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Predicting malignancy in small testicular lesions

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Introduction Small testicular lesions ≤20 mm (STL) detected by ultrasound (US), usually non-palpable, have been reported to be benign in up to 80% of cases. Thus, partial orchiectomy with or without frozen section examination and surveillance has been advocated for these kinds of lesions. We seek to report the proportion of benign lesions in testicular tumors ≤20 mm detected by US in our population and explore the predicting factors of malignancy.

Material and methods A retrospective descriptive study of orchiectomies performed for testicular tumors in patients older than 15 years between 2005 and 2019 was performed, including all patients with lesions ≤20 mm on US imaging.

Results A total of 70 patients with STL were included (mean age 34.6 ±10.8 years). Overall, 69% of the lesions were malignant while the smallest lesions (≤10 mm) showed 61% of cancer. Moreover, in the subgroup of non-palpable lesions ≤10 mm, 50% were malignant. Multifocal tumors were found in 18 subjects with a malignancy rate of 88%. There was a significant association between maximum size on US, multifocality and malignancy. Neither tumor markers nor palpability foretold a malignant lesion. A predictive model including size and multifocality was created showing a positive predictive value of 83.3%.

Conclusions US maximum size and multifocality were predictors of malignancy in STL. However, even the smallest lesions showed a 50% chance of being malignant, thus surgery with or without intraoperative biopsy is warranted in most cases.

Key Words: testicular neoplasms ‹› ultrasonography ‹› biopsy ‹› testis ‹› orchiectomy ‹› small testicular mass

INTRODUCTION

"All testicular tumors are cancer until proven otherwise". This urologic statement has been endorsed for decades because allegedly more than 90% of testicular masses are malignant, making radical orchiectomy the standard management. Moreover, partial orchiectomy with frozen section examination (FSE) has been proposed for patients with bilateral tumors or with a single testicle in order to preserve testicular function [1]. However, with ultrasound testing (US) popularization, more and more small non-palpable testicular tumors are being detected and therefore, some benign lesions may be at risk of being over-treated with radical orchiectomy. This treatment might lead to some adverse effects, including increased risk of infertility [2, 3] and gonadal dysfunction [4]. On the other hand, small non-palpable testicular lesions (STL) ≤20 mm have been reported to be benign in up to 80% of cases [5, 6]. Thus, conservative approaches to these STL have been advocated such as ultrasound-guided testicular biopsy with FSE or even US surveillance [5, 7, 8, 9]. Some authors have proposed that small non-palpable testicular tumors, found during infertility workup along with normal tumor markers could undergo US surveillance [10, 11, 12]. Currently, there is a lack of consensus about the surgical approach for small incidental testicular lesions.

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Our country, Chile, has one of the highest incidences and mortality rates for testicular cancer in the world [13], hence these approaches must be considered very carefully in our environment. It would be of great interest to elucidate if there is some subgroup of patients for which conservative approaches could be safely recommended.

The aim of this study was to report the proportion of malignant lesions in small testicular lesions ≤20 mm. We seeked to identify clinical predictors of malignancy, which might help to establish criteria for radical or conservative approaches in our population.

MATERIAL AND METHODS

A retrospective review of patients undergoing orchiectomy for testicular tumors at Pontificate Catholic University of Chile Hospital, between 2005 and 2019 was performed. All US-detected ≤20 mm testicular lesions in subjects older than 15 years old were included. Most of the patients were referred to a urologist because of an incidental finding of patients complaining of testicular pain and a few while undergoing infertility diagnosis. The data collected included age, preoperative diagnosis, palpability, tumor size on US, number of tumors, tumor markers: alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), lactate dehydrogenase (LDH), histologic tumor size and histologic diagnosis.

Statistical analysis was performed with SPSS v22 and Epidat v4.2. Comparisons of continuous variables were done with non-parametric analysis (Mann-Whitney U test) and categorical variables with Chi-square test. Correlation between histologic and US size was evaluated by Spearman's correlation coefficient and Bland-Altman method. P-value <0.05 was considered statistically significant.

