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ORIGINAL ARTICLE

Male Infertility

Testicular sperm extraction (TESE) outcomes in the context of malignant disease: a systematic review

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Advances in the oncology field have led to improved survival rates. Consequently, quality of life after remission is anticipated, which includes the possibility to conceive children. Since cancer treatments are potentially gonadotoxic, fertility preservation must be proposed. Male fertility preservation is mainly based on ejaculated sperm cryopreservation. When this is not possible, testicular sperm extraction (TESE) may be planned. To identify situations in which TESE has been beneficial, a systematic review was conducted. The search was carried out on the PubMed, Scopus, Google Scholar, and CISMeF databases from 1 January 2000 to 19 March 2020. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were followed in selecting items of interest. Thirty-four articles were included in the systematic review, including 15 articles on oncological testicular sperm extraction (oncoTESE), 18 articles on postgonadotoxic treatment TESE and 1 article on both oncoTESE and postgonadotoxic treatment TESE. Testicular sperm freezing was possible for 42.9% to 57.7% of patients before gonadotoxic treatment and for 32.4% to 75.5% of patients after gonadotoxic treatment, depending on the type of malignant disease. Although no formal conclusion could be drawn about the chances to obtain sperm in specific situations, our results suggest that TESE can be proposed before and after gonadotoxic treatment. Before treatment, TESE is more often proposed for men with testicular cancer presenting with azoospermia since TESE can be performed simultaneously with tumor removal or orchiectomy. After chemotherapy, TESE may be planned if the patient presents with persistent azoospermia.

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INTRODUCTION

Current advances in early diagnosis and new treatments have led to improved survival rates in patients with cancer.[1] Consequently, many patients and health-care professionals anticipate the quality of life after remission, which includes the possibility to conceive healthy children.[2] However, all treatments prescribed in oncology (*e.g.*, chemotherapy, radiotherapy, and/or surgery) are potentially gonadotoxic.[3] Gonadotoxicity depends on several factors such as the type and dose of chemotherapy or radiation, the type of cancer, and the age of the patient. Counseling about fertility preservation before treatment initiation is, therefore, essential. International guidelines recommend that patients be informed as early as possible of the adverse effects of treatments on their fertility and of the possibility of fertility preservation.[4]

Male fertility preservation is mainly based on the cryopreservation of ejaculated sperm,[5] with semen collection performed after masturbation. Nevertheless, obtaining sperm samples through masturbation may be challenging under various conditions, such as if the patient is young or has a severe illness or there are ethnic or religious barriers. Although electroejaculation could then be an option to collect a semen sample,[6] it is not readily available in all centers.

Moreover, some men with cancer may present with sperm alteration at the time of fertility preservation;[7] specifically, azoospermia is found in 3% to 18% of men before surgery or chemotherapy initiation.[8,9] In the case of testicular cancer, different physiopathological hypotheses have been proposed, including testicular dysgenesis syndrome, testicular developmental disorders, systemic effects, endocrine effects, and immunity, which may impact spermatogenesis.[10] Local effects (inflammation and oxidative stress) may also disrupt the seminiferous tubes adjacent to the tumor.[11] For other cancers such as lymphomas or hematological diseases, a significant alteration in the patient's general state at diagnosis, systemic inflammation, hyperthermia (frequently observed during lymphomas), or testicular infiltration (as in acute leukemia) could explain sperm parameter impairments.[9]

In patients presenting with azoospermia or cryptozoospermia, ejaculated sperm freezing is not possible, and testicular sperm extraction (TESE) may be planned. TESE involves a surgical procedure to remove a small portion of testicular tissue for extracting spermatozoa. For some years now, this procedure has been performed through optical magnification using a surgical microscope. This procedure, named microsurgical testicular sperm extraction (microTESE), allows for the identification of spermatogenesis areas and requires a smaller testicular tissue sample.[12] Regardless of the surgical technique, TESE

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should be performed before the initiation of gonadotoxic treatment. Nevertheless, some situations, such as therapeutic urgency or medical constraints, may make this procedure impossible. Consequently, TESE is sometimes proposed to collect spermatozoa after remission if the patient still presents with azoospermia, cryptozoospermia, or severe oligozoospermia with no mobile spermatozoa. Hence, "oncological testicular sperm extraction (oncoTESE)" is used for testicular sperm extraction performed before any gonadotoxic treatment (surgery, chemotherapy, or radiotherapy), whereas "postgonadotoxic treatment TESE" is used for TESE performed after gonadotoxic treatment in the context of oncological pathology.

