

**Identifying infertile men who may be amenable to a limited testicular dissection at microdissection testicular sperm extraction**David Bouhadana<sup>1</sup>, Mélanie Chow-Shi-Yée<sup>2</sup>, Isaac-Jacques Kadoch<sup>2,3</sup>, Armand Zini<sup>1,2</sup><sup>1</sup>Division of Urology, McGill University, Montreal, QC, Canada; <sup>2</sup>OVO Clinic, Montreal, QC, Canada; <sup>3</sup>Division of Obstetrics Gynecology, Université de Montréal, Montreal, QC, Canada

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**ABSTRACT**

**Introduction:** We aimed to compare clinical characteristics of men with non-obstructive azoospermia (NOA) and cryptozoospermia with a successful sperm retrieval after a limited dissection micro-TESE to identify clinical parameters that may help find patients most likely to undergo a limited dissection.

**Methods:** We retrospectively analyzed a prospective database of 208 infertile men undergoing a first microdissection testicular sperm extraction (micro-TESE) at a high-volume fertility center (March 2015 to June 2025). The stepwise approach begins with five targeted micro-biopsies through a 1 cm tunica albuginea incision. The incision is extended only if sperm are not initially identified.

**Results:** Among 208 patients, 51 (25%) required a mini-incision micro-TESE with limited dissection, and 157 (75%) underwent an extensive dissection. NOA patients with a successful retrieval after mini-incision dissection had lower follicle-stimulating hormone (FSH) levels than those requiring extensive dissection ( $15 \pm 13$  vs.  $22 \pm 13$ ,  $p < 0.05$ ). Successful cryptozoospermic patients had higher testosterone levels than those requiring extensive dissection ( $14 \pm 5$  vs.  $8 \pm 4$  nmol/L,  $p < 0.05$ ). Receiver operating characteristic (ROC) analysis suggested thresholds of testosterone  $\geq 10$  nmol/L for cryptozoospermia (sensitivity 0.91, specificity of 0.58) and FSH  $\leq 19$  IU/L for men with NOA (sensitivity: 0.81, specificity of 0.52).

**Conclusions:** A stepwise approach to micro-TESE starting with a mini-incision can frequently allow for successful sperm retrieval with limited testicular dissection. Preoperative serum FSH

(in NOA) and testosterone (in cryptozoospermia) may help identify candidates most likely to undergo limited testicular dissection at micro-TESE.

## INTRODUCTION

Male factor infertility is a prevalent and growing concern affecting up to 50% of infertile couples.<sup>1</sup> Multiple studies report declining sperm quality and sperm count worldwide, making it a growing public health concern.<sup>2</sup> Male factor infertility can be caused by a disturbance in sperm transport, production or function. Non-obstructive azoospermia (NOA) and cryptozoospermia are semen abnormalities generally associated with severe defects in spermatogenic function. NOA is a form of primary testicular failure resulting in the absence of spermatozoa due to decreased spermatogenesis. Cryptozoospermia is a variant of the latter wherein a small number of spermatozoa is only noted after centrifugation and would not be found on initial semen analysis.<sup>3</sup>

The gold standard approach to treat men with limited sperm production is with intracytoplasmic sperm injection (ICSI).<sup>4</sup> Often, these men will require surgical sperm retrieval together with ICSI. Common sperm retrieval techniques used for men with limited sperm production include testicular sperm aspiration (TESA), testicular sperm extraction through open biopsy (TESE), and microdissection testicular sperm extraction (micro-TESE). The TESA method is usually not recommended among men with azoospermia as it can be inefficient and traumatic when attempting to retrieve spermatozoa.<sup>5</sup> In comparison to TESE, which consists of arbitrarily making incisions within the testicular parenchyma, micro-TESE is a more invasive but also a more targeted approach that uses microsurgical exploration to target regions within the testicular parenchyma that are more likely to yield developing spermatozoa.<sup>6-8</sup> In men with NOA, micro-TESE allows for sperm retrieval rates as high as 60%.<sup>9</sup> In a previous publication, Alrabeeah et al. reported the development of a stepwise strategy to micro-TESE starting with a mini-incision along the tunica albuginea to decrease tissue scarring and inflammation.<sup>10,11</sup> In a follow-up study, the authors demonstrated that the mini-incision micro-TESE technique was successful among 58% of men with cryptozoospermia and 26% of men with NOA.<sup>10</sup> However, this study was limited by its smaller sample size. In addition, there is limited data guiding clinicians on how to determine which patients would be successful with only a limited dissection.

