Spermatogenesis in Testicles with Germ Cell Tumors

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ABSTRACT: **Background:** Almost 50% of patients with germ-cell tumors (GCT) are subfertile, and every step of the treatment may further impair fertility. As a result, sperm banking is often advised prior to radical orchiectomy. However, whether affected testes contribute to fertility is unclear.

Objectives: To determine whether maximal tumor diameter (MTD) is correlated with ipsilateral fertility (IF) in patients treated for GCT.

Methods: We reviewed medical charts for demographic and clinical data of patients with GCT who had undergone orchiectomy at our institution between 1999 and 2015. The extent of spermatogenesis was categorized into three groups: full spermatogenesis, hypospermatogenesis, and absence of spermatogenesis. The presence of mature spermatozoa in the epididymis tail was also assessed. We defined IF as the combination of full spermatogenesis in more than 100 tubules and the presence of mature spermatozoa in the epididymis tail. Mann–Whitney was applied to determine the correlation between MTD and IF.

Results: Of 57 patients, IF was present in 28 (49%). Mean patient age was 32.8 years in patients with positive IF and 33.4 years those with negative IF. Seminoma was diagnosed in 46.4% of patients with positive IF and in 65.5% of patients with negative IF. Full spermatogenesis was observed in 33 patients (57.8%). In 48 (82.7%), mature epididymal spermatozoa were found. No correlation was found between MTD and IF.

Conclusions: IF is present in almost half of the patients undergoing radical orchiectomy. Because IF cannot be predicted by MTD, routine pre-orchiectomy sperm banking is suggested.

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KEY WORDS: fertility, germ-cell tumors (GCT), nonseminoma germ-cell tumor, seminoma, spermatogenesis

Over 90% of intratesticular solid masses in adults are malignant germ-cell tumors (GCT), and radical orchiectomy is the standard initial approach. GCT occur most often in young men [1] between 20 and 40 years of age [2], when fertility and family planning are most relevant.

Unfortunately, GCT have a negative impact on patient fertility [3,4] as 50% of patients have abnormal sperm counts at presentation [5]. Further therapy, which may be indicated for GCT, includes systemic chemotherapy, radiation therapy, or retroperitoneal lymphadenectomy. All of these therapies have the potential to further impair fertility [6-14].

Because residual spermatogenesis is possible in the uninvolved resected testicular parenchyma, there is concern that orchiectomy itself may compromise a patient's fertility. Consequently, sperm banking prior to orchiectomy has become common practice despite no available evidence to support or object to such policy.

Readily available routine sperm banking has its downsides, which include delay of surgery until an adequate quantity of sperm has been retrieved and preserved as well as increased costs. We therefore sought to determine whether testicles with GCT manifest characteristics suggestive of IF, thereby indicating whether or not to perform routine preoperative sperm banking.

PATIENTS AND METHODS

After receiving institutional research and ethics board approval, we reviewed medical charts of all patients diagnosed with GCT who had undergone surgery in our hospital between 1999 and 2015. We abstracted demographic, clinical, and pathology data. Patients younger than 18 year of age or presenting with pathology reports other than GCT were excluded [Table 1].

All archived pathology slides were reviewed by a single uropathologist who confirmed the diagnosis of GCT. Maximal tumor diameter was measured and the quality of spermatogenesis in the resected testes was assessed. The quality of spermatogenesis was observed in at least 100 tubules per unit area of pathological slide and classified into the following three categories [15]:

- Full spermatogenesis: complete spermatogenesis in the entire pathological specimen
- Hypospermatogenesis: presence of all stages of spermatogenesis but reduced to varying degree
- Absence of spermatogenesis: no mature spermatozoa found in tubules

Table 1. Patient baseline demographic characteristics for the entire cohort (N=57)

