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Multiple, synchronous lesions of differing histology within the same testis: ultrasonographic and pathologic correlations

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2 Multiple, synchronous lesions of differing histology within the same testis: ultrasonographic  
3 and pathologic correlations

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## Abstract

### Objective

To describe ultrasound (US) and pathologic findings in 11 patients with multiple, synchronous lesions of different histology within the same testis.

### Materials and methods.

We reviewed US and pathologic findings in 11 patients with multiple, synchronous lesions of different histology within the same testis. Lesions were classified as separate or adjacent one to another and attempt was made to predict tumor type on their US textures. Pathologic review assessed presence of normal tissue between adjacent lesions and of Germ Cell Neoplasia In Situ (GCNIS) in surrounding parenchyma. Nine cases were from files specifically dedicated to testicular tumors and estimated prevalence was calculated.

### Results.

Two nodules were seen in nine patients and 3 in remaining two. Nine had tumors of different histology; two had one malignancy and one focal benign lesion. GCNIS was seen in 7/11 cases. In dedicated archives, these lesions had 1.83% prevalence.

### Conclusion

Multiple focal lesions identified at imaging within the testis are not always of same histology. This can be suspected in some cases basing on US texture. Recognition that lesions are multiple and indication of their locations within the testis is most important role of imaging and may help pathologists correctly sample the specimen to establish nature of each of them. Presence of multiple lesions is regarded as contraindication to testicular sparing surgery. In two of our patients one lesion was benign. Then, when the procedure is indicated all lesions have to be sampled and assessed by pathologists before deciding between conservative or radical technique.

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## Introduction

Testicular tumors account for less than 1% of all cancers and have an incidence of 0.005% in the general population. They are, however, the most common neoplasm affecting males in the 15 – 34 age range (1). Most of these lesions are testicular germ cells tumors (TGCTs) and it is known that up to 5% patients with a TGCT may develop a second tumor, be it metachronous or synchronous (2, 3). In about 38.6% of cases of metachronous lesions and in about 31.6% of synchronous lesions, the two tumors are of different histologic nature (3).

Multiple, synchronous tumors within the same testis are a known possible occurrence in the pathologic literature and a distinct tumor, separate from the main mass, has been reported in 12% - 22.83% of cases (4, 5). There have been no details of the histology of these multiple synchronous tumors, whether concordant or discordant with that of the dominant mass (4, 5). However, a number of cases with multiple, separate tumors of differing histology in the same testis have been reported (6 - 8).

Multiple tumors within the same testis may be identified on preoperative imaging and are normally considered to be of the same underlying histologic nature. On occasion these are well separate one from another and demonstrate differing echotexture, raising the possibility of histological differences (8).

The aim of this report is to present the imaging and pathologic findings observed in a series of patients with multiple, synchronous tumors of different histology within the same testis, to assess whether ultrasonography (US) can recognize they are actually of different nature and to provide an estimate of their prevalence.

1 Materials and methods

2

3 A request for cases of multiple, synchronous tumors of different histology within the same  
4 testis was announced on the website of the European Society of Urogenital Radiology  
5 (ESUR) in October 2016 as a “call for scientific cooperation”. Eleven cases from 7 different  
6 institutions were collected. All were from teaching files; nine were from files specifically  
7 dedicated to testicular tumors; two were from more general archives. Imaging and  
8 pathologic findings, as well as limited patients’ data (age, clinical signs and symptoms)  
9 were collected and retrospectively reviewed.

10 All patients were examined by ultrasonography (US) only, and both the reports and all the  
11 US images obtained during the studies were available for review in all cases. Pathologic  
12 confirmation of the nature of all the different tumors was obtained in all cases; the original  
13 pathology report was available in all and microscopic images (digital copies of the original  
14 slides) were available for review in 9/11 cases.

15 Given the multicentric and retrospective nature of the study, a variety of US equipment  
16 was used, but all equipment was considered state-of-the-art. All examinations had been  
17 performed with linear, broadband transducers with central frequency higher than 10MHz.  
18 Both B-mode and color-Doppler images were obtained in all cases; US elastography was  
19 performed in one and one case was subject to contrast-enhanced US examination.

