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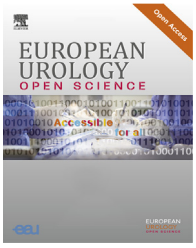

European Association of Urology

Brief Correspondence

Metastatic Potential of Small Testicular Germ Cell Tumors: Implications for Surveillance of Small Testicular Masses

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Abstract

Incidental detection of urogenital tumors has increased in recent decades owing to the greater use of ultrasonography and cross-sectional imaging. For patients with low-risk prostate cancer or small renal masses, active surveillance represents a valid treatment option. Similarly, for men with small testicular masses <10 mm, active surveillance has been discussed as an alternative to surgery, although little is known regarding the behavior of small testicular germ cell tumors (GCTs). In the Swiss Austrian German Testicular Cancer Cohort Study we identified 849 patients (546 seminoma, 303 nonseminoma) treated with radical inguinal orchiectomy for GCT with a median tumor diameter of 35 mm. A tumor diameter <10 mm was observed in 25 patients (13 seminoma, 12 nonseminoma). Of these, five patients (20%) presented with primary metastatic disease, all of whom had elevated tumor markers and nonseminomatous GCTs. Two patients (8%) with initially localized disease (1 seminoma, 1 nonseminoma) and without elevated tumor markers experienced relapse at 4 mo (nonseminoma) and 14 mo (seminoma) after orchiectomy, despite the fact that the latter had received adjuvant chemotherapy. These findings highlight the metastatic potential of small testicular GCTs and raise the question of whether active surveillance for small testicular masses is safe.

Patient summary: This study on testicular cancer assesses the metastatic potential of small testicular germ cell tumors. Men with small testicular masses should be counseled about the malignant potential of small testicular germ cell tumors.

Incidental detection of small testicular tumors has increased in recent decades owing to the greater use of ultrasonographic examination of the testes [1]. Radical orchiectomy constitutes the standard of care for men with testicular germ cell tumors (GCTs) and is curative for patients with localized disease [2]. The management of men with incidentally detected testicular masses and negative tumor markers can be challenging, as the majority of

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incidentally detected testicular masses are benign (e.g., epidermoid cysts, fibrothecoma, post-traumatic scar tissue) [1]. Assessment of tumor size or volume, fertility disorders, duration of symptoms, history of cryptorchidism, and testosterone levels can help in predicting the risk of malignancy [3].

It has been shown that in cases of uncertainty, tumor enucleation with intraoperative frozen-section examination (FSE) has high diagnostic accuracy in identifying malignant tumors [4]. To further eliminate the risk and burden of surgical interventions and reduce unnecessary orchiectomies for benign testicular tumors, active surveillance has been discussed as an approach for small, incidentally detected testicular masses. An upper limit of 10 mm has been proposed as a cutoff for immediate surgical intervention [5,6], as the risk of malignancy increases with testicular mass size [7]. In order for active surveillance to be safe, the risk of metastasis needs to be low for small testicular masses. In contrast to low-risk prostate cancer [8] and small renal masses [9], little is known regarding the risk of metastatic disease or recurrence for small testicular GCTs. The aim of this study was to assess the risk of metastatic disease for men with testicular GCTs <10 mm.

The Swiss Austrian German Testicular Cancer Cohort Study (SAG TCCS) is a prospective, multinational cohort study enrolling curatively treated patients with GCTs in follow-up since December 2013 (NCT02229916). For all patients included, treatment is at the discretion of the local investigators in accordance with international guidelines for the treatment of GCT. The aim is to provide comprehensive long-term data regarding follow-up of patients with GCTs.

Patients treated with radical inguinal orchiectomy and histologically verified testicular GCT were included in this analysis. Patients with extragonadal GCTs or contralateral GCTs were excluded from the analysis. A total of 849 patients with malignant testicular GCTs were enrolled between December 2013 and December 2021 and were included in this analysis. Of these, 546 (64%) had seminoma and 303 (36%) had nonseminoma. Regarding tumor stage, 465 patients (85%) with seminoma and 207 (68%) with nonseminoma presented with localized disease (stage I). Primary tumor size was determined on histological analysis and corresponded to the largest tumor diameter. The median tumor size for all patients included was 35 mm (Supplementary Fig. 1).

