THE DEFENSE OF MESOTHELIOMA TUNICA VAGINALIS TESTIS CASES FROM A TO Z

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A. Intervention.

Malignant mesothelioma of the tunica vaginalis testis is an extremely rare but aggressive cancer of the outpocketing of the peritoneum within the scrotum, normally lined by a single layer of mesothelial cells. During normal embryonic development, an outpouching of the peritoneum, called the processus vaginalis, descends into the scrotum to form the cover of the testis. See generally Hassan and Alexander, 2005." A few weeks later, the cranial end of the processus vaginalis closes, resulting in a cavity called the tunica vaginalis testis thus the tunica vaginalis testis ("TVT") is of mesothelial origin, similar to the pleura, peritoneum and pericardium." Bertolotto, et al. 2016.

Most of these mesotheliomas sometimes referred to a paratesticular mesotheliomas are of the tunica vaginalis testis. However, there are a few which actually arise in the spermatic cord. See generally Park, et al. 2011; Hai, et al. 2012; Ahmed, et al. 2016, citing Meng and Bing, 2013; D'Antonio, et al. 2016.

B. Incidence.

The superb review article by Mezei, Chang, Mowat, Moolgavakar, 2017 provides information on the incidence of mesothelioma of the tunica vaginalis in the United States based upon an analysis of the U.S. Surveillance, Epidemiology and End Results Cancer Registry Data between 1973 and 2013 maintained by the National Cancer Institute (treating all mesotheliomas of male genital sites as mTVTs), there were 52 (0.7%) of 7,101 malignant mesotheliomas diagnosed among males. Mezei, et al. 2017 at p. 353. In the period between 2003 and 2013, the incidence rate of mTVT was 0.66 per 10 million. As with the vast majority of cancers, the incidence of mTVT for males ages 50-59 was 4.9 times higher than for males under the age of 50. The incidence rate continues to increase with age and males over the age of 80 have an 18.6 times higher incidence rates that males under the age of 50. Id. at 353.

A study on extrapleural malignant mesothelioma from the Italian National Mesothelioma Registry reported by Marinaccio, et al. in 2010 reported a similar percentage with pleural mesotheliomas representing 92.6% of all malignant mesothelioma cases, peritoneal - 6.7%, pericardial - 0.4% and testicular - 0.3%.

Of 11,629 malignant mesothelioma deaths recorded in the United Kingdom Health and Safety Executive Mesothelioma Register from 1968 to 1991, only 0.09% of the deaths were caused by mesothelioma of the tunica vaginalis (Attanoos and Gibbs, 2000). Some of difference could be accounted for by the fact that the survival rate for mTVT is substantial, even though a significant percentage of patients ultimately die of the disease.

A recent case series in Japan identified 105 diffuse malignant mesotheliomas diagnosed between January 2005 and December 2007 in the Rosai group and related facilities. Among them, 94 (89.5%) originated in the pleura, 7 (6.7%) in the peritoneum, 2 (1.9%) in the pericardium, and 1 (.09%) in the tunica vaginalis testis. Fujimoto, et al. 2010 at p. 1755.

In the Annual of the pathological autopsy cases in Japanese Society of Pathology from 1958 to 1996, a total of 1,846 malignant mesothelioma cases were registered - 1,213 pleural
mesotheliomas (68%), 431 peritoneal (24.1%), 108 pericardial (6.1%) and 6 tunica vaginalis testis (0.3%) and 28 "others" (1.6%). Murai, 2010.

C. State-of-the-Art.

Dr. Newton Evans published a report on 4 cases of "mesotheliomas of the uterine and tubal serosa and the tunica vaginalis testis in 1943 in the American Journal of Pathology. However, all of these tumors were characterized by Evans as "essentially being benign. . ."(Id. at 465). He did conclude that "these tumors represent a type not here before generally recognized, and that the facts presented justify the view that the characteristic cell structure is mesothelial and that the tumors may properly be considered to be mesotheliomas." Id at 466.

There have been scattered case reports of mTVTs since at least the 1950s. A number of articles, including Mezei, 2017, identified Barbera and Rubino, 1957, as the first case report in the literature concerning mTVT. In this case, which more closely resembled a well-differentiated papillary mesothelioma of the tunica vaginalis, no asbestos exposure was specified.

There were a few case reports prior to 1976, including Kasdon, 1969 (two cases of mTVT) and Johnson, et al., 1973 (23-year old male with mTVT). The first case report of a person with a history of asbestos exposure was not published until 1976. Fligiel, et al. 1976. The patient had worked as an insulator for 40 years, and the authors of the case reported noted:

"Malignant mesotheliomas of the tunica vaginalis are rare and have not been associated with asbestos exposure as have pleural and pericardial mesotheliomas, citing Evans, 1943; Selikoff, et al. 1964; Selikoff, et al. 1965." Fligiel, 1976 p. 1478.

The Selikoff references are two seminal publications by Dr. Irving Selikoff of his study of the Heat and Frost Insulators Union in North American. The 1964 publication focused on asbestos and neoplasia while the 1965 publication specifically focused on mesothelioma. Neither of these articles identified any cases of mTVT in insulators.

The Fligiel and co-authors pointed out that:

"This is the first report, to our knowledge, of a malignant mesothelioma of the tunica vaginalis associated with asbestos exposure, and his epidemiologically as well as clinically important." Id at 1481.

In the same year, Margaret Becklake, a professor of epidemiology at McGill University in Montreal, Quebec published a very influential state-of-the-art review article in the American Review of Respiratory Disease. Table 1 contains a list of organs affected by asbestos and it includes mesothelioma of the pleural and peritoneum. mTVT is not included. For both pleural and peritoneal mesothelioma, it noted that the association with asbestos exposure is "established", but defined "established" for this purpose as "association" not "cause, established".
The next case report that associated a case of mTVT with asbestos exposure was not published until Japko, 1982. In the Japko case report, the patient had been a pipefitter at an oil refinery and his worked involved "placing thick asbestos insulation around large pipelines, straddling the pipes and their insulation in the process." Id. at 119. Japko, et al. 1982 the authors include a table summarizing all of the prior case reports. In 3 cases, there was no history of asbestos exposure, in 6 there was no information, and 2 included a history of exposure - the Fligiel, 1976 report of an insulator and the current case of a pipefitter.

The Japko case report and review of the literature was closely followed by an influential case report by Karen Antman, et al. which was published in 1984. Antman, et al. describes 6 additional patients with mTVT, 4 of whom had significant asbestos exposure. Atman, et al. included a table summarizing case reports of patients with mTVT in order of survival:
"Since the first malignant mesothelioma of the tunica vaginalis testis was described by Barbera and Rubino in 1957, 17 additional cases have appeared in the literature. Only 2 of these previously reported cases had a well-documented history of asbestos exposure. We described 6 additional patients with malignant mesothelioma of the tunica vaginalis, 4 of whom were heavily exposed to asbestos." Id. at 447.

