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Para- and Intratesticular Aspects of Malignant Mesothelioma

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1. Introduction

While the pleural and pericardial forms of malignant mesothelioma account for the majority of cases, this tumor has important and often overlooked urological implications. Embryologically, the vaginal process is an evagination of the peritoneum and indents the scrotal swelling to form the inguinal canal. During migration from the abdomen, the testes are covered by reflected folds of the vaginal process and subsequently form the visceral and parietal layers of the tunica vaginalis. Given this continual lining of epithelial cells of endodermal origin, the potential for transformation into malignant mesothelioma is possible from the peritoneal cavity to the tunica vaginalis covering the testis (Lane, 2001). Although the majority of literature is dedicated to malignant mesothelioma of the tunica vaginalis, relationships between other genitourinary organs and this disease have been described and will be discussed. This chapter will focus on the epidemiology, physical examination findings, diagnostic modalities, histopathologic analysis, treatment, recurrence rates, follow-up guidelines and prognostic factors for male patients with genitourinary malignant mesothelioma.

2. Malignant mesothelioma by genitourinary anatomic location

2.1 Tunica vaginalis testis

The most common urologic site of mesothelioma is the tunica vaginalis testis, accounting for ~1% of all mesothelioma cases (Attanoos & Gibbs, 2000) and the majority of urologic cases (Plas et al., 1998). The tunica vaginalis is an embryonic evagination of the abdominal peritoneum residing in the scrotum, and similar to thoracic mesothelioma, risk factors for malignant mesothelioma include a history of asbestos exposure or a family member with a history of asbestos exposure (may be present in up to 1/3 of patients) (Plas et al., 1998; Vianna & Polan, 1978). Other possible etiological factors that have been suggested for malignant disease include previous testicular trauma and hernia repair; however these factors have not been corroborated (Amin, 1995; Antman et al., 1984). In the few cases reported in patients in the first three decades of life, no history of asbestos exposure was

reported in the patient or family and the etiological factor in these cases remains unclear (Antman et al., 1984; Johnson et al., 1973; Jones et al., 1995; Linn et al., 1988; McDonald et al., 1983; Plas et al., 1998; Stein and Henkes, 1986).

In their report of 74 patients, Plas et al. (1998) reported that the highest incidence of disease is noted in the 6th and 7th decades of life, although 1/3 of cases have been reported in patients less than 44 years of age. Among 16 patients identified in The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (2009) with disease of the tunica vaginalis the mean age was 68 ± 12 years with a range of 44 to 88 years. Furthermore, 15 of these 16 patients were Caucasian, suggesting a possible race predilection. No predilection for the right or left tunica vaginalis has been elucidated to date (Plas et al., 1998), however two cases of malignant bilateral disease have been reported (McDonald et al., 1983; Menut et al., 1996).

2.2 Spermatic cord

Malignant mesothelioma of the spermatic cord is an extremely rare tumor with less than 10 cases reported in the literature (Arlen et al., 1969; Leiber et al., 2000; Pizzolato & Lamberty, 1976; Silberblatt & Gellman, 1974; Tobioka et al., 1995; Torbati et al., 2005; Tuttle Jr et al., 1977; Vyas et al., 1990) including 4 patients identified in the SEER database (National Cancer Institute, 2009). Tuttle et al. (1977) have suggested that a mesothelial histogenesis of the spermatic cord should not be surprising as the testis descend to the scrotum giving the opportunity for nests of mesothelial cells from the urogenital ridge to implant along this route. Furthermore the spermatic cord is in immediate contact with tunica vaginalis.

Men of all ages may be affected as cases from the literature have a median age of 46 years of age (range: 37-60 years), while patients from the SEER Program have identified young (one patient 11 years of age) and elderly patients (three patients >60 years of age). In all studies reviewed from the literature and 3 of 4 patients identified in the SEER database presented with right-sided disease, however due to the paucity of cases, any causal anatomic relationship would be speculative.

2.3 Epididymis/testis

Although the literature does not explicitly report cases of malignant mesothelioma confined to the true testis or epididymis (perhaps diagnosed and/or conglomerated with malignant mesothelioma of the tunica vaginalis), the SEER database identified three patients with disease of the epididymis and 12 patients with testicular disease between 1973 and 2007 (National Cancer Institute, 2009). Comparable to other urologic anatomic sites, elderly patients are more susceptible (mean age – 59 ± 21 years of age; median 65 years of age), however younger patients are not without risk (one patient 24 years of age). Among 13 of 15 patients the database reported laterality of the lesion, 7 (54%) patients had right sided and 6 (46%) patients had left sided lesions. Furthermore, 9 patients had a reported tumor size, ranging from 0.9 to 11.2 cm (mean ± SD, 3.9 ± 3.2). Comparable to disease of the tunica vaginalis testis, 14 of 15 (94%) patients with disease of the epididymis or testis were Caucasian, further suggesting a race predilection for malignant mesothelioma.

3. Physical examination and diagnostic modalities

The majority of patients present to their primary care physician or urologist with a scrotum that has been enlarging over the course of several months and patients typically receive a preoperative diagnosis of hydrocele or testicular tumor (Figure 1) (Spiess et al., 2005). Patients with spermatic cord disease commonly present with scrotal or inguinal swelling or mass that may be assumed to be inguinal hernia and go undiagnosed for years (Leiber et al., 2000).

