Predictors of spermatogenesis in radical orchiectomy specimen and potential implications for patients with testicular cancer

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Objective: To assess the ability of semen analysis and other patients' characteristics to predict the presence of spermatozoa in radical orchiectomy pathological specimen, and describe potential implications for patients with azoospermia and testis cancer.
Design: Retrospective cohort study.
Setting: Tertiary hospital.
Patient(s): A total of 214 consecutive patients with testicular cancer who underwent radical orchiectomy between 1997 and 2015.
Intervention(s): None.
Main Outcome Measure(s): Histologic slides were reviewed and the presence of mature spermatozoa was documented. Clinical, laboratory, and radiographic characteristics were recorded. Logistic regression analyses were used to identify factors associated with the presence of spermatozoa in the noninvolved ipsilateral testicular parenchyma.
Result(s): Spermatozoa were found in the pathological specimen of 145 patients (67.8%). At multivariate analysis, increased tumor size was the only factor associated with lower rates of spermatozoa in the specimen. Mean tumor diameter was 4.06 cm, and spermatozoa were found in 83% and 49% of testes with tumor diameters <4 and ≥ 4 cm, respectively. Preoperative semen analysis records were available for 107 patients. Oligozoospermia, severe oligozoospermia, azoospermia, and cryptozoospermia were observed in 17 (16%), 18 (17%), 9 (8%) and 3 (3%) patients, respectively. Sperm concentration and motility were not associated with complete spermatogenesis. Seven of 12 patients (58%) with either azoospermia or cryptozoospermia had mature sperm in their pathological sections.
Conclusion(s): Larger testicular cancers are associated with lower rates of spermatozoa in the ipsilateral testis. Given the substantial likelihood (~60%) of spermatozoa to be present in the cancerous testis of patients with azoospermia and cryptozoospermia, concomitant oncologic testicular sperm extraction (TESE) can be considered in these selected patients. (Fertil Steril® 2016;106:70–4. ©2016 by American Society for Reproductive Medicine.)
Key Words: Testis cancer, spermatogenesis, fertility preservation, onco-TESE

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Testicular germ cell tumors constitute the most common solid tumor in men between the ages of 20 and 34 years, and its incidence has been rising in the past 2 decades (1). Because modern therapies yield excellent results in most patients (long-term overall survival rates, >95%), attention has focused on quality of life issues. Fertility preservation and paternity are significant issues in men diagnosed with testicular cancer (TC). Up to 50% of TC patients present with abnormal semen analysis at diagnosis (2, 3). Furthermore, decreased fertility is well documented among survivors of TC (4, 5). Because many of these young patients have not yet accomplished their reproductive desires, preservation of fertility has become an integral part of comprehensive oncology management.

Sperm cryopreservation is an effective method to increase fertility rates among patients with TC. It is recommended by the American Society of Clinical Oncology 2013 guidelines that sperm banking will be offered to postpubertal males receiving cancer treatment (6). However, up to 15% of

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patients with TC present with azoospermia, and are unable to provide sperm for cryostorage through ejaculation (7–9).

The concept of oncologic testicular sperm extraction ("onco-TESE") has been described 13 years ago (10, 11). Ever since, there is a growing acceptance of TESE as a "preemptive" procedure in patients with azoospermia before therapy, and concomitantly with orchiectomy. Several groups of investigators (12–19) have published their experience with onco-TESE in patients with azoospermia and TC, and demonstrated successful utilization of the sperm in assisted reproduction, resulting in the birth of healthy children. Estimating the probability of finding sperm in the cancerous testis could be of value when discussing fertility preservation options with the patient in the preorchiectomy setting. Only few studies, with a limited number of patients, have evaluated possible predictors of complete spermatogenesis in the cancerous testis. Two studies (20, 21) highlighted the need to examine the correlation between semen analysis and the presence of mature spermatozoa in the resected testicle.

In the present study we sought to evaluate potential predictors of complete spermatogenesis in a larger cohort of patients with TC. We also investigated the association between semen analysis and the presence of spermatozoa in the pathological specimen, and provided potential implications for the patients with azoospermia and TC.