In both situations, when spermatozoa are isolated from the testicular tissue, they are cryopreserved for later use through *in vitro* fertilization techniques such as intracytoplasmic sperm injection (ICSI).

Since TESE is an invasive surgical procedure, it should only be proposed for well-established indications. Literature on this subject remains scarce and includes a limited number of patients. Thus, this study aims to conduct a systematic review to identify situations in which TESE in a malignant disease context has made it possible to obtain spermatozoa and situations in which TESE has not been beneficial, both before the initiation of gonadotoxic treatments and after treatment and remission.

METHODS

Literature search and eligibility criteria

A search was carried out on the PubMed, Scopus, Google Scholar and CISMeF databases from 1 January 2000 to 19 March 2020. The search strategy was based on the following combined search terms: "((fertility preservation [title/abstract]) or (fertility preservation [mesh terms]) or (chemotherapy [title/abstract]) or (chemotherapy [mesh terms]) or (radiotherapy [title/abstract]) or (radiotherapy [mesh terms]) or (gonadotoxic [title/abstract]) or (gonadotoxic [mesh terms]) or (cancer [title/abstract]) or (cancer [mesh terms]) or (oncology [title/abstract]) or (oncology [mesh terms])) AND ((testicular sperm extraction [title/abstract]) or (testicular sperm extraction [mesh terms]) or (testicular sperm retrieval [title/abstract]) or (testicular sperm retrieval [mesh terms]) or (sperm extraction [title/abstract]) or (sperm extraction [mesh terms]) or (sperm retrieval [title/abstract]) or (sperm retrieval [mesh terms]) or (TESE [title/abstract]) or (TESE [mesh terms]) or (microTESE [title/abstract]) or (microTESE [mesh terms]) or (oncoTESE [title/abstract]) or (oncoTESE [mesh terms]))". We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations when selecting items of interest.[13]

Study selection and data extraction

After eliminating duplicates, articles were preselected through 2 independent readers (LO and CD), who read titles and abstracts. Preselected articles were then classified as "excluded", "doubtful" or "retained". "Doubtful" articles were further discussed between LO and CD, and a third reader (NS) intervened to resolve any disagreement or uncertainty. LO and CD then read the full text of the "retained" articles.

Data synthesis

The articles were classified according to whether they dealt with oncoTESE (TESE performed before any gonadotoxic treatment) or postgonadotoxic treatment TESE. Pretreatment oncoTESE included all TESEs performed before the initiation of any potentially gonadotoxic cancer treatment (chemotherapy, radiotherapy or testicular surgery). Moreover, TESE performed simultaneously with testicular tumor surgery were considered pretreatment oncoTESE in this study. Finally, postgonadotoxic treatment TESE were procedures conducted after the end of a potentially gonadotoxic cancer treatment.

To characterize the included studies, the following details were extracted: year of publication, country, sample size, cancer diagnosis, the indication of TESE, TESE technique, TESE outcomes, and assisted reproductive technique (ART) outcomes after cryopreserved spermatozoa use. TESE outcomes according to the type of cancer were also reported. In this analysis, only retrospective studies were included to avoid publication bias linked to case reports since successful stories are more often published. Chi-square tests were used to compare the chances of freezing spermatozoa after TESE according to the cancer diagnosis. Statistical analyses were performed using Prism 6 software (GraphPad Software Inc., La Jolla, CA, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

Study selection

The search strategy identified a total of 194 articles, including duplicates and articles that had no relevance to the primary research questions. After reviewing 56 titles and abstracts, 38 full-text articles were assessed for eligibility. Among them, 34 articles were included in the systematic review, including 15 articles on oncoTESE, 18 articles on postgonadotoxic treatment TESE and 1 article on both oncoTESE and postgonadotoxic treatment TESE, and cited in both sections (**Figure 1**).