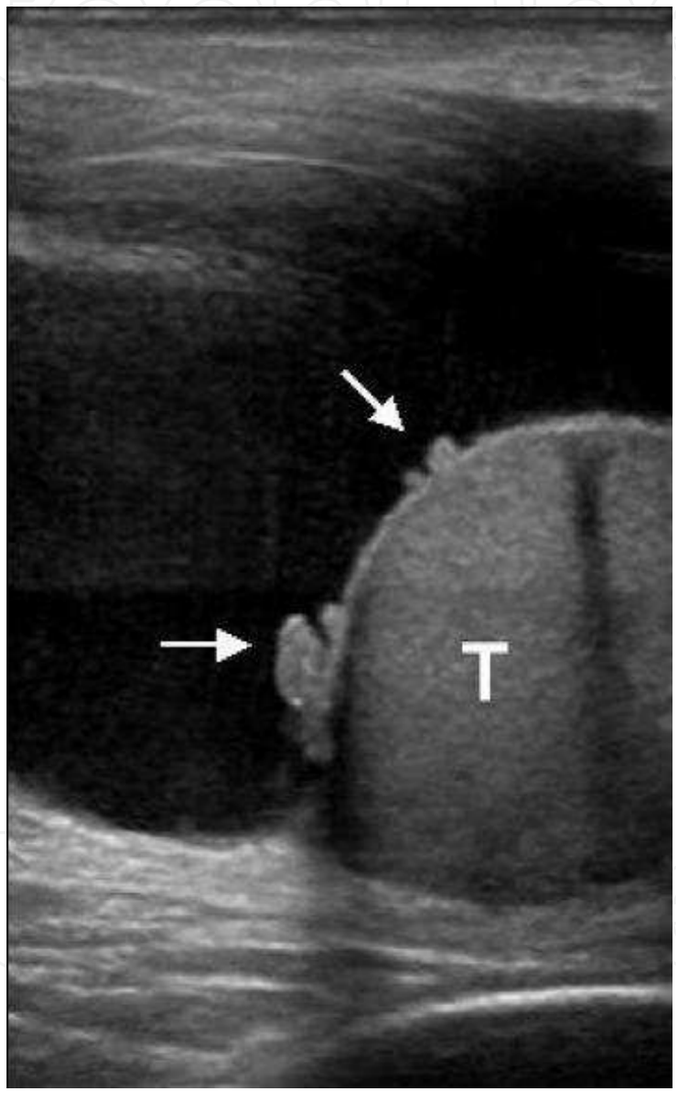

Fig. 1. Preoperative ultrasonography demonstrating the testicle (T) and a paratesticular mass (arrows - mesothelioma of the tunica vaginalis testis).

One of the most significant issues with managing patients with malignant disease is accurate preoperative diagnosis [less than 3% of cases of malignant mesothelioma of the tunica vaginalis (Plas et al., 1998)]. Although relatively nonspecific, typical sonographic appearance of malignant mesothelioma is a paratesticular papillary excrescence or

nodularity that is often associated with hydrocele (Boyum & Wasserman, 2008). Recently, color Doppler sonography has emerged as a possible imaging modality for preoperative diagnosis. Initial studies (Mak et al., 2004; Wang et al., 2005; Wolanske & Nino-Murcia, 2001) documented an intratesticular mass that was hypovascular in comparison to surrounding testicular tissue, and 2 recent cases (Aggarwal et al., 2010; Boyum and Wasserman, 2008) report hypervascularity within a paratesticular nodule or stalk arising from the tunica vaginalis. Thus, discrepancies in color Doppler sonography, whether hypovascularity or hypervascularity of paratesticular nodules, may increase preoperative diagnosis of malignant mesotheliomas (Klaassen & Lehrhoff, 2010).

4. Histopathology

Malignant mesothelioma of the tunica vaginalis comprise the histopathological reports to date and are generally subclassified into epithelial type and biphasic or mixed type (Figure 2). Sarcomatous type is generally found in the pleural cavity however there has been one

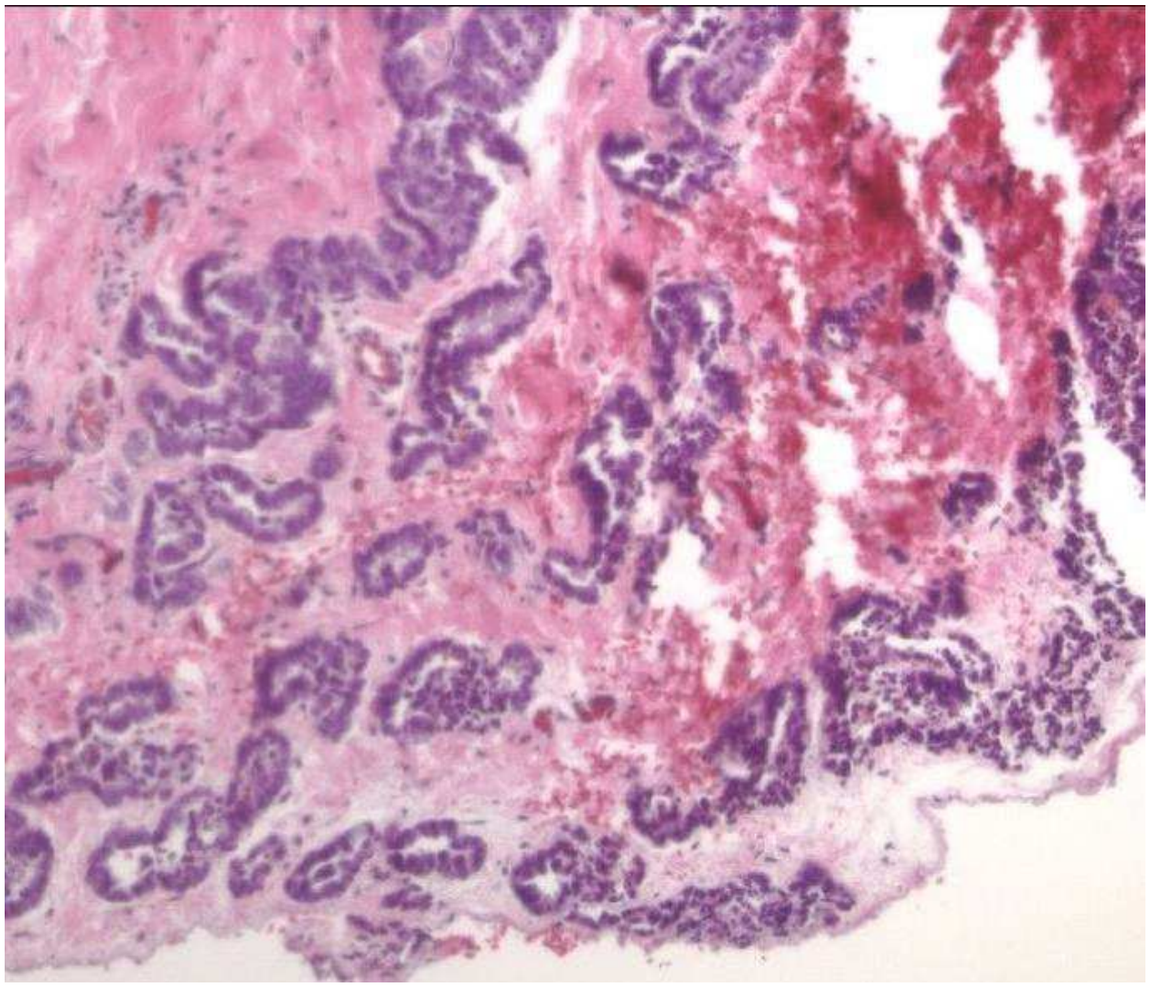

Fig. 2. Malignant mesothelioma of the tunica vaginalis testis (Hematoxylin and Eosin stain 100x). The tumor is predominantly epitheliod, which is the most common histological type.