20 The review process was performed by two radiologists (40 years and 25 years of  
21 experience in US) and two pathologists (one dedicated uropathologist with 30 years of  
22 experience and a 3<sup>rd</sup> year resident in pathology). Radiologists evaluated the US images for  
23 number of lesions within the testis, their position, relationships and echotexture. All  
24 interpretations were compared to the original report and an attempt was made to predict  
25 type of tumor based on B-mode findings. Lesions were classified as well separate or  
26 adjacent one to another; the first were at the opposite aspects of the testis or only visible

1 along a scan plane that did not include the main lesion; the second were close one to  
2 another and were either divided by a visible cleavage plane or seen as two rounded  
3 lesions which did not merge at point of contact. Pathologic images were assessed for  
4 confirmation of the nature of each tumor and for presence of normal tissue between  
5 adjacent ones, therefore confirming that lesions were actually separate nodules of different  
6 histology and not “mixed” TGCTs and for presence of Germ Cell Neoplasia In Situ  
7 (GCNIS) in the testicular parenchyma.

8 The study was approved by the Ethics Committee of the corresponding author and the  
9 need for informed consent was waived, given its retrospective nature.

10

## 11 Results

12

13 We collected the images from 11 different patients from 7 different institutions. All had  
14 been referred to US because of presence of a palpable mass; all had both testes; all  
15 lesions were unilateral only. All patients had multiple nodules and, at review, a 1 mm  
16 lesion that had not been described in the original US report was detected (Case #2). Nine  
17 patients had 2 lesions; two had 3 lesions, with a total number of 24 lesions reviewed.  
18 Lesions seen at US were described as well separated in 7 cases (Fig. 1) and closely  
19 adjacent in 4 cases (Fig. 2). Two patients had one tumor and a concomitant benign lesion  
20 (1 Sertoli cell hyperplasia; 1 focal area of hyaline degeneration) (Fig. 3). Nine had multiple  
21 germ-cell tumors. The most common association (7/11 cases) was seminoma and  
22 embryonal-cell carcinoma.

23 A preoperative hypothesis of lesions of different histologic nature on the US examination  
24 was suggested in the original report in 4/11 cases only. At consensus central review, in the  
25 9 patients with two lesions, there were 6 in whom these had different echotexture,  
26 considered to be possibly of different histologic nature; similar appearances were

1 observed in the remaining 3 cases. In both patients with 3 nodules there were two lesions  
2 that had similar echotexture and a third one that was clearly different.

3 No discrepancies were observed between the diagnostic interpretation of each nodule in  
4 the pathology reports and the findings observed during the review process.

5 Presence of GCNIS within the testicular parenchyma was described in 7/11 cases (all with  
6 multiple malignancies) and confirmed at review of pathological images. As regards the  
7 remaining 4 patients, GCNIS were not visible in the two of whom pathological images were  
8 available for review (one with two malignancies; one with one malignant tumor and a focus  
9 of Sertoli cell hyperplasia), while only the pathology report, with no mention of GCNIS, was  
10 available in the other two (one with two malignancies; 1 with one malignant tumor and one  
11 area of focal hyaline degeneration). No differences in echotexture of the testicular  
12 parenchyma were found between the patients with and without GCNIS; however, some  
13 intraparenchymal microcalcifications were seen in 3/7 cases with GCNIS.

14 Nine cases were from files specifically dedicated to testicular tumors in 7 different  
15 institutions, which overall banked a total number of 492 malignancies. Based on this total  
16 figure, an estimate of prevalence of multiple lesions with different histology in this  
17 subgroup was 1.83%. Two cases were from more general archives and were not  
18 considered to calculate prevalence.

19 The findings observed in all patients are summarized in Table I.

## 20 21 Discussion

22  
23 Ultrasound imaging is commonly used in patients with a scrotal mass to demonstrate  
24 whether lesions are unilateral or bilateral, intra- or extra-testicular and, if applicable, to  
25 recognize their nature.

