Role of Frozen Section Examination in the Management of Testicular Nodules: A Useful Procedure to Identify Benign Lesions

Giorgio Bozzini,[1] Barbara Rubino,[2] Serena Maruccia,[1] Carlo Marenghi,[1] Stefano Casellato,[1] Stefano Picozzi,[1] Luca Carmignani[1]

[1] Academic Department of Urology, Istituto Di Ricovero e Cura a Carattere Scientifico, Policlinico San Donato, University of Milan, Milan, Italy.
[2] Pathology Unit, Istituto Di Ricovero e Cura a Carattere Scientifico, Policlinico San Donato, University of Milan, Milan, Italy.

Corresponding Author:

Giorgio Bozzini, MD
Academic Department of Urology, Istituto Di Ricovero e Cura a Carattere Scientifico, Policlinico San Donato, University of Milan, Milan, Italy.

Tel: +39 34 7794 5956
Fax: +39 02 5277 4329
E-mail: gioboz@yahoo.it

Received February 2013
Accepted December 2013

Purpose: To assess the validity of frozen section examination (FSE) on testis nodules.

Materials and Methods: A series of 86 preselected patients with testicular nodules were recruited in this study. Nodules smaller than 2 cm had been surgically removed and biopsies of the margins performed. Larger nodules were just biopsied. Orchiectomy was the treatment of choice for malignant lesions and stromal tumors. Conservative surgery was performed on 2 previously monorchid patients with Leydig cell tumor because of the presence of just one testis. Conservative surgery was the treatment of choice for benign lesions in 32 cases.

Results: At FSE we observed that nodules were malignant germinal tumors in 47% of the cases, stromal tumors in 7% of the cases, benign lesions in 45% of the cases and doubtful for lymphoproliferative lesion in 1 case. The diagnosis made by FSE were confirmed in the definitive ones in all of them, we reported just 2 cases of Leydig cell tumor and benign fibrosis lesion. In these 2 cases, definitive histology of the collected specimens revealed areas of Leydig cell hyperplasia and seminomatous foci, respectively.

Conclusion: Our data suggest that FSE is a valid tool to discriminate between benign and malignant neoplastic lesions, particularly when an adequate sample is available.

Keywords: testicular nodules; testis; pathology; testicular neoplasms; diagnosis; abnormalities; frozen sections; biopsy.

INTRODUCTION

Orchiectomy has represented for a long time the only surgical treatment approved for testicular tumors. This practice was justified by the high proportion of malignant testicular tumors reported in literature (80-90%) among all nodules. However, more recent data indicate that the prevalence of benign lesions (mainly about non palpable incidental lesions) ranges between 8% and 80% in different series.[1-8]

Similarly, the feasibility of organ-sparing surgery on malignant[9] and stromal testicular tumors[10] warrants a more careful evaluation of a radical approach. In particular, we note that, in 1986, Haas and colleagues[6] reviewed their series of over 2800 patients undergoing orchiectomy and reported a 31% prevalence of benign testicular lesions. These results have prompted many investigator to reconsider the opportunity of radical surgery and to search for novel sensitive tools to discriminate between benign and malignant nodules.

Advances in ultrasonographic techniques allow a sensitivity exceeding 90% in the detection of non-palpable testicular lesions; however, the specificity of the test towards benign conditions (i.e. infarction, inflammation, atrophy, hematoma, and benign tumors) remains low.[2] About 70% of these benign lesions are smaller than 2 cm.[2,10]

While the use of intraoperative histological frozen section examination (FSE) has been widely investigated and this procedure is common in several human malignancies, its role in testis tumors is still debated. In fact, some reports encourage FSE use indicating its validity to discriminate between adult[3-5,8,11] and children[12] benign and malignant lesions. The aim of our study was to assess FSE validity in the diagnosis and management of different sized testis nodules.

MATERIALS AND METHODS

Between October 2007 and February 2012, 86 preselected patients (mean age 38 years, range 5-76) were referred to our Academic Division of Urology in Milan for palpable testicular lesions and/or ultrasonography (US) examination (83.72% US evidence, clinically negative). For this reason, after tumor markers evaluation and signed the consent form, they underwent inguinal explorative surgery.