A binary logistic regression was conducted to look for independent predictors of malignancy. Variables that were statically associated on the bivariate analysis were included in the model. A receiver operating characteristic (ROC) curve was developed and the Youden index was used to select the best sensitivity/specificity cut-off value.

The study was approved by the institutional review board of Pontificate Catholic University of Chile.

RESULTS

Out of 442 orchiectomies reviewed, 70 patients met the inclusion criteria. Overall, 48 patients presented with malignant lesions on final pathology report (69.6%). Histological diagnoses are shown in Table 1. Mean age in our sample was 34.6 ±10.8 years. Malignant lesions were bigger (median 10 mm vs 7 mm, p <0.002) and more likely to be multifocal; single lesions had 62% chance of being malignant while multiple lesions were 89% malignant (p: 0.03). Although 74.4% of palpable tumors were found to be malignant compared to only 55.6% in those with non-palpable lesions, tumor palpability was not associated with malignancy (p: 0.111) (Table 2).

In lesions ≤10 mm (N: 43) size was not significantly associated with malignancy. In the subgroup of lesions measuring ≤10 mm and non-palpable (N: 24)

Table 1. *Histologic diagnosis of testicular tumors*

Benign	22	Malignant	48
Atrophic and fibrotic lesions	5	Seminoma GCT	28
Leydig's cell tumors	4	Non-seminoma GCT	14
Sertoli's cell tumors	4	Burn out Cancer	5
Leydig's cells hyperplasia	3	Plasmatic cells neoplasia	1
Arterial thrombosis	1		
Epidermoid cyst	1		
Adenomatoid tumor	1		
Nonspecific inflammation	1		
Haemangioma	1		
Mixed and unclassified benign sex cord-stromal tumor	1		

GCT – germ cell tumor

Table 2. *Characteristics of testicular tumors*

	Total	Benign	Malignant	p
Total	70	22 (31.4%)	48 (68.6%)	
Age (years)*	34.6 ±10.8	37.4 ±12.2	33.3 ±10.1	0.147
Size (mm)**	10 (7–15)	7 (6–10.25)	10 (8–15)	0.002
Palpable				
Yes	39	10 (25.6%)	29 (74.4%)	0.111
No	27	12 (44.4%)	15 (55.6%)	
Number of tumors				
1	52	20 (38.5%)	32 (61.5%)	0.031
2+	18	2 (11.1%)	16 (88.9%)	
Tumor markers				
All normal	51	18 (35.3%)	33 (64.7%)	0.140
Any abnormal	18	3 (16.7%)	15 (83.3%)	
AFP				
Normal	61	20 (32.8%)	41 (67.2%)	0.241
Abnormal	8	1 (12.5%)	7 (87.5%)	
HCG				
Normal	62	20 (32.3%)	42 (67.7%)	0.098
Abnormal	6	0 (0%)	6 (100%)	
LDH				
Normal	58	19 (32.8%)	39 (67.2%)	0.335
Abnormal	11	2 (18.2%)	9 (81.8%)	

AFP – alpha-fetoprotein; HCG – human chorionic gonadotropin; LDH – lactate dehydrogenases
*Mean ±SD; **Median (IQR)

Table 3. *Logistic regression of predictors for malignancy*

Variable	OR	CI 95%	P value
Size (mm)	1.2	1.041–1.394	0.012
Multifocal tumor	5.12	1.01–25.9	0.049

OR – odds ratio; CI – confidence interval

were less likely to be malignant than the whole cohort, however 50% of them were still malignant. There was a significant association between size in US and malignancy in tumors less than 20 mm (p: 0.002).

Multifocal tumors were found in 18 subjects (25.7%), with a malignancy rate of 88%, this being a parameter significantly associated with malignancy (p:0.031).