In this study, we provide the largest dataset to date evaluating clinical predictors of success with a stepwise, mini-incision micro-TESE, aiming to refine patient selection and optimize counseling before surgery.

## METHODS

A retrospective analysis of a prospective database from a high-volume center of all infertile men who underwent a primary micro-TESE between March 2015 and June 2025 was performed. All

patients were evaluated and screened by a fellowship-trained male infertility specialist with a detailed history, physical examination and appropriate laboratory testing. Almost all men had genetic testing with karyotype and Y chromosome microdeletion studies done. In addition, all procedures were performed by the same physician, a high-volume micro-TESE surgeon.

### Patient characteristics

We categorized all men into two groups, including men with NOA and cryptozoospermia. Men with cryptozoospermia were defined as men with no spermatozoa noted in wet semen preparations, but for whom spermatozoa were then noted in pellets obtained following centrifugation at 3000g for 15 minutes. To meet this criterion, men needed two semen samples that demonstrated the latter. We excluded men with a potentially reversible cause of cryptozoospermia (i.e., presence of a varicocele, febrile illness, or recent toxin exposure) and men with suspected partial genital tract obstruction (i.e post-vaso-vasostomy, post-vasoepididymostomy, and low volume cryptozoospermia with ejaculatory duct obstruction). Patients were also excluded if they had previously undergone a micro-TESE, TESA or TESE procedure. Hypogonadal men with a testosterone level <9nmol/L were treated with a selective estrogen receptor modulator (SERM) (e.g., clomiphene citrate) or an aromatase inhibitor to enhance testosterone and sperm production before the micro-TESE was planned.

### Micro-TESE

All procedures were performed at our fertility center and were reviewed by the clinical team, which consists of a urologist, gynecologist and embryologist. When counselling patients, we discuss the following options: providing multiple ejaculated semen samples, extended sperm search and cryopreservation of motile sperm (if found), before proceeding to micro-TESE. We offer cryptozoospermic men the following options, including (1) cryopreservation of motile sperm (if found) prior to ICSI, (2) an extended ejaculate sperm search at ICSI and/or (3) a micro-TESE. Most of the men attempted to cryopreserve motile sperm (prior to ICSI), but none had adequate sperm for freezing. All included patients opted to undergo a micro-TESE. None of the patients selected the strategy of extended ejaculate sperm search at ICSI so this was not a criterion required for surgery. All patients with cryptozoospermia understood that this semen abnormality represents a relative indication for sperm retrieval, with some studies preferring the use of ejaculated sperm for ICSI.<sup>12</sup> Before beginning the procedure, all patients were re-examined to determine the initial testicle that would be explored according to real-time testicular volume measurement and prior ultrasound imaging. The procedures were carried out under intravenous sedation and local anesthesia in an operating room within the IVF centre. This consists of 50–100 mg of IV fentanyl and 1–2 mg of IV midazolam for sedation and a spermatic cord block using 5cc of 1% xylocaine and 5cc of 0.5% bupivacaine. The procedure will typically take between 1 and 3.5 hours, depending on the outcome of the micro-TESE. This is a shorter procedure if a unilateral mini-incision is performed and will take longer if an extensive bilateral micro-TESE is required.

The procedure begins with a 1.5-3cm unilateral transverse incision along the scrotal folds. The dartos and tunica vaginalis layers are then opened to expose the tunica albuginea. Once the testicle is delivered, the microscope is brought into the field. We begin with a 1cm equatorial incision (mini-incision) through the tunica albuginea. The exposed parenchyma is then examined using up to 30x magnification to identify dilated seminiferous tubules. If these are detected, three to five micro-biopsies are taken and transferred to a sterile dish containing HEPES [4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid] buffered sperm medium. This sample is then promptly sent to the laboratory embryologist located adjacent to the operating room to begin manual dissection of the harvested tissue biopsies. The biopsies are dissected by teasing them apart with fine needles and cutting with sharp scissors to obtain small clusters of cells. No chemical agents are used for tissue dissection. The dissected samples are then examined under high-power microscopy to identify sperm. The surgeon will re-examine the images with the embryologist to confirm the presence of spermatozoa. If no sperm are detected, the surgeon is informed and proceeds to extend the mini-incision by an additional 1-1.5cm on each side of the initial 1cm mini-incision. Further dissection of the testicular parenchyma along the testis lobules is undertaken, and additional biopsies are taken from the newly exposed tubules. The report on microscopic findings is updated every 15 minutes as additional biopsies are examined. There was no standardized embryology search duration per specimen however the maximal search duration was up to 3 hours (in cases where an extensive micro-TESE was performed). The procedure is terminated once a total of at least five spermatozoa (motile or non-motile) are identified within the retrieved micro-biopsies.

