Malignant Mesothelioma of the Tunica Vaginalis Testis

Review of the Literature and Assessment of Prognostic Parameters

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BACKGROUND. Only 73 cases of malignant mesothelioma of the tunica vaginalis testis have been reported in the last 30 years. Although these tumors were most often seen in patients between ages 55 and 75 years, 10% of the patients were younger than 25 years. Because prognostic parameters have not yet been reported, the authors present another case of a male age 14 years and a review of the available literature, which they conducted to determine prognostic parameters.

METHODS. The medical literature about malignant mesothelioma of the tunica vaginalis testis was reviewed. For the determination of prognostic parameters, a univariate and multivariate Cox regression model was used to assess the relevance of the patient's age, history of asbestos exposure, tumor histology, primary therapeutic approach, and presence of metastatic disease to survival.

RESULTS. Previous exposure to asbestos or asbestos-containing materials must be considered a risk factor for the development of malignant mesothelioma. The major difficulty in managing patients with malignant mesothelioma of the tunica vaginalis testis was determining an accurate preoperative diagnosis, which was reported in only two cases. Due to the lack of characteristic symptoms, 97.3% of the cases were diagnosed intraoperatively. Of patients who underwent local resection of the hydrocele wall, 35.7% experienced local tumor recurrence, as compared with 10.5% after scrotal orchiectomy and 11.5% after inguinal orchiectomy. Therefore, radical orchiectomy should be the first-line therapy. The median survival of the patients was 23 months, which decreased to 14 months in cases of recurrence. The overall recurrence rate (local and disseminated) was 52.5%. More than 60% of recurrences developed within the first 2 years of the follow-up. In some cases of disseminated mesothelioma, adjuvant chemotherapy or radiotherapy was given. Although reports on adjuvant treatments were limited, radiotherapy appeared to be more effective than chemotherapy. However, 37.9% died of disease progression. Assessment of prognostic parameters revealed a significant correlation of patient's age with survival ($P < 0.01$), with a better outcome for younger patients and a worse disease course for patients with primary disseminated disease ($P < 0.05$) in univariate analysis. A multivariate Cox regression model of prognostic parameters concerning survival did not yield statistically significant results.

CONCLUSIONS. Malignant mesotheliomas of the tunica vaginalis testis rarely occur, but the possibility should be considered for all age groups. Univariate analysis determined that a patient's age and the presence of primary disseminated disease were prognostic parameters related to survival. Due to the invasive potential of this disease and the risk of tumor recurrence, radical orchiectomy and close follow-up are strongly recommended. ***Cancer* 1998;83:2437–46.**
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KEYWORDS: malignant mesothelioma, tunica vaginalis testis, asbestos exposure, therapy, prognosis.

Malignant mesothelioma of the tunica vaginalis testis is considered a rare scrotal tumor, with only 73 cases reported in the literature.[1–47] