], Carmignani et al [49], Giannarini et al [50], and Suardi et al [51]. After a mean/median follow-up of approximately 4–8 yr, no patients experienced local or distant recurrence. The only case of locally recurrent Leydig cell tumour was reported by Wegner et al [54] in a 26-yr-old man 6 mo after TSS, despite small size and negative surgical margins.

Only five cases of Sertoli cell tumour managed with TSS have been reported so far [10,17,28,55], with three of them providing follow-up data as to absent local recurrence. Thus no evidence-based recommendations can be given regarding TSS for sex cord/gonadal stromal tumours other than Leydig cell tumours.

3.2.3. Nonpalpable tumours

The incidental detection of asymptomatic, nonpalpable, and small testis tumours by scrotal ultrasound is an increasingly encountered scenario. Several series are available, reporting on the management of such patients with TSS as an alternative to radical orchidectomy [10,16,17,22,36,56–63]. Most of these studies demonstrated that, contrary to palpable testis tumours that are malignant in >90% of cases [9], a high (approximately 80%) prevalence of benign histology has to be expected in nonpalpable masses (Table 2).

In a series of 27 men with ultrasound-detected testis tumours, Carmignani et al [10] reported an overall 52% prevalence of benign disease at definitive histology, with 80% of nonpalpable tumours being benign. Similarly, Sheynkin et al [58] reported a 75% prevalence of benign tumours among eight nonpalpable testis tumours. It has also been shown that smaller (<2 cm) nonpalpable tumours are more likely to be benign [23,64]. Of note, many of the nonpalpable testis tumours in these series were Leydig cell tumours, which have a benign behaviour, especially if they are small and occur at a younger age [46].

Remarkably, most patients included in this category of testis tumours were treated with TSS for an elective indication, that is, tumours in the presence of healthy

Table 3 – Series specifically reporting complications after testis-sparing surgery for tumours of different histology

First author	Year	Procedures, No.	Type of complication, No.			Complications treated with orchidectomy, No.
			Haematoma	Infection/Inflammation	Atrophy	
Heidenreich [19]	2001	73	–	–	4	4
Elert [9]	2002	37	3	3	1	–
Steiner [28]	2003	32	–	–	1	1
Carmignani [10]	2003	15	1	–	–	–
Connolly [23]	2006	25	–	–	–	–
Rolle [60]	2006	7	–	–	–	–
Carmignani [49]	2007	4	–	–	–	–
Giannarini [50]	2007	17	1	–	–	–
Suardi [51]	2009	28	–	–	–	–
Hallak [17]	2009	6	–	–	–	–
Total		244	5	3	6	5

contralateral testes. Thus TSS may be considered a viable option for all patients with nonpalpable tumours, particularly small ones, with the advantage of sparing an unnecessary radical orchidectomy in most of them. Clearly, FSE is a mandatory prerequisite in these cases.

3.3. Complications

TSS is associated with a low incidence of early and delayed postoperative complications, with an overall rate of <6% (Table 3). The main concern relates to the potential negative effect of TSS on the viability of the remaining testis. Testis atrophy was indeed reported in 3–5% of the performed procedures. It is intuitive, albeit not yet proven, that lesions amenable to TSS should be relatively small (<20 mm according to Heidenreich et al [19]), and surgical manoeuvres should respect intratesticular arterial anatomy. In a small series of four patients with GCTs and a tumour size <2 cm, testes were evaluated with magnetic resonance imaging before and 6 mo after TSS (K.-P. Dieckmann, personal communication, Hamburg, Germany). The image analysis revealed that size, shape, internal structure, and vascularisation were preserved in all patients (Fig. 2).

3.4. Functional outcome

The loss of testis parenchyma has potential negative consequences on long-term exocrine and endocrine function, as well as on psychosocial well-being. Although the detrimental effects of bilateral orchidectomy are well documented [19], the impact of unilateral orchidectomy has not been widely addressed in the literature so far. Some evidence indicates that the loss of only one testis is associated with impaired spermatogenesis [65–67], altered endocrine function [68–70], and reduced male body image [71,72].

Consequently, it appears reasonable to preserve as much testicular parenchyma as possible by pursuing TSS whenever possible, provided that cancer control is not jeopardised. These considerations hold particularly true for patients with malignant GCTs because a significant proportion of them have impaired spermatogenesis at the time of diagnosis [73]. Moreover, patients with GCTs are at risk to experience late-onset hypogonadism prematurely [69,70]. Furthermore, most of them receive local adjuvant radiotherapy after TSS, which may compromise the gonadal function [41].

In the largest TSS series reported so far with a mean follow-up of 80 mo, 84 of 101 patients treated with TSS for GCTs had a normal postoperative testosterone level [38]. Only 10 patients developed de novo hypogonadism and consequently received androgen supplementation; 6 had a low testosterone level as before surgery. An initial analysis of the series [19] revealed that among seven patients developing de novo hypogonadism, four had a large tumour size >20 mm and three had undergone surgery in warm ischaemia. Thus a significant proportion of hypogonadism cases could have resulted from an unfavourable selection of

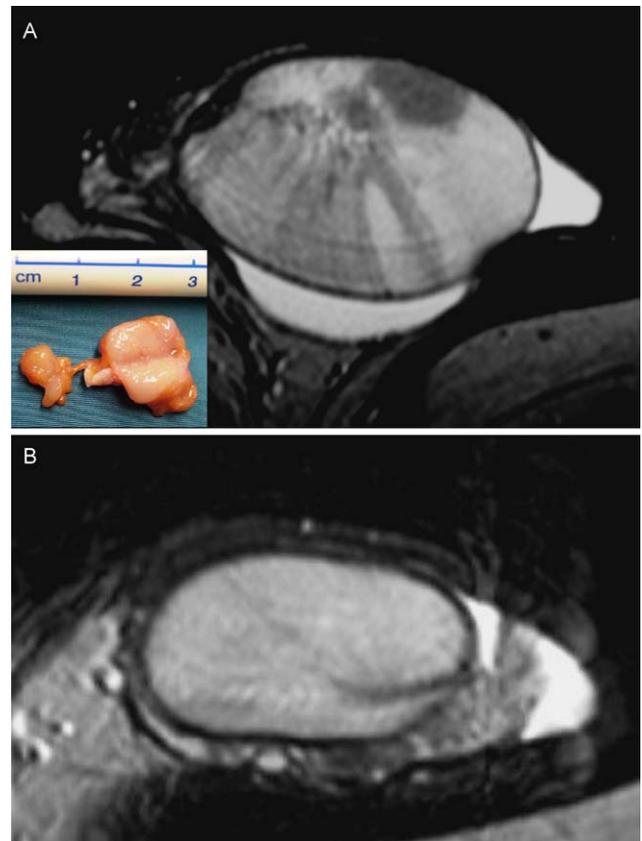


Fig. 2 – Sagittal T2-weighted magnetic resonance image of a testis (A) before and (B) after organ-sparing surgery for a segmented seminoma. No changes in testicular parenchyma are detectable after surgery. In the insert, the surgical specimen clearly corresponds to the preoperative image.

candidate patients and from an inappropriate surgical technique, respectively. However, in the updated series [38], four of six patients who postponed local adjuvant radiotherapy succeeded in achieving paternity.

In the series by Steiner et al [28], all patients had normal preoperative testosterone levels. Approximately 60 mo after TSS, all patients but one had a normal testosterone level. In the only patient developing androgen insufficiency (testosterone level: 0.4 ng/ml) and testicular atrophy, a comparatively large 30-mm mixed GCT was removed and local adjuvant radiotherapy was administered.

Grouping together the remaining individual case reports, providing functional data after TSS with a follow-up reaching 93 mo [17,29–37], it emerges that most patients did not require androgen supplementation and had a satisfactory sexual function but were infertile (Table 1). These data, however, should be interpreted with some caution because the combined evaluation of individual cases carries the inherent potential for positively inflated outcome due to publication bias.

Concerns regarding the possible functional advantages of TSS have been raised as far as patients with malignant GCTs are concerned because their gonadal function may be impaired due to a number of reasons [74].

First, ischaemia to the testis following spermatic cord clamping has the potential of damaging the exocrine and endocrine function. However, although this is incontrovertibly true for a long-lasting decrease in blood supply (ie, prolonged acute testicular torsion), sufficient experimental and clinical evidence suggests that no irreversible damage occurs, even under warm ischaemia, when spermatic cord clamping time does not exceed 30 min [19,75]. In two series, TSS with FSE was shown to be technically feasible during this time window [23,50]. Because the presumed benefit of spermatic cord clamping has never been formally proven, however, some experts have recently started to systematically refrain from spermatic cord clamping and testis cooling (P. Albers, personal communication, Düsseldorf, Germany). Although this procedure does clearly represent a paradigm shift in testis cancer surgery, it appears rational when the goal is to preserve gonadal function to the greatest extent in the case of TSS in solitary testes.