reported case of this histological subtype for the tunica vaginalis (Eimoto and Inoue, 1977). A large immunohistochemical profile by Winstanley et al. (2006) reported 18 cases of malignant mesothelioma specific to the tunica vaginalis from the UK between 1959 and 2004. They found that all cases were positive for calretinin (Figure 3) and EMA, 16 cases were positive for thrombomodulin, 15 cases were positive for CK7, 13 cases were positive for CK5-CK6, and all cases were negative for CK20 and carcinoembryonic antigen (CEA). Furthermore, tumors are characteristically vimentin positive (Figure 4) and MOC 31 negative (Figure 5). On gross examination, the tumor is usually poorly demarcated, with intermittent firm and friable whitish and yellowish regions (Richie & Steele, 2007).

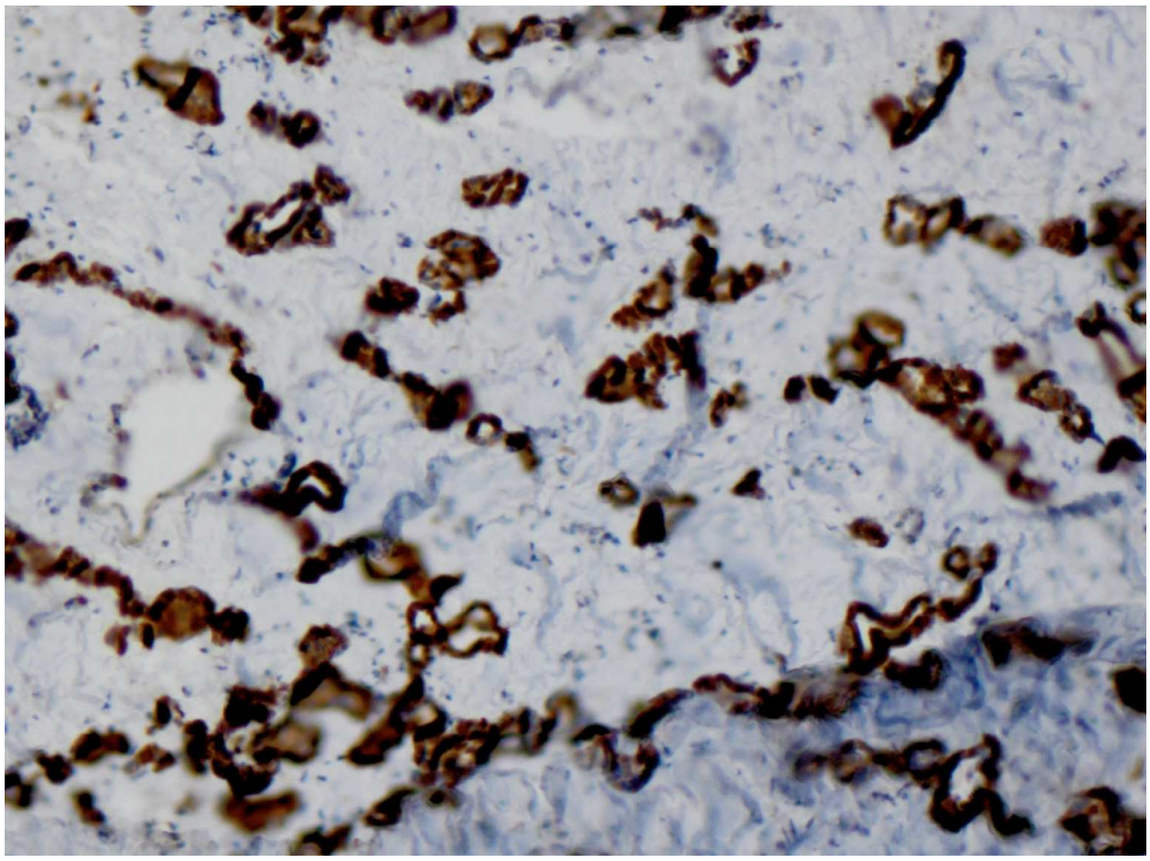

Fig. 3. Malignant mesothelioma of the tunica vaginalis testis staining positive for calretinin (100x).