This was followed by several additional case reports, some of which reported cases of mTVT with no asbestos exposure. Prescott, et al. 1988 (61-year old retired salesman with no history of asbestos exposure); Grove, et al. 1989 (case series including a 58-year old and 79-year old with no evidence of asbestos exposure); Carp, et al. 1990 (54-year old with no history of asbestos exposure); Kamiya and Eimoto, 1990 (32-year old Japanese male with no history of exposure to asbestos); Kuwabara, et al. 1991 (60-year old with no history of asbestos exposure);
Moch, et al. 1994 (80-year old male with no history of asbestos exposure); Amin, 1995 (59-year old who had not been exposed to asbestos); Eden, et al. 1995 (62-year old who had no known occupational exposure to asbestos). On the other hand, there were a few additional case reports prior to a significant case series published in 1994 which contained a history of asbestos exposure: Karunaharan, 1986 (40-year old male who had been regularly exposed to asbestos for 20 years performing maintenance and modification work in a phenol formaldehyde plant); Huncharek, et al. 1995 (45-year old male previously employed as an electrical power plant worker with possible exposure to asbestos in insulation materials). There were scattered additional case reports in this timeframe without any information on whether the patient had a history of asbestos exposure.

An influential case series was published by Jones, Young and Scully in the American Journal of Surgical Pathology in 1995. It included a clinical pathologic analysis of 11 cases with review of the literature. This was the largest case series to date, and while the authors commented that a number of individual case reports and occasional small series have documented the occurrence of mesotheliomas of the tunica vaginalis, "The issue of asbestos exposure has been specifically addressed in only 27 of the reported 64 cases of testicular mesothelioma. Of these 27 cases, 11 (41%) were associated with an occupational history of exposure ranging from 'several' to 40 years before the diagnosis of mesothelioma." Id. at 819. The authors noted (incorrectly) that "the figure of 41% is similar to the frequency of asbestos exposure of patients with pleural mesothelioma." Id. at 819. In their case series, only 5 of the 11 cases had information available regarding asbestos exposure, and in only 1 of the 5 was there history of exposure to asbestos (10 year history of exposure as a pipefitter). The other 4 cases had no history of asbestos exposure.

D. Epidemiology/Case Reports/Case Series

Given the rarity of mTVT, there are no epidemiological studies (case control or cohort). However, over 100 case reports/case series have been published in the peer-reviewed medical literature. Appendix A (which will be available online) contains a brief summary of each of these reports as well as review articles and book chapters relevant to mTVT. However, if the case was reported in a foreign journal with no English translation, it was not included.

Dr. Suresh Moolgavkar and colleagues at Exponent recently published an outstanding review on the epidemiology of both mesothelioma of the pericardium and tunica vaginalis testis in the Annals of Epidemiology. Among the 89 reported cases with mTVT that Mezei et al. identified as not having been previously been included in literature reviews of mTVT case reports, "the possibility of asbestos exposure was considered for 50 cases (56%). "Of these 50 cases of mTVT, asbestos exposure was confirmed or assumed for 15 (30%)." Mezei, et al. 2017 at p. 353. In other reviews, the estimated percentage of cases in which there has been a history of asbestos exposure has generally been in the range of 30 to 40%. For example, in Segura-Gonzalez, et al. 2015, the authors noted that "only 34.2% of patients with mesothelioma of tunica vaginalis have a positive history of asbestos exposure", citing Guney, et al. 2007 and Ikegami, et al. 2008. The authors included a useful chart summarizing review of cases of paratesticular mesothelioma of tunica vaginalis:
Several other reviews have provided similar estimates of the percentage of cases where there has been a history of asbestos exposure: Bisceglia, et al. 2010; Pesatori and Mensi, 2005; Hatzinger, et al. 2006. However, several reviewers have pointed out that the real prevalence of asbestos exposure could be underestimated because many case reports published before 2000 lacks sufficient clinical information. Hatzinger, 2006; Plas, et al. 1998.

As in the case of pericardial mesothelioma, Marinaccio, et al. 2010, is an outlier, estimating that 70 to 80% of subjects with MTDT had a prior history of asbestos exposure.

Mezei, et al. 2017 identified 89 individuals with primary malignant mTVT reported between 1964 and 2015 "who apparently had not been included in prior literature reviews of case reports (case series were generally reported with insufficient detail to determine whether some of the patients were also described separately in case reports). Of these case reports, 56% were from Europe (including Istanbul), 30% from Asia, 10% from North America, 2% from Africa, and 1% from South America. The mean age at diagnosis was 58 years and the median was 63.5 years, with a range from 7 to 91 years." Id. at 353.

Mezei, et al. included a very helpful chart summarizing case series and literature reviews of malignant mesothelioma of the tunica vaginalis testis in Table S2 (supplemental materials) of their article. It is reproduced with permission as Appendix B to this outline.

Most recently, researchers at the Memorial Sloan Kettering Cancer Center in New York published a case series of all patients with pathologically confirmed mTVT over a 17-year period (1997-2014). Recabal, et al. 2017. Overall, 15 patients with pathologically confirmed mTVT were included. Of particular interest is the fact that asbestos exposure was recorded in only 2 of

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<table>
<thead>
<tr>
<th>Study</th>
<th>No. and Age of Patients</th>
<th>Asbestos</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
<th>Histology</th>
<th>Follow-up and Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yen¹¹</td>
<td>1 patient, 53 years</td>
<td>No</td>
<td>Hydrocele with tumor mass</td>
<td>Surgery (radical orchietomy with wide excision of the homocrotal root)</td>
<td>Epithelial (well-differentiated papillary)</td>
<td>3 years</td>
</tr>
<tr>
<td>Mensi²⁸</td>
<td>13 patients, mean 74 years</td>
<td>Yes (n = 9)</td>
<td>Hydrocele</td>
<td>Surgery only (radical orchietomy)</td>
<td>7 epithelial, 3 sarcomatosus, 3 biphacic</td>
<td>NR: 3-year OS 33%</td>
</tr>
<tr>
<td>Jones²⁹</td>
<td>11 patients, mean 54.1 years</td>
<td>Yes (n = 1)</td>
<td>Hydrocele with or without associated mass</td>
<td>Surgery only (radical orchietomy)</td>
<td>6 epithelial, 5 biphacic</td>
<td>Mean 4.3 years</td>
</tr>
<tr>
<td>Erdogan³⁰</td>
<td>1 patient, 48 years</td>
<td>No</td>
<td>Hydrocele</td>
<td>Surgery (radical orchietomy)</td>
<td>Epithelial (papillary)</td>
<td>OS 3 years</td>
</tr>
<tr>
<td>Yang³¹</td>
<td>1 patient, 68 years</td>
<td>No</td>
<td>Hydrocele</td>
<td>Surgery (radical orchietomy)</td>
<td>Epithelial</td>
<td>OS 6 months</td>
</tr>
<tr>
<td>Garcia de Jalón³²</td>
<td>1 patient, 78 years</td>
<td>No</td>
<td>Hydrocele with tumor mass</td>
<td>Surgery (radical orchietomy) + RT</td>
<td>Biphasic</td>
<td>3 months</td>
</tr>
<tr>
<td>Brima³³</td>
<td>8 patients, mean 52.5 years</td>
<td>NR</td>
<td>Hydrocele</td>
<td>Surgery (radical orchietomy, hydroceleotomy)</td>
<td>Epithelial (papillary, tubulopapillary)</td>
<td>NR</td>
</tr>
<tr>
<td>Present study</td>
<td>1 patient, 58 years</td>
<td>No</td>
<td>Hydrocele/DVT</td>
<td>Surgery (radical orchietomy) + chemotherapy + RT</td>
<td>Epithelial</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Abbreviations: DVT = deep venous thrombosis; NR = not reported; OS = overall survival; RT = radiotherapy.