Patients with multifocal lesions or lesions involving the whole testis were excluded from this study.

The technique used included inguinal clamping of the spermatic cord and incision of the tunica albuginea in the corresponding area identified by intraoperative US and/or palpation. Nodules less than 2 cm in diameter were surgically removed and biopsies of the margins of resection were performed. On larger nodules an incisional biopsy was performed. Obtained specimens were evaluated using FSE.

Briefly, samples were frozen using the Leica CM 3000 cryostat (JUNG CM 3000; Leica Microsystems GmbH, Wetzlas, Germany); three 4 µm thick sections were then obtained and stained with hematoxylin and eosin. The time necessary for the histological diagnosis ranged between 10 and 15 minutes. Two different genitor-urinary pathologists examined the specimens. Lesions were then divided into germinal, stromal, benign, and doubtful. All samples were then routinely formalin fixed, paraffin embedded and comparatively reviewed.

RESULTS

Patient's age ranged from 5 to 76 years (average 37.7 years). The nodule size of all nodules included in the present study ranged between 0.44 cm and 10 cm (mean 2.4 cm), with a mean value of 3.7 cm for malignant tumors, 1.12 cm for benign lesions and 0.99 cm for stromal tumors.

At FSE we diagnosed 40/86 (47%) malignant germinal tumors, 1/86 (1%) case doubtful for lymphoproliferative lesion, 6/86 (7%) stromal tumors, and 39/86 (45%) benign lesions. Malignant germinal tumors were represented from further defined as seminomas in 32 cases (80%), embryonal carcinomas in 7 (17%) cases, and choriocarcinoma in 1 (3%) case. Mean diameters of specific lesions were 3.7 cm for malignant tumors, 1.12 cm for benign lesions and 0.99 cm for stromal tumors.

The histological examination on paraffin-embedded sections confirmed the diagnosis of malignant germinal tumors made by FSE in all cases, revealing a mixed nature in 5 seminomas (with teratomatous, embryonal, and yolk sack tumors components), in 2 embryonal carcinomas (with teratomatous and choriocarcinomatous components) and in the only case of choriocarcinoma (with teratomatous component). The one case that was judged doubtful for lymphoprolifera-

Table . Pathological characteristics of studied testicular nodules.

Pathological Characteristics	No.	%
Malignant tumors		
Seminoma*	**32**	80
Embryonal cell carcinoma	**7**	17.5
Mixed (Immature teratoma, choriocarcinoma)	1	2.5
Doubtful		
Non-Hodgkin lymphoma	**1**	100
Stromal tumors		
Leydig cell tumor	5	83
Calcifying large Sertoli cell tumor	1	17
Benign lesions		
Adenomatoid tumor	4	10
Nodular periorchitis	1	3
Epidermoid cyst	1	3
Leydig cell hyperplasia*	6	15
Mesothelial hyperplasia	1	3
Mesothelioma cystic benign	1	3
Infarction	5	12
Fibrosis	12	30.5
Granulomatous inflammation	4	10
Edema	3	7.5
Epididymal appendix	1	3

* These values include cases with changed diagnosis.

tive lesion was confirmed to be the intratesticular localization of a non-Hodgkin lymphoma.

In all the patients with a diagnosis of malignant germinal tumor an orchiectomy was performed. The patient with a testicular localization of a non-Hodgkin lymphoma was treated with conservative surgery. The diagnosis of stromal tumor was made at FSE in 6 cases; 5 (83%) were Leydig cell tumors and one of them (17%) was a large cell calcifying Sertoli cell tumor. The diagnosis of stromal tumors made by FSE was confirmed in the case of large cell calcifying Sertoli cell tumor and in 4 of Leydig cell Tumors. Only in one case a more extensive examination of the paraffin-embedded samples was needed and revealed a more diffuse Leydig cell proliferation with intermixed atrophic tubules, allowing the diagnosis to be changed into a Leydig cell hyperplasia.