Characteristics	Positive IF	Negative IF	*P* value
Patients	28 (49%)	29 (51%)	
Mean age, years	32.8	33.4	0.82
Seminoma	46.4%	65.5%	0.15
Testicular specimen volume, ml	36	45	0.35
Pathological testicular specimen MTD, mm	50	55	0.49
Pathological tumor MTD, mm	30	31	0.56
Median LDH, IU/L	409	504	0.192
Alpha-fetoprotein	3	3.2	0.73
Median b-hCG, mIU/ml	5	5	0.99
Mean tumor-to-testicle ratio	0.63	0.65	0.55

IF = ipsilateral fertility, hCG = Human chorionic gonadotropin, LDH = lactate dehydrogenase, MDT = maximal tumor diameter

In addition, we looked for the presence of mature spermatozoa in the epididymis tail. Because tumor growth is a gradual process, we considered that mature spermatozoa could be detected in testicles with absent spermatogenesis indicating that effective spermatogenesis had been present until the time when the extent of the tumor caused complete cessation of sperm production. Similarly, a centrally located tumor obstructing the rete testis could prevent transport of sperm cells to the epididymis, thus rendering any residual spermatogenesis in the affected gonad ineffective and resulting in the absence of sperm in the epididymis tail. We therefore defined IF as the combination of both full spermatogenesis in testicular tubules and the presence of mature spermatozoa in the epididymis [Figure 1].

STATISTICAL ANALYSIS

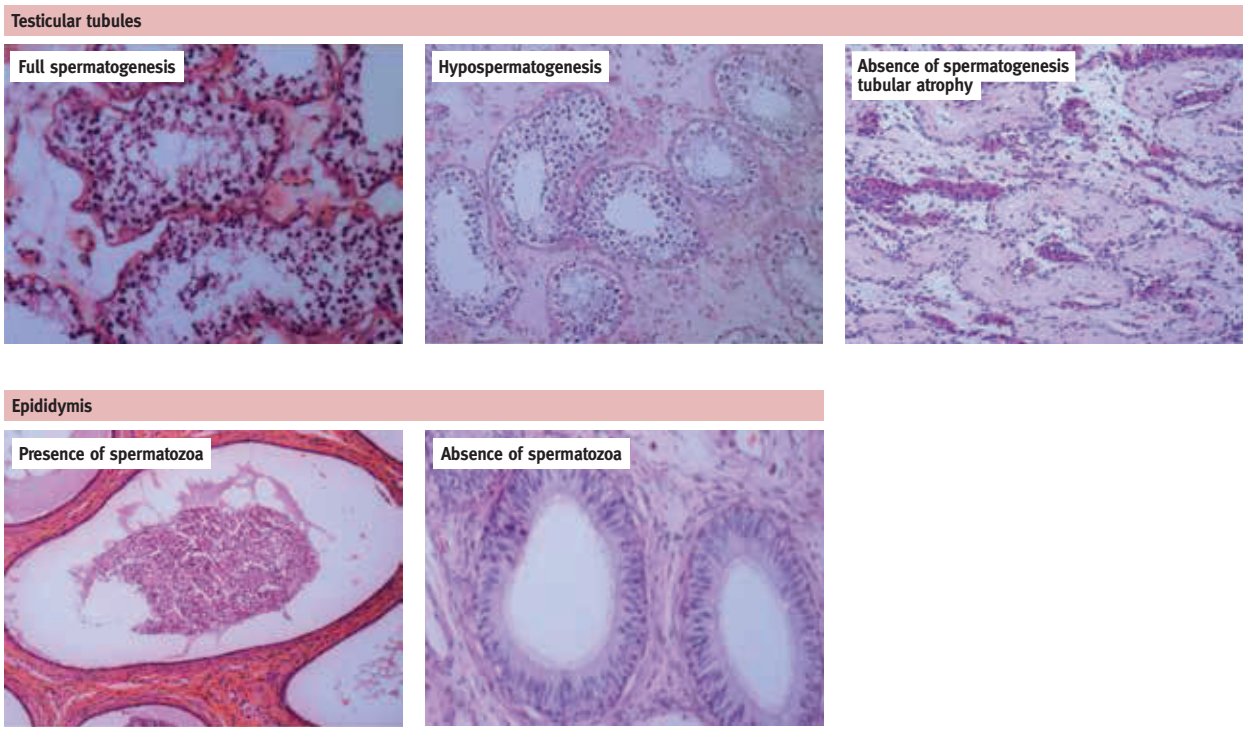
The Mann–Whitney test was applied to determine the correlation between maximal tumor diameter and IF. $P = 0.05$ was considered significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