We have previously shown that the procedure may be stopped after at least five spermatozoa are identified, as this has been associated with sufficient spermatozoa for ICSI.<sup>13</sup> If no spermatozoa (or fewer than five spermatozoa) are identified after exploration of the first testicle, exploration of the contralateral testis is undertaken. The micro-TESE is terminated when at least five spermatozoa are observed in the biopsied samples, or after thorough examination of the entire testicular parenchyma. However, at the end of the procedure, retrieval of any number of mature spermatozoa is deemed a successful sperm retrieval. After completion of the micro-dissection, the layers are closed sequentially, beginning with the closure of the tunica albuginea using 6-0 Prolene suture, the tunica vaginalis using 3-0 catgut, the dartos muscle layer with 3-0 catgut, and scrotal skin with 4-0 plain suture. The surgical setup, demonstrating the key steps of the procedure, is highlighted in Supplementary Figure 1.

### Statistical analysis

Descriptive analyses were used to describe the baseline parameters. Continuous variables (age, follicle-stimulating hormone (FSH), testosterone, and testicular volume) are presented as means ( $\pm$ SD). Independent sample t-tests were used to compare continuous variables among patient groups. Multivariable logistic regression was used to identify factors associated with successful mini-incision. Age, FSH, and testosterone were included a priori based on clinical relevance. Given the limited number of events, only a small number of variables were included to reduce the risk of overfitting. Analyses were restricted to complete cases with no missing data

for the variables included in the model. A p-value of  $<.05$  was used as the threshold of significance. Receiver operating characteristic (ROC) curves were plotted to evaluate the performance of all statistically significant variables as predictors of limited micro-TESE success. We present ROC curves with an area under the curve (AUC) greater than 0.5, and report an optimal threshold value using Youden's J. We report sensitivity and specificity at the selected optimal threshold value. All statistical analyses were carried out using the SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Baseline demographics

The 208 patients in this study included 156 (75%) men with NOA and 52 (25%) with cryptozoospermia. All patients had an initial attempt of mini-incision micro-TESE, which was converted to conventional micro-TESE if no spermatozoa were identified. The overall sperm retrieval rate (SRR) was 46% (71/156) in the NOA group and 87% (45/52) in the cryptozoospermia group. Of the 208 patients, 157 (75%) underwent an extensive micro-TESE and 51 (25%) underwent a mini-incision micro-TESE with limited dissection. Among the 156 patients with NOA, 27 (17%) underwent a mini-incision limited dissection micro-TESE, and 129 (83%) underwent an extensive dissection (34 unilateral and 95 bilateral micro-TESEs). Of the 52 patients with cryptozoospermia, 24 (46%) underwent a mini-incision limited dissection micro-TESE, and 28 (54%) underwent an extensive dissection (15 unilateral and 13 bilateral micro-TESEs). In men with a successful mini-incision micro-TESE (NOA and cryptozoospermia), we observed homogeneously dilated seminiferous tubules or multiple foci of dilated seminiferous tubules. Micro-biopsies of these dilated tubules demonstrated the presence of mature spermatozoa. In contrast, in men that required extensive microdissection we generally observed homogeneously dilated seminiferous tubules or homogeneously thin tubules with or without rare foci of markedly dilated tubules. Micro-biopsies of the markedly dilated tubules often demonstrated the presence of mature spermatozoa. The baseline demographics for the entire group of patients who underwent an extensive or a mini-incision micro-TESE can be found in Table 1.

### Genetic variants

We found that 14% (22/156) of men with NOA and 17% (9/52) of men with cryptozoospermia had a genetic abnormality ( $p=0.65$ ). Among the patients that underwent an extensive micro-TESE, 18% (28/157) had a genetic abnormality, which included 18 patients with Klinefelter Syndrome (47,XXY), six patients with an AZFc Y chromosome microdeletion, and four who either had a chromosomal translocation or an inversion (**Table 1**). In comparison, 6% (3/51) of men undergoing a mini-incision micro-TESE had a genetic abnormality, which included one with an AZFc Y chromosome microdeletion and two who either had a translocation or an inversion (Table 1). The proportion of men with Klinefelter Syndrome (47, XXY) was significantly greater in men with extensive micro-TESE compared to men with mini-incision micro-TESE (11%

[18/157] vs. 0% [0/51], respectively,  $p=0.017$ ) (Table 1). Among men with NOA, genetic abnormalities were identified in 16% (21/129) of those with extensive dissection and 4% (1/27) with limited dissection. Among men with cryptozoospermia, genetic abnormalities were identified in 25% (7/28) of those undergoing extensive dissection and 8% (2/24) with limited dissection.