The mitotic rate observed for large cell calcifying Sertoli tumor was of 3 × 10 high power field (HPF), for Leydig cell tumors varied between 1 to and 2 × 10 HPF. The mitotic count was in the whole study confirmed by definitive histological examination. Orchiectomy was the treatment performed for these kind of lesions, although in two patients with Leydig cell tumors the Urologist decided to spare the remaining testicular parenchyma because they were monorchids.

The benign lesions diagnosed on FSE were, fibrosis in 12 cases (32%), Leydig cell hyperplasia in 5 (13%), adenomatoid tumors in 4 (10%), infarction in 5 cases (12%), granulomatous inflammation in 4 (10%), nodular periorchititis in 1 case (3%), epidermoid cyst in 1 case (3%), mesothelial hyperplasia in 1 case (3%), cystic benign mesothelioma in 1 case (3%), edema in 3 cases (8%) and epididymal appendix in 1 (3%) case. All the diagnosis were confirmed by definitive non-FSE histological examination.

For benign lesions, an organ sparing surgery was performed in all the cases except in one patient with Leydig cell hyperplasia, 2 patients with adenomatoid tumor, and in 1 pa-

tient with fibrosis. This decision was made in these 4 cases because of their past history of cryptorchidism (see Table). In the last case a more extensive analysis of the testicular parenchyma revealed a seminomatous areas besides the known fibrosis. Orchiectomy was also performed in 2 patients with parenchymal infarction and in one patient with a granulomatous inflammation for its widespread extension.

During the follow-up period (1 to 36 months) no relapses were noted in patients with malignant germinal tumors and Leydig cell tumors who underwent organ sparing surgery.

DISCUSSION

The increased incidence of benign testicular tumors determines a review of the radical surgical approach and led to consider the organ-sparing surgery as a valid option[8,9] for selected patients. However, the conservative management of testis requires to ensure the surgeon about the benign nature of the lesion.

Although US has a very high sensitivity, its low specificity represents a limit to select eligible patients for organ-sparing surgery. The FSE could offer a valid support to discriminate between benign and malignant lesions. In the literature the FSE specificity is reported to be ranging from 81% to 100%. In our study, using the FSE procedure, we identified 40 on 40 malignant lesions (100%), 44 on 45 (98%) benign lesions and 5 on 6 (98%) stromal tumors.

Our results are similar to the ones reported in literature. Tokuc and colleagues[11] showed a specificity of 100% to properly identify 24 malignant lesions by FSE; Leroy and colleagues[4], evaluating 15 patients, reported a specificity of 81% for benign lesions and 100% for malignant lesions. Similar results were reported by Elert and colleagues[5] on 354 patients, in which malignant and benign lesions were correctly identified on FSE with a specificity of 100%. An aspect to take into account in performing FSE is the adequacy of the biopsy submitted for FSE. Apparently in our study we had two discording diagnosis: one Leydig cell tumor and one fibrosis. In both cases the urologist decided to perform the orchiectomy because the patients had a retained testis presenting with non-homogeneous US pattern. In the first case the histological examination revealed a more diffuse Leydig cell proliferation with intermixed atrophic tubules and in the second case diffusely atrophic seminomatous foci were detected into the analyzed testicular parenchyma. These results, in our opinion, underline the importance to obtain an adequate sample and point out how submitting multiple samples of testicular parenchyma, in case of cryptorchidism, could help in having a proper pathological report. In our study the most of benign lesions had diameters under cm 2 (mean 1.12 cm), only the epidermoid cyst had the dimension of 10 cm. These results confirmed what postulated by other authors,[2,10] given the high percentage of benign lesions the FSE is strongly recommended.

Another point of discussion is represented by spermatic cord stromal tumors, because actually we still do not really know what is their biological and pathological potential. In fact they represent the hardest histological lesion to be correctly diagnosed by FSE. Very few are the malignant cases reported in literature; 6 cases of malignant Leydig cell tumor were described, one of them was in association with the adrenogenital syndrome.[13-15] Sertoli cell tumors with malignant pattern have also been described.[16] In all these cases the features[17] described to confirm the malignant nature of the lesions were, dimension more than 5 cm, mitosis rate greater than 3 × 10 HPF, presence of angio/lymphatic invasion and necrosis. On FSE we evaluated these parameters and no one of them was present. During the follow-up period no relapse of metastasis were observed in any case. These last data allowed us to hypothesize, as was done by other authors,[9] that a conservative surgery for stromal tumors, in absence of aspects of malignancy and clinical syndromes correlated, is feasible and risk-free.

CONCLUSIONS

Our results confirm that benign testicular lesions are becoming even more frequent. We found benign lesions in 45% of the cases analyzed. More frequently the benign nodules have dimension under 2 cm. In these cases FSE is strongly recommended because it represents a valid tool to select the patients for organ sparing surgery. It is important to point out that the sample sent to pathologist must be adequate. Moreover this technique may also be used to identify stromal tumors without malignant features.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Chang SY, Ma CP, Tzeng CC. Benign testicular tumours. Eur Urol. 1987;13:242-5.
2. Passarella M, Usta MF, Bivalacqua TJ, Hellstrom WJG, Davis R. Testicular sparing surgery: a reasonable option in selected patients with testicular lesions. BJU Int. 2003;91:337-40.
3. Carmignani L, Gadda F, Gazzano G, et al. High Incidence of benign testicular neoplasms diagnosed by ultrasound. J Urol. 2003;170:1783-6.
4. Leroy XL, Rigot JM, Aubert S, Ballereau C, Gosselin B. Value of frozen section examination for the management of nonpalpable incidental testicular tumors. Eur Urol. 2003;44:458-60.
5. Elert A, Olbert P, Hegele A, Barth P, Hofmann R, Heidenreich A. Accuracy of frozen section examination of testicular tumors of uncertain origin. Eur Urol. 2002;41:290-3.
6. Haas GP, Shumaker BP, Cerny JC. The high incidence of benign testicular tumours. J Urol. 1986;136:1219-20.
7. Sheynkin YR, Sukkarieh T, Lipke M, Cohen HL, Schulsinger DA. Management of nonpalpable testicular tumors. Urology. 2004;63:1163-7.
8. Horstman WG, Haluszka MM, Burkhard TK. Management of testicular masses incidentally discovered by ultrasound. J Urol. 1994;151:1263-5.
9. Steiner H, Holtl L, Maneschg C, et al. Frozen section analysis-guided organ-sparing approach in testicular tumours: technique, feasibility, and long-term results. Urology. 2003;62:508-13.
10. Masoudi JF, Van Arsdalen K, Rovner ES. Organ-sparing surgery for bilateral Leydig cell tumor of the testis. Urology. 1999;54:744.
11. Tokuc R, Sakr W, Pontes JE, Haas GP. Accuracy of frozen section examination of testicular tumors. Urology. 1992;40:512-6.
12. Valla JS for the Group D'Etude en Urologie Pédiatrique. Testis-sparing surgery for benign testicular tumors in children. J Urol. 2001;165:2280-3.
13. Comiter CV, Benson CJ, Capelouto CC, et al. Nonpalpable intratesticular masses detected sonographically. J Urol. 1995;154:1367-9.
14. Kratzer SS, Ulbright TM, Talerman A, et al. Large Cell Calcifying Sertoli cell tumor of the testis: contrasting features of six malignant and six benign tumors and a review of the literature. Am J Surg Pathol. 1997;21:1271-80.
15. Cheville JC, Sebo TJ, Lager DJ, Bostwick dg, Farrow GM. Leydig cell tumor of the testis: a clinicopathologic, DNA content, and MIB-1 comparison of non-metastasizing tumours. Am J Surg Pathol. 1998;22:1361-7.
16. Hopps CV, Goldstein M. Ultrasound guided needle localization and microsurgical exploration for incidental nonpalpable testicular tumors. J Urol. 2002;168:1084-7.
17. Coret A, Leibovitch I, Heyman Z, Goldwasser B, Itzchak Y. Ultrasonographic and clinical correlation of intratesticular lesions: a series of 39 cases. Br J Urol. 1995;76:216-9.