MATERIALS AND METHODS

After obtaining institutional review board approval, we retrospectively reviewed our surgical registry and identified 245 patients who underwent radical orchiectomy for germ cell tumors between June 1997 and June 2015. Pathological slides were available for 214 patients (87%) who comprised the study cohort. A dedicated uro-pathologist (M.Y.), blinded to clinical data, reviewed the slides and determined whether mature spermatozoa were present in the orchiectomy specimen. Preoperative data were obtained from the medical charts and included age, body mass index (BMI), smoking status, history of undescended testis, physical examination, fertility status, sonographically measured testes and tumor size (maximal diameter, as continuous variable), and tumor marker levels (α-fetoprotein [AFP], β-hCG, and lactate dehydrogenase). All tumor marker levels were analyzed by a single laboratory, and abnormal levels were defined as β-hCG >5 IU/L and AFP >7 ng/mL. Radiographic stage was determined based on computerized tomography and chest roentgenogram, according to the American Joint Committee on Cancer TNM system (7th edition) (22). Histologic tumor type and features were retrieved from the pathological reports. All patients were preoperatively counseled on cryopreservation of sperm, which is offered free of cost for oncologic patients in Israel. Preoperative semen analysis results were available for 107 patients who elected to cryopreserve sperm before orchiectomy. Consequently, most patients had one semen sample. Data collected included semen volume, sperm concentration, motility, and morphology. When no sperm was found on wet mount examination, the whole sample was centrifuged and the pellet was examined for the presence of sperm. Azoospermic, cryptozoospermic, and some severe oligozoospermic men had at least one additional semen analysis. In these cases, we selected the best semen specimen to be included. Normal semen values were defined according to World Health Organization 2010 reference values (23). Severe oligozoospermia was defined as total motile count of ≤ 5 million/mL. Because morphology data were missing for most patients, it was excluded from the analysis. Univariate and multivariate logistic regression analyses were used to identify factors associated with the presence of spermatozoa in the noninvolved testicular parenchyma. Patient, tumor, and preoperative sperm count parameters were included in the models. All variables associated with a univariate P value $\leq .1$ were included in the multivariate model. Statistical tests were two-sided and were considered statistically significant when $P<.05$. Analyses were performed with Stata 10 (Statacorp).

RESULTS

Summary characteristics of patients and their tumors are presented in Table 1. A total of 214 men with a median age of 32 years (interquartile range, 26.5–39 years) were included. Of these patients, 129 (60%) were diagnosed with localized disease. The average tumor diameter was 4.06 cm (range, 0.5–10 cm). Final surgical pathology was seminoma in 121 patients (56.5%) and nonseminoma in 93 patients (43.5%). Mature spermatozoa were found in the pathological specimen of 145 patients (67.8%).

TABLE 1

Demographics, clinical, and tumor characteristics.

Characteristic	Value
Age (y), median (IQR)	32 (26.5–39)
BMI (kg/m^2), median (IQR)	25 (21.5–28)
Smoking, n (%)	47 (22)
History of primary infertility	16 (7.5)
History of undescended testis, n (%)	18 (8.4)
Hypotrophic contralateral testis, n (%)	16 (6.5)
Tumor maximal diameter (cm), mean ± SD (range)	4.06 ± 2.33 (0–10)
Histology, n (%)	
Seminoma	121 (56.5)
Non-seminoma	93 (43.5)
Lymphovascular invasion, n (%)	41 (19.2)
Multi-focal disease, n (%)	43 (20.1)
Abnormal tumor marker levels, n (%)	
FPA	75 (35)
β-hCG	91 (42.5)
LDH	145 (67.8)
Radiologic stage, n (%)	
Stage I	129 (60)
Stage II	56 (26)
Stage III	16 (8)
Unknown	13 (6)

Note: FPA = α-fetoprotein; IQR = interquartile range; LDH = lactate dehydrogenase.

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