Second, local adjuvant radiotherapy after TSS determines sterility but may be safely postponed if fathering a child is desired, provided that follow-up is stringent [19]. Patients should be counselled to bank their sperm even in the presence of severe oligozoospermia. In addition, local radiotherapy has also been shown to impair Leydig cell function, and up to 40% of patients undergoing local radiotherapy may require testosterone supplementation in the long term regardless of the radiation dose [41]. One has to consider, however, that Leydig cell function may indeed be reduced as a preexisting abnormality in patients with testis cancer [41]. As a result, patients with low preoperative testosterone levels are usually excluded from TSS.

Third, incision of the tunica albuginea invariably violates the blood–testis barrier, which may subsequently induce the production of antisperm antibodies causing autoimmune infertility. However, this appears to be a rather theoretical concern. Leonhartsberger et al [76] observed comparable postoperative levels of antiserum sperm antibodies in patients with malignant GCTs treated with either radical orchidectomy or TSS.

Clearly, further research is urgently needed to ascertain whether these considerations also apply to patients treated with TSS for a benign tumour.

3.5. Guidelines

As a consequence of the paucity of published data, specific guidelines and recommendations by experts are scarce. In the 2009 EAU guidelines [2], TSS for GCTs is considered as an *alternative* to radical orchidectomy only in patients with synchronous bilateral tumours, metachronous contralateral tumours or tumour in solitary testis, tumour volume <30% of the testis volume, and normal preoperative testosterone levels. Adjuvant radiotherapy to the remaining testis with a 20-Gy dose is recommended to *all* patients *at some point* after TSS. The time span, however, remains unspecified. Furthermore, only *experienced* centres are advised to perform TSS. This could be a potential element deterring urologists from performing TSS. We acknowledge that

indications for TSS should be strict, but we invite all urologists to consider TSS as part of their routine surgical armamentarium. Additionally, when examining sex cord/gonadal stromal tumours, the guidelines state that TSS should be performed for *every small* intraparenchymal lesion to obtain the histologic diagnosis, and that a delayed radical orchidectomy can be performed if the definitive pathology reveals malignancy. However, no cut-off for tumour size is offered, and no specific studies are quoted.

The 2008 European Germ Cell Cancer Consensus Group report [1] endorses the same recommendations as the EAU guidelines, with the only exception the absence of indications concerning the tumour size cut-off to perform TSS.

In the 2009 NCCN guidelines [77], TSS is not mentioned. The ASCO and the AUA have released no guidelines on testis cancer so far.

4. Conclusions

The traditional dogma equating the diagnosis of any testis tumour to immediate radical orchidectomy has been challenged by the clinical experience accumulated in the last two decades.

Due to the low incidence of testis tumours and the long accrual time, no randomised controlled trials comparing TSS and radical orchidectomy are available and will hardly ever be conducted. However, increasing evidence from retrospective outcome studies with medium- and long-term follow-up suggests that TSS is a safe treatment option for selected cases of testis tumours of different histology in the adult population.

TSS should be considered for (1) small malignant GCTs with imperative indications for surgery and normal preoperative endocrine function; (2) small Leydig cell tumours even with elective indications, and (3) small nonpalpable, ultrasound-detected tumours with elective indications, provided that definitive histology fails to reveal malignancy. In the case of malignant GCTs, TSS should be coupled with local adjuvant radiotherapy.

Although functional advantages, namely preservation of fertility, endocrine function, and male body image, represent a strong theoretical argument to support the use of TSS for the treatment of testis tumours under appropriate conditions, currently available published data are immature. Prospective cooperative studies exploring health-related quality-of-life issues are therefore eagerly awaited to further qualify TSS as a recommendable treatment option.

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Study concept and design: Giannarini, Dieckmann, Albers, Heidenreich, Pizzocaro.

Acquisition of data: Giannarini, Dieckmann.

Analysis and interpretation of data: Giannarini, Dieckmann, Albers, Heidenreich, Pizzocaro.

Drafting of the manuscript: Giannarini.

Critical revision of the manuscript for important intellectual content: Dieckmann, Albers, Heidenreich, Pizzocaro.

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