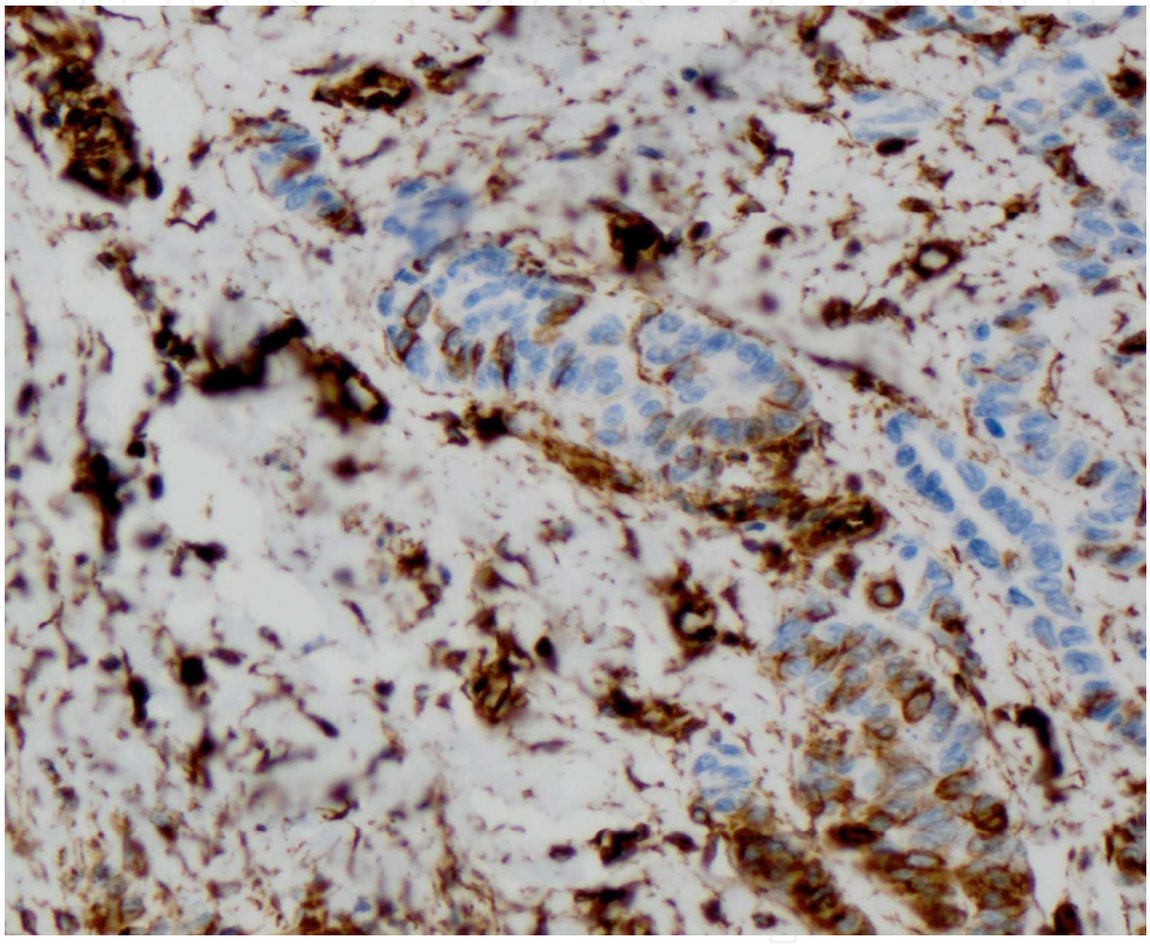

Fig. 4. Malignant mesothelioma of the tunica vaginalis testis staining positive for vimentin (100x).

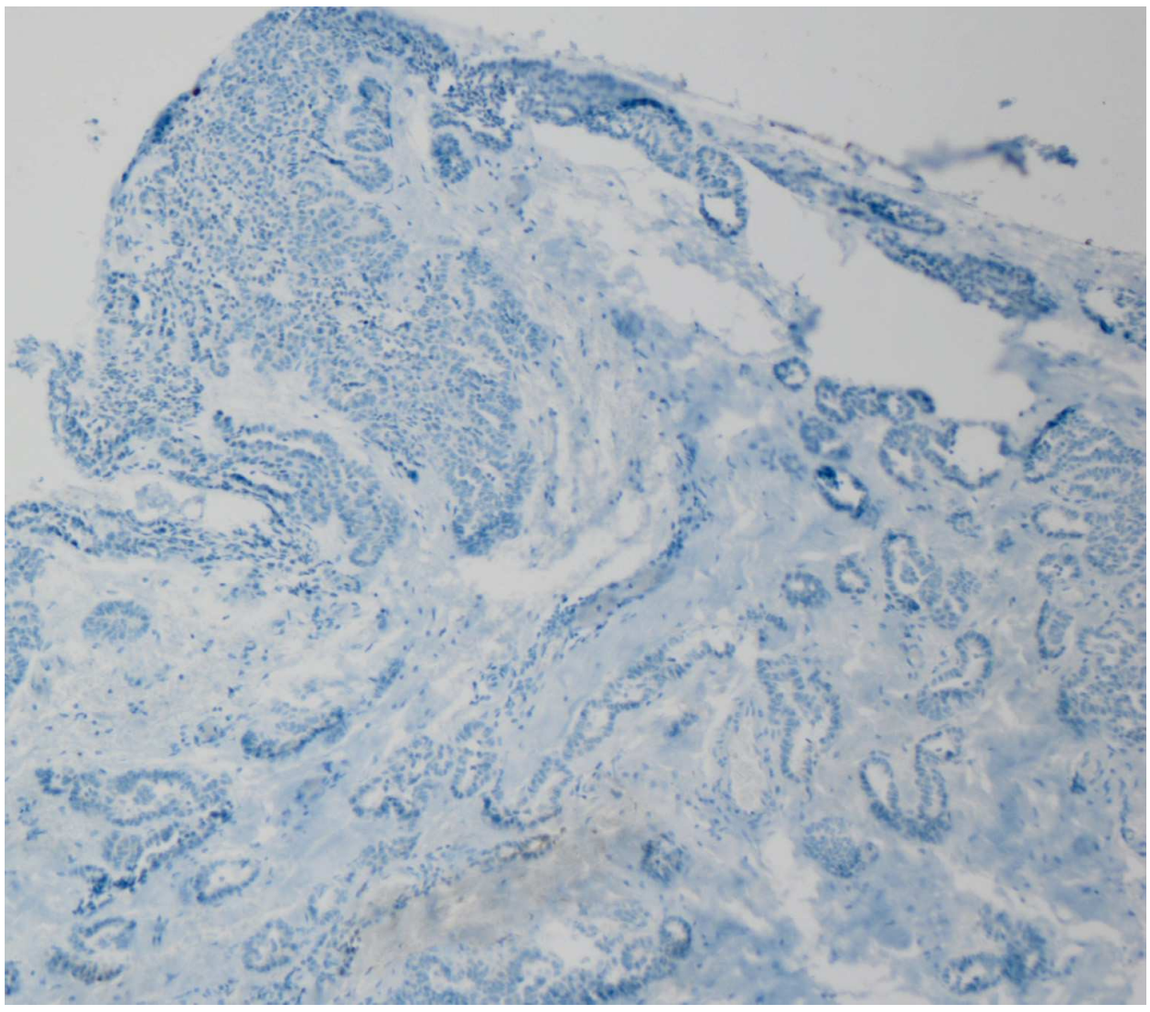

Fig. 5. Malignant mesothelioma of the tunica vaginalis testis staining negative for MOC 31 (40x).