Among the men who underwent an extensive or mini-incision micro-TESE, we then compared the baseline characteristics of men with NOA and cryptozoospermia. In men with NOA, FSH levels were significantly lower in those undergoing a mini-incision micro-TESE compared to extensive micro-TESE ( $15 \pm 12$ ; vs  $22 \pm 15$  IU/L,  $p=0.02$ ). Among men with cryptozoospermia, men undergoing a mini-incision micro-TESE had significantly higher serum testosterone levels than those undergoing an extensive micro-TESE ( $14 \pm 5$  vs.  $8 \pm 4$  nmol/L;  $p=0.001$ ). These findings were consistent with multivariable analysis demonstrating that FSH levels were lower among men with NOA undergoing a successful mini-incision micro-TESE (OR 0.94, 95% CI 0.89–0.98;  $p=0.008$ ). In addition, our multivariable analysis also showed that cryptozoospermic men undergoing a successful limited micro-TESE had higher testosterone levels (OR 1.52, 95% CI 1.19–2.23;  $p=0.006$ ). Overall, there were significantly fewer biopsies done for all men undergoing a mini-incision micro-TESE ( $10 \pm 3$ ;  $p<0.001$ ) compared to those undergoing an extensive micro-TESE ( $26 \pm 12$ ;  $p<0.001$ ). The clinical characteristics of men with NOA and cryptozoospermia undergoing extensive or mini micro-testicular sperm extraction can be found in Table 2.

### Receiver operating characteristic (ROC) curves

Among men with cryptozoospermia and men with NOA, we carried out ROC analysis. For men with cryptozoospermia serum total testosterone levels showed moderate discrimination, with an area under the curve (AUC) of 0.753 (95% CI 0.601–0.880), consistent with higher testosterone levels corresponding to a greater likelihood of sperm retrieval with a limited microdissection. The optimal threshold identified by Youden's J was a testosterone level  $\geq 10$  nmol/L. This threshold demonstrated a sensitivity of 0.905 (95% CI 0.70–0.99) and specificity of 0.577 (95% CI 0.37–0.77), along with a positive predictive value (PPV) of 0.633 (95% CI 0.44–0.80) and negative predictive value (NPV) of 0.882 (95% CI 0.64–0.99) (Figure 1). When carrying out the same analysis for men with NOA and FSH levels, FSH demonstrated moderate discrimination for success with an AUC of 0.683 (95% CI 0.560–0.791). The optimal cutoff by Youden's J was an FSH level  $\leq 19$  IU/L. At this threshold, the model demonstrated a sensitivity of 0.81 (95% CI 0.61–0.93) and specificity of 0.52 (95% CI 0.43–0.61), along with a PPV 0.26 (95% CI 0.17–0.36) and NPV 0.93 (95% CI 0.84–0.98) (Figure 2).

### DISCUSSION

In men with NOA or cryptozoospermia, micro-TESE is associated with high sperm retrieval rates in comparison to alternative methods, including a standard TESE or TESA.<sup>14</sup> However, micro-TESE remains relatively invasive and may require extensive tissue dissection that can lead to testicular injury. Our group previously described the development of a novel stepwise

approach that aims to decrease the need for extensive tissue dissection by making a smaller equatorial tunica albuginea incision and only extending it to 3-4cm if no spermatozoa are found.<sup>10,15</sup> Our group initially demonstrated that 60% of men with cryptozoospermia and 13% of men with NOA are amenable to a limited micro-dissection without the need for extensive testicular dissection.<sup>11</sup>