26 Multiple lesions may be identified at imaging within the testis, and are usually considered



1 of the same histology but, as seen in our series, this is not always true. We have seen  
2 that, in our subgroup coming from teaching files specifically dedicated to testicular tumors,  
3 9/492 (1.83%) had multiple lesions within the same testis that were of different histology.  
4 Correct identification of the nature of all lesions within the testis is quite important since, in  
5 patients with multiple lesions of different histology, the subsequent therapeutic approach is  
6 targeted to the most aggressive lesion (9). US does not allow to identify with certainty the  
7 histologic nature of testicular masses. However, it is known that a lesion presenting with a  
8 hypoechoic and homogeneous echotexture is more likely a seminoma, more  
9 heterogeneous and echogenic lesions suggest non-seminomatous neoplasms, and  
10 teratomas commonly show internal cystic areas (10). It must be underlined that, although  
11 presence of different US characteristics may suggest the histology of the lesion, the role of  
12 preoperative imaging is limited in this respect; what is paramount is confirmation of the  
13 nature of each lesion at pathologic examination.

14 Some considerations can be done on our findings.

15 In our series, 7 out of our 11 cases had lesions that were clearly separated one from  
16 another, and 4 of these had lesions that were at the two opposite poles of the testis or that  
17 were not seen in the same image plane as the main lesion. Preoperative identification at  
18 imaging of a lesion distant from the proposed main lesion may help the pathologist  
19 correctly sample the appropriate section of the surgical specimen to identify and analyze  
20 all of them. Then, radiologists have to describe all lesions and their location within the  
21 testicular parenchyma in their report, and all reported lesions have to be specifically  
22 searched for at pathology so that proof of the nature of each of them can be established.

23 Presence of multiple, synchronous lesions within the same testis has been suggested as a  
24 possible contraindication to conservative surgery (4, 5). In fact, when testicular sparing  
25 surgery is planned, US imaging is used to assess lesion size and position within the testis  
26 and to analyze the surrounding parenchyma to check for further lesions (11). However, we

1 believe presence of multiple nodules is not an absolute contraindication to this therapeutic  
2 approach, at least in principle: if the procedure is clinically indicated (patient with single  
3 testis or bilateral tumors) and technically feasible (largest lesion smaller than 2 cm) (12),  
4 all lesions have to be sampled at the operative table and their nature assessed by the  
5 pathologist before deciding to carry on with conservative surgery or to proceed with an  
6 orchidectomy. In 2/11 cases of our series, in fact, a small benign nodule was associated  
7 with the main neoplasm.

8 A high number of testicular malignancies of small size was observed in our patients. It is  
9 known that there is an association between small size of testicular nodules and benign  
10 histology, and in a series of 131 consecutive patients, Shilo et al. reported that 38.5%  
11 nodules below the size threshold of 18.5 mm were benign (13). On the contrary, 16 out of  
12 24 lesions observed in our patients were smaller than that cut-off value and 14 of them  
13 (87.5%) were malignant. The low number of patients in our series makes difficult to draw  
14 conclusions about this higher proportion of malignancies of small size in patients with  
15 multiple lesions in the same testis. Larger studies are needed to understand whether  
16 multiplicity is actually a risk factor for malignancy. Furthermore, it must be underlined that  
17 many studies reporting high proportion of benign lesions in small masses are from  
18 infertility clinics, where patients without palpable abnormalities are usually evaluated (14).  
19 All patients from our series had scrotal symptoms and none of these lesions was found  
20 during US examinations performed without a palpable abnormality.

21 GCNIS in the testicular parenchyma surrounding the lesions were found in 7 patients of  
22 our series. US did not show any differences in testicular structure between patients with  
23 and without GCNIS. However, in 3/7 of our patients in whom these cells were confirmed at  
24 pathology, microcalcifications were found. The clinical significance of testicular  
25 microcalcifications is not clearly understood and they are not always found in patients with  
26 GCNIS. However, their presence may be regarded, in some cases, as indicative of pre-

1 malignant changes, especially when associated with additional risk factors such as  
2 testicular atrophy, history of cryptorchidism, presence of testicular neoplasm. At  
3 orchidectomy in men with germ cell tumor, if there is testicular microlithiasis in the  
4 contralateral testis, or if the contralateral testis is atrophic, biopsy may be indicated to look  
5 for GCNIS (15, 16).