5. Treatment

Intraoperative or postoperative diagnosis of malignant mesothelioma most commonly results in inguinal orchiectomy, orchiectomy, or hydrocele wall excision of the tumor (Figure 6).

In their review of 74 cases of malignant mesothelioma of the tunica vaginalis, Plas et al. (1998) reported first-line surgical approach (available for 62 patients) as inguinal orchiectomy in 26 patients, orchiectomy in 19 patients, resection of hydrocele wall in 15 cases and individual cases of hemiscrotectomy and local excision of the tumor. Following histologically proven malignant mesothelioma inguinal orchiectomy was performed as a second procedure for 14 patients and hemiscrotectomy in 12 patients (Plas et al., 1998). Furthermore, lymphadenectomy was performed in 17 patients (N=8 retroperitoneal, N=5 inguinal, N=4 iliac) with evidence of metastasis in 11 of these patients (Plas et al., 1998). Fifty of 51 patients identified in the SEER database (National Cancer Institute, 2009) underwent

surgical excision of the tumor. Black et al. (2003) advocate early aggressive local resection for palliation in patients who have significant symptoms, as they described a patient who underwent multiple aggressive resections and experienced a remarkable, albeit transient, improvement in symptoms following each resection.

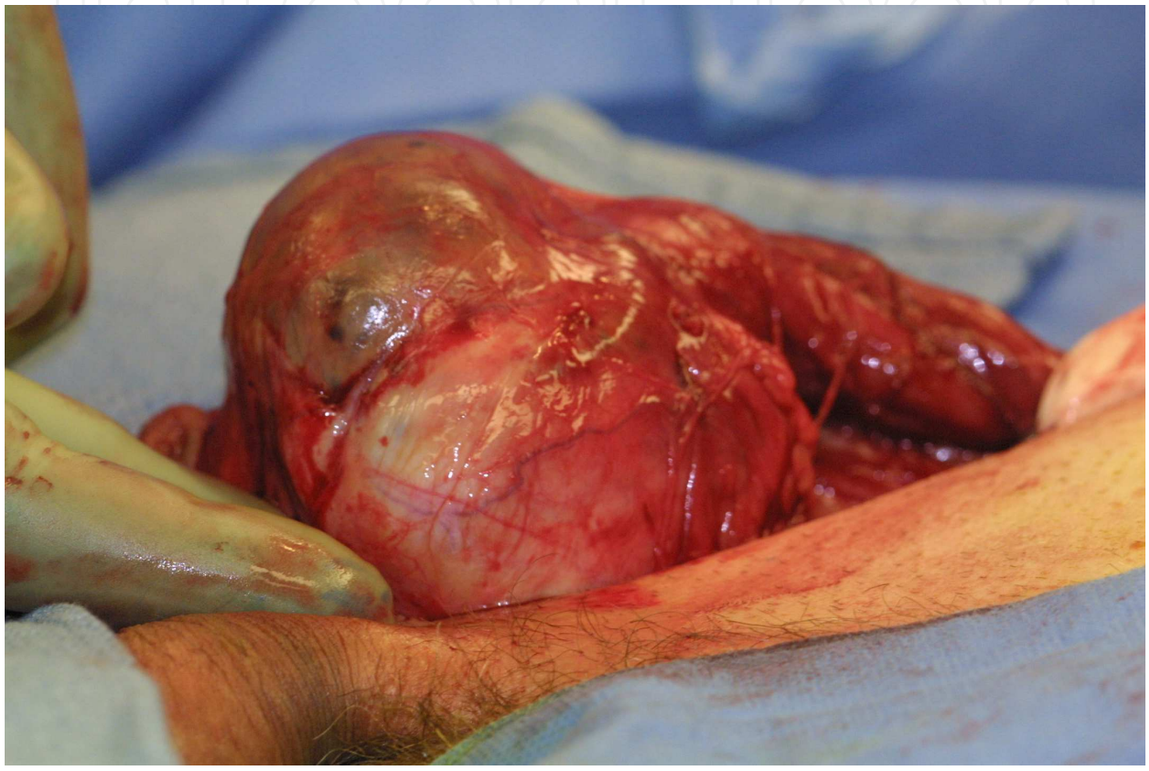

Fig. 6. An intraoperative image demonstrating a paratesticular mass during orchiectomy (mesothelioma of the tunica vaginalis testis).

Adjuvant treatment strategies include chemotherapy, radiotherapy or a combination of chemotherapy and radiotherapy, with heterogenous regimens and outcomes reported (Plas et al., 1998). Plas et al. (1998) identified 10 patients who underwent chemotherapy (most commonly doxorubicin and cyclophosphamide) 2 of which had partial remission and 6 of which had no improvement in symptoms. Plas et al. (1998) also identified 10 patient who underwent radiotherapy (40-60 gray; varying duration of therapy), reporting complete remission with 12 months of follow up in 5 patients, partial remission in 1 patient and no change in tumor size in 2 patients. Among 6 patients who underwent chemotherapy and radiotherapy, Plas et al. (1998) reported no cases of complete remission however 3 patients had partial remission. At the present time, adjuvant treatment of malignant mesothelioma remains experimental and physician dependent with no set guidelines or appropriate follow-up analysis available.

6. Recurrence, follow-up guidelines and prognosis

6.1 Recurrence

To date, Plas et al. (1998) have reported the only comprehensive study identifying factors that may influence local recurrence. In their report, patients with a positive histology of asbestos exposure (N=2) had a significantly shorter interval before tumor recurrence than patients with no history of exposure (N=7) ($p < 0.05$). Furthermore, Plas et al. (1998) reported an increased incidence of local recurrence after resection of the hydrocele wall alone compared to scrotal excision and inguinal orchiectomy, however there was no survival advantage when more radical excision was performed.