While a mini-incision allows for successful sperm retrieval in up to 25% of patients with NOA and cryptozoospermia, to the best of our knowledge, no study has examined the clinical characteristics of men with NOA or cryptozoospermia that may help identify patients who may only require a limited dissection at micro-TESE. In the current analysis, we further expanded the dataset to include 208 patients (156 with NOA and 52 with cryptozoospermia) of whom 157 underwent an extensive micro-TESE and 51 underwent a mini-incision micro-TESE. Among these patients, a mini-incision, limited dissection micro-TESE allowed for sperm retrieval in 17% (27/156) of men with NOA and 46% (24/52) of men with cryptozoospermia. We found that FSH levels were lower among NOA men undergoing a successful mini-incision micro-TESE than those requiring an extensive micro-TESE. Using a threshold FSH level of  $\leq 19$  IU/L in men with NOA, we obtained a PPV of 26% and an NPV of 93%. Therefore, the probability of a successful limited dissection, mini-incision micro-TESE is estimated at 26% when there is an FSH level  $\leq 19$  IU/L and at 7% when there is an elevated FSH ( $> 20$  IU/L). We also found that cryptozoospermic men with a successful mini-incision micro-TESE had significantly higher serum testosterone levels than those requiring an extensive micro-TESE. Using a threshold testosterone level of  $\geq 10$  nmol/L in men with cryptozoospermia, we obtained a PPV of 63% and NPV of 88%. This suggests that the probability of a successful limited dissection, mini-incision micro-TESE, is estimated at 63% when testosterone levels are  $\geq 10$  nmol/L and at 12% when testosterone levels are  $< 10$  nmol/L. While this data alone should not be used to propose a surgical plan, it can help counsel patients regarding their likelihood of a successful limited dissection at the time of micro-TESE. Of note, using these thresholds, 25% (21/83) of men with NOA and FSH  $\leq 19$  IU/L, and 61% (19/31) of men with cryptozoospermia and serum testosterone  $\geq 10$  nmol/L, underwent successful limited dissection micro-TESE, respectively. Conversely, these thresholds were wrong for 42% (66/156) of men with NOA and 27% (14/52) of men with cryptozoospermia, respectively. While these predictive cut-off scores may not be generalizable due to the study's limitations, they provide insightful and unique information that is currently not yet published and warrants further investigation and validation in larger randomized studies.

In a systematic review conducted by Li et al. FSH was not predictive of sperm retrieval rates.<sup>16</sup> While testosterone and FSH levels may not be useful in predicting micro-TESE SRR, our findings suggest that these parameters may help predict those men most likely amenable to a successful retrieval with a mini-incision micro-TESE alone. Using serum FSH in men with NOA is of limited value, as this presents a low PPV, which could lead to multiple false positives. However, it can serve as a useful tool for determining patients who will not undergo a successful limited dissection, given its high NPV. Another more recent systematic review and meta-analysis

led by Pozzi et al. evaluated the influence of FSH, inhibin B and anti-Müllerian hormone (AMH) to predict sperm retrieval rates among men with NOA.<sup>17</sup> They found that FSH was not predictive of successful sperm retrieval rates, but mentioned that AMH levels can help predict successful sperm retrieval rates among men with NOA.<sup>17</sup> While the role of AMH in males is not completely understood, they hypothesize that AMH can serve as a marker of Sertoli cell maturation, wherein AMH levels decrease as sperm cells mature.<sup>18</sup> Of note, this study excluded all patients with Y chromosome microdeletions and those with Klinefelter syndrome due to the rarity of these conditions, which warrant dedicated studies specific to these subgroups.

Overall, there were significantly fewer biopsies performed for all men undergoing a mini-incision micro-TESE compared to those undergoing an extensive micro-TESE. This offers patients a tangible clinical advantage with less tissue trauma, fewer biopsies, and preserved testicular architecture, while maintaining comparable retrieval success. This is especially important for patients with NOA and cryptozoospermia as they can often develop testicular atrophy and hypogonadism post-operatively.<sup>19,20</sup> Studies have shown that testicular sperm extraction procedures can lead to anatomical changes detected on ultrasound. These physical changes are drastically reduced with a micro-TESE in comparison to a conventional TESE, as there is less testicular tissue being dissected.<sup>19</sup>

Although prospective, controlled studies are needed to demonstrate a benefit of mini-incision micro-TESE compared to conventional micro-TESE, a mini-incision micro-TESE can in theory minimize anatomical disturbances, as the technique can help spare a larger amount of testicular tissue from being manipulated during surgery. This may reduce testicular damage, inflammation and hematoma formation that can limit further sperm retrieval success.<sup>21,22</sup> In fact, it has been shown that a repeat micro-TESE after a successful primary micro-TESE is associated with an 82% sperm retrieval rate.<sup>23</sup> However, it is not known whether adopting a stepwise approach to micro-TESE (starting with mini-incision) would increase the sperm retrieval rate beyond 82% at redo micro-TESE.

Reports on the distribution of active spermatogenesis in men with NOA have been inconsistent, with some studies suggesting a patchy distribution and others a diffuse, homogeneous distribution.<sup>24,25</sup> Our data suggest that men with NOA, as well as those with cryptozoospermia, have different patterns of spermatogenesis distribution within the testicle. We observed that men with NOA amenable to successful sperm retrieval with a limited dissection mini-incision micro-TESE (17% of men with NOA) exhibit one of two patterns of seminiferous tubule appearance: homogeneously dilated seminiferous tubules (with active but quantitatively reduced spermatogenesis on biopsy) or heterogeneous seminiferous tubule appearance with multiple foci of dilated tubules (with active spermatogenesis on biopsy). It is important to note that none of these men had typical features of obstructive azoospermia (none had normal serum FSH and normal testicular volume with full epididymides) but some may have a component of obstructive azoospermia, as observed in azoospermic men with surgically repaired cryptorchidism.<sup>26</sup>

In contrast, the data suggest that a larger subset of men with NOA (83%) exhibit absent spermatogenesis or rare foci of active spermatogenesis (often found in isolated foci of dilated seminiferous tubules) requiring extensive dissection for sperm recovery. Our findings for cryptozoospermic men indicate that close to 50% of these men have one of two patterns of seminiferous tubule appearance: homogeneously dilated seminiferous tubules (with active but quantitatively reduced spermatogenesis on biopsy) or heterogeneous seminiferous tubule appearance with multiple foci of dilated tubules (with active spermatogenesis on biopsy). In contrast, approximately 50% of cryptozoospermic men either have absent spermatogenesis or rare areas of active spermatogenesis (in dilated tubules) requiring extensive dissection for sperm recovery.

### Limitations

Limitations of this study include the single-center retrospective design and lack of systematic follow-up for complications, as it limits the generalizability of our results and introduces an operator-dependent bias. However, the consistency of findings across subgroups and the large patient cohort strengthens the reliability of our conclusions. Of note, the sample size of our mini-incision subgroup limits the robustness of our ROC curves and increases our risk of overfitting. However, to the best of our knowledge, this is the largest dataset to date evaluating clinical predictors of success with a stepwise, mini-incision micro-TESE.

We also recognize that pre-operative hormonal optimization with a SERM or aromatase inhibitor could have confounded our results. However, these medications were only administered to a small subset of men in our study, specifically hypogonadal men with a testosterone level  $<9\text{nmol/L}$ . In addition, we did not measure AMH levels or obtain a formal histopathologic diagnosis (at micro-TESE), a parameter that can help better characterize the severity of spermatogenic dysfunction and possibly predict sperm retrieval rates if a redo micro-TESE is contemplated.<sup>17,27</sup> Histological data is also relevant as patients with severe spermatogenic disorders may have an increased risk of germ cell neoplasia in situ that is not noted on ultrasound.<sup>27,28</sup> However, we have not submitted tissue for histological assessment to preserve all harvested tissue for therapeutic purposes and avoid potentially losing areas with sperm production.<sup>27</sup>

Lastly, the occurrence of post-operative complications was not documented systematically due to limited long-term patient follow-up, as many of the patients live far away from our center.

### CONCLUSIONS

This large single-surgeon series demonstrates that a stepwise micro-TESE beginning with a mini-incision represents an effective, less invasive strategy for men with NOA and cryptozoospermia. We found actionable clinical thresholds to help guide physicians when counselling patients and selecting patients who may undergo a successful limited dissection. The thresholds included FSH levels  $\text{FSH} \leq 19\text{ IU/L}$  for men with NOA and testosterone  $\geq 10\text{ nmol/L}$  for men with cryptozoospermia.

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**Conflict of interest:** AZ and IJK are shareholders of YAD technologies (nutraceuticals).

**Declaration of generative AI and AI-assisted technologies in the writing process:**

During the preparation of this work, the authors used Chat GPT 5.0 in order to review the grammar, spelling and overall flow of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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## FIGURES AND TABLES

**Figure 1.** Receiver operating characteristic (ROC) curve identifying optimal testosterone cutoff value for men with cryptozoospermia. ROC curve for serum testosterone predicting mini-incision micro-TESE success (AUC 0.753, 95% CI 0.601–0.880). The point corresponding to the Youden-optimal threshold cutoff ( $\geq 10.0$  nmol/L) is indicated, with sensitivity 91% and specificity 58%.