6 There are some limitations to this case series. The most important are the low number of  
7 patients we were able to collect and the retrospective nature. As regards the first point, it  
8 must be underlined that our request on the ESUR website was quite specific (multiple,  
9 synchronous lesions of different histology in the same testis), and implied knowledge of  
10 both the imaging and pathologic results in each case. Thus, we have been able to retrieve  
11 only a low number of cases even after posting a “call for scientific cooperation” to  
12 radiologists dedicated to genito-urinary imaging. As regards the second point it has to be  
13 noted that, although all the US images that were in the archives for each of our patient  
14 were available for review, these formed those that had been previously selected for  
15 archiving according to the criteria of the radiologist who examined the patient. The same  
16 can be said for the pathologic images found in the archives: we reviewed digital copies of  
17 the slides that were selected for archiving according to the criteria of the reporting  
18 pathologist while preparing and reading them. We did not obtain the original paraffin  
19 embedded blocks and did not totally section and review them.

20 Furthermore, our patients were pooled from the databases of many institutions, and  
21 cannot therefore be considered as a series of consecutive cases. Although nine patients  
22 were recorded in databases specifically dedicated to testicular tumors in seven different  
23 institutions and we believe that the majority, if not all, of such lesions encountered in each  
24 institution was archived, we cannot be sure this was the practice. Then, the 1.83%  
25 prevalence of multiple, synchronous lesions in the same testis we have calculated can be  
26 considered only as a broad estimate of the rate of such lesions among all testicular

1 tumors.

2 It is however important to understand that multiple, synchronous lesions in the same testis  
3 are "rare" and that there are difficulties in gathering experience with regards to any rare  
4 abnormality. In patients with rare tumors, the results of studies like the present one reflect  
5 the need for retrospective and multi-institutional review, with their inherent bias.  
6 Nonetheless these case series may represent the highest level of evidence available for  
7 these conditions, for which knowledge of imaging appearances and clinical characteristics  
8 is usually based only on case reports or very small case series (17).

9

10

#### 11 CONFLICT OF INTEREST

12

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22 (a) Source of Funding

23 (b) Paid consultant to Sponsor

24 (c) Study Investigator Funded by Sponsor

25 (d) Employee of Sponsor

26 (e) Board Membership with Sponsor

27 (f) Stock Holder for Mentioned Product/Company

28 (g) Patent Inventor for Mentioned Product

29 (h) Any Financial Relationship to Competitors of Mentioned Product

30 (i) Other (please specify)

31

32 This information will be kept confidential. The Editor will discuss the method of disclosure of  
33 any potential conflict of interest with the corresponding author on an individual basis.

34

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2 9) Carlo Toncini: none  
3 10) Lorenzo E. Derchi: none

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5 I accept the responsibility for the completion of this document and attest to its validity on  
6 behalf of the co-authors.

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8 Lorenzo E. Derchi 24.07.18.  
9 (Type name above) (Date)

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19 Figures

20  
21 Fig. 1 A - C. Case #2. 28year old man with palpable mass at right testis. A. Sagittal US  
22 shows three lesions: a large, heterogeneous one at upper pole (open arrows) and two  
23 small, solid and hypoechoic at lower pole (arrows). B) The large lesion was a teratoma  
24 showing both keratinized (open arrows) and cartilaginous (arrows) components  
25 (Ematoxylin Eosin 40x). C) Both small lesions were seminomas, made of homogeneous,  
26 round or polygonal cells with sharp membranes and clear to eosinophilic cytoplasm. The

1 two small lesions were close one to another, but divided by a thin layer of normal tissue  
2 (Ematoxylin Eosin 100x).

