The seminiferous tubule caliber pattern as evaluated at high magnification during microdissection testicular sperm extraction predicts sperm retrieval in patients with non-obstructive azoospermia

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ABSTRACT

Background: microTESE proved to be the gold standard surgical approach for patients with non-obstructive azoospermia (NOA), but sperm retrieval rates (SRRs) vary considerably among centers. Some authors compared their SRRs with the pattern of seminiferous tubule caliber found at high magnification, but none provided diagnostic accuracy measures.

Objective: The present retrospective study sought to verify the diagnostic accuracy of the pattern of seminiferous tubule caliber in predicting the sperm retrieval in NOA patients.

Materials and Methods: Data from 143 infertile NOA men undergoing unilateral (64) or bilateral (79) microTESE (222 testes) were retrospectively evaluated. During microTESE, if present, dilated tubules (DTs) were retrieved, otherwise tubules with slightly larger caliber (SDT) (>24) than that of the surroundings were removed. When no DT or SDT were found, not dilated tubules (NDTs) were excised.

Results: Spermatozoa were retrieved in 95 of 222 testes (42.8%); sperm retrieval was successful in 90% of testes with DTs, in 47% of those with SDTs, and only in 7% of those with NDTs (p < 0.0001). Stepwise binary logistic regression revealed that the combination of seminiferous tubule pattern and testis histology was significantly predictive of SSR, being able to classify 86.8% of testes, with an excellent diagnostic accuracy (AUC 0.93). The median number of spermatozoa retrieved was significantly higher in DTs compared with SDTs and NDTs.

Discussion: The results of the present study provide reliable accuracy measures in support of the relationship between seminiferous tubule caliber and SSR in patients with non-obstructive azoospermia. We are proposing for the first time that spermatozoa may be retrieved even from slightly dilated tubules in about half of cases. The pattern of tubules retrieved, together with histology, may represent an additional outcome measure of microTESE.

Conclusion: The pattern of seminiferous tubules together with testis histology predicts sperm retrieval with an excellent diagnostic accuracy.
tubules, which are presumed to contain mature germ cells (Schlegel, 1999).

Although the microTESE technique has been introduced two decades ago, still the reported sperm retrieval rates differ between authors: Such a variability could be ascribed to several factors, not the least being the surgeon’s skill and experience (Ishikawa et al., 2010). Very recently, a letter to the Editor (Song, 2017) and then two Editorials (Jensen et al., 2017; Carrell & Simoni, 2017) appearing in Andrology pointed out that the results of microTESE could be affected by several confoundings, including different tissue processing methods and the time, the skill and effort dedicated to the identification of spermatozoa in the testicular specimen, and patient characteristics, and therefore may account for the broad range of reported sperm retrieval rates, so that they asked for improved outcomes measures for microTESE success, in order to address the remaining questions in using such a technique more effectively in patients care.

Among the potential factors able to explain the outcome of microTESE in individual NOA subjects, the evaluation of the prevalent seminiferous tubule caliber pattern found at high magnification has attracted the attention of few authors in the past decade (Okada et al., 2002; Tsujimura et al., 2002; Amer et al., 2008), but none provided an evaluation of its diagnostic accuracy in predicting the sperm retrieval success in NOA patients.

The present study sought to determine, by providing diagnostic accuracy measures, whether the pattern of seminiferous tubule caliber found at high magnification during microdissection testicular sperm extraction (microTESE) may represent a reliable outcome measure of such a surgical procedure.

MATERIALS AND METHODS

Ethical approval

All procedures were carried out in accordance with the international and national guidelines and regulations on the diagnosis and treatment of non-obstructive azoospermia. No additional diagnostic or therapeutically procedure was carried out for research purposes.

This study has been approved by the Ethics Committee Ticino, Switzerland (email dss-ce@ti.ch), protocol no. 2018-00213.

Inclusion criteria

All patients with NOA who underwent microTESE whose tubule caliber pattern was described in the case history and stored in electronic format were included in the study.

Exclusion criteria

Patients with NOA with an history of testicular torsion, mumps, or bacterial orchitis were excluded from the study.