A total of 57 patients who had undergone unilateral orchiectomy for GCT at our center between 1999 and 2016 were included. The mean age at presentation was 32.8 years for patients with positive IF and 33.4 years for patients with negative IF. Patient baseline characteristics are listed in Table 1.

Seminoma was present in 46.4% of patients with positive IF and 65.5% of patients with negative IF ($P = 0.15$). Full spermatogenesis was observed in 50% of patients, while presence of mature spermatozoa in epididymis was found in 84%

Figure 1. Descriptions of specimen analysis according to the level of spermatogenesis. Ipsilateral fertility is defined as the combination of both full spermatogenesis in testicular tubules and the presence of mature spermatozoa in epididymis



of patients. In 15 of 25 nonseminoma patients (60%) IF was detected compared to 15 of 32 seminoma patients (46%). This difference was not statistically significant.

No correlation was found between MTD and IF.

DISCUSSION

Considering that of all necessary treatment modalities for GCT, chemotherapy has the worst impact on fertility, sperm banking prior to systemic chemotherapy has become a standard treatment. The impact of unilateral orchiectomy on patient fertility remains unclear. In this study, we showed that IF may be detected in 50% of the patients undergoing orchiectomy for GCT. In our sample, IF was not affected by patient age, tumor histology, or MTD. As a result, preoperative clinical data did not predict IF before orchiectomy. Therefore, our findings support the concept that affected testes have the potential to contribute to patient fertility [10,16]. Despite the aggressiveness of GCT and the presence of large testicular tumors, either normal or decreased spermatogenesis was observed in 48 (82%) of the specimens. This finding suggests that most gonads affected with GCT preserve some of their reproductive function.

Our definition of IF was restrictive. The presence of spermatozoa in the epididymis tail reflects the immediate capacity of that gonad to contribute to fertility if sperm banking is to be performed. It is these sperm cells in the epididymis tail and downstream in the vas deferens that appear in the next ejaculations. Conversely, full spermatogenesis seems to predict further fertility potential of the testicle in the near future. If we used only the endpoint of spermatozoa in the epididymis tail as a marker of IF, we would have reported residual fertility in 48 of the 57 patients (84%), making the point for routine pre-orchiectomy sperm banking stronger.

To date there is no direct measurement of the relative contribution of each gonad to overall fertility. Therefore, our definition of IF is merely a surrogate indicator of fertility suggesting whether the affected testicle might contribute to fertility.

One limitation of our study is the retrospective nature of the analysis. We did not have sperm counts before versus after surgery, and we did not have data on actual fertility of our patients following treatment. In our cohort, four patients (6.8%) had a history of undescended testis. While cryptorchidism is a known risk factor for GCT, it is also a risk factor for subfertility in the affected testis [17].

Despite these obvious shortcomings, our data suggest that the affected gonad might contribute to overall fertility in roughly half of the patients. Considering this high proportion of IF and the inability to predict IF according to clinical data, we believe that sperm banking should be considered in all patients with GCT prior to orchiectomy. Further studies with larger patient samples are needed to determine clinical predictors for patient subsets that might benefit most from sperm banking versus others in whom banking might prove unnecessary.

CONCLUSIONS

Because IF can be found in almost half of the patients undergoing unilateral orchiectomy for GCT, sperm banking should be discussed with patients prior to surgery.

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"Don't judge each day by the harvest you reap, but by the seeds you plant"

Robert Louis Stevenson, (1850–1894), Scottish novelist, poet, travel writer