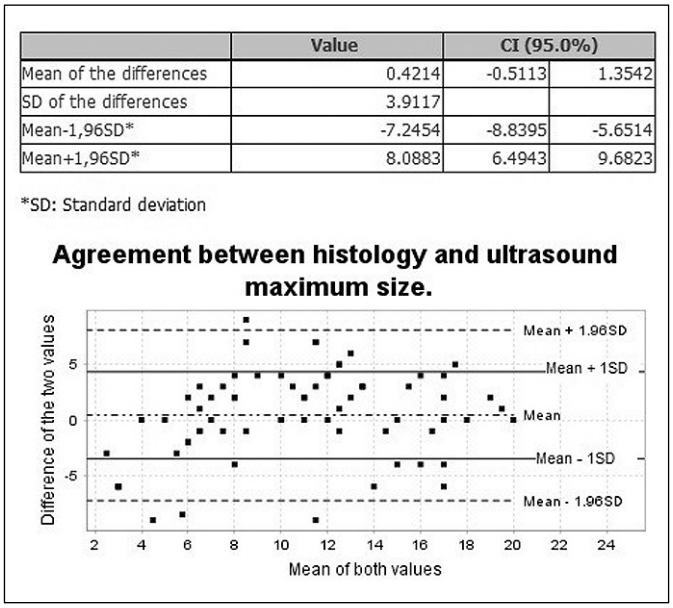
Elevation of the tumor markers LDH, AFP, or HCG was not associated with malignancy (p:0.14). Of patients with normal tumor markers, 64.7% presented with cancer. Analyzed separately, none of the tumor markers alone were associated with malignancy, although, all the patients with elevated HCG had malignant histology.

Multivariate analysis showed that size as a continuous variable [OR 1.2 (CI 1.041–1.394) p:0.012] and multifocality [OR 5.12 (CI 1.01–25.9) p:0.049] were independent predictors of malignancy (Table 3). Derived from this model a score was calculated.

Score = Size (mm) x 18.3 + (163.3 if unifocal + 326.3 if multifocal) – 138.1

Applying this formula in our population we obtained scores from 98 to 542. The area under the ROC curve for predicting malignancy using the formula was 0.753. Applying the Youden index, we found that the best cut-off value was 202 which achieved a sensitivity of 83% and specificity of 74%, with a positive predictive value of 83.3% and negative predictive value of 63.6%.

Correlation between US size and final size on histology by Spearman's rank coefficient was 0.73. The Bland-Altman method showed an agreement between US and histology maximum size, with a mean of the differences of 0.42, a standard deviation of the differences of 3.91 mm and a 1.96 standard deviation of 7.67 mm (Figure 1). However, this parameter is too wide to be clinical useful, so we established a stricter criterion: 20% variation in size as significant. In this case, US underestimates size in 33% of cases and overestimates size in 24%.



	Value	CI (95.0%)	
Mean of the differences	0.4214	-0.5113	1.3542
SD of the differences	3.9117		
Mean-1,96SD*	-7.2454	-8.8395	-5.6514
Mean+1,96SD*	8.0883	6.4943	9.6823

*SD: Standard deviation

Figure 1. *The Bland-Altman method.*
CI – confidence interval

DISCUSSION

This study shows that in our population, patients with STL have a high chance of harboring malignant histology.

Even in the smallest (≤10 mm) non-palpable lesions the chance of malignancy is still 50%. Hence, we do not recommend observation of these lesions. Surgery with FSE should be proposed especially for patients with one testicle or for those unwilling to undergo upfront orchiectomy on dubious cases.

Also, this research shows that the size of the lesion is directly related to the probability of cancer. The described model states that each millimeter increases the risk of malignancy by 20% and multifocality gives 5 times more risk of cancer. Then, using our model with clinically available information before orchiectomy, we can predict reasonably well the chance of malignancy and thus counsel patients on the best option for their STL.

Several studies have shown that size is a good predictor of malignancy. In a study including all testicular tumors irrespective of size, Gang et al. showed that size was directly associated with malignancy [14]. Additionally, Gentile et al. showed that size was a predictor of testicular cancer: the risk of finding a malignant lesion increased sevenfold per mm, and with a cutoff of 8.5 mm on tumor diameter the sensitivity was 81%, specificity 58%, positive predictive value 24% and negative predictive value 95% [15].