Segura -Gonzales, et al. 2015 p. e404

<table>
<thead>
<tr>
<th>Study</th>
<th>No. and Age of Patients</th>
<th>Asbestos</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
<th>Histology</th>
<th>Follow-up and Survival</th>
</tr>
</thead>
</table>
15 (13%) patients. the authors noted that "prevalence of asbestos exposure was lower than previously reported" but cautioned that "however this variable was not documented in a standardized fashion in medical records, so it may be under-reported in our study." Id. at 169. Finally, the authors noted that "Although this cohort is very small, it represents the largest single-institution series presented to date." Id. at p. 5. (online version).

E. Reviews Published in the Peer-Reviewed Medical Literature.

The following are the most informative and useful reviews published in the medical literature: Antman, et al. 1984; Jones, Young and Scully, 1995; Plas, et al. 1998; Attanoos and Gibbs, 2000; Andrew Churg, 2003; Hassan and Alexander, 2005; Winstanley, et al. 2006; Bisceglia, et al. 2010; Segura-Gonzalez, et al. 2015. Winstanley, 2006, as well as the Hassan and Alexander, 2005 are helpful general reviews, including diagnostic issues. By far, the most exhaustive review is the more recent systematic review by Mezei, Chang, Mowat, and Moolgavkar published in 2017. With the authors' permission, included as Appendix B is Table S2 which provides an excellent summary and chart form of case series of malignant mesothelioma of the tunica vaginalis testis.

From the defense perspective, the reviews by Attanoos and Gibbs, 2000; Andrew Churg, 2003 and Mezei, et al. 2017 are particularly relevant. In the Attanoos and Gibbs review published in 2000, they provide some useful information on the pathology of what they term "Gonadal mesotheliomas", as well as immunohistic chemical details. More importantly, they provided a discussion of etiology:

"Similarly the largest published study of tunica vaginalis mesotheliomas comprises 11 cases and the authors identified approximately 75 further cases from the literature [citing Jones, Young and Scully, 1995]. However, this is not an accurate representation of the prevalence of these tumors for a number of reasons. First, cases identified at surgical resection are not counted unless the patient has died and 'mesothelioma' was recorded on the death certificate. Secondly, on account of the etiological association with asbestos and the potential for medicolegal litigation, most mesothelioma studies are prone to selection bias. In this way, subjects working with, or exposed to asbestos via a non-occupational means are more likely to have a tumor diagnosed as mesothelioma, than individuals developing neoplasms in a non-asbestos exposed cohort. To support this, the authors note that in 5 of 8 (63%) register testicular mesotheliomas, and in 2 of 3 (67%) registered ovarian mesotheliomas there was a history of asbestos exposure. This association with asbestos is stronger than in other series collated from surgical resections. Thirdly, on account of the morphological diversity of malignant mesothelioma, there is potential for misdiagnosis. The World Health Organization classification of ovarian and testicular tumours each recognize 'mesothelioma' as a diagnostic category although and awareness of the occurrence of the tumour at these sites is not widely known. Two of 10 (20%) testicular mesotheliomas and 2 of 3 (67%) ovarian mesotheliomas present in the Mesothelioma Register were available for diagnostic confirmation by use of adjunct techniques.
In contrast to pleural and peritoneal mesothelioma, where some 85 to 90% cases are associated with prior amphibole asbestos exposure, the association between asbestos and Gonadal mesotheliomas has not been well made. In the larger series of mesotheliomas of the tunica vaginalis testis, only 1 of 11 (9%) cases had a history of asbestos exposure [citing Jones, et al. 1995] and many single case reports document no asbestos history." Id. at 155.

Drs. Attanoos and Gibbs summarized their review of 7 primary malignant Gonadal mesotheliomas. (tunica vaginalis and ovarian):

"These tumours represent a poorly described tumour category in both sites. An awareness of their existence is important to prevent misdiagnosis. In both genders the tumours show a similar age distribution (with median onset in the 6th decade), an association with asbestos (in approximately 50% of cases), a diverse histological spectrum (with predominately tubulo papillary epithelial subtype tumours) and immunophenotype that is comparable with malignant pleural and peritoneal mesothelioma." Id. at 158

Dr. Andrew Churg published a very important review article on paratesticular mesothelial proliferations in 2003, with sections addressing both well-differentiated papillary mesotheliomas of the tunica vaginalis (to be discussed later) and malignant mesothelioma of the tunica vaginalis. He summarized the evidence regarding asbestos and mTVT as follows:

"A proportion of MMTV cases do appear to be associated with occupational-level asbestos with occupational-level asbestos exposure. Plas, et al. reported a history of asbestos exposure in 34% of cases. However, few details are available regarding the associated occupations and the quality of the data is quite unclear. That is a particular problem with regard to attribution, because asbestos-associated malignant peritoneal mesotheliomas, which are the closest analogs to MMTV, are only induced with extremely high exposures to amosite or crocidolite-type asbestos. [citing Churg and Green textbook on Pathology of Occupational Lung Disease, Second Edition, 1998, p. 277-338]. In fact, it is very likely that less than the reported 34% of MMTVs are actually caused by asbestos, and the majority of paratesticular mesotheliomas appear to be idiopathic in nature." Id. at 276.

One final note regarding reviews. One of the more unusual articles to make its way into the medical literature, a plaintiffs’ asbestos attorney and plaintiff expert teamed up to publish a case series on mTVT. Meisenkothen and Finkelstein, 2013. It is not known whether "OA case reports", the journal in which the article appeared, is a peer-reviewed journal.

**F. Textbook Discussions of Mesothelioma of the Tunica Vaginalis Testis.**

There have been a number of textbooks which have discussed in varying detail mTVT. Here is a list of some of them. Summaries of the discussion and nature of these textbooks can be found in Appendix A, which will be available online:


IARC, “Tumours of the Testis and Paratesticular Tissue, Chapter 4,” Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs, IARC Press, Lyon, pp. 217-278, 2004


Moolgavkar, S., Chang, E., Mezei, G., Mowat, F., “Epidemiology of Mesothelioma, Chapter 3,” Asbestos and Mesothelioma, Testa, J. (Ed.), Springer, pp. 43-72, 2017


G. Useful Quotes for Use in Direct and Cross Examination of Experts As Well As Openings and Closings

Fligiel and Kaneko, et al 1976

"Malignant mesotheliomas of the tunica vaginalis are rare and have not been associated with asbestos exposure as have the pleural and peritoneal mesotheliomas." p. 1478. [caution: Uses only for state-of-the-art as this is a case report where the authors identified asbestos exposure and stated "this is the first report to our knowledge of a malignant mesothelioma of the tunica vaginalis associated with asbestos exposure, and is epidemiologically as well as clinically important."] p. 1481

McDonald, et al. 1983
"The etiology of these tumors is unknown. an association with hydrocele or prior scrotal procedures is common in case reports of malignant mesothelioma." (p. 360.

