Outcomes of operative sperm retrieval strategies for fertility preservation among males scheduled to undergo cancer treatment

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Objective: To describe the outcomes of electroejaculation (EEJ) and testicular sperm extraction (TESE) performed for fertility preservation among male patients who are unable to ejaculate or have nonobstructive azoospermia/severe oligospermia before definitive cancer therapy.
Design: Retrospective cohort study.
Setting: Tertiary cancer referral center.
Patient(s): Forty-nine patients seeking fertility preservation before definitive cancer therapy, with anejaculation, religious or cultural objections to masturbation, azoospermia, or severe oligospermia requiring either EEJ or TESE.
Intervention(s): EEJ and TESE.
Main Outcome Measure(s): Sperm retrieval rates.
Result(s): Fifty-nine percent of patients overall and 60% of adolescents/young adults had sperm retrieved for cryopreservation. EEJ was successful in retrieving sperm in 60% of adolescents. Of all adolescents and young adults undergoing TESE, 33% had sperm retrieved for cryopreservation. No complications were reported. Chemotherapy was commenced without delay in all patients requiring it, frequently on the same day as the sperm retrieval.
Conclusion(s): EEJ and TESE can be safely and successfully used for fertility preservation before cancer therapy among boys and young adult men who are unable to provide a semen specimen or have nonobstructive azoospermia, and they should be considered in all men meeting this patient profile. (Fertil Steril® 2014;101:805–11. ©2014 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, adolescent, electroejaculation, testicular sperm extraction, cancer

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Infertility, particularly nonobstructive azoospermia, is a well recognized effect of chemotherapeutic regimens for the treatment of male patients with cancer (1–3). In the United States, ~60% of male patients aged 15–29 years experience 20-year survival after diagnosis of invasive cancer, with an almost 50% 20-year survival rate in the 30–44-year-old age group (4). Increasing survival rates are expected in the future as oncologic care continues to improve, making the likelihood of future fertility an important component of the treatment of these patients. Given these survival rates, fertility preservation among patients with newly diagnosed cancer is gaining increasing clinical attention. In addition, 43%–71% of adolescent patients and their parents, across cancer risk groups, report a concern regarding fertility potential after cancer diagnosis (5). Despite this, referral rates for fertility preservation among oncologists remain low, with recent surveys reporting only 38%–47% of oncologists providing in-depth material or referring patients to fertility specialists for patients of "child-bearing" age (6, 7).

Among post-pubertal males, fertility preservation before the use of potentially gonadotoxic chemotherapeutic and radiotherapy agents is

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frequently a straightforward procedure, consisting of cryopreservation of masturbation-assisted ejaculated semen. Obtaining semen samples by masturbation poses a clinical dilemma in some of these patients, who report having never masturbated secondary to young age, religious or cultural objections, severe pain limiting the ability to ejaculate, or anatomic derangements due to tumor mass leading to anejaculation.

Additionally, recent literature confirms that some men with cancer are already oligospermic/azoospermic before any therapeutic intervention (8, 9). The mechanism of this tumor-induced impairment in spermatogenesis is not fully understood at this time; it may be caused by local effects of testicular tumors on nearby seminiferous tubules owing to paracrine action of secretory substances of the tumor, disruption of the blood-testis barrier, endocrine effects from production of β-hCG and α-fetoprotein (AFP), and systemic responses from cytokines, including interleukins and tumor necrosis factors (10). Patients with testicular cancer may in fact be presenting along a spectrum of disease known as the testicular dysgenesis syndrome, supported by epidemiologic and histologic links between cryptorchidism, hypospadias, male infertility, and testicular cancer (11). It should be noted, however, that patients presenting with these factors are frequently normospermic, highlighting a lack of true understanding of the factors leading to subfertility in these men.

To date, sperm obtained by electroejaculation (EEJ) for cryopreservation among teenagers has been reported in only three case series, all with small patient cohorts (12–14). Similarly, testicular sperm extraction (TESE) before cancer treatment among azoospermic adults has been reported in a variety of case series, also all with small patient populations (15–20). We report our experience with surgical sperm retrieval, via EEJ and TESE, for patients unable to produce a semen specimen or with azoospermia who sought fertility preservation before definitive oncologic therapy. Additionally, we performed a subset analysis to report outcomes of surgical sperm retrieval for fertility preservation in adolescents and young adults aged 11–19 years.

MATERIALS AND METHODS

Patient Population

A retrospective review was performed of all male patients referred for evaluation for surgical sperm retrieval for fertility preservation before definitive cancer therapy at a tertiary referral cancer center. Males were referred for evaluation at a single center for surgical sperm retrieval because of inability to ejaculate (anejaculation), religious or cultural objections to masturbation, azoospermia, or severe oligospermia (<1 million sperm/mL of semen) before cancer treatment. The database was registered with, and the study approved by, the Institutional Ethics Committee.

Owing to the tertiary referral center nature of the institution, patients are frequently referred for definitive treatment on an urgent or emergent basis, rendering a complete preoperative work-up for nonobstructive azoospermia difficult to complete in all patients. Patients who were able to provide a semen specimen had at least a single semen analysis reviewed. Azoospermic and severely oligospermic patients were additionally evaluated with a karyotype and analysis for Y chromosome microdeletions when time permitted. All patients had a complete physical examination performed with assessment of Tanner pubertal stage and use of a Prader orchidometer to evaluate testicular volumes. Hormonal evaluation including total serum testosterone and FSH was obtained, when possible, before sperm retrieval. Surgical sperm retrieval was generally scheduled at the time of other surgical procedures in all patients scheduled for adjunctive procedures for cancer therapy (radical orchiectomy, insertion of a central venous access infusion device, bone marrow biopsies).

Electroejaculation

Among patients who were either anejaculatory or could not otherwise produce a semen specimen, EEJ was performed under general anesthesia. In some cases, especially among Orthodox Jewish patients, consultation was held with the patient's rabbi in an effort to define what was rabbinically permitted regarding semen retrieval. When EEJ was permitted, the procedure commenced with bladder catheterization and instillation of 30 mL sperm transport medium into the bladder. The patient was then placed in the lateral decubitus position, and a digital rectal examination and anoscopy were performed. EEJ was performed with the use of the Seager Model 14 Electroejaculator (Dalzell USA Medical Systems), by inserting a 1.25-inch transrectal probe (with longitudinally oriented electrodes). The probe was inserted and the electrodes were oriented anteriorly to be placed in contact with the rectal mucosa in the region of the prostate and seminal vesicles. A pulsatile pattern of electrical stimulation was administered with 20–25 V and 0.4–0.6 A until ejaculation occurred. Stimulations were administered in cycles of five stimulations while attention was paid to the rectal temperature. If the temperature were to rise above 37°C the procedure would be aborted. The ejaculate was collected in a sterile plastic cup with a wide mouth. This was mixed with sperm transport medium and was then evaluated for the presence of sperm with the use of phase-contrast microscopy at $\times$400 magnification. Wet preparation of the semen sample was performed by the operating surgeon at the time of EEJ to evaluate semen quality. The number of sperm and their motility were recorded. Total number of vials cryopreserved was ultimately decided by the embryologist at the local sperm bank, with a recommendation by the operating surgeon to maximize number of vials cryopreserved whenever possible. The patient was then returned to the supine position, the bladder was catheterized, and the resulting urine sample was collected. Both antegrade and retrograde specimens were sent to the sperm bank for evaluation.

Testicular Sperm Extraction

In patients in whom EEJ was not permitted for religious reasons, or in whom EEJ procured an inadequate specimen (azoospermia, or <1 sperm per 10 high-power fields,or absence of motility), or who were azoospermic or severely

oligospermic on post-masturbation semen analysis, TESE was performed. Given that most of these patients were to commence chemotherapy within 24 hours of sperm retrieval, testis delivery and bivalving (which is routine for our post-chemotherapy TESE procedures) was not performed because of concerns for wound healing. A midline scrotal raphe incision, ~2 cm in length, was made to access the testis for TESE. After identification of the tunica albuginea, a 1-cm incision was made in the tunica albuginea to expose the seminiferous tissue. After achieving hemostasis, tubules were extruded through the incision in the tunica albuginea and excised. The resulting specimen was completely minced with scissors in sperm transport medium in a Petri dish and sequentially passed through a 24-gauge angiocatheter. A sample of this tissue was examined with the use of phase-contrast microscopy at ×400 magnification to detect spermatozoa. Patients with no sperm identified on wet preparation performed by the operating surgeon had an identical procedure performed on the contralateral side. Specimens were placed in sperm transport medium and sent for formal evaluation and cryopreservation by an embryologist at the sperm bank.