A total of 25 patients (3%) had a primary tumor <10 mm, of which 13 (52%) were seminoma and 12 (48%) were nonseminoma. Seven of these patients (28%) presented with marker-positive disease and five (20%) had primary metastatic disease, all of which were nonseminomas. The median age of the patients at diagnosis was 35 yr (range 21–64). Baseline characteristics for patients with testicular GCTs <10 mm are listed in Table 1. Three of the twenty patients (15%) with stage I disease received adjuvant chemotherapy. Two patients with marker-negative stage I disease experienced relapse with lymph node metastasis, one at 4 mo (nonseminoma, no adjuvant chemotherapy) and one at 14 mo (seminoma, adjuvant chemotherapy) after orchiectomy. The median follow-up at analysis was 28 mo (range 3–62).

Table 1 – Characteristics of patients with a testicular germ cell tumor <10 mm from the Swiss Austrian German Testicular Cancer Cohort Study

	Overall	Seminoma	Nonseminoma
Patients, *n* (%)	25 (100)	13 (52)	12 (48)
Median tumor diameter, mm (range)	8 (3–9)	7 (3–9)	8 (5–9)
Clinical stage, *n* (%)			
Stage I without adjuvant chemotherapy	17 (68)	12 (92)	5 (43)
Stage I with adjuvant chemotherapy	3 (12)	1 (8)	2 (16)
Stage >I (metastatic disease)	5 (20)	0 (0)	5 (41)
Preoperative tumor markers, *n* (%)[a]			
Normal	16 (64)	11 (85)	5 (41)
At least one elevated	7 (28)	0 (0)	7 (59)
Missing	2 (8)	2 (15)	0 (0)
Relapse of stage I, *n* (%)[b]	2 (10)	1 (8)	1 (14)

[a] α-Fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase.
[b] Median follow-up 28 mo.

Two large retrospective studies assessed the rate of incidental testicular masses <10 mm detected on evaluation for male infertility. Bieniek et al. [10] identified a <10 mm incidental testicular mass in 120 out of 4088 men evaluated (3%). Surgery was performed in 18 of these patients during follow-up, with malignancy found in six cases, all of which were localized seminomas. Similarly, Toren et al. [5] detected a <10 mm incidental testicular mass in 46 of 4418 men (1%) evaluated for male infertility. Serial ultrasound follow-up was available for 38 men, with mean growth of 0.5 mm/yr noted. Eight of these men were ultimately treated surgically, with a localized seminoma detected in one patient [5]. In a cohort of 20 men with very small incidental testicular masses ($\leq$5 mm) and negative tumor markers who underwent surgical exploration and FSE, a malignant GCT was detected in four (20%) men [6]. Similarly, a retrospective analysis of men undergoing surgery for testicular masses demonstrated a higher rate of benign histology for small testicular masses, with half of the testicular tumors <10 mm being benign [7].

In this analysis, we assessed the metastatic potential of <10 mm testicular GCTs in the SAG TCCS. The rate of primary metastatic disease was similar for small testicular GCTs (20%) and the overall cohort (21%). All five patients (20%) presenting with primary metastatic small GCTs had marker-positive disease. Two further patients (10%) with initially marker-negative disease developed early relapse despite being treated with radical orchiectomy and in one case even adjuvant chemotherapy. These findings highlight the metastatic potential of small testicular GCTs. Furthermore, our results show that initially negative results for tumor markers did not preclude the risk of early relapse for small testicular GCTs, even when detected and treated early. As this study exclusively assessed patients with histologically confirmed testicular GCTs, it does not assess the relative risk of malignant disease or metastasis for small testicular masses. Furthermore, the number of patients with small GCTs pose a limitation of this analysis.

Given the risk of progression in size and the metastatic potential of small GCTs, we recommend swift work-up for testicular masses. Surgical exploration with tumor

enucleation and histological examination via FSE is a reasonable approach in men with small testicular masses and negative tumor markers. If a malignant GCT is confirmed, radical orchiectomy remains the standard of care for men with bilateral testes.

Author contributions: Manolis Pratsinis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: M. Pratsinis, Fankhauser, Rothermundt.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.03.013.

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