6.2 Follow-up guidelines

Presently, there are no established follow-up guidelines for malignant mesothelioma. We agree with Plas et al. (1998) who have suggested clinical examinations and CT scan or retroperitoneal ultrasound every 3 months for the first 2 years, followed by yearly observation for the subsequent 3 years. Since malignant mesothelioma of the genitourinary tract may be diagnosed at any age, the fact that there are no established tumor markers to use during the follow-up period, and due to the possibility of recurrence up to 15 years after primary therapy (Jones et al., 1995), there is an argument that surveillance should continue for up to 10 years and perhaps for the rest of the patient's life.

6.3 Prognosis (Table 1)

The SEER database (National Cancer Institute, 2009) and Plas et al. (1998) provide the largest sample size and provide the most significant analyses for determining prognosis of genitourinary malignant mesothelioma.

	Age			
	≤ 40	**41-69**	**≥ 70**	***p*-value**
Patients, N=(%)	7 (14)	24 (47)	20 (39)	<0.0001
Age (mean ± SD)	23.3 ± 7.6	59.2 ± 7.7	76.1 ± 5.2	
Location, N=(%)	Testis - 3 (43) Penis - 1 (14) Scrotum - 1 (14) Spermatic Cord - 1 (14) Overlapping Lesion - 1 (14)	Tunica vaginalis - 8 (33) Overlapping Lesion - 8 (33) Testis - 3 (13) Spermatic Cord - 2 (8) Epididymis - 2 (8) Scrotum - 1 (4)	Tunica vaginalis - 8 (40) Testis - 6 (30) Overlapping Lesion - 2 (10) Scrotum - 2 (10) Spermatic Cord - 1 (5) Epididymis - 1 (5)	
Mean Survival, years (95% CI)	16.1 (8.0-24.2)	12.3 (6.2-18.4)	5.0 (3.0-7.0)	0.06
Median Survival, years (95% CI)	14.7 (4.2-25.3)	7.0 (1.2-12.8)	3.3 (2.7-3.9)	

	Stage[a]			
	Localized	**Regional**	**Distant**	***p*-value**
Patients, N=(%)	23 (47)	18 (37)	8 (16)	<0.0001
Age (mean ± SD)	61.9 ± 14.0	62.8 ± 17.6	63.6 ± 23.5	
Location, N=(%)	Tunica vaginalis - 6 (26) Overlapping Lesion - 5 (22) Testis - 5 (22) Scrotum - 3 (13) Spermatic Cord - 2 (9) Epididymis - 2 (9)	Tunica vaginalis - 7 (39) Testis - 5 (28) Overlapping Lesion - 4 (22) Spermatic Cord - 1 (6) Epididymis - 1 (6)	Tunica vaginalis - 3 (38) Overlapping Lesion - 2 (25) Scrotum - 1 (13) Spermatic Cord - 1 (13) Testis - 1 (13)	
Mean Survival, years (95% CI)	16.7 (10.4-23.0)	7.7 (3.5-11.9)	2.4 (0.7-4.1)	0.02
Median Survival, years (95% CI)	8.0 (NR)	3.4 (2.3-4.5)	1.3 (0-3.2)	

Abbreviations: SD, standard deviation; CI, confidence interval; NR, not reported
[a] Two patients unstaged (one penile and one testis mesothelioma)

Table 1. Clinical outcomes of male patients with malignant mesothelioma stratified by age and stage of disease, from the Surveillance, Epidemiology, and End Results (SEER) database (2009).

6.3.1 Age (Figure 7)

Among the 51 patients identified in the SEER database (National Cancer Institute, 2009), 7 (14%) were ≤40, 24 (47%) were 41-69 and 20 (39%) were ≥70 years of age ($p < 0.0001$). Mean survival was progressively worse for older patients, with mean survival rates of 16.1 (95% CI 8.0-24.2), 12.3 (95% CI 6.2-18.4) and 5.0 years (95% CI 3.0-7.0), respectively ($p = 0.06$). The 3- and 5-year survival rate for patients ≤40 years of age was 100% and 80%, for patients 41-69 was 56% and 38%, and for >70 was 29% and 23%, respectively. In their meta-analysis patients with malignant mesothelioma of the tunica vaginalis, Plas et al. (1998) reported that univariate analysis revealed a significant correlation of age with survival ($p < 0.01$), emphasizing longer survival for younger patients (N=29, <60 years of age) compared to older patients (N=29, ≥60 years of age). Among these two sample populations, it is evident that elderly patients have a survival disadvantage compared to younger patients with genitourinary malignant mesothelioma.

6.3.2 Extent of disease (Figure 8)

Among the 51 patients in the SEER database (National Cancer Institute, 2009), 49 patients were categorized as having localized (N=23, 47%), regional (N=18, 37%) or distant (N=8, 16%) disease ($p < 0.0001$). Mean survival was significantly worse for patients with non-localized disease, with mean survival rates of 16.7 (95% CI 10.4-23.0), 7.7 (95% CI 3.5-11.9) and 2.4 years (95% CI 0.7-4.1), respectively ($p = 0.02$). The 3- and 5-year survival rate for patients with localized disease was 65% and 48%, for patients with regional disease was 40%