Ex vivo TESE was performed in those patients undergoing concomitant radical orchiectomy. Following radical orchiectomy, the specimen was evaluated on a back table. A transverse incision, extending from the upper pole to the lower pole of the testis, was made through the tunica albuginea, and the testis was opened widely. Samples of seminiferous tubules identified to be well away from grossly visible tumor sites were excised and sent to the embryologist for evaluation and cryopreservation.

RESULTS

Patient Population

A total of 49 patients met the inclusion criteria and are the subject of this analysis. Thirty-six patients were unable to provide a semen specimen owing to: religious/cultural objections to masturbation (13 patients), pain (7 patients), lack of a history of masturbation or nocturnal emission (8 patients), psychogenic anejaculation (4 patients), and anejaculation secondary to previous retroperitoneal lymphadenectomy, sacral sarcoma, prostatic rhabdomyosarcoma, or remote history of childhood cancer requiring extensive chemotherapy (1 patient each). Eleven patients were noted to be azoospermic on semen analysis. Two patients, 1 adult and 1 adolescent, had severe oligospermia (0.0013×10^6 and 0.01×10^6 total viable sperm, respectively) prompting surgical sperm retrieval. The mean age was 22.1 ± 9.5 years (range 11–53 years). The mean testis volume was 14.1 ± 3.7 mL. Mean serum testosterone was 308 ± 199 ng/dL (range 10–671 ng/dL), and mean serum FSH was 9.6 ± 10.5 mU/mL (range 0.2–37.3 mU/mL). Cancer/tumor diagnoses are presented in Table 1.

A schematic representation of our treatment algorithm is presented in Figure 1. The overall (EEJ plus TESE) sperm retrieval rate (SRR) among all patients was 59.2% (Table 2). Twenty-eight patients underwent EEJ, with an SRR of 64.3%. Three teenage patients failed to ejaculate with EEJ, although in two the anesthesiologist administered short-acting paralytic agents despite being asked to forgo such agents. Among those patients undergoing successful EEJ, the mean antegrade sperm concentration was 12.9×10^6/mL (range $0.005–100 \times 10^6$/mL). The mean number of vials for sperm cryopreservation from sperm retrieved with EEJ was 4.6 (range 2–9). All patients with a positive retrograde ejaculate after EEJ had sperm present in their antegrade samples. TESE was performed as the only method of sperm retrieval in 21 patients (13 because of azoospermia/severe oligospermia, 6 because of rabbinic permission for TESE only, 1 because of anejaculation due to prostatic rhabdomyosarcoma, and 1 because of anejaculation due to childhood chemotherapy). Patients undergoing TESE alone had an SRR of 38.1%. Mean sperm concentrations among patients successfully undergoing TESE alone was 0.28×10^6/mL (range $0.0025–2 \times 10^6$/mL). This group included three patients who underwent ex vivo TESE on an orchiectomy specimen immediately after removal of the testis, none of whom had sperm retrieved in their specimens (two of these patients had metachronous testis cancer and were rendered anorchic after orchiectomy). One adult patient undergoing TESE with failed retrieval was noted to have Klinefelter syndrome, diagnosed after the procedure owing to the delay in laboratory testing. A total of 18 patients had both TESE and EEJ performed, with an overall SRR of 50%. There were no reported complications among patients undergoing either EEJ or TESE.

TABLE 1

Cancer/tumor diagnosis in the patient population.

Diagnosis	n (%)
Overall cohort	
Sarcoma	23 (47)
Lymphoma	10 (20)
Testicular germ cell tumor	8 (16)
Leukemia	3 (6)
Leydig cell tumor	2 (4)
Extragonadal germ cell tumor	1 (2)
Rectal adenocarcinoma	1 (2)
Metastatic renal cell carcinoma	1 (2)
Adolescent/young adult population	
Sarcoma	18 (60)
Lymphoma	9 (30)
Leukemia	3 (10)