3

4 Fig. 2 A - G. Case #3. 24year old man with palpable mass at lower pole of left testis. A.  
5 Axial US image showing two lesions, one adjacent to another; the largest is 22 mm; the  
6 smaller is 16 mm; both have mixed echotexture, with solid and cystic areas. A cleavage  
7 plane is seen between them (arrowheads). B. Sagittal image along largest lesion (open  
8 arrow). C. Sagittal image along other one (curved open arrow) shows an additional,  
9 smaller (9 mm), lesion (arrow) with solid echotexture and internal calcification. The two  
10 lesions are adjacent, with no cleavage plane dividing them, but seen as two rounded  
11 lesions which do not merge at their point of contact. D. Mixed GCT. Tissue from largest  
12 lesion shows embryonal cell carcinoma with focal necrosis and hemorrhage as well as  
13 adjacent residual didymal tissue. The cystic teratoma component is shown in Fig. 3G  
14 (Ematoxylin Eosin 100x). E. Mixed GCT. Intermediate lesion: mixed area of cystic  
15 teratoma surrounded by embryonal cell carcinoma (Ematoxylin Eosin 100x). F. Small  
16 lesion: cystic teratoma with small cystic areas lined by monostratified epithelium  
17 surrounded by markedly haemorrhagic stroma (Ematoxylin Eosin 100x). G. Normal  
18 testicular tissue (between arrows) dividing largest and intermediate lesions: the one at left  
19 of the image (the largest) shows features of cystic teratoma; the one at right (the  
20 intermediate) shows area of embryonal cell carcinoma (Ematoxylin Eosin 20X).

21

22 Fig. 3 A – D. Case #7. A. 32year old male with palpable mass in left testis. Axial US shows  
23 2 cm hypoechoic solid lesion with well defined, lobulated margins (open arrows). B.  
24 Sagittal image along a plane that did not include main lesion demonstrates a 3 mm  
25 hypoechoic, additional one with thin hyperechoic rim (arrow). C. Large lesion was  
26 seminoma with homogeneous polygonal cells with cleared out cytoplasm and prominent



- 1 nucleoli (Ematoxylin Eosin 100X). D. Small one was area of well circumscribed  
 2 proliferation of Sertoli cells in tubular architecture (arrows) (Ematoxylin Eosin 200X).

3

	Age	# of lesions	Separate vs adjacent	Histology	Echotexture and max diameter	GCNIS
1	37	2	Adjacent	Seminoma	Echogenic, homogeneous, 10mm	yes
				Embryonal	Echogenic, homogeneous, 30mm	
2	28	3	Separate *	Teratoma	Heterogeneous, cystic spaces, 30mm	yes
				Seminoma	Hypoechoic, 3.5mm	
				Seminoma	Hypoechoic, 1mm	
3	29	3	Adjacent	Mixed GCT	Heterogeneous, cysts, 22mm	yes
				Mixed GCT	Heterogeneous, cysts, 16mm	
				Teratoma	Solid, calcification, 9mm	
4	13	2	Separate *	Seminoma	Hypoechoic, homogeneous, 12 mm	No
				Hyaline degeneration	Hypoechoic, homogeneous, 6 mm	
5	34	2	Adjacent	Seminoma	Hypoechoic, homogeneous, 20mm	yes
				Embryonal	Echogenic, homogeneous, 35mm	
6	28	2	Separate	Seminoma	Hypoechoic, homogeneous, 33mm	No
				Embryonal	Echogenic, homogeneous, 13mm	
7	32	2	Separate *	Seminoma	Hypoechoic, homogeneous, 19mm	No
				Sertoli cell hyperplasia	Hypoechoic, thin perinodular hyperechoic rim, 3mm	
8	n.a	2	Separate *	Seminoma	Hypoechoic, homogeneous, 5mm	yes
				Embryonal	Echogenic, heterogeneous, 17mm	
9	n.a.	2	Adjacent	Seminoma	Hypoechoic, homogeneous, 13mm	No
				Embryonal	Echogenic, homogeneous, 14 mm	
10	28	2	Separate	Seminoma	Echogenic, homogeneous 3mm	yes
				Embryonal	Hypoechoic, homogeneous 10mm	
11	28	2	Separate	Seminoma	Hypoechoic, homogeneous, 15mm	yes
				Embryonal	Hypoechoic, homogeneous, 20mm	

4 Table I. Patients' age, number of lesions and US characteristics

1 \* indicates that the smaller lesions were far from the main ones.

2 n.a. Age was not available for these two patients

3 GCT = germ cell tumor

4 GCNIS = germ cell neoplasia in situ

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