OncoTESE before the initiation of gonadotoxic treatment

Study characteristics

Sixteen articles evaluating oncoTESE before the initiation of gonadotoxic treatment were included, most of which were case reports or case series ($n = 12$),[14–25] with only 4 retrospective studies.[6,26–28]

The case reports mainly reported TESE that allowed for spermatozoa retrieval and cryopreservation,[14–25] while the retrospective studies reported 38.1% and 57.8%,[6] 66.7%,[26] 80%,[27] and 45.2%[28] positive TESEs, respectively. Sperm utilization was evaluated in 3 retrospective studies and 7 case reports, corresponding to 11 ICSI cycles reported to have resulted in 10 pregnancies or live births (**Table 1**).

Many oncoTESEs were performed simultaneously with an orchiectomy or lumpectomy in the context of a testicular tumor. TESE was the most widely used procedure compared to microTESE.

Results according to the type of cancer

Cancer types were classified into 5 categories: testicular tumor (TT), Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), leukemia (LK), and other cancers. Case reports and case series were eliminated from the analysis to limit bias.

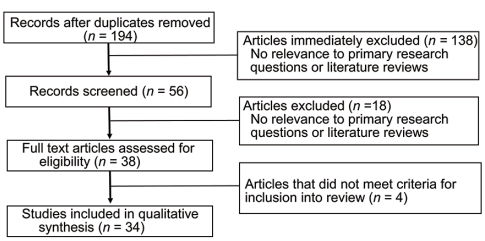

Figure 1: Flowchart of study selection for systematic review with PubMed, Scopus, Google Scholar, and CISMeF database between 1 January 2000 to 19 March 2020.

Table 1: Characteristics of studies reporting oncological testicular sperm extraction performed before gonadotoxic treatment

Study	*Study type (n)*	*Sample size (n)*	*Azoospermia (n)*	*OAT or Crypt (n)*	*Others (n)*	*Cancer type*	*Sperm extraction procedure*	*Positive TESE, n (%)*	*ART and LB*
Berookhim and Mulhall 2014;[6] USA	Retrospective study	39	15	16	8	NA	TESE	TESE: 8 (38.1) EEJ + TESE: 10 (57.8)	None
Furuhashi *et al*. 2013;[26] Japan	Retrospective study	3	2	1	0	1 SGCT, 1 NSGCT, 1 NGTT	TESE	2 (66.7)	1 ICSI (1 pregnancy)
Hallak *et al*. 2009;[27] Brazil	Retrospective study	5	5	0	0	1 SGCT, 5 NGTT (1 bilateral TT)	mTESE	4 (80.0)	1 ICSI (1 LB)
Schrader *et al*. 2003;[28] Germany and Japan	Retrospective study	31	31	0	0	8 SGCT, 6 NSGCT, 7 HD, 10 NHL	TESE	14 (45.2)	2 ICSI (1 miscarriage and 1 LB)
Sener *et al*. 2018;[14] Turkey	Case report	1	0	1	0	1 SGCT	TESE	1 (100.0)	None
Kuroda *et al*. 2018;[15] Japan	Case report	1	1	0	0	1 SGCT	mTESE	1 (100.0)	None
Tsutsumi *et al*. 2017;[16] Japan	Case report	2	2	0	0	2 SGCT	TESE	1 (50.0)	None
Pindoria *et al*. 2016;[17] UK	Case report	1	1	0	0	1 epididymal papillary cystadenocarcinoma	TESE and mTESE	1 (100.0)	1 ICSI (1 LB)
Luján *et al*. 2016;[18] Spain	Case report	1	1	0	0	1 SGCT	TESE	1 (100.0)	1 ICSI (1 LB)
Roque *et al*. 2015;[19] Brazil	Case report	1	1	0	0	1 SGCT	TESE	1 (100.0)	1 ICSI (1 LB)
Haddad *et al*. 2014;[20] Canada	Case report	1	0	1	0	1 SGCT	TESE	1 (100.0)	None
Safsaf *et al*. 2011;[21] France	Case report	1	1	0	0	1 SGCT	TESE	1 (100.0)	None
Descombe *et al*. 2008;[22] France	Case report	2	1	1	0	1 SGCT, 1 NSGCT	TESE	2 (100.0)	1 ICSI (1 LB)
Carmignani *et al*. 2007;[23] Italy	Case report	4	4	0	0	2 SGCT, 2 NGTT	mTESE	3 (75.0)	1 ICSI (no LB, sperm donation)
Binsaleh *et al*. 2004;[24] Canada	Case report	2	2	0	0	2 NGTT	mTESE	1 (50.0)	1 ICSI (1 pregnancy)
Res *et al*. 2000;[25] Slovenia	Case report	1	1	0	0	1 SGCT	TESE	1 (100.0)	1 ICSI (1 LB)