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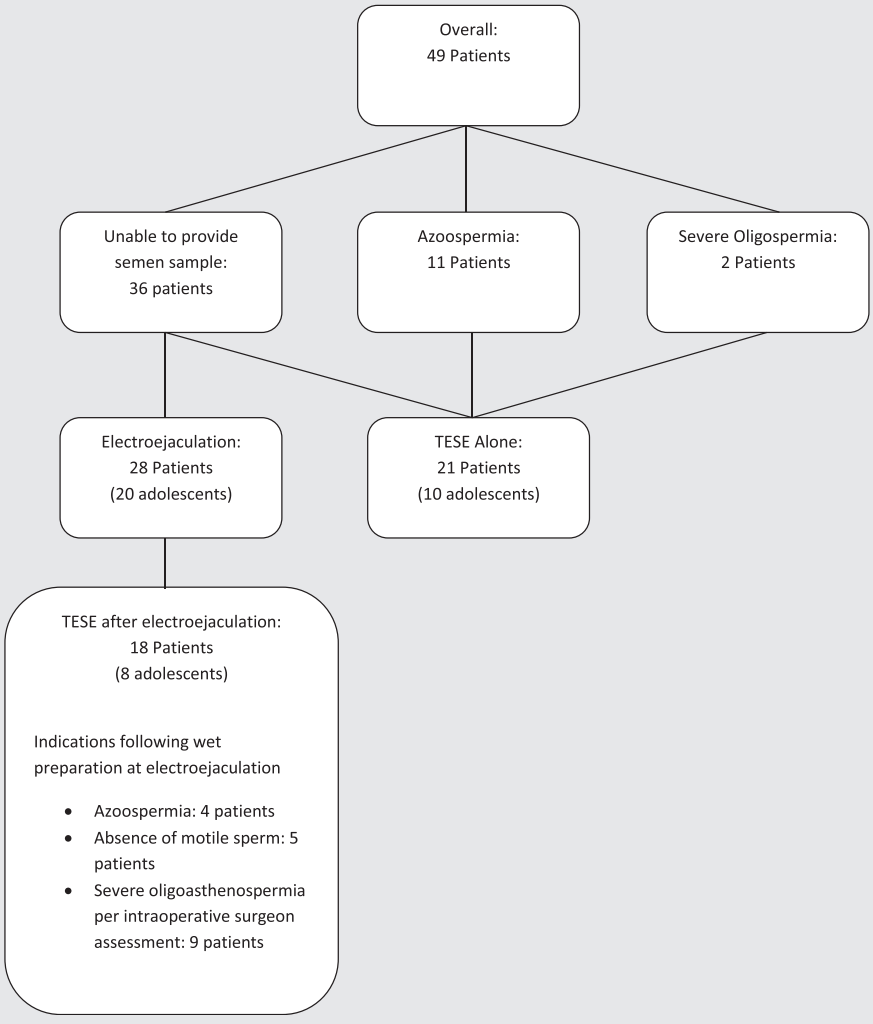
Subpopulation Analysis—Adolescents and Young Adults

A subset analysis was performed for the 30 adolescents and young adults within this patient population. Indications for surgical fertility preservation included no history of masturbation in 19 patients, pain in 6 patients, azoospermia or severe oligospermia in 3 patients, and failure to provide a semen specimen in 2 patients. The mean age was 16.2 ± 2.6 years (range 11–19 years). These patients were stratified according to Tanner developmental stages: Tanner 2 in 3 patients, Tanner 3 in 9 patients, Tanner 4 in 5 patients, and Tanner 5 in 13 patients. The mean testis volume was 14.3 ± 2.8 mL. Mean serum testosterone was 210.2 ng/dL and mean serum FSH 4.2 ± 4.9 mU/mL. Oncologic diagnoses in these patients are listed in Table 1.

FIGURE 1



Schematic representation of treatment algorithm. TESE = testicular sperm extraction.

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The SRR among adolescent males was 60%. Twenty patients underwent EEJ with an SRR of 60% and an ejaculation rate of 85%. The mean antegrade sperm concentration was 4.75 $\times$ 10^6/mL (range 0.005–10.5 $\times$ 10^6/mL). TESE was performed in the eight patients who either failed to ejaculate or were azoospermic with EEJ, with a retrieval rate of 25%, although one patient, who was azoospermic with EEJ and sperm was retrieved with TESE, did not have sperm noted on a post-thaw analysis. The other patient had failed to ejaculate with EEJ. Patients undergoing TESE alone had an SRR of 50%, with mean sperm concentrations of 0.42 $\times$ 10^6/mL (range 0.003–2 $\times$ 10^6/mL). Seven of these patients had TESE performed bilaterally, with sperm retrieved in three patients (noted to be unilateral in two patients). SRR stratified by patient age and Tanner developmental stage is presented in Table 3.