Prescott, et al. 1988

"Malignant mesotheliomas are uncommon tumors that arise from the serosal surfaces of the pleural, pericardial and peritoneal cavities. Origin in the tunica vaginalis is rare. From the first reported case by Barbera and Rubino in 1957 until the World Literature Review by Antman and associates in 1984, only 24 cases had been described. Further cases have since been reported by McDonald and associates (2 cases, including the only bilateral case) and Karunaharan (1 case). The peak incidence of presentation is in the seventh decade and hydrocele is the most common presentation. A history of asbestos exposure was obtained in 7 of the previously reported 27 cases, 4 of which were in the 6 new cases described by Antman and associates, although no attempt has been made to obtain information about lung asbestos content at autopsy." pp. 623-624

Grove, et al. 1989

"Asbestos exposure has been described in one of the 17 patients in the clinically benign group (Japko, et al. 1982), and in 3 of the patients with malignant running tumors (Antman, et al. 1984; Fliegel and Kaneko, 1976, our case number 2). Unfortunately, an occupational history has not been emphasized in all the cases. Interestingly, too, prior trauma or herniotomy were recorded in 5 of the 17 patients in the clinically benign group [cites omitted], and in the latter case talc crystals were demonstrated. Radiation, which has also been suggested a causal agent for mesothelioma was not recorded in any of the clinical reports. Asbestos bodies could not be identified in any of the cases, where special examination has been performed (Fliegel and Kaneko, 1976; Japko, et al. 1982; Kasdon, 1969, cases 1 through 3." at p. 290

Jones, Young and Scully, 1995

"As the reported experience with this tumor comprises only approximately 53 cases, the natural history and pathological spectrum of malignant mesothelioma of the tunica vaginalis are still not completely understood." at p. 815

Attanoos and Gibbs, 2000

"In contrast to pleural and peritoneal mesothelioma, where some 85-90% cases are associated with prior amphibole asbestos exposure, the association between asbestos and Gonadal mesotheliomas has not been well made." p. 155

Xiao, Rizzo and Carbone, 2000

"The etiology for tumorigenesis of benign mesothelioma of the tunica vaginalis remains unknown." p. 146
Chetty, 1992

"Well differentiated papillary mesothelioma is usually a small lesion in both the peritoneum and tunica vaginalis. Most occur in the peritoneum, and very rarely in the tunica vaginalis with only two definite cases having been reported so far. Other sites include the epicardium and pleura. Peritoneal lesions are more common in females, but cases have been described in the peritoneum in males.

... 

"Probably not associated with exposure to asbestos, the precise aetiology is not clear." p. 1030

Gurdal and Erol, 2001

"The development of malignant mesothelioma has been proven to be related to exposure to asbestos or different asbestos-containing materials (34.2%). Trauma and inguinal herniotomy are also considered predisposing factors. It is most associated with hydrocele in 56.3% of the cases." p. 689

Andrew Churg, 2003

"A proportion of MMTV cases do appear to be associated with occupation-level asbestos exposure. Plas, et al., reported the history of asbestos exposure in 34% of cases. However, few details are available regarding the associated occupations and the quality of the data is quite unclear. That is a particular problem with regarding to attribution, because asbestos-associated malignant peritoneal mesotheliomas, which are the closest analogues to MMTV, are only induced with extremely high exposures to amosite or crocidolite-type asbestos. In fact, it is very likely that less than the reported 34% of MMTVs are actually caused by asbestos and the majority of paratesticular mesotheliomas appear to be idiopathic in nature." p. 276

Hassan and Alexander, 2005

"Mesotheliomas that involve the pericardium or originate from the tunica vaginalis are rare tumors. Given the rarity of these tumors, it is difficult to obtain precise information regarding their incidence, natural history, and optimal management." p. 1067

Pasquotti, 2005

"In contrast to pleural mesothelioma, the association between asbestos and malignant mesothelioma of the tunica vaginalis has not been well-described." p. 758

Al-Qahtani, et al. 2007
"Unlike other malignant mesotheliomas, no clear etiological factor has been established for those arising from the tunica vaginalis. However a positive history of exposure to asbestos was present in up to 41% of cases according to Jones and colleagues and Pass and colleagues. Our patient did not have any personal or family history of asbestos exposure, and no other etiological factor was identified. Due to the rarity of this tumor type, it will likely be difficult to identify other potential causative factors associated with it." at p. 3516

**Guney, et al. 2007**

"One of the major difficulties in managing malignant mesothelioma of tunica vaginalis is making an accurate preoperative diagnosis. Due to there are no characteristic clinical symptoms or tunica markers available." p. 450

**Gibbs and Craighead, 2008**

"Knowledge of the natural history and etiology of these lesions [MMs of the tunica vaginalis and in the testicular and ovarian parenchyma] is limited because of their rarity and poor documentation. Only 50% (or less) appear to be associated with exposure to commercial amphibole asbestos and the clinical course is more favorable than the pleural and peritoneal MM." p. 212

**Attanoos, 2014**

"Pericardial mesotheliomas and Gonadal mesotheliomas are very rare, and consequently the role of asbestos in their etiology is not yet defined." p. 276

**Lowry and Weiss, 2016**

Abstract

Conclusions: "The results of this ecologic study do not support a role for asbestos exposure in the etiologies of either pericardial or paratesticular mesotheliomas; however, this study was limited by small numbers and was unable to directly ascertain asbestos exposure." p. 1487

"This study found no association between the incidence of either pericardial or paratesticular mesothelioma and that of pleural mesothelioma, across 9 regions of the USA. This is, however, an ecologic study based on very small numbers of cases, which was unable to directly ascertain asbestos exposure, and thus, the strength of evidence is limited. The absence of a correlation in this study suggested that the association between asbestos exposure and these raring forms of mesothelioma, if there is one, may not be as strong as the association with pleural mesothelioma." p. 1489

**Mezei, et al. 2017**

Abstract
Conclusions: "In the absence of analytic epidemiologic studies, the etiologic role of environmental risk factors for mesothelioma of the pericardium and TVT remains elusive." p. 348

"In our evaluation of SEER data, the incidence trends for pericardial mesothelioma and mTVT did not correspond, with sufficient latency taken into account to trends in commercial asbestos use in the United States, which would be expect of pericardial mesothelioma or mTVT were causally associated with exposure to asbestos." p. 355

"Our findings are consistent with those of a recently published analysis of geographic distribution of mesothelioma incidence in SEER data shown no increases in incidence of pericardial mesothelioma and mTVT in the San Francisco-Oakland and the Seattle-Puget Sound areas that would mirror the increases in pleural mesothelioma incidence in these areas." p. 355

"In summary, pericardial mesothelioma and mTVT are rare forms of mesothelioma, constituting less than 1% of mesotheliomas overall. Similar to pleural and peritoneal mesothelioma, the etiologic role of asbestos exposure has been hypothesized for these rare forms of mesotheliomas, but no analytical case-control epidemiological studies exist to support the hypothesis of a causal relationship between inhalation [of] asbestos exposure and pericardial mesothelioma or mTVT. In large occupational cohorts with heavy exposures to asbestos, no cases of pericardial mesothelioma or mTVT have been reported. The lack of temporal trends in incidence of pericardial mesothelioma or mTVT that would correspond, with due consideration of sufficient induction time, to historical trends of commercial asbestos use, and the lack of differences in incidence rates of pericardial mesothelioma among men and women, argue against the etiologic role of inhalation asbestos exposure in the development of these rare forms of extrapleural mesotheliomas. The epidemiologic evidence also remains elusive for other risk factors for these disease entities." p. 356

Maheshwari, 2017

"Exposure to asbestos is considered a risk factor for its development with some stray reports of malignant mesothelioma developing in long duration hydrocele. Furthermore, trauma and herniorrhaphy have been reported as other possible predisposing factors, however, not all reported cases of mesothelioma of the tunica vaginalis were associated with exposure to asbestos." p. 3 (online version).

Recabal, et al. 2017

"MMTV usually presents between ages 55 and 75, and is less frequent among younger patients. This disease poses a diagnostic challenge and usually goes unrecognized as it lacks specific clinical features, and can mimic common
inguinal or scrotal diseases such as a hydrocele or an inguinal hernia." p. 1 (online version).


"In conclusion, epidemiological studies show that there is a site-specific gradient in the mesothelioma risk associated with inhalation exposure to asbestos. Pleural mesothelioma is most strongly associated with asbestos exposure. Peritoneal mesothelioma is less strongly associated with asbestos exposure, and when it is, it is associated with high exposure to amphibole asbestos. There is no evidence that mesotheliomas of the pericardium and the TVT are associated inhalation exposure to asbestos, a conclusion that is supported by a recent analysis of SEER data (Lowry and Weiss, 2016). p. 55

**H. Diagnosis of Mesothelioma of the Tunica Vaginalis**

1. **Symptoms**

   The most common presenting symptoms are hydrocele, i.e., an accumulation of fluids in the sack surrounding the testicle that causes swelling in the scrotum and scrotal masses. These non-specific symptoms make the diagnosis more difficult. See generally Pasquotti, 2005.

2. **Differential Diagnosis**

   The differential diagnoses include mesothelial hyperplasia, either spontaneous or secondary to inflammatory processes, primary carcinoma of the testis, which according to Roggli 2014, shares gross and histological similarities with mesothelioma, well-differentiated papillary mesothelioma, and metastatic tumors from a number of sites, including lung and prostate.

3. **Immunohistochemistry**

   Roggli, et al. 2014 noted that the "histologic spectrum and immunophenotype are similar to that of malignant mesotheliomas from other sites." p. 120. According to the WHO Classification of Tumours - Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs, 2004, "by immunohistochemistry these cells are uniformly reacted with cytokeratin (AE1/AE3) in both epithelial and spindle cell elements. ENA and vimentin are also usually positive and calretinin has been invariably positive. CEA, B72.3, Leu M1 and Ber-Ep4 have been negative." WHO, 2004, at 268-269. In a subsequently published immunohistochemical profile of malignant mesotheliomas of the tunica vaginalis, Winstanley, et al. found that "all cases were positive for calretinin and EMA (100%), 16 of 18 (89%) were positive for thrombomodulin and 15 of 18 (83%) were positive for CK7. Winstanley, 2006 at p. 1 (online version). However, Shelton and Dalal, 2012 in a letter to the editor to the Journal of Clinical Pathology cautioned that Ber-Ep4 and Leu M1 may actually stain positive.

   Lee et al. 2014 summarized the experience at Johns Hopkins University Hospital and cautioned that florid mesothelial hyperplasia can mimic mesothelioma of the tunica
vaginalis. See Chekol and Sun, 2012 for an excellent summary of the diagnostic studies and differential diagnosis for malignant mesothelioma of the tunica vaginalis testis.

I. Unusual Variants of Primary of the Mesothelioma of the Tunica Vaginalis

1. Well Differentiated Papillary Mesothelioma

There have been a number of case reports of well-differentiated papillary mesothelioma of the tunica vaginalis reported in the medical literature. See generally Grove, 1989; Chetty, 1992; Xiao, et al. 2000; Butnor, et al. 2001; WHO 2004; Tollhurst, et al. 2005; Fukunaga, 2010; Tan, et al. 2016; Parcescepe, et al. 2016. Parcescepe, et al. estimated that only 17 cases of WDPM of the tunica vaginalis had been published as of the time of their case report in 2016. The mean age of patients with well-differentiated papillary mesotheliomas of the tunica vaginalis (43 years) is significantly younger than for diffuse malignant mesotheliomas of the tunica vaginalis. In Table 1 on page 446, the authors summarize all of the cases of well-differentiated papillary mesothelioma of tunica vaginalis reported in the literature in a very useful chart format.

At least 2 case reports have been published on a variant of well-differentiated papillary mesothelioma labeled "mesothelioma of uncertain malignant potential". See Brimo, et al. 2010 and Tripkov, et al. 2011. Brimo, et al. summarized the case for distinction in stating:

"The morphological continuum noted between our cases and the classic well-differentiated papillary mesotheliomas, combined with their immunohistochemical profile and indolent behavior, contrasts with that of diffuse malignant mesotheliomas. We propose that these tunica vaginalis mesotheliomas, which are more complex than the classic well-differentiated papillary mesotheliomas, and yet are not overtly histologically malignant, be classified as 'mesotheliomas of uncertain malignant potential'." Id. at 1165.

As in the case of well-differentiated papillary mesotheliomas of the peritoneum, there seems to be a general consensus that well-differentiated papillary mesotheliomas of the tunica vaginalis are not causally related to asbestos exposure.

2. Deciduoid Malignant Mesothelioma of the Tunica Vaginalis Testis

At least one case has been described by Ahmed, et al. 2012.

J. Fiber Burden Analysis

1. Results of Asbestos Body Counts/Fiber Digestions of Lung Tissue

There have been only a few references to searches for asbestos bodies or fiber burden analysis of lung tissue in the case reports/case series of mTVT. One of the earliest was Prescott, 1988 which summarized the case of a 61-year old retired salesman with no history of asbestos exposure being diagnosed with mTVT. He died 21 months after diagnosis and an autopsy revealed, among other things, numerous hyalinized plaques consistent with prior exposure to asbestos present in the parietal surfaces. "No asbestos fibers were found on microscopy of
several sections of lung parenchyma. However, after dissolving a specimen of lung tissue in 1% sodium hypochlorite solution, according to the method of Smith and Naylor, asbestos fibers were found in low concentration." Id. at 623. Subsequently, Kuwabara, et al. 1991 reported on a 60-year old man with no history of asbestos exposure diagnosed with mTVT. After death, an autopsy was performed and "asbestos bodies were not found in the lung or parietal plaque by usual observation methods. Additionally, asbestos body counts in the pulmonary parenchyma were carried out by a modification of Smith and Naylor's method, but no asbestos bodies were found." p. 859.

2. Identification of Asbestos Bodies/Asbestos Fibers in Tumor and Surrounding Tissue

The earliest reference to examination of tumor tissue for the presence or absence of asbestos bodies/asbestos fibers was the report by Kasdon on 2 cases published in 1969. In both cases, asbestos particles were not identified in the tumor tissue. Kasdon, 1969 at p. 1145-1146.

In the case report by Fligiel and Kaneko, 1976, a case of mTVT was diagnosed at Mount Sinai Hospital. While the case was not published until 1976, the diagnosis was initially made in 1969 and the patient underwent surgery in July 1971. He died shortly thereafter and permission for autopsy was not granted. Asbestos bodies were not identified in either the tissue from the surgery or two small lymph node fragments obtained at mediastinoscopy. However, the patient had a history of 40 years in plumbing as an insulator with regular exposure to asbestos. In the second published case of mTVT in a person with a history of asbestos exposure, cytological examination of smears in a cell block revealed no asbestos bodies. Japko, et al., 1982. However, the 30-year old male had been a pipefitter at an oil refinery working around asbestos insulation for 8 years until 2 years prior to admission. A latency period of 10 years is extremely suspect and therefore it seems highly probable that this case had nothing to do with his prior employment.