OAT: oligoasthenoteratospermia; Crypt: cryptozoospermia; Others: sperm collection failures, sperm collection refusal, anejaculation, or retrograde ejaculation; ART: assisted reproductive technology; LB: live birth; NA: not available; TESE: testicular sperm extraction; mTESE: microsurgical TESE; TGCT: testicular germ cell tumor; SGCT: seminomatous germ cell tumor; NSGCT: non-SGCT; NGTT: nongerminal testicular tumor; HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma; EEJ: electroejaculation; ICSI: intracytoplasmic sperm injection

Table 2: Oncological testicular sperm extraction before treatment: positive testicular sperm extraction according to the disease

Reference	*Sperm extraction procedure*	*TESE⁺, n/ total (%)*
Testicular tumor		
Schrader *et al*. 2003[28]	TESE	6/14
Carmignani *et al*. 2007[23]	mTESE	3/4
Hallak *et al*. 2009[27]	mTESE	4/5
Furuhashi *et al*. 2013[26]	TESE	2/3
Total		15/26 (57.7)
Hodgkin's disease		
Schrader *et al*. 2003[28]	TESE	3/7
Total		3/7 (42.9)
Non-Hodgkin's lymphoma		
Schrader *et al*. 2003[28]	TESE	5/10
Total		5/10 (50.0)
Leukemia		
NA		
Total		NA
Other cancers		
NA		
Total		NA

NA: not available; TESE: testicular sperm extraction; mTESE: microsurgical TESE; TESE⁺: positive TESE

Pretreatment oncoTESEs were mostly performed in men presenting with a TT, and TESE was positive in 57.7% of cases. For men with HL and NHL, spermatozoa were found in 42.9% and 50.0% of TESEs, respectively. The differences were not significant for these 3 indications ($P > 0.05$; **Table 2**). OncoTESEs for other indications were only reported in case reports.

Postgonadotoxic treatment TESE

Study characteristics

Eleven retrospective studies[26,29–38] and 8 case reports or case series[39–46] reported results for postgonadotoxic treatment TESE. The case reports and case series mainly reported TESEs that allowed for spermatozoa retrieval, while the retrospective studies reported between 33.3% and 76.2% positive TESEs (**Table 3**).

Most of the articles described the outcomes of ICSI-TESE cycles, with highly heterogeneous live birth rates across studies. Both TESE and microTESE were proposed to collect spermatozoa.

Results according to the type of cancer

Cancer types were classified into 5 categories: TT, HD, NHL, LK, and other cancers. Case reports and case series were eliminated from the analysis to limit bias. Postgonadotoxic treatment TESE were positive in 75.5% of men with TT, whereas they were positive in 34.6%, 32.4%, 32.6%, and 44.4% of men with HL, NHL, L, and other cancers, respectively (all $P < 0.001$; **Table 4**).

DISCUSSION

This systematic review confirmed the feasibility of TESE in the context of malignant diseases leading to sperm cryopreservation for about half of patients. This result is close to those obtained after TESE and microTESE in an ART context.[47]

Before initiating chemotherapy, it is important to discuss the possibility of TESE in the cases of azoospermia, severe oligozoospermia, cryptozoospermia, or sperm collection failure. Nevertheless, numerous constraints such as organizational issues, contraindication to anesthesia, or an urgent need to initiate treatment can make this procedure impossible. In this review, it was highlighted that TESE performed before gonadotoxic treatment is mainly applicable

Table 3: Characteristics of studies reporting testicular sperm extraction performed after gonadotoxic treatment