DISCUSSION

The role of fertility preservation among patients scheduled to undergo potentially gonadotoxic therapy for the treatment of cancer has been well established. An estimated 1.6 million people will have been diagnosed with cancer in the United States in 2013, with a 1-in-69 likelihood of developing invasive cancer in male individuals from birth to age 39 years, and a 1-in-11 likelihood in men aged 40–59 years (21). Significant overall improvements have been noted in survival after cancer treatment across all ages in the past three decades, with particularly significant improvements among children aged 1–14 years (21). Given the success of treatment regarding survival, attention has turned to the reproductive potential of these patients, who are often leading full lives after cancer treatment. The American Society of Clinical Oncology convened an expert panel to update its recommendations regarding fertility preservation in 2012, and recommended that health care providers should address the possibility of infertility in patients treated during their reproductive years and discuss fertility preservation options with all eligible patients before cancer therapy (22). In addition, the Children's Oncology Group has recommended semen collection in all peripubertal boys, with penile vibratory stimulation or EEJ

TABLE 2

Sperm retrieval rates (SRRs; %) stratified by mode of sperm retrieval and patient age.

	n	Overall	EEJ	TESE only	EEJ + TESE
Overall	49	59.2	64.3	38.1	57.8
Adolescents (11–19 y)	30	60	60	50	70
Adults (≥20 y)	19	57.9	75	27	100

Note: EEJ = electroejaculation; TESE = testicular sperm extraction.

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in those who fail to collect a specimen with masturbation (23). These authors additionally suggest the use of TESE in patients where other options for sperm retrieval have failed.

Given the role of our institution as a tertiary cancer referral center, fertility preservation is prioritized and is the focus of a dedicated team. Our institution has made a concerted effort to educate practitioners about the importance of fertility preservation from the viewpoint of cancer survivorship, providing educational resources for patients and easy access to visible consultant services and reproductive specialists within the hospital to assist patients looking to explore fertility options. Inpatients frequently consult with a clinical nurse specialist focused on fertility preservation before initiation of gonadotoxic treatment, who refers to our service in the event of concerns for pretreatment subfertility according to semen analysis results. Semen cryopreservation in all male patients interested in future reproductive potential is strongly encouraged, and patients are provided ready access to a number of cryobanks in the region. In addition, our service is given preferential access for operating room time for surgical sperm retrieval in patients due to undergo urgent or emergent cancer therapy.

EEJ has long been used in the treatment of anejaculation due to spinal cord injury and results in sperm retrieval in ~90% of such patients (24). A rectal probe is used to transmit electrical stimulation to the short postsynaptic sympathetic fibers in the walls of the ejaculatory organs, leading to ejaculation (25). Complications are noted to be rare, with reports of no instances of mechanical or thermal rectal injuries in 915 EEJ procedures reported by experienced authors performing the procedure (26).

TABLE 3

Sperm retrieval rates (SSRs) stratified by Tanner developmental stage and age among adolescents.

	No. of patients	SSR (%)
Tanner stage[a]		
2	3	0
3	9	44
4	5	80
5	13	69
Age range (y)		
11–13	10	30
14–16	7	71
17–19	13	69

[a] No Tanner 1 patients were treated.

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In our patient population, we report an almost 60% SRR among boys and young men requiring surgical sperm retrieval for fertility preservation before cancer therapy, with successful sperm retrieval with EEJ in 64% and with TESE in 38% of our patients. Successful sperm retrieval was noted with EEJ in 60% of boys aged 11–19 years among our patients. Our results confirm earlier reports (study group sizes ranging from one to eleven boys) describing the utility of EEJ in the adolescent and young adult cancer population (12–14). The youngest patient in our study to undergo EEJ with successful sperm retrieval was Tanner stage 3 and 12.7 years old, and he denied a history of masturbation or nocturnal emission.