Subjects

We reviewed the clinical data of all infertile male patients with non-obstructive azoospermia referring to the IVF unit from January 2015 through July 2017 to undergo microdissection testicular sperm extraction. During all microTESE procedures, following our consolidated clinical procedure, we carefully recorded the caliber pattern of all tubules retrieved and took some pictures (about 20–40× patient) of the tubules themselves.

Every patient’s tubule caliber pattern as observed at high magnification was annotated in the patients’ case history and stored in an Excel dataset; data collection and analysis were retrospectively conducted.

The criteria for the diagnosis of NOA were similar to those applied in a previous study from our group (Caroppi et al., 2017). Briefly, patients were defined to have NOA if semen analysis showed azoospermia without spermatozoa in the pellet, ejaculate volume and pH were higher than 1 mL and 7.2, respectively, and no sign of obstruction of the seminal tract was detected on physical examination, scrotal, and transrectal ultrasound.

All patients underwent a careful physical evaluation, and blood samples were obtained to assay their FSH, LH, and total testosterone (TT) levels. Testis volume was measured by scrotal ultrasound. An additional semen sample was obtained on the day of planned surgical procedure in order to confirm the absence of spermatozoa in the pellet.

Patients who gave their informed consent to the surgical procedure were included in the study.

Surgical procedure and sample processing

microTESE was performed under general anesthesia through a transversal incision of the testis covering from two-thirds to three-quarters of its circumference, according to a line preserving as much as possible the transversal subalbugineal vessels. Intra- or subalbugineal vessel bleeding, if any, was cauterized with a microsurgical bipolar thermal device (with 0.3 mm wide tips). The testis was opened like a book by a gradual and very gentle separation of the lobular tissue of both sides with a spatula or a Vannas micro-forceps, in order to avoid tissue stretching and to preserve the caliber of the underlying seminiferous tubules. Next, the tissue was observed under the operating microscope at 10–24× magnification in the search for areas containing the tubules that appeared clearly dilated, that is, those tubules with a diameter larger than all the surrounding ones constituting most of the parenchyma (Fig. 1A). These tubules can be found grouped in a tiny heap, sometimes lie solitary surrounded by smaller size tubules, or more rarely occupy a small part of a lobule. Dilated tubules (DTs) were removed and given to the embryologists in the surgical theater for the immediate identification of spermatozoa. If no normal, dilated, tubules were identified, then any tubule whose caliber appeared slightly larger than that of the surroundings (at ×24 magnification) was removed (slightly dilated tubules—SDTs; Fig. 1B). After examining the surface, if necessary, the deeper part of the testicular parenchyma was explored, and tubules were examined both along the septa and by delicately detaching groups of them from the adjacent ones by Vannas micro-forceps, again retrieving all those areas with clearly dilated or only apparently dilated seminiferous tubules, according to the protocol described by Schlegel, (1999). When such a procedure did not yield spermatozoa, and because of the volume of the testis, a moderate part of the gland had remained unexplored, a second albugineal incision, parallel to the preceding one, was performed. When no dilated or slightly dilated tubules were found in the different areas of the testis, not dilated tubules (NDTs) were excised according to a sort of mapping, by removing tiny fragments of testicular tissue from the two separated surfaces, at different depths from the albuginea to the hilum (Fig. 1C). The surgical procedure lasted...
for 1.5–4 h, bilateral microTESE being more time-consuming than unilateral.

The embryologists were blinded to the pattern of tubules retrieved during microTESE. The removed tubules were washed in Hepes-buffered medium to remove the blood. The tiny fragments of testicular tissue were placed in sterile petri dishes with 0.5 mL sperm washing medium and meticulously minced using microscissors. The resulting fragments were then passed through a intravenous angiocatheter for 3–5 min, until a homogeneous pulverized suspension was obtained. Small aliquots of the suspension were directly examined under an optical microscope. The meticulous search for spermatozoa could last up to 4 h. Only afterward, the testicular tissue surfaces were irrigated for antisepsis with Ringer solution (plus 80 mg gentamycin/100 mL). Hemostasis was then performed with the patient's blood pressure being normalized by the anesthetist, by gently pressing the testicular tissue for 4 min using gauze wet with the antiseptic solution, and eventually (but rarely) using the microsurgical bipolar thermal device. The albuginea incision was closed with a continuous suture of Vicryl 5/0 or 4/0, involving only its external layer in order to avoid any additional damage to the subalbugineal vessels. The tunica vaginalis opening was repaired by a continuous Vicryl 4/0 after instillation into the vaginalis cavity of 1.5 mg betamethasone (a 2 mL ampoule) to prevent pain and tunica vaginalis adhesions. Dartos and skin were closed by separate stitches with Vicryl 3/0 suture.

If an appropriate sperm yield was obtained, dissection of the contralateral testicle was avoided, otherwise dissection of the contralateral side proceeded.

All surgical procedures were performed by the same urologist (GMC), with about 900 microTESE surgical procedures performed in the past twenty years. Processing of all testis specimens was made by the same two embryologists with 17 years of experience in the field.

Testicular histology

All the histopathology specimens were evaluated by an unique pathologist (GG) with about 17 years of experience in the field.

A fragment of one or more of the tubules of the same diameter (DT, SDT, or NDT) found in each single testis was fixed in Bouin’s solution and sent to the pathologist. Histological analysis was conducted by examining at least 100 different tubule sections. The histopathological results were defined as: (i) Sertoli cell-only syndrome (SCO) when the seminiferous tubules were exclusively populated by Sertoli cells; (ii) focal SCO when tubules with SCO were interspersed with rare tubule containing germ cells; (iii) early and late maturation arrest (MA), characterized with an arrest of the spermatogenetic maturation sequence at spermatogonia/spermatocytes or round spermatid level respectively; (iv) hypospermatogenesis (HYPO), when all stages of germ cells (spermatogonia, spermatocytes, and spermatids) were present although reduced in number; (v) hyalinosis when peritubular fibrosis with peritubular and intratubular hyalinosis were found together with absence of Sertoli and germ cells; and (vi) intraepithelial neoplasia (IN) when malignant germ cells were identified within the seminiferous tubules.

Statistical analysis

The difference in serum hormonal level and testicular size in patients stratified according to sperm retrieval success was evaluated by Mann-Whitney U-test, as the variables were not normally distributed according to one-sample Kolmogorov-Smirnov test. The frequencies of histopathological patterns in patients with and without SSR and per tubule pattern were computed by chi-squared test. The distribution of tubule caliber
pattern in patients with and without SSR was computed by Kruskal–Wallis test. The predictive ability of clinical parameters, tubule caliber pattern, and histology on sperm retrieval success was evaluated by binary logistic regression with stepwise selection method, the entry testing being based on the significance of the statistic score: SSR was set as binary-dependent variable, while tubule pattern and testicular histology as categorical (nominal) variables utilizing the simple contrast coding, with ‘DT’ and ‘SCO’ as reference category, respectively. The obtained predictive probabilities were used as the test variable to obtain area under curve (AUC) estimates derived from receiving operator characteristic (ROC) curve.

The predictive ability of clinical parameters and histology on tubule caliber pattern was evaluated by binary logistic regression using two dummy binary-dependent variables (DT plus SDT or SDT plus NDT). The obtained predictive probabilities were used as the test variable to obtain AUC estimates.

Statistical significance was set at $p < 0.05$ for all analyses. All computations were performed using IBM SPSS for WINDOWS (Chicago, IL, USA).

### Sample size estimation

The sample size requested for binary logistic regression was calculated according to Peduzzi and coworkers (Peduzzi et al., 1996). Given that the proportion of positive cases ($p$) was 42.8% (sperm retrieval per testes) and the number of independent variables ($k = \text{testis histology and tubule seminiferous caliber pattern}$) was two, the minimum number of cases to include in this study to obtain a statistical power of 80% with $\alpha$ set at 0.05 was 46.7 ($N = 10 k/p$).

### RESULTS

One hundred and forty-three male patients with non-obstructive azoospermia were included in this study: 64 underwent unilateral and 79 bilateral microTESE. Patients clinical, hormonal, and histopathological findings are displayed in Table 1.

Sperm retrieval was successful for 79 of 143 patients (55.2%), 23 of 79 (29%) after bilateral, and 57 of 64 (89%) after unilateral microTESE, respectively. Sperm retrieval was successful in one of six patients with non-mosaic Klinefelter syndrome, in patient with 45X/46XXY mosaicism, and in all patients with translocations. Three patients had deletion of AZFc region and one of AZFb and AZFc of the Y chromosome. Sperm retrieval was successful in all three patients with AZFc deletion following unilateral microTESE, but not in the patient with AZFb and AZFc deletion despite bilateral microTESE.