Study characteristics			*TESE indication (n)*			*Cancer and treatment characteristics*			*TESE characteristics*		*Number of ART procedures and LB (n)*
Study	*Study type*	*Sample size (n)*	*Azoospermia*	*OAT or Crytp*	*Others*	*Cancer type*	*Treatment received before TESE*	*Delay (end of treatment-TESE), year*	*Sperm extraction procedure*	*Positive TESE, n (%)*	
Levi-Setti *et al*. 2020;[29] Italy	Retrospective study (case-control)	88	67	0	21	26 SGCT, 25 NSGCT, 14 HD, 8 NHL, 15 others	CT, RT, SUR	Mean ± s.d.: 8.7±8.6	TESE	55 (62.5): 34 (50.7, azoospermia) and 21 (100 others)	88 ICSI (22 LB [25.0%])
Dar *et al*. 2018;[30] Israel	Retrospective study	36	36	0	0	4 SGCT, 13 HD, 3 NHL, 5 LK, 11 others	CT, RT	Mean ± s.d.: 8.2±2.6 Minimum: 1	mTESE	12 (33.3)	17 ICSI (10 LB [58.8%])
Shin *et al*. 2016;[31] Japan	Retrospective study	65	65	0	0	21 TT, 9 HD, 7 NHL, 16 LK, 12 others	CT, BMT	Mean (range): 8.8 (1–30)	mTESE	31 (47.7)	31 ICSI (18 LB [58.1%])
Shiraishi and Matsuyama 2014;[32] Japan	Retrospective study	26	26	0	0	8 TT, 5 HD, 4 NHL, 5 LK, 4 others	CT	Mean: 14.8	mTESE	12 (46.1)	58 ICSI (5 LB [8.6%]; cumulative LB [19.0%])
Furuhashi *et al*. 2013;[26] Japan	Retrospective study	3	2	1	0	2 SGCT, 1 NSGCT	CT, SUR	Mean (range): 10.5 (1–20)	TESE	2 (66.7)	1 ICSI (1 pregnancy [100.0%])
Hsiao *et al*. 2012;[33] USA	Retrospective study	21	7	12	2	21 NSGCT	SUR	NA	TESE	16 (76.2)	None
Hsiao *et al*. 2011;[34] USA	Retrospective study	73	73	0	0	7 TT, 27 HD, 11 NHL, 12 LK, 16 others	CT	Mean ± s.d. (range): 19±7.7 (1–34)	TESE then mTESE	27 (37.0)	36 ICSI (15 LB [41.7%])
Hibi *et al*. 2007;[35] Japan	Retrospective study	5	5	0	0	1 SGCT, 1 NSGCT, 1 NHL, 2 sarcoma	CT, RT, SUR	Mean (range): 10.4 (2.5–18)	mTESE	3 (60.0)	7 ICSI (2 LB [28.6%])
Zorn *et al*. 2006;[36] Slovenia	Retrospective study	30	18	0	12	4 SGCT, 16 NSGCT, 5 HD, 1 LK, 4 others	CT, RT, SUR	Mean (range): 9.4 (2–19)	TESE	21 (70.0)	39 ICSI (4 LB [10.2%])
Meseguer *et al*. 2003;[37] Spain	Retrospective study	12	12	0	0	6 NSGCT, 3 HD, 1 NHL, 1 LK, 1 sarcoma	CT, RT, SUR	Mean (range): 10.8 (4–24)	TESE	5 (41.7)	8 ICSI (1 LB [12.5%])
Damani *et al*. 2002;[38] USA	Retrospective study	21	21	0	0	12 TT, 2 HD, 2 NHL, 1 LK, 4 others	CT	NA	TESE	15 (71.4)	26 ICSI (8 LB; 2 miscarriages)
Jacobsen *et al*. 2019;[39] Denmark	Case report	1	1	0	0	1 NHL + other	CT, RT, BMT	5	mTESE	1 (100.0)	1 ICSI (1 miscarriage)
Chen *et al*. 2019;[40] China	Case report	3	3	0	0	NA	CT	NA	mTESE	2 (66.7)	2 ICSI (NA)
Hamano *et al*. 2018;[41] Japan	Case report	1	1	0	0	1 TT	SUR	5	TESE	1 (100.0)	14 ICSI (0 LB [0])
Carrasquillo *et al*. 2018;[42] USA	Case report	1	1	0	0	1 SGCT	SUR	NA	mTESE	1 (100.0)	None
Wood *et al*. 2017;[43] USA	Case report	1	0	0	1	1 prostatic ADK	RT, SUR	11	TESE	1 (100.0)	2 ICSI (1 LB [50.0%])
Sakamoto *et al*. 2007;[44] Japan	Case report	2	1	0	1	1 SGCT, 1 NSGCT	CT, SUR	Range: 1–5.7	TESE	2 (100.0)	3 ICSI (1 pregnancy [33.3%])
Choi *et al*. 2005;[45] USA	Case report	2	1	1	0	1 SGCT, 1 NA	RT, SUR	NA	mTESE	2 (100.0)	3 ICSI (2 LB [66.7%])
Kohn *et al*. 2001;[46] Germany	Case report	1	1	0	0	1 NSGCT	SUR	17	TESE	1 (100.0)	2 ICSI (0 LB [0])