No published article was found in our search identifying asbestos or asbestos bodies in mTVT or surrounding tissue.

K. Other Potential Risk Factors for Mesotheliomas of the Tunica Vaginalis Testis

1. Radiation Therapy and mTVT

Mezei, et al., 2017 noted that "receipt of localized ionizing radiation has been reported as a postulated cause of mTVT, citing Plas, et al. 1998; Esen, et al., 2012 and Mrinakova, et al., 2016. Mezei, et al. pointed out that there is less likely that the radiation-related, non-asbestos etiology for mTVT "where prior radiation therapy in the inguinal area is rare and likely more localized." Id. at 356. However, since an increased risk of radiation induced mesothelioma has been found epidemiologically even when administered away from the primary site, "an etiologic link with the development of pericardial and mTVT mesotheliomas is also possible." Ibid.
2. **Other Possible Causes**

Trauma and previous herniorrhaphy have been proposed by Chen, et al. 1982 and Plas, et al. 1998, as possible etiologic factors. Longstanding hydrocele have also been proposed as a possible predisposing factor. Hai, et al. 2012; Goel, and Gupta, 2008.

The bottom line is that mesotheliomas of the tunica vaginalis are so rare, establishing etiologic factors will continue to be exceedingly difficult and most will likely remain idiopathic.

3. **Germline BAP1/Mesothelioma of the Tunica Vaginalis**

Thus far, no cases of TVT in individuals with a Germline BAP1 mutations have been identified and published in the medical literature.

L. **Reasons Why Asbestos Exposure is not a Significant Cause of mTVT**

1. There are no epidemiological studies (case-control or cohort) studies of mTVT and therefore no epidemiological support for a causal association between asbestos exposure and mTVT.

2. In the absence of epidemiological studies there have been a number of case reports and case series of patients with mTVT. Bisceglia, et al. 2010 tallied a total of 223 paratesticular mesothelioma cases identified in the published literature between 1957 and 2009. As pointed out by Mezei et al. 2017, this total included mesotheliomas of the spermatic cord as well as a number of well-differentiated papillary mesotheliomas. Mezei, et al. 2017 identified another 24 to 74 cases in 11 case series published since 2009 up through 2015. A number of additional case reports have been published since 2015, many of which identified no positive history of asbestos exposure. Overall, it appears that the percentage of reported cases with a history of asbestos exposure is significantly less than 50% and more likely in the 30 to 35% or lower range. However, as Andrew Churg pointed out in his review in 2003, there is good reason to be suspicious of an asbestos etiology in many of these cases, since "asbestos-associated malignant peritoneal mesotheliomas, which are the closest analogues to MMTV, are only induced with extremely high exposures to amosite or crocidolite-type asbestos. In fact, it is very likely that less than the reported 34% of MMTVs are actually caused by asbestos, and the majority of paratesticular mesotheliomas appear to be idiopathic in nature." Churg, 2003 at p. 276. The most recent case series reported only 13% of cases had a history of asbestos exposure. Recabal, et al. 2017.

3. No mTVTs have been reported in several of the largest asbestos cohorts with heavy exposure to asbestos. (chrysotile only; mixed; and amphibole only).

4. **There is evidence that mTVTs occurs spontaneously in the absence of any contribution from asbestos exposure.**

   a. **mTVTS have been identified in young boys without asbestos exposure**

   Plas, et al. 1998 and Jones, et al. 1995 both identify a case of mTVT in a 7-year old boy. In Plas, et al. 1998, they estimated that 10% occurred in patients younger than 25 years
of age, whereas in Jones, et al. 1995, they estimated that less than 7% were under the age of 20. A number of other case reports or case series have a reported mTVTs in young males: Velasco, et al. 1988; Fukunaga, 2010; Khan, et al. 1997; Mirabella, 1991; Mrinakova, et al. 2012 (20-year old male); Maheshwari, et al. 2017 (20-year old male with absence of etiologic factors, including no asbestos).

b. There are case reports in the medical literature of a variety of animals without asbestos exposure developing mTVT.

**Dogs**

Vascellari, et al. 2011

**F344/N Rats**

Blackshear, et al., 2014

5. The incidence trend over time is inconsistent with asbestos being a significant cause factor in mTVTs.

In Mezei, et al. 2017's analysis of the SEER database (i.e. SEER nine registries), there was some evidence of an increase in incidence trend between 1973 and 2010, but it was none significant:

0.35 per 10,000 million in 1973-1982;

0.66 per 10,000 million in 2003-2013 (IRR=1.9; 95% Competence Interval = 0.8-4.9)

Mezei, et al. concluded:

"In our evaluation of SEER data, the incidence trends for pericardial mesothelioma and mTVT did not correspond with sufficient latency period taken into account, to trends in commercial asbestos use in the United States, which would be expected if pericardial mesothelioma mTVT were causally associated with exposure to asbestos." p. 355

6. Analysis of geographic distribution of incidence of mTVT in the United States is consistent with asbestos exposure not being a significant factor in mTVT.

Lowry and Weiss, 2016 utilized age-adjusted incidence data from the SEER data base for the period 1973-2011. They compared the incidence of mesothelioma among men greater than 50 years of age in the San Francisco-Oakland and Seattle-Puget Sound areas compared to other regions in the SEER data base. Whereas the rate of pleural mesothelioma was twice as high in the San Francisco and Seattle-Puget Regions compared to other areas, in contrast, the rate of pericardial mesothelioma was not elevated in either compared to other regions. The authors "hypothesized that the regional patterns in incidence of paratesticular and pericardial mesotheliomas would parallel those of pleural mesotheliomas if in fact occupational asbestos exposures causes those rarer types as well." (p. 1487). The authors limited their study
population to men aged greater than or equal to 50 years at diagnosis "because most occupational exposure to asbestos has historically occurred in men." (Id. at 1488). On the basis of their analysis showing distinctly different trends between pleural and pericardial (as well as paratesticular) mesothelioma, the authors concluded:

"The results of this ecologic study do not support a role for asbestos exposure in the etiologies of either pericardial or paratesticular mesotheliomas; however, this study was limited by small number and was unable to directly ascertain asbestos exposure." Id. at 1487.

7. The failure to identify asbestos in tunica vaginalis tissue weighs against a significant role for asbestos in the causation of mTVT mesothelioma.

As previously stated, asbestos fibers or bodies have not been identified in tunica vaginalis tissue. There is a general consensus among plaintiff experts that asbestos has to make its way to the target organ in order to contribute to the development of cancer (in this case mTVT). The apparent inability of asbestos fibers to do so weighs against the significant role for asbestos in the causation of mTVT. As was summarized by Mezei, et al. 2017.

"Some considerations of anatomy and embryonic development may also be used to support the apparent lack of a causal relationship between inhalation of asbestos exposure and pericardial mesothelioma. . . . Using a similar argument, anatomical considerations regarding mTVT can also be made. Although the TVT forms from the processus vaginalis of the nascent peritoneal cavity, the connection between the peritoneal cavity and the processus vaginalis is obliterated during normal development, leaving no direct communication between the peritoneal (abdominal) cavity and the TVT [citing Garriga, V, et al., "US of the Tunica Vaginalis Testis: Anatomic Relationships and Pathologic Conditions," Radiographics 29(7) 2017-32, 2009; this would limit the potential migration of asbestos fibers from the peritoneum to the TVT. In addition, as with the pericardium, asbestos fibers would have to travel in a retrograde manner against the lymph circulation to access the TVT [cites omitted]." Id. at 356.