Rates of azoospermia before initiation of chemotherapy have been reviewed by Tournaye et al. and vary from 3% to 18% depending on patient population and underlying cancer diagnosis (27). Concerns of genetic mutations and chromosomal aneuploidies induced by chemotherapy both in short- and long-term follow-up provide one rationale for offering TESE in this setting (27). Furthermore, sperm cryopreservation before cancer therapy has been demonstrated to encourage patients during and after cancer treatment, with 80% of respondents to a questionnaire reporting that cryopreservation emotionally "helped in the battle against cancer" (28).

TESE as a means of fertility preservation among azoospermic men scheduled to receive cancer therapy has been recently evaluated by a few investigators (15, 16, 29, 30). Our results further confirm the feasibility of "onco-TESE," with successful retrieval in 41% of patients either failing EEJ or with azoospermia, compared with earlier reports describing retrieved sperm in 42% (14 patients evaluated) and 67% (6 patients evaluated) among patients with testicular germ cell tumors (15, 16). TESE has been safely performed for fertility preservation in adolescents with Klinefelter syndrome, with a retrieval rate of 20% among five patients aged 15–17 years undergoing the procedure (31). To our knowledge, we are the first to report TESE performed for fertility preservation before cancer therapy in the pubertal adolescent/young adult patient population. TESE, whether combined with EEJ or performed alone, led to successful sperm retrieval in 33% of our adolescent/young adult population, with successful retrieval in a boy as young as 11.0 years. Our center is currently enrolling prepubertal boys in a multi-institutional, Institutional Review Board–approved protocol for evaluation and identification of spermatogonial stem cells for potential expansion and in vitro culture. The safety and acceptability of such a treatment protocol in prepubertal boys has been reported previously (32).

At our center, we do not have an embryologist available intraoperatively for a complete real-time assessment of total viable sperm counts. As such, the decision to proceed with TESE in EEJ patients is based on the operating surgeon's assessment at the time of intraoperative wet preparation. The final decision as to number of vials cryopreserved following surgical sperm retrieval is made by an embryologist at the sperm bank who works closely with the surgical team. The objective at cryopreservation is to maximize the number of vials available for possible use with assisted reproductive technologies at a

future date. Patients without viable sperm identified after TESE and in-depth analysis by the embryologist are not recommended to proceed with cryopreservation.

TESE in a cancerous testis at the time of orchiectomy has been reported in a number of case reports (19, 20, 33–35). Although ex vivo TESE failed in the three patients in our population who underwent ochiectomy, it should be noted that two of the patients had a history of metachronous testis cancer. Given their presentation of bilateral testicular cancer, it is possible that these patients had always had spermatogenic failure, and may therefore not have had successful sperm extraction even at their initial orchiectomy.

Challenges in sperm retrieval in patients with post-chemotherapy azoospermia serve as an additional factor driving the use of TESE for the sake of fertility preservation. Hsiao et al. reported the largest cohort of azoospermic men (73 patients) undergoing microdissection TESE at a mean of 19 years after chemotherapy, and noted successful sperm retrieval in 37% of patients (36). Although this retrieval rate is similar to what we achieved in a pretreatment population, it should be noted that TESE was performed at our institution with the use of a single incision without the use of multiple samples, given concerns for wound healing in patients due to undergo immediate extensive chemotherapy.

Of note, patients undergoing either EEJ or TESE did not have any complications. There was no delay in initiation of chemotherapeutic regimens among those scheduled for urgent/emergent chemotherapy, and patients frequently began chemotherapy on the same day as EEJ and/or TESE. It is possible, however, that with increased sampling at the time of fertility preservation, higher retrieval rates may be observed. Additional research is needed to identify the safety and efficacy of more extensive TESE with multiple samples in this patient population.

CONCLUSION

In our patient population, almost 60% of men presenting for surgical sperm retrieval for fertility preservation, because of pretreatment anejaculation or azoospermia, had sperm found and cryopreserved with the use of EEJ and/or TESE. Successful sperm retrieval rates were similar in the adolescent and young adult population, including successful TESE in an 11-year-old patient. To our knowledge, we report the first experience with TESE in adolescents for the sake of fertility preservation before definitive cancer therapy. EEJ and TESE can be safely performed immediately before the initiation of chemotherapy, without delaying necessary definitive cancer treatment.

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