Spermatozoa were retrieved in 95 of 222 testes (sperm retrieval per testes 42.8%). For the purpose of this study, from now onward data will be reported as per testes rather than per patients.

Table 2 displays the results as obtained in testes with or without SSR. No difference was seen in testis volume, FSH and LH serum levels between cases with SSR or sperm retrieval failure (SRF); individual AUC estimates confirmed that none of the above parameters was predictive of SSR (0.48, 0.50, and 0.55 for FSH, LH, and testis volume, respectively). On the other hand, total testosterone serum level was significantly lower in testes with SRF compared to those with SSR ($p = 0.007$), but its predictive value was poor (AUC 0.61).

Histopathological findings differed significantly among testes with SSR or SRF (Pearson’s chi-squared test 54.170, $p < 0.0001$). SCO and hyalinosis were the prevalent finding in testes with SRF, while focal SCO was found only in testes with SSR, and SSR was associated with HYPO in the 96.4% of cases.

The tubule caliber pattern differed significantly among testes with or without SSR (Pearson’s chi-squared test 114.690, $p < 0.0001$). About 90% of dilated tubules were found in testes with SSR, while only 7% of non-dilated tubules contained viable sperm cells. On the other hand, the percentage of slightly dilated tubules were roughly comparable among testes with or without SSR. The number of spermatozoa retrieved was significantly higher when dilated tubules were retrieved compared with the other two caliber categories ($p < 0.001$; Table 2).

Binary logistic regression with stepwise selection for the prediction of sperm retrieval excluded FSH, LH, testosterone, and testicular volume, as they were not significant to the model. On the other hand, the combination of histology plus tubule caliber pattern was significantly predictive of SSR with a diagnostic accuracy of 86.8% (Table 3). The tubule caliber pattern, when computed as the sole predictive factor, allowed the correct classification of 82.4% of testes, while histology classified 72.7% of them. Individually, AUC estimates as obtained from the computed predictive probabilities demonstrated that histology had a fair diagnostic accuracy (0.7), while tubule caliber pattern accuracy was good (AUC 0.89); the combination of both variates had an excellent discriminatory power (AUC 0.93). Table 4 displays the combination between tubule caliber pattern, histology, and successful sperm retrieval.

Binary logistic regression for the prediction of tubule caliber pattern was run with two dummy binary-dependent variables (dummy 1 = DT plus SDT and dummy 2 = SDT plus NDT); the dummy variable that performed better was the dummy 2. Stepwise selection excluded all variates but histology, which corrected classified 75.9% of testes (Table 3), although with a poor diagnostic accuracy (AUC 0.67).

### DISCUSSION

The results of the present study confirm that the seminiferous tubule caliber pattern as found at high magnification during microTESE is predictive of sperm retrieval in patients with NOA.

| Table 1 Clinical parameters of 143 patients undergoing unilateral or bilateral microTESE |
|---------------------------------|-----------------|
| **Parameter**                   | **Results**     |
| Age (years)                     | 36 (33–39) [26–62] |
| Non-mosaic Klinefelter S (%)    | 6 (4)          |
| 45X/46XXY (%)                   | 1 (0.7)        |
| Robertsonian translocations (%) | 4 (2.8)        |
| Testis volume (mL)              | 7.3 (6–9) [1.5–17] |
| FSH mIU/mL                      | 21 (14.8–28) [1.47–68.7] |
| LH mIU/mL                       | 6.3 (4.4–10.8) [0.2–48] |
| Total testosterone (ng/dL)      | 390 (300–525) [134–890] |
| Testis histology                | 220 reports (per testis) |
| SCO (%)                         | 143 (65)       |
| Focal SCO (%)                   | 9 (4.1)        |
| MA                              | 29 (13.1%)     |
| HYPO                            | 28 (12.8)      |
| Hyalinosis                      | 9 (4.1%)       |
| IN                              | 2 (0.9)        |

Data are displayed as median and interquartile range with ranges in squared parentheses or as count with percentages in parentheses.
This finding, being already anticipated by previous studies (Schlegel, 1999; Okada et al., 2002; Tsujimura et al., 2002; Amer et al., 2008), is now fully supported by the diagnostic accuracy measures provided by the present study.