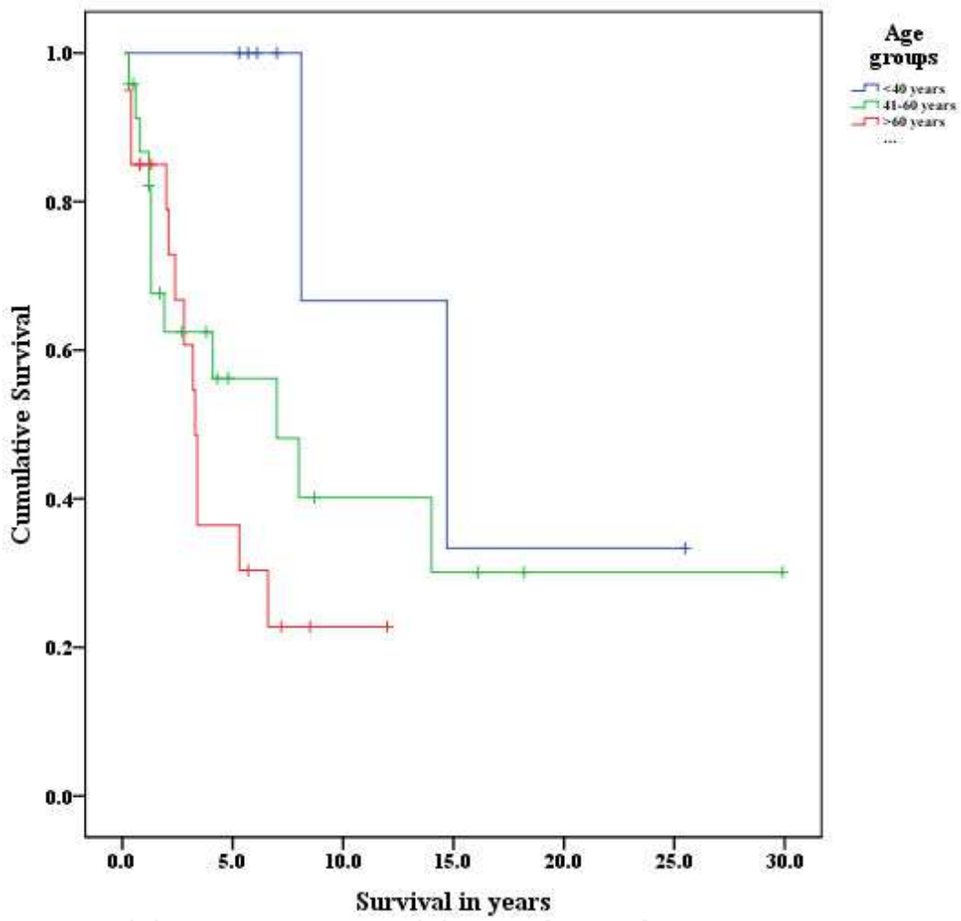

Fig. 7. Kaplan-Meier survival analysis of male patients with urologic malignant mesothelioma stratified by patients <40, 41-60 and >60 years of age from the Surveillance, Epidemiology, and End Results (SEER) database (2009) (p = 0.06).

and 35% and for patients with distant disease was 29% and 29%, respectively. Comparatively, Plas et al. (1998) also found a significant correlation between the presence of primary metastatic disease and survival ($p < 0.05$, N=11 metastatic disease; N=46 organ confined disease). Not surprisingly, patients with advanced malignant mesothelioma have significantly poorer outcomes compared to patients with locoregional controlled disease.

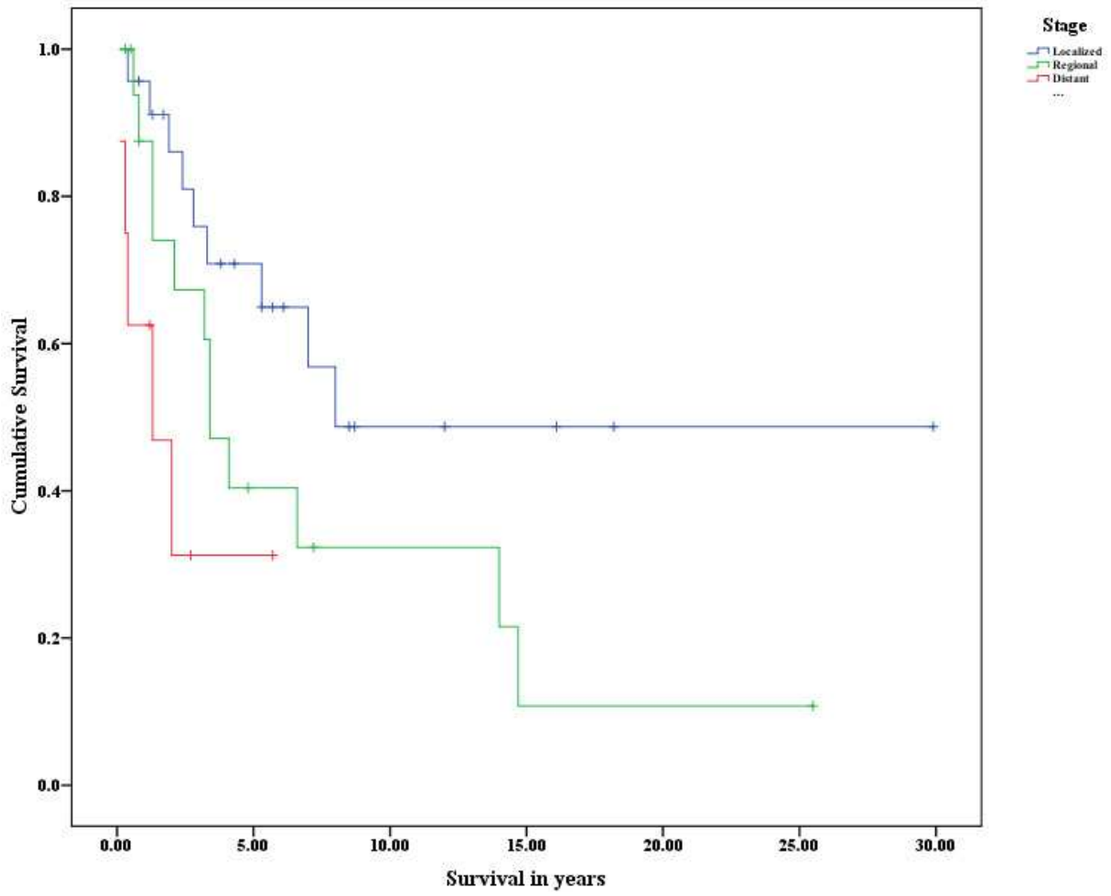

Fig. 8. Kaplan-Meier survival analysis of male patients with urologic malignant mesothelioma stratified by localized, regional and distant disease from the Surveillance, Epidemiology, and End Results (SEER) database (2009) (p = 0.02).

6.3.3 Other variables

Since there are no tumor markers available for patients with malignant mesothelioma, other factors have been tested for prognostic significance. Competing-risks regression analyses performed for the 51 patients in the SEER database (National Cancer Institute, 2009) did not identify a significant prognostic correlation for disease of the tunica vaginalis, patients of non-Caucasian race, year of diagnosis before 2001 and tumor size. Plas et al. (1998) reported that a history of asbestos exposure, tumor histology or primary therapy did not correlate with survival.