s.d.: standard deviation; OAT: oligoasthenoteratospermia; Crypt: cryptozoospermia; Others: sperm collection failures, sperm collection refusal, anejaculation, or retrograde ejaculation; ART: assisted reproductive technology; LB: live birth; NA: not available; TESE: testicular sperm extraction; mTESE: microsurgical TESE; TT: testicular tumor; GCT: germ cell tumor; TGCT: testicular GCT; SGCT: seminomatous GCT; NSGCT: non-SGCT; NGTT: nongerminal testicular tumor; HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma; LK: leukemia; ADK: adenocarcinoma; CT: chemotherapy; RT: radiotherapy; SUR: surgery; BMT: bone marrow transplantation; ICSI: intracytoplasmic sperm injection

Table 4: Testicular sperm extraction after treatment: positive testicular sperm extraction according to the disease

Reference	*Sperm extraction procedure*	*TESE⁺, n/total (%)*
Testicular tumor		
Levi-Setti *et al*. 2020[29]	TESE	37/51
Dar *et al*. 2018[30]	mTESE	4/4
Shin *et al*. 2016[31]	mTESE	11/21
Furuhashi *et al*. 2013[26]	TESE	2/3
Shiraishi and Matsuyama 2014[32]	mTESE	7/8
Hsiao *et al*. 2012[33]	TESE	16/21
Hsiao *et al*. 2011[34]	TESE/mTESE	6/7
Hibi *et al*. 2007[35]	TESE	2/2
Zorn *et al*. 2006[36]	TESE	19/20
Meseguer *et al*. 2003[37]	TESE	4/6
Damani *et al*. 2002[38]	TESE	9/12
Total		117/155 (75.5)
Hodgkin's disease		
Levi-Setti *et al*. 2020[29]	TESE	6/14
Dar *et al*. 2018[30]	mTESE	3/13
Shin *et al*. 2016[31]	mTESE	6/9
Shiraishi and Matsuyama 2014[32]	mTESE	1/5
Hsiao *et al*. 2011[34]	TESE/mTESE	7/27
Zorn *et al*. 2006[36]	TESE	2/5
Meseguer *et al*. 2003[37]	TESE	1/3
Damani *et al*. 2002[38]	TESE	1/2
Total		27/78 (34.2)
Non-Hodgkin's lymphoma		
Levi-Setti *et al*. 2020[29]	TESE	2/8
Dar *et al*. 2018	mTESE	1/3
Shin *et al*. 2016[31]	mTESE	3/7
Shiraishi and Matsuyama 2014[32]	mTESE	1/4
Hsiao *et al*. 2011[34]	TESE/mTESE	4/11
Hibi *et al*. 2007[35]	mTESE	0/1
Meseguer *et al*. 2003[37]	TESE	0/1
Damani *et al*. 2002[38]	TESE	1/2
Total		12/37 (32.4)
Leukemia		
Levi-Setti *et al*. 2020[29]	TESE	2/5
Dar *et al*. 2018[30]	mTESE	0/5
Shin *et al*. 2016[31]	mTESE	6/16
Shiraishi and Matsuyama 2014[32]	mTESE	1/5
Hsiao *et al*. 2011[34]	TESE/mTESE	6/12
Zorn *et al*. 2006[36]	TESE	0/1
Meseguer *et al*. 2003[37]	TESE	0/1
Damani *et al*. 2002[38]	TESE	0/1
Total		15/46 (32.6)
Other cancers		
Levi-Setti *et al*. 2020[29]	TESE	8/10
Dar *et al*. 2018[30]	mTESE	4/11
Shin *et al*. 2016[31]	mTESE	5/11
Shiraishi and Matsuyama 2014[32]	mTESE	2/4
Hsiao *et al*. 2011[34]	TESE/mTESE	4/16
Hibi *et al*. 2007[35]	mTESE	1/2
Zorn *et al*. 2006[36]	TESE	0/4
Meseguer *et al*. 2003[37]	TESE	0/1
Damani *et al*. 2002[38]	TESE	4/4
Total		28/63 (44.4)