8. Since low dose chrysotile does not increase the risk for pleural mesothelioma, it certainly would not be expected to increase the risk of mTVT.

Andrew Churg pointed in his 2003 review that mTVT is closely analogous to peritoneal mesothelioma. If chrysotile does not cause peritoneal mesothelioma then there is no reason to believe it will cause mTVT. As Mezei, et al. pointed out:

"Even in heavily exposed populations, such as insulators and pipefitters, cases of pericardial mesothelioma and mTVT are not observed. In several large cohorts with heavy occupational exposures to either chrysotile or amphibole asbestos, or both, and with several decades of follow-up, rather there are no reports of pericardial mesothelioma or mTVT [cites omitted]. The background incidence of pleural and peritoneal mesotheliomas has been estimated to be about 3 to million person-years, which is about 30 to 60 fold the incidence of pericardial or TVT
mesothelioma (approximately 0.5 to 1 per 10,000 million person-years as estimated in our paper). Therefore, if in highly exposed occupational cohorts the RR is the same as that for pleural and peritoneal mesotheliomas, approximately 1.6% to 3% of mesotheliomas should occur at each of the two sites of interest (pericardium and TVT). According to Hodgson and Darnton, there were 453 cases of pleural and peritoneal mesotheliomas in the U.S./Canada insulators cohort evaluated by Selikoff and colleagues, which is one of the largest asbestos-exposed cohorts. In that cohort, one would have expected to observe between 8 and 16 cases of each of pericardial mesothelioma and mTVT, under the assumption that the RR imposed by the exposure was the same as that for pleural and peritoneal mesotheliomas. Even if the RR associated with heavy exposure were in order of magnitude lower, one would still expect to find one to two cases of each of pericardial mesothelioma and mTVT. If we consider all the occupational cohorts in Hodgson and Darnton as distinct and independent studies, we should certainly expect to see some cases of pericardial mesothelioma in mTVT if inhaled asbestos exposure were associated with increased risk - yet no such cases have been reported.” Id. at 355.

9. Since chrysotile does not cause peritoneal mesothelioma, there is no reason to believe that it would cause mesothelioma of the tunica vaginalis testis.

See the section of the peritoneal mesothelioma outline which addresses chrysotile and peritoneal mesothelioma.

M. The Defense Response to Plaintiff's Key Argument/Literature on Chrysotile/mTVT


The Marianaccio, et al. analysis of data from the Italian National Register reported that 70% of testicular mesothelioma cases diagnosed between 1993 and 2004 were classified as having definite, probably or possible asbestos exposure versus 81% of pleural mesothelioma cases. Plaintiffs' counsel attempt to use Marianaccio in support of their claim that a significant percentage of mTVTs are asbestos-related.

Defense Response:

a. As emphasized in Mezei, et al. 2017, "The registry study of Marianaccio, et al. provides no direct evidence that pericardial and TVT mesotheliomas are associated with inhaled asbestos exposure." Id. at 356.

b. The Marianaccio study does not have any controls and therefore does not calculate any risk ratio.

c. Most importantly, Table 3 provides the number of cases of mesothelioma of the peritoneum, pericardium, and tunica vaginalis by the industry. There is only one case in the highest risk industries (i.e., and industries in which asbestos exposure is significant and in
which the highest rates of pleural mesothelioma are seen). The highest risk of asbestos-associated mesotheliomas, as judged by the number of peritoneal mesotheliomas per person-year of observation are seen in the asbestos cement, national defense, shipbuilding and railway industries, in that order. There is only one reported case of mTVT in these industries. Therefore, there is no correlation between the risk of peritoneal mesothelioma and the risks of pericardial and TVT mesotheliomas in Marianaccio, et al. suggesting that inhaled asbestos is not associated with pericardial and TVT mesotheliomas." Mezei, et al. 2017 at 356. Even Marianaccio, et al. admitted that "the absence of exposures in the shipbuilding, railway, and asbestos-cement industries (the sectors 'traditionally' involved in asbestos exposure for pleural MM) for all the 67 pericardial and testicular cases is note-worthy", but then not easy to interpret and these findings need to be confirmed in a larger sample." Marianaccio, et al. 2010 at 764.


The objective of this study was to describe cases of mesothelioma of the tunica vaginalis testis (mTVT) recording in the Lombardi Mesothelioma Registry between 2000 and 2010. Thirteen cases of mTVT were reported between 2000 and 2010 and the authors claim that asbestos exposure was documented in 8 of the 12 (67%), confirming the etiological role for asbestos in the pathogenesis of mTVT.

Defense Response:

a. The authors noted that asbestos exposure has only been associated with 30 to 40% of reported mTVT cases in the medical literature.

b. As in the cases identified by Marianaccio in 2010, none of the jobs with possible asbestos exposure identified for the cases of mTVT were in the highest risk industries such as shipbuilding and asbestos cement.

c. There was no information on whether any of the cases had asbestos bodies or fibers in lung tissue.


The authors reviewed records for 6,030 cases of death due to malignant mesothelioma between 2003 and 2008. Of all these cases, a clinical diagnosis of malignant mesothelioma was confirmed for 928 - 794 pleural (85.5%), 123 peritoneal (12.2%), 7 pericardial (0.8%) and 5 testicular tunica vaginal testis (0.5%). Id. at 483.

Examination of lung tissue for asbestos "particles" was determined in 103 malignant mesothelioma cases (92 of the pleural and 11 of the peritoneum), but in none of the testicular mesotheliomas.

Table 4 provided information on occupational categories associated with asbestos exposure by site of mesothelioma. For 3 mesothelioma of the tunica vaginalis (apparently 2 had
no occupation with potential asbestos exposure), there was one case each in the occupations of construction, shipbuilding and steel production.

**Defense Response:**

a. The assessment of accuracy of diagnosis was less than satisfactory. It was based entirely upon the review of medical records, x-rays, and CT images rather than an independent pathological review of the pathology specimens. Mesothelioma is a pathological diagnosis and the diagnosis of mTVT can be challenging. While the authors provide numbers and percentages for the method of pathological diagnosis of mesotheliomas of the pleura and peritoneum, they provide no such information for mesothelioma of the tunica vaginalis.

b. There were simply too few cases to draw any firm conclusions on.

**N. Survival**

While mesotheliomas of the tunica vaginalis testis are described as aggressive tumors, it is possible they can be surgically resected if diagnosed early enough before there has been any metastases. The median survival period is 24 months compared with 5 to 6 months for mesotheliomas of the pericardium. However, it tends to reoccur in the majority of patients. See Bisceglia, et al. 2010; Plas, et al. 1998. Based upon their analysis of the literature, Plas et al. estimated that 38% of patients died of localized or disseminated tumor. Consequently, a significant percentage of patients survived for an extended period of time.

**O. Bibliography**


104. Englehart, A., Email Correspondence to Erick Falk and Kevin Greene re: Dr. Hammar-Meso of the Tunica Vaginalis Testis, 4/17/09.


149. Zanker, F., Zellner, M., Busche, J., Woziwodski, J., [Paratesticular mesothelioma – Article in German – Abstract only], Urologe A 54(3):394-6, 2015.