Palpability has also been related to malignancy. Carmignani et al. reported 27 cases of testicular tumors up to 24 mm, of which 17 were palpable and 10 were non-palpable, reporting an overall percentage of benign lesions of 47% and 80% in the subgroup of non-palpable [5]. In a review by Giannarini et al. of non-palpable testicular tumors of up to

20 mm, 75% were benign [8]. Scandura et al. reports 81 cases of tumors ≤10 mm (in this case by histology) of them, 69% were benign, and in the subgroup of ≤5 mm all were benign, determining that the limit to predict benign lesions by biopsy is 5 mm [6]. Eifler et al. published that patients with non-palpable testicular lesions with negative tumor markers, less than 5 mm and without hypervascularity could undergo US surveillance or testicular biopsy [7]. Paffenholz et al. propose that testicular tumors less than 2.8 cm^3, without tumor maker elevations, with a history of infertility or hormone disorders and long duration of symptoms could undergo testis sparing surgery [10]. Bieniek et al. suggested that testicular lesions discovered during infertility work-up less than 10 mm on US, non-palpable and without elevation of tumor markers could be referred to US surveillance [11]. Our series differs significantly as we have found that the chance of malignancy in our cohort was significantly higher; 69% overall and 50% in non-palpable lesions less than 10 mm.

Reasons for these discrepancies may be related to several factors. On the one hand, we focused on US size and not on histological size, as in Scanduras's study, which is more clinically relevant information. The correlation between both measurements in the clinical setting is less than optimal and according to our results, US underestimates size by 20% in 33% of patients. Similar results were reported by Shtricker et al. concluding that US underestimates size in 25% of the malignant cases [16], thus these results are not necessarily comparable. On the other hand, several of these studies with a high incidence of benign lesions include a high proportion of patients with incidentally discovered STL during infertility work-up or related to hormone disorders unlike our series.

Tumor markers were unhelpful in differentiating between benign and malignant pathology, however, it is remarkable that all patients who had elevated HCG had cancer. Unfortunately, this was not statistically significant (p:0.098). Counterintuitively, Scandura et al. reported that in their series all the patients with raised tumor markers were benign, but none had elevated HCG [6]. Paffenholz et al. also reported that none of the benign cases had alteration in HCG [10]. The study of Gang et al. showed that elevated HCG was significantly associated with malignant histology, but as we have already alluded to, they included all testicular tumors and not only STL [14]. It seems that HCG is the only tumor marker that is never elevated in benign pathology, hence having this parameter altered may be a predictor of cancer, but this must be confirmed with other studies.

Although Gang et al. also proposes a model to predict malignancy, they included all tumors undergoing surgery independent of size. Our model is based exclusively on STL excluding larger lesions and thus is more relevant for this population. Our model shows that tumors that have a score more than 202 are more likely to be malignant with a positive predictive value of 83.3%, therefore it is advisable for them to perform surgery.

Considering our high rate of malignancy even in non-palpable tumor less than 10 mm (50%), US surveillance for these lesions seems to be a poor choice in our country and performing a partial orchiectomy with FSE would more advisable.

Although, the correlation between FSE and definite histology was not assessed, the performance of FSE is reported to be as high as 100% for detecting malignant tumors [17, 18]. Nonetheless, we had one case of a patient who underwent a partial orchiectomy with an intraoperative FSE ruling out malignancy, although a seminoma was diagnosed at the final pathology report, thus radical orchiectomy was performed.

Limitations of this research are inherent to its retrospective nature. Only patients undergoing surgery were included, hence there is a small chance that some lesions were surveilled and left out of the analysis. However, that is an unusual conduct in our group of urologists. Also, US was performed by many different radiologists and we did not have all the information on vascularity and echogenicity of the STL, however all of them were solid lesions.

CONCLUSIONS

According to our study, maximum size at ultrasound and multifocal lesions are predictors of cancer in STL. In our population, these tumors should be routinely operated as even the smallest non-palpable lesions harbor a non-negligible risk of malignancy. In patients with STL, our model might help to identify candidates for partial orchiectomy with FSE.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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