TESE: testicular sperm extraction; mTESE: microsurgical TESE; TESE⁺: positive TESE

to testicular tumors since the TESE can be performed simultaneously with tumor removal or orchiectomy. Only 1 study reported diseases other than a testicular tumor,[28] making it impossible to compare the outcomes of sperm extraction across cancer types. Few studies reported the effectiveness of the procedure in terms of a live birth following ART, and no formal conclusion can be drawn from the numerous case reports published on the subject due to major publication bias.

For TESE performed after gonadotoxic treatment, retrospective studies highlighted that sperm recovery rates are favorable. Nevertheless, differences were observed according to the type of cancer. Patients in remission of testicular cancer are much more likely to have spermatozoa in their testicular tissue than patients in remission of hematological cancers, Hodgkin's disease, or lymphoma. These differences may be due to the intensity and severity of treatment, which vary according to the cancer type. Indeed, concerning testicular tumors, only excisional surgery, with or without lymph node removal, may be proposed. Moreover, when chemotherapy is needed, it is often a combination of bleomycin, etoposide, and cisplatin (BEP), which has an estimated 20% risk of intermediate prolonged infertility.[8] In comparison, treatments used for Hodgkin's disease, such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (BEACOPP), may lead to a high risk of permanent infertility.[8,48] Nevertheless, some studies reported positive sperm retrieval in patients with a history of lymphoma or leukemia (**Table 4**), and a case of positive TESE after bone marrow transplantation was even published.[39] Consequently, although it is difficult to propose guidelines for patients in remission of cancer presenting with persistent azoospermia, TESE is an option to consider. Each case should be discussed based on the overall outcome, even though the prognosis of TESE remains poorly known. The time interval between the end of chemotherapy or radiotherapy should also be discussed since an increased risk of sperm aneuploidy is present up to 12 months after radiotherapy and 24 months after chemotherapy.[49,50] Even if azoospermia is usually the consequence of gonadotoxic treatments when it is diagnosed after remission (this is posttreatment, nonobstructive azoospermia [NOA] or posttreatment NOA),[30] some patients may have suffered from azoospermia before their malignant diseases. A complete exploration of azoospermia, including a hormonal status evaluation, testicular examination, and genetic screening, should be proposed.

When testicular spermatozoa are frozen, ICSI outcomes seem similar to those obtained with ejaculated spermatozoa or testicular spermatozoa in nonmalignant situations. Many factors, including female partners' characteristics, may influence ICSI-TESE outcomes. Nevertheless, the long-term impact of chemotherapy or radiotherapy on spermatozoa quality remains controversial.[49]

Concerning the surgical procedure, an increased risk of hematoma, as well as additional difficulties in organizing microTESE in an emergency context, is to be weighed against a possible higher extraction rate. To date, it seems impossible to formally conclude that microTESE is superior to conventional TESE.

This systematic review had some limitations. The number of patients was quite low, data were missing and many case reports were included. Therefore, it seems important to continue collecting data on the subject to better inform professionals and patients.

CONCLUSIONS

This review shows that TESE can be proposed before and after gonadotoxic treatment. Before treatment, TESE is more often proposed for men with testicular cancer since TESE can be performed simultaneously with tumor removal or orchiectomy. Nevertheless, it can

also be proposed for men with other cancers. After chemotherapy, TESE may be planned if the patient presents with persistent azoospermia, but hormonal, genetic, and testicular status evaluations are required to evaluate the benefit–risk balance.

AUTHOR CONTRIBUTIONS

LO and CD reviewed the literature, collected data, and wrote the manuscript. IB, RL, RHH, MP, MA, and NS collaborated in writing, revising, and editing the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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