We found that sperm retrieval was successful in 90% of cases when dilated tubules were found at high magnification, but only in 7% of cases when not dilated tubules were retrieved. The binary logistic regression analysis, as well as the resulting predictive probabilities used to obtain AUC estimates, confirmed that the tubule caliber pattern had a good diagnostic accuracy in predicting SSR. Since the first report on microTESE procedure (Schlegel, 1999), it was suggested that the recovery of opaque and dilated seminiferous tubules would result in a higher chance of obtaining viable spermatozoa for ICSI. Three years later, Okada and coworkers (Okada et al., 2002) evaluated 74 patients with NOA undergoing microTESE and found dilated tubules in 20 of 33 patients with SSR (60%), while Tsujimura (Tsujimura et al., 2002) evaluated 56 patients with NOA and found homogeneous dilated tubules in seven, all of them with SSR (100%), 23 patients with homogeneous non-dilated tubules, all with failed sperm retrieval, and 26 with heterogeneous tubule thickness (the pattern of seminiferous tubules retrieved was not specified), 17 (65%) of whom had SSR. Amer and colleagues (Amer et al., 2008) provided a measure of tubule caliber using a micrometer fixed to the eyepiece of the operating microscope. They reported that sperm retrieval rate was significantly higher in cases with tubule diameter >150 µm (SSR 49.2% vs. 31.4% respectively), reaching 84.2% when tubule diameter exceeded 300 µm.

Our data show that sperm retrieval was unsuccessful only in seven cases when dilated tubules were retrieved, showing...
heterogeneous histological characteristics (MA in three cases, SCO in two cases, and HYPO and hyalinosis in the two remaining cases). As shown by a morphometric study (Volkmann et al., 2011), sometimes highly dilated tubules (diameter $>400$ $\mu$m) may be found in the testes of patients with NOA, showing impaired spermatogenesis together with thickened lamina propria because of the increased extracellular matrix. The differential diagnosis between these tubules and those with intact spermatogenesis could be hard even for an expert surgeon, especially when such tubules are found by chance in testes with otherwise predominantly non-dilated tubules.

Notably, the present study suggests that it could be worthless to retrieve not dilated tubules, as the chance of finding spermatozoa is around 7%. On the other hand, in the absence of clearly dilated tubules, the retrieval of tubules with a larger diameter compared with that of the surroundings (NDT) may result in SSR in about half of cases, according to our results. It has to be specified, however, that the identification of such tubules, which requires the highest optical magnification ($\times24$), can result easier to skilled and experienced surgeons. Dabaja and Schlegel (Dabaja & Schlegel, 2013) argued that the identification of dilated tubules becomes easier, the operative time decreases, and the SSR increases when a surgeon exceeds experience with more than 500 microTESE procedures.

Our data suggest also that when testis histology is coupled to the tubule pattern, SSR is predicted with an excellent diagnostic accuracy (AUC 0.93). Histology has been previously found to be the unique parameter able to predict the outcome of microTESE (Abdel Raheem et al., 2013; Bernie et al., 2013; Althakafi et al., 2017; Li et al., 2018), though with a poor/fair diagnostic accuracy (Li et al., 2018). The only limit of testis histology is that it may be available when conventional TESE or, in rare cases, testis biopsy has been performed prior to microTESE, but this is not a rare event for NOA patients.

On the other hand, histology showed a poor diagnostic accuracy in predicting the tubule caliber pattern. As displayed in Table 4, SCO was more prevalently found in not dilated tubule, while HYPO was associated with dilated tubules in 71.4% of cases. Okada and coworkers found dilated and opaque seminiferous tubules in all cases with HYPO, but only in two of nine and 12 of 19 patients with MA and SCO, respectively (Okada et al., 2002), while Tsujimura et al. found that all testes showing an homogeneous pattern of dilated tubules had HYPO, while those with homogeneous thin tubules had SCOS (95.6%) or MA (0.4%) (Tsujimura et al., 2002). The discrepancy between these data and ours may be explained by the study selection criteria: we, in fact, included patients with different clinical conditions, including those with known cytogenetic abnormalities. Data from morphometric studies suggest that several clinical conditions (varicocele, cryptorchidism, Klinefelter syndrome) may have an impact on tubule structure and size, regardless of testicular histology (Sato et al., 2008).

