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Determining an Approach to Small Testicular Masses by Examining Scrotal Doppler Ultrasonography and Serum Tumor Markers

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What's known on the subject? and What does the study add?

The place and importance of ultrasound in testicular masses is indisputable in the literature, as in our study. However, radical orchiectomy is often performed in small testicular masses due to low patient compliance and insufficient diagnostic differentiation of ultrasound. In this study, we found that very few testicular masses were malignant in our clinic, so we emphasized the necessity of a conservative approach in patients.

Abstract

Objective: In our study, we retrospectively analyzed the pathology results of radical orchiectomy operations performed in our clinic and to correlate preoperative color Doppler ultrasonography (CDUSG) findings with small-testicular masses (SmTM) with negative serum tumor markers (STM).

Materials and Methods: Male patients (n=98) who underwent radical orchiectomy between January 2010 and January 2021 to treat intratesticular solid lesions that were detected via CDUSG were evaluated retrospectively. All patients were evaluated in terms of age, atrophic testis, echogenicity, size of tumoral lesions, testicular palpability, preoperative STM and postoperative pathology results.

Results: Expression of at least one STM was elevated in 58 (59.2%) patients preoperatively. STM elevation continued to occur in 25 (25.5%) patients postoperatively; furthermore, 81 (82.7%) patients presented with malignant pathology. The mean age of patients was 39.47±15.20 years, whereas the mean age of patients with benign pathology was higher than patients with malignant pathology (p=0.008). The mean size of malignant lesions was significantly greater than that of benign lesions (5.4 vs 3.5 cm; p=0.033). Statistically elevated STM, lower age, heterogeneity in CDUSG, and large lesion size were found as parameters predicting malignancy. Although lesions in 9 (45%) of 20 STM-negative patients with a lesion smaller than 3 cm were benign, benign pathology was detected in 6 (75%) of 8 STM-negative patients with a lesion smaller than 1.5 cm.

Conclusion: CDUSG plays an important role in detecting small non-palpable masses. Especially in STM-negative patients with a SmTM, CDUSG can reasonably guide the decision-making phase although it cannot provide definitive diagnosis. Radical orchiectomy, which is the traditional approach for all solid testicular lesions, leads to unnecessary treatment in patients with benign lesions, so testicular-sparing surgery should be preferred in STM-negative non-palpable SmTMs because the risk of cancer is low.

Keywords: Testicular cancer, ultrasonography, small testicular masses, testis-sparing surgery, radical orchiectomy

Introduction

Germ cell tumor (GCT) of the testis is the most common solid tumor in men aged 15-35 years. GCT is a unique neoplasm where biochemical markers play a critical role. Biochemical serum tumor markers (STM) in testicular tumor are alpha-fetoprotein, b-human chorionic gonadotropin and lactate dehydrogenase. At the time of diagnosis, approximately 60% of patients with GCT appear to have at least one of these 3 tumor markers elevated (1). STM in patients with testicular cancer is integral in patient management, contributing to diagnosis, staging and risk assessment, evaluation of response to therapy, and detection of relapse. Historically, approximately 90% of testicular palpable solid masses were found to be malignant GCT, but today it has been reported that >60% of SmTM are benign (2). According to the European Association of Urology (EAU) guidelines, radical

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orchiectomy is still considered the gold standard approach to treat malignant testicular masses or masses of unknown origin (3). Most of these tumors are palpable and 95% of palpable masses are malignant (4,5). Owing to the increasing use of scrotal ultrasound in the evaluation of urological problems such as infertility, scrotal pain, or trauma, the number of incidentally detected non-palpable testicular masses is increasing and most of these masses are hypoechoic (6,7). However, over the last two decades, the treatment of testicular tumors has begun to shift in favor of conservative surgery. SmTM, defined in the literature as non-palpable masses <2 cm in diameter, is a constant dilemma for urologists. Owing to the existing oncological evidence in the literature (additional treatment with radical orchiectomy) and the side effects of radical orchiectomy-such as hypogonadism, infertility, and male body image deterioration-there has been a shift from radical inguinal orchiectomy, which has been the general approach to intratesticular masses (8). In the study, we retrospectively examined the pathological results of radical orchiectomy patients in our clinic, compare these results with preoperative correlate preoperative color Doppler ultrasonography (CDUSG) findings and determine the most accurate surgical approach that should be considered for these patients, especially in STM-negative patients with SmTM.

Materials and Methods

Male patients who underwent inguinal radical orchiectomy between January 2010 and January 2021 due of intratesticular solid lesions detected in CDUSG were evaluated retrospectively. Our study was conducted at a single tertiary center. All patients were evaluated in terms of age, atrophic testis, vascularity, echogenicity, size of testicular masses, testicular palpability, before the operation STM and postoperative pathology results. Parameters correlated with malignancy were determined according to the results. Pathological subtypes and incidence rates were determined. CDUSG characteristics of pathological subtypes were compared. The probability of malignancy was determined by forming two separate groups for non-palpable STM-negative SmTM smaller than 3 cm and smaller than 1.5 cm. Patients previously diagnosed with testicular cancer (n=2), patients with a history of previous inguinal/scrotal surgery (n=1), a history of other concomitant malignancies (n=1), and chronic diseases [cirrhosis (n=1), hepatosteatosis (n=1), gynecomastia (n=0), or hormonal disorder (n=1)] that may lead to elevated marker levels were excluded from the study.

Statistical Analysis

Independent samples t-test was used to compare the numerical preoperative parameters (the age and lesion diameters) between malignant and benign solid lesions and chi-square was used for categorical parameters (ultrasonic features and pathological results). $P<0.05$ indicated statistical significance. Statistical analysis was performed using SPSS v24.0 statistics software.

Results

The demographic information of the patients and their preoperative STM and postoperative tumor pathologies are shown in Table 1. At least one STM was elevated in 58 (59.2%) patients preoperatively. Tumor marker elevation continued in 25 (25.5%) patients postoperatively. In total, 81 (82.7%) of 98 patients had a malignant pathology. Although the mean age of all patients was 39.47 ± 15.20 years, the mean age of patients with benign pathology was higher than the patients with malignant pathology (p=0.008). The mean size of malignant lesions was significantly larger than benign lesions (5.4 vs 3.5 cm) (p=0.033). In the preoperative CDUSG evaluation of the patients, vascularity increase was detected in 74 (75.5%) patients, whereas microcalcification was found in 28 (28.8%) patients. Hypervascularization was detected in 62 (76%) patients (p=0.6) and microcalcification was found in 22 (27%) patients (p=0.49) with malignant lesions. CDUSG echogenicity showed that 5 (29.4%) of the benign masses were hyperechoic, whereas only 3 (3.7%) of the malignant masses were hyperechoic (p=0.00). While 32 (39%) of malignant masses were heterogeneous, only 2 (11%) of benign masses were heterogeneous. Statistically elevated tumor markers, lower age, heterogeneity, and large lesion size were found as parameters predicting malignancy (Table 1). Pathological subtypes of all malignant and benign lesions are shown in Table 2. The most common pathological subtype was MGCT (mixed-GCT) detected in 33 (33.6%) patients. The second most common subtype was seminoma in 31 (31.6%) patients. Seventeen of the MGCT cases (51.5%) and 21 of the seminomas (67.7%) were hypoechoic. In other words, the most common CDUSG finding in both subtypes was hypoechogenicity. Although 13 of the patients had other pathologies such as atrophy or epididymorchitis, lymphoma was detected in 5 patients, NGCT (non-germ cell) in 5 patients, and paratesticular tumor (liposarcoma) was detected in 1 patient. Heterogeneity was the most common finding in 4 (80%) patients with lymphoma. Although the lesions in 11 (48%) of 20 STM-negative patients with a lesion smaller than 3 cm were considered benign, lesions in 6 (75%) of 8 STM-negative patients with a lesion smaller than 1.5 cm were benign (p=0.00).

Discussion

Historically, approximately 95% of testicular palpable solid lesions were found to be malignant GCT. Today, early-stage GCT is a highly curable malignancy, with a reported 5-year survival rate of approximately 91% (9). Despite these good oncological evidence, it is also important to consider the side

effects of radical orchiectomy (testosterone deficiency, sexual dysfunction, infertility, and modified body appearance) and avoid overtreatment in patients with benign masses. More than 60% of SmTM cases were reported to be benign (10). EAU guidelines state that testis-sparing surgery can be performed in meta-synchronous contralateral tumors or in cases with normal preoperative testosterone levels, solitary testis, and tumor volume of less than approximately 30% of testicular volume, but even in these cases, testicular intraepithelial neoplasia (TIN) rate in the same testis is high (at least up to 82%). The TIN rate is 3-5% in the contralateral testis, and malignancy is observed in half of these cases within 5 years (11-14). This requires long-term follow-up after testis-sparing surgery. Conservative surgery is avoided in SmTM owing to low patient compliance, the pathologist's lack of experience in frozen section evaluation, and the surgeon's lack of partial orchiectomy experience (14).

In addition to these challenging conditions, conservative surgery is a viable alternative to radical surgery, particularly in selected patients with normal contralateral testis. Important points are the size of the mass, clinical picture, non-palpable feature, tumor marker negativity, or absence of radiological suspicion of malignancy. This approach has increased the importance of SmTM recently. This is because SmTMs are generally non-palpable, STM-negative, and it is difficult to distinguish whether they are malignant or benign using CDUSG or magnetic resonance imaging (15,16).

Table 1. Demographic characteristics and lesion-related pre-op CDUSG characteristics of benign and malignant patients

Parameters	All	Malignant	Benign	p
Number	98	81 (82.7%)	17 (17.3%)	
Age (years)	39.47±15.20	37.63±13.94	48.24±18.16	0.008[t]
Lesion diameter (cm)		5.40±3.29	3.50±3.22	0.033[t]
Side				
Right	59 (60.7%)			
Left	37 (37.8%)			
Bilateral	2 (2%)			
USG findings of the mass echogenicity				
Hypoechoic	52 (53%)	43 (53%)	9 (52%)	0.06[k]
Hyperechoic	8 (8.1%)	3 (3.7%)	5 (29.4%)	0.00[k]
Heterogeneous	34 (34.6%)	32 (39%)	2 (11%)	0.02[k]
Isoechoic	4 (4%)	3 (3.7%)	1 (5.8%)	0.14[k]
Vascularity	74 (75.5%)	62 (77%)	12 (70%)	0.6[k]
Microcalcification	28 (28.5%)	22 (27%)	6 (35%)	0.49[k]
Pre-op STM-positive	58 (59.2%)	58 (59.2%)	0 (0%)	0.00[k]
Post-op STM-positive	25 (25.5%)	25 (25.5%)	0 (0%)	0.00[k]
≤1.5 cm STM-negative*	8 (8.2%)	2 (25%)	6 (75%)	0.00[k]
≤3 cm STM-negative*	23 (23.5%)	12 (52%)	11 (48%)	0.00[k]

[t]: Independent sample t-test, [k]: Chi-square statistic, *: Non-palpable, STM: Serum tumor marker, CDUSG: Correlate preoperative color Doppler ultrasonography, USG: Ultrasonography

Table 2. Pathological subtypes and preoperative CDUSG characteristics

Pathological subtypes	Heterogeneous	Hyperechoic	Hypoechoic	Isoechoic	Total	p-value
Seminomatous	6 (19.4%)	2 (6.5%)	21 (67.7%)	2 (6.5%)	31 (31%)	
NSGCT	6 (60.0%)	1 (10%)	3 (30%)	0 (0%)	10 (10%)	
MGCT	15 (45.5%)	0 (0%)	17 (51.5%)	1 (3%)	33 (33%)	
Other	2 (15.4%)	4 (30.8%)	6 (46.2%)	1 (7.7%)	13 (13%)	
NGCT	0 (0%)	1 (20%)	4 (80%)	0 (0%)	5 (5%)	
Lymphoma	4 (80%)	0 (0%)	1 (20%)	0 (0%)	5 (5%)	
Paratesticular tumor	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	p=0.028[k]
Total	34 (34.7%)	8 (8.2%)	52 (53.1%)	4 (4.1%)	98 (100%)	

CDUSG: Color Doppler ultrasonography characteristics, MGCT: Mixed germ cell tumor, NSGCT: Non-seminamatous germ cell tumor other (atrophic testis, epididymorchitis...), paratesticular tumor: Liposarcoma, [k]: Chi-square statistic

A recent systematic review reported that approximately 80% of non-palpable masses had a benign histology (17). Corrie et al. (18) reported that the incidence of benign mass was 51.8% among 27 non-palpable testicular masses detected by CDUSG. In a similar study by Sheynkin et al. (19), tumor prevalence was found to be 75%. In a recent study by Shilo et al. (20), 69% (palpable and non-palpable) of testicular tumors smaller than 2.5 cm were benign. Esen et al. (21) found that 7 (53.8%) of 13 non-palpable lesions were benign. Gentile et al. (22) reported that 86.7% (13/15) of the patients had benign pathology, while De Stefani et al. (10) reported that only 2 (9.5%) of 21 cases were malignant. Ates et al. (23) reported that 93.3% of patients with tumors <2.5 cm had benign pathology (14/15). High % of benign pathologies in this series is due in part to the exclusion of lesions with malignant sonographic features. Bojanic et al. (24) found that 35.7% of the patients had GCT, whereas stromal tumors and various lesions were found in 64.3% of the patients, specific data on the differentiation of malignant and benign lesions were not reported. In this study, 11 (48%) of 23 STM-negative patients with a lesion smaller than 3 cm had benign pathology, whereas this rate was 75% in STM-negative patients with a lesion smaller than 1.5 cm (6 of 8 patients) (p=0.00). This result is in agreement with previous studies. The fact that we encountered only 2 STM-negative patients with a lesion smaller than 1.5 cm (25%) makes us question the applicability of over- and more severe treatments, such as radical orchiectomy, in these patients (worsening cosmetic body appearance, organ loss, decreased hormone levels, and fertility). We believe that conservative treatments (ultrasonography, marker close follow-up or partial orchiectomy with simultaneous frozen) should be preferred in these patients.

Of course, not all non-palpable masses should be considered benign, but the fact that the vast majority of these tumors are benign and they are suitable for organ-sparing surgery in terms of size makes radical orchiectomy overtreatment in these cases (24). The small number of cases and the lack of long-term follow-up makes it impossible to establish a guideline for non-palpable testicular tumors. After informing the patient in detail before the operation (letting the patient know that radical orchiectomy may be preferred during the procedure, radiotherapy may be needed, infertility may occur, etc.), performing inguinal exploration, partial orchiectomy and frozen pathological evaluation (25), completion of partial orchiectomy in patients with benign results, and performing radical orchiectomy otherwise may be considered a good option.

The overall incidence of testicular tumors is reported to be 2-3 per 100,000 and shows an increasing trend, albeit slowly (26). Apart from hematological malignancies, testicular tumors are the most common malignancies in men in the 3rd and 4th decades (27,28). In this study, the mean age of 98 testicular tumors was 39.47±15.20, which was consistent with the literature. The incidence of bilateral involvement in testicular tumors is reported to be 1-4% (2,3). In this study, bilateral involvement was observed in 2 (2%) patients. It has been reported that most testicular tumors are GCT with a high rate of 90-95% (29). In our series, the pathology of 13 (13%) patients resulted as atrophic testis, epididymorchitis, and ischemic necrosis (other). The remaining 85 patients had tumoral pathologies. 74 (87%) of these patients were reported as GCT. However, the rate of lymphomas, which is reported as 2-3%, in the literature, was 5% in our series (30). In this study, the rates of both lymphoma and GCT were similar to those reported in the literature. Secondary tumors of the testis are very rare. No secondary tumors were detected in our series. Metastases of the prostate, lung, and gastrointestinal system carcinomas are the most common metastases, which constitute 2.3% of all testicular tumors (26,31). No carcinoma metastasis was observed in our series.

In the general approach to intratesticular solid lesions, all lesions are considered malignant unless otherwise indicated (3). The first step in further evaluation is to identify for STM and perform a CDUS (6). Ultrasound is a valuable tool for distinguishing intratesticular masses from paratesticular masses and distinguishing solid masses from cystic masses (32). CDUSG is used to show the vascularity and echogenicity of the masses, and presence of microcalcification. Based on CDUSG findings, the surgeon determines the treatment process (radical orchiectomy, partial orchiectomy, or close follow-up of the mass). Hypoechoic findings increase the suspicion of testicular cancer. 95% of testicular cancer cases have hypoechoic features (33). In our study, we found that approximately 92% of malignant pathologies had hypoechoic (pure hypoechoic + heterogeneous) features. Generally, studies report that non-cystic seminoma subtypes are more homogeneous and hypoechoic, whereas non-seminoma and cystic tumors are more heterogeneous and hyperechoic (34). In our series, 21 (67.7%) of 31 patients with seminomatous GCT (SGHT) and 17 (51.5%) of 33 patients with MGCT were pure hypoechoic, whereas 6 (60%) of 10 patients with non-seminamatous GCTs were heterogeneous. We found that hypoechoicity, heterogeneity, vascularity, and microcalcification in CDUSG was more common in malignant pathologies. However, except for heterogeneity, the difference was not statistically significant (p>0.05). These results cannot be generalized to the whole population; thus, none of these features alone is sufficient to diagnose a malignant testicular mass, but these features play an important role in the surgeon's decision for radical orchiectomy.

Study Limitations

The biggest limitation of our study is the small number of patients and its retrospective nature. In order for these results

to be valid for the whole population, multicenter prospective studies with more patients are needed.

Conclusion

CDUSG plays an important role in detecting small non-palpable masses. Especially in STM-negative patients with an SmTM, CDUSG can reasonably guide the decision-making phase although it cannot provide a definitive diagnosis. Radical orchiectomy, which is the traditional approach for all testicular solid masses, may lead to unnecessary overtreatment in patients with benign masses. Conservative treatments provide good hormonal, sexual and body appearance results in patients with benign lesions. For this reason, partial orchiectomy or close follow-up can be considered in the first place if the patient is compatible and willing, if there is no evidence of metastatic disease, if non-palpable and incidentally detected, if STB is negative, if frozen pathological evaluation can also be performed.

Ethics

Ethics Committee Approval: Our study is retrospective and was prepared using data from our hospital system, so ethics committee approval was not required.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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