Appendix A

(Will be Available Online)
## Appendix B

### Table S2

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Data Source</th>
<th>Time Period Reviewed</th>
<th>% of Cases</th>
<th>Age, Years (Range)</th>
<th>Adriamycin Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramson et al., 1994 [224]</td>
<td>Literature review (with case series included in later reviews)</td>
<td>Cases of malignant mesothelioma of the TVT (source not specified) + 18 cases from literature review</td>
<td>1957–1982</td>
<td>24%</td>
<td>Median: 61 (24–78); 9/24 (37.5%)</td>
<td>Yes</td>
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<tr>
<td>Mieschel et al., 1995 [235]</td>
<td>Literature review</td>
<td>Cases of malignant mesothelioma of the TVT from literature review</td>
<td>1941–1989</td>
<td>45%</td>
<td>Median: 58 (14–66); 11/45 (24%)</td>
<td>Yes</td>
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<tr>
<td>Jones et al., 1995 [236]</td>
<td>Literature review (with case series included in later reviews)</td>
<td>11 cases of malignant mesothelioma of the TVT retrieved from doctors' convolution films and hospital's surgical pathology files + 55 cases of VAT TVT from literature review</td>
<td>1957–1994</td>
<td>64%</td>
<td>Mean: 55.7 (7–80); 11/64 (17%)</td>
<td>Yes</td>
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<tr>
<td>Perez-Olmedo et al., 1998 [237]</td>
<td>Case series (abstract)</td>
<td>18 cases of malignant mesothelioma of the TVT, including 42 seen at the Canadian Reference Center for Cancer</td>
<td>1967–1993</td>
<td>13%</td>
<td>Mean: 64 (31–84); 3/13 (23%); 10/13 (77%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pik et al., 1998 [238]</td>
<td>Literature review (with case report)</td>
<td>1 case of malignant mesothelioma of the TVT + 75 cases from literature review</td>
<td>1966–1997</td>
<td>74%</td>
<td>Median: 60 (7–87); 34/74 (46%) and 17%</td>
<td>Yes</td>
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<tr>
<td>Attanasio and Gibbs, 2000 [239]</td>
<td>Registry-based case series</td>
<td>Deaths from malignant mesothelioma of the TVT identified from death certificates filed in UK Health and Safety Executive Mesothelioma Register + 1 case from routine surgical practice</td>
<td>1988–1994</td>
<td>10%</td>
<td>Median: 71 (23–77); 1/10 (10%); 2/10 (20%); 7/10 (70%)</td>
<td>Yes</td>
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<tr>
<td>Maca et al., 2000 [6]</td>
<td>Registry-based case series</td>
<td>Deaths from malignant mesothelioma of the TVT reported in the Annual of the Pathological Autopsy Care in Japan</td>
<td>1958–1996</td>
<td>6%</td>
<td>Median: 60 (45–80); 1/6 (16%); 5/6 (83%)</td>
<td>Yes</td>
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<tr>
<td>Biccioglia et al., 2010 [218]</td>
<td>Literature review (with case report)</td>
<td>1 case of malignant mesothelioma of the TVT from authors' hospital + 3 cases malignant mesothelioma of the TVT and peritoneal mesothelioma from literature review</td>
<td>2003–2008</td>
<td>54%</td>
<td>Median: 45 (21–84); 14/54 (26%); 15/54 (28%)</td>
<td>Yes</td>
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<tr>
<td>Marincola et al., 2010, 2015 [192,219]</td>
<td>Registry-based case series</td>
<td>Cases of malignant mesothelioma of the TVT identified from Italian National Mesothelioma Register</td>
<td>1950–2004 or 1950–2008</td>
<td>50%</td>
<td>Median: 67 (28–73); 14/50 (28%); 15/50 (30%); 7/50 (14%)</td>
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<td>Grema et al., 2012 [14]</td>
<td>Registry-based case series</td>
<td>Deaths from malignant mesothelioma of the TVT identified from death certificates filed in UK Health and Safety Executive Mesothelioma Register</td>
<td>2000–2008</td>
<td>5%</td>
<td>Median: 60 (45–80); 1/6 (16%); 5/6 (83%)</td>
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<tr>
<td>Hat et al., 2012 [240]</td>
<td>Case series</td>
<td>Cases of malignant mesothelioma of the TVT identified from pathology archives at a single hospital</td>
<td>1990–2000</td>
<td>6%</td>
<td>Median: 62 (26–78); 1/6 (16%); 5/6 (83%)</td>
<td>Yes</td>
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<tr>
<td>Menni et al. 2012 [241]</td>
<td>Registry-based case series</td>
<td>Cases of malignant mesothelioma of the TVT identified from Italian National Mesothelioma Registry</td>
<td>2000–2010</td>
<td>13%</td>
<td>Median: 74 (38–85); 8/13 (62%); 0/13 (0%); 5/13 (38%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Fan et al., 2012 [242]</td>
<td>Case series</td>
<td>Cases of malignant mesothelioma of the TVT identified from pathology archives at a single hospital</td>
<td>1988–2013</td>
<td>6%</td>
<td>Median: 68 (25–71); 0/6 (0%); 0/6 (0%); 6/6 (100%)</td>
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<tbody>
<tr>
<td>Modellese and Buchholz, 2013 [243]</td>
<td>Case series</td>
<td>Cases of malignant mesothelioma of the TVT identified at having sought legal representation with U.S. law firms, with adriamycin exposure as an implied precondition for inclusion</td>
<td>Nil</td>
<td>9%</td>
<td>Median: 60 (44–74); 0/6 (0%)</td>
<td>No</td>
</tr>
<tr>
<td>Bertolotto et al., 2015 [244]</td>
<td>Case series</td>
<td>Cases of malignant mesothelioma of the TVT identified from Italian National Mesothelioma Registry</td>
<td>Nil</td>
<td>9%</td>
<td>Median: 64.5 (34–82); 0/9 (0%); 0/9 (0%); 9/9 (100%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Current literature review*</td>
<td>Literature review</td>
<td>Cases of malignant mesothelioma of the TVT previously included in published literature reviews</td>
<td>1954–2015</td>
<td>89%</td>
<td>Median: 63.5 (7–91); 13/89 (14%); 25/89 (28%); 28/89 (44%)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA, not applicable; Nil, not reported; TVT, tunica vaginalis testis.

* All included published literature reviews are partially but not completely overlapping, except for Biccioglia et al. [218], which has no overlap with other reviews.

† Authors stated that adriamycin exposure was reported in 34.2% of patients with malignant mesothelioma of the TVT in the literature and that sufficient information on adriamycin exposure was available in 54.45 of cases, implying that 17.2% were not exposed to adriamycin. However, 12.3% of 75 cases (or 74 cases, correcting the additional case reported by Pik et al. [238]) is not a whole number. Therefore, only percentages are provided here.

‡ Information on age and adriamycin exposure was provided for three cases with biopsy tissue and/or post-mortem material.

§ Authors also identified case reports published between 1957 and 2001, but did not include these in their table summarizing reported adriamycin exposure. All such case reports that were not described in other included literature reviews (except foreign and intermediate tumors) are summarized in the last row of this table.

∥ Six cases were interviewed about adriamycin exposure and classified as having “unknown” or “improbable” exposure. Eleven cases were not interviewed.

¶ Four cases were interviewed about adriamycin exposure and classified as having “unknown” exposure. One case was not interviewed.

* Case reports of malignant mesothelioma of the TVT that were not described in other included literature reviews are summarized in this row [9,12,242,244–327].