Indeed, the predictive factors evaluated in the present study are intraoperative (tubule pattern) and post-operative (testis histology) and therefore require surgery to be obtained. Yet, pre-operative clinical parameters are hardly predictive of microTESE success. Our data confirm that the microTESE outcome cannot be predicted on the basis of patients FSH, LH and testicular volume; relevantly, microTESE was found to be successful in patients with very high serum FSH levels (Ramasamy et al., 2009) and/or severe testicular atrophy (Bryson et al., 2014). We found that such parameters did not even predict the tubule pattern (Table S1). In spite of the lack of pre-operative predictive factors, we are providing an intraoperative predictor of microTESE success that may assist the surgeon during the surgical procedure: The knowledge that even slightly, apparent dilated tubules may harbor spermatozoa in about half of cases would compel him or her to extensively search for those tubules in the case of failure to detect dilated tubules at high magnification. We would highlight that the present study is providing for the first time ever sperm retrieval rates in tubules which are neither ‘dilated’ nor ‘not dilated’. In addition, we are suggesting to add the seminiferous tubule caliber pattern to the microTESE outcome report in order to provide the patients (and the referred urologist/clinical andrologist as well) with valuable information about the degree of their spermatogenesis impairment, given that the classical yes or not microTESE report is poorly informative about that, being the chance of retrieving spermatozoa not fully related to the spermatogenesis integrity, but also to the surgeon skill and experience, and to the time spent in the laboratory in the identification of the spermatozoa in the testicular specimens. Such a report would help the counseling of patients referring for a redo microTESE: If the previous surgical evaluation at high magnification, in the hand of a skilled urologist, identified only not dilated tubules, the patient would be counseled about the relatively scarce chance of having his spermatozoa retrieved with another microTESE attempt.

This study has some limitations. The tubule pattern was subjectively evaluated. Najary and coworkers performed an experimental pilot study aiming at evaluating the accuracy of multiphoton microscopy (MM) in detecting tubules with intact spermatogenesis, and found a concordance rate of 86% between MM and histology, but acknowledged that MM needs to be miniaturized and its safety has to be ensured before its introduction in the clinical practice (Najari et al., 2012). In the lack of such a potentially innovative diagnostic tool, the surgeon’s skill and experience remains the only factor that can account for the reliability of the results: In this light, the circumstance that all surgical procedures were performed by the same highly experienced urologist may represent a methodological strength, as both the identification of tubule caliber and the sperm retrieval rate could not have been affected by interoperator variability. Another limitation of the study is that data were retrospectively collected and analyzed; however, data collection was easy as all data were annotated in patients’ clinical history and in an Excel dataset, following our consolidated clinical procedure, and for the same reason, the risk of selection bias was negligible.

In conclusion, the present study suggests that the seminiferous tubule caliber pattern as observed at high magnification during microTESE is strictly correlated with the chances of retrieving spermatozoa in patients with NOA. We are providing an intraoperative predictor of microTESE success and suggest to add the tubule pattern and testis histology to the microTESE outcome report in order to render it more informative to the patient.

**CONFLICT OF INTEREST**

The authors have no conflict of interests to disclose.
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AUTHORS’ CONTRIBUTIONS
E. C. designed the study, analyzed and interpreted the data, and drafted the article. E.M.C. contributed to the acquisition of data and critically revised the manuscript. G.G. performed all the tests histology evaluation, substantially contributed to the conception and the design of the study, and critically revised the manuscript. L.V. contributed to the acquisition of data, prepared the figure, and critically revised the manuscript. E.P. contributed to the manuscript drafting, and critically revised the manuscript. G.D. critically revised the manuscript. G.M.C. conceived and designed the study, performed all the surgical procedures, identified the seminiferous tubule pattern and collected the results, contributed to the manuscript drafting, and critically revised the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Clinical parameters as stratified per tubules caliber pattern.