7. Conclusions

Malignant mesotheliomas with urologic connotations need to be considered as these tumors have been termed "well described pathologies at unusual sites" (Lane, 2001). At this point in time, analysis suggests a predilection for Caucasian males (however, without a survival disadvantage) and poorer prognosis for elderly patients and patients without locoregional control. The advent of color Doppler sonography will potentially increase the rate of correct

preoperative diagnosis and allow for the appropriate primary surgical approach to be performed (Boyum & Wasserman, 2008; Wolanske & Nino-Murcia, 2001; Mak et al., 2004; Wang et al., 2005) (Figure 9). Surgical therapy remains the cornerstone of initial treatment with a need for further analysis and resources directed toward identifying appropriate adjuvant treatment regimens. This disease is rare but has the potential for aggressive and deadly behavior necessitating a correct preoperative diagnosis, aggressive surgical management and likely lifelong surveillance.

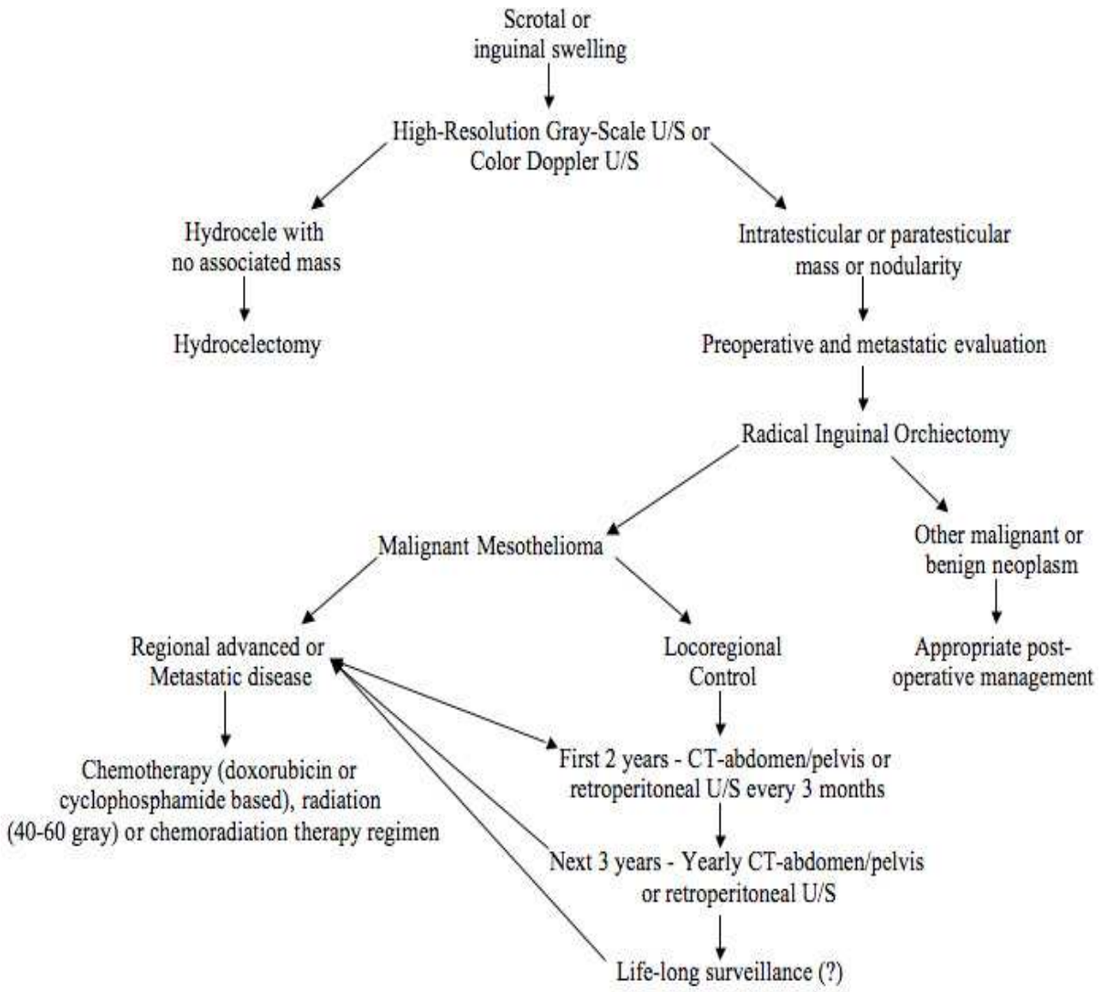

Fig. 9. An evidence-based algorithm for the diagnosis, treatment and follow-up of malignant mesothelioma of the male genitourinary tract (U/S – ultrasonography; CT – computed tomography

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9. References

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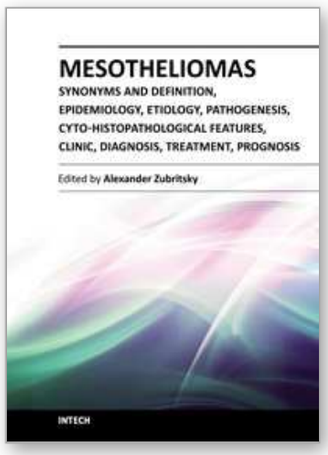

Mesotheliomas - Synonyms and Definition, Epidemiology, Etiology, Pathogenesis, Cyto-Histopathological Features, Clinic, Diagnosis, Treatment, Prognosis

Edited by Dr Alexander Zubritsky

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Mesotheliomas are mysterious mesothelial tumors in that they are relatively rare, difficult to diagnose, with a large number of synonyms, and the etiology and pathogenesis of the disease are still not fully disclosed. This problem attracts the attention of various specialists in the field of medicine and biology every year. In recent years there has been a significant increase of mesothelioma morbidity in most of the countries, due to the further industrialization of society. In this regard, this book has been published with the participation of an international group of experts with rich experience from around the world . The book consists of 14 chapters containing the most advanced achievements of all aspects of the various types of mesotheliomas, both in humans and domestic animals, at a high methodological level. This book is intended for biologists and all health care workers, mostly oncologists of different profiles, as well as students of medical educational institutions engaged or even just interested in the problems of mesotheliomas.

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