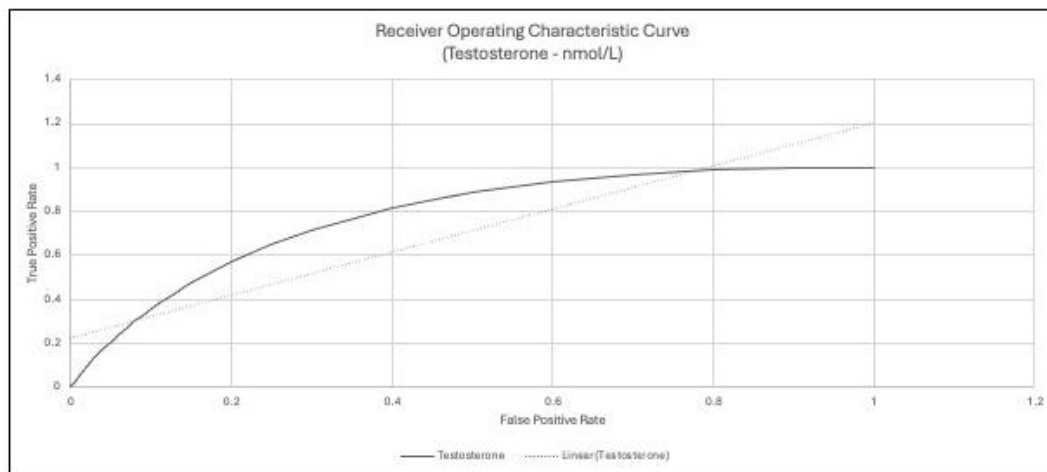
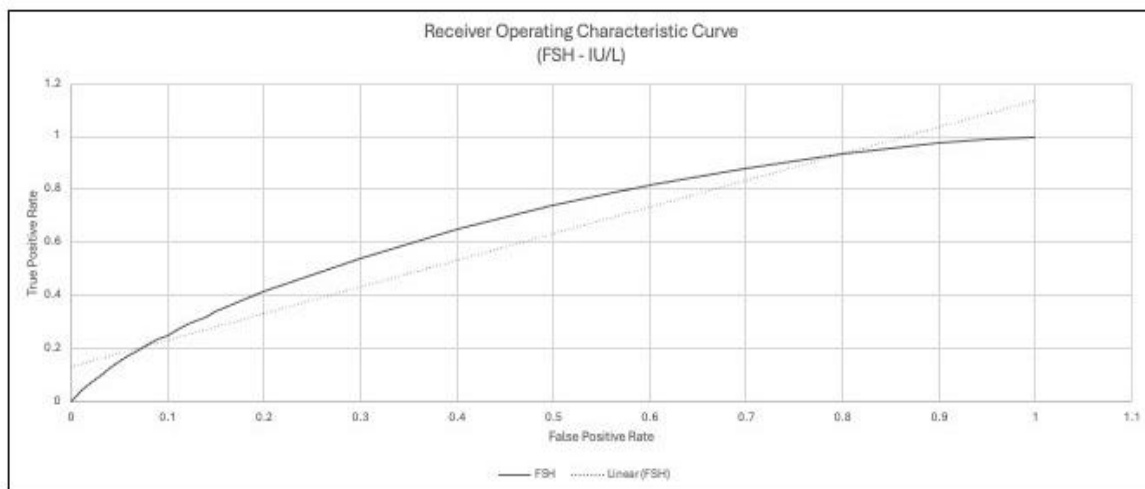


**Figure 2.** Receiver operating characteristic curve identifying optimal follicle-stimulating hormone (FSH) cutoff value for men with non-obstructive azoospermia. ROC curve for FSH levels predicting mini-incision micro-TESE success among men with non-obstructive azoospermia (AUC 0.683, 95% CI 0.560–0.791). The Youden-optimal cutoff ( $\leq 19.0$  IU/L) is indicated, with sensitivity 81% and specificity 52%.



| <b>Table 1. Clinical characteristics of men undergoing extensive or mini micro-testicular sperm extraction (micro-TESE)</b> |                             |                        |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------|
|                                                                                                                             | <b>Extensive micro-TESE</b> | <b>Mini micro-TESE</b> |
|                                                                                                                             | 157                         | 51                     |
| Age (years), mean ( $\pm$ SD)                                                                                               | 36 (7)                      | 37 (6)                 |
| Genetic abnormalities (%) <sup>a</sup>                                                                                      | 18                          | 6                      |
| Klinefelter diagnosis (%) <sup>*</sup>                                                                                      | <b>11</b>                   | <b>0</b>               |
| Presence of AZFc microdeletion (%)                                                                                          | 4                           | 2                      |
| Testicular volume (right) (ml), mean ( $\pm$ SD)                                                                            | 12 (6)                      | 13 (4)                 |
| Testicular volume (left) (ml), mean ( $\pm$ SD)                                                                             | 11 (5)                      | 14 (4)                 |
| FSH (IU/L), mean ( $\pm$ SD)                                                                                                | 21 (13)                     | 15 (11)                |
| Total testosterone (nmol/L), mean ( $\pm$ SD)                                                                               | 11 (6)                      | 12 (4)                 |
| Unilateral procedures (%)                                                                                                   | 31                          | 100                    |
| Total number of biopsies, mean ( $\pm$ SD)                                                                                  | 26 (12)                     | 10 (3)                 |
| Successful sperm retrieval (%)                                                                                              | 41                          | 100                    |

<sup>a</sup>Percentage of men with detected genetic abnormalities, including Klinefelter syndrome, AZFc microdeletion, and chromosomal translocation or inversion. <sup>\*</sup>Statistically significant difference (p=0.017).

| <b>Table 2. Clinical characteristics of men with non-obstructive azoospermia and cryptozoospermia undergoing extensive or mini micro-testicular sperm extraction (micro-TESE)</b> |                             |                        |                         |              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|------------------------|-------------------------|--------------|
|                                                                                                                                                                                   | <b>Extensive micro-TESE</b> | <b>Mini micro-TESE</b> | <b>OR (95% CI)</b>      | <b>p</b>     |
| Non-obstructive azoospermia (n=156)                                                                                                                                               | 129                         | 27                     |                         |              |
| Age (years), mean ( $\pm$ SD)                                                                                                                                                     | 36 (7)                      | 37 (6)                 | 1.06 (0.97–1.15)        | 0.190        |
| Genetic abnormalities (%) <sup>a</sup>                                                                                                                                            | 16                          | 4                      |                         |              |
| Klinefelter diagnosis (%) <sup>*</sup>                                                                                                                                            | <b>13</b>                   | <b>0</b>               |                         |              |
| Presence of AZFc microdeletion (%)                                                                                                                                                | 2                           | 0                      |                         |              |
| Testicular volume (right) (ml), mean ( $\pm$ SD)                                                                                                                                  | 12 (6)                      | 13 (5)                 |                         |              |
| Testicular volume (left) (ml) <sup>*</sup> , mean ( $\pm$ SD)                                                                                                                     | <b>11 (5)</b>               | <b>15 (3)</b>          |                         |              |
| FSH (IU/L) <sup>*</sup> , mean ( $\pm$ SD)                                                                                                                                        | <b>22 (15)</b>              | <b>15 (12)</b>         | <b>0.94 (0.89–0.98)</b> | <b>0.008</b> |
| Total testosterone (nmol/L), mean ( $\pm$ SD)                                                                                                                                     | 12 (6)                      | 11 (5)                 | 0.95 (0.86–1.04)        | 0.311        |
| Unilateral procedures (%)                                                                                                                                                         | 26                          | 100%                   |                         |              |
| Total number of biopsies <sup>*</sup> , mean ( $\pm$ SD)                                                                                                                          | <b>27 (12)</b>              | <b>10 (4)</b>          |                         |              |
| Successful sperm retrieval (%)                                                                                                                                                    | 34                          | 100                    |                         |              |
| Cryptozoospermia (n=52)                                                                                                                                                           | 28                          | 24                     |                         |              |
| Age (years)                                                                                                                                                                       | 35 (6)                      | 38 (7)                 | 1.14 (1.01–1.34)        | 0.049        |
| Genetic abnormalities (%) <sup>a</sup>                                                                                                                                            | 25                          | 8                      |                         |              |
| Klinefelter diagnosis (%)                                                                                                                                                         | 4                           | 0                      |                         |              |
| Presence of AZFc microdeletion (%)                                                                                                                                                | 11                          | 4                      |                         |              |
| Testicular volume (right) (ml), mean ( $\pm$ SD)                                                                                                                                  | 12 (5)                      | 12 (4)                 |                         |              |
| Testicular volume (left) (ml), mean ( $\pm$ SD)                                                                                                                                   | 12 (5)                      | 12 (4)                 |                         |              |
| FSH (IU/L), mean ( $\pm$ SD)                                                                                                                                                      | 17 (13)                     | 16 (10)                | 1.00 (0.93–1.09)        | 0.951        |
| Total testosterone (nmol/L) <sup>*</sup> , mean ( $\pm$ SD)                                                                                                                       | <b>8 (4)</b>                | <b>14 (5)</b>          | <b>1.52 (1.19–2.23)</b> | <b>0.006</b> |
| Unilateral procedures (%)                                                                                                                                                         | 54                          | 100                    |                         |              |

|                                                |                |               |  |  |
|------------------------------------------------|----------------|---------------|--|--|
| Total number of biopsies*,<br>mean ( $\pm$ SD) | <b>24 (12)</b> | <b>10 (3)</b> |  |  |
| Successful sperm retrieval (%)                 | 75             | 100           |  |  |

<sup>a</sup>Percentage of men with detected genetic abnormalities, including Klinefelter syndrome, AZFc microdeletion, and chromosomal translocation or inversion. \*Statistically significant result that yielded a  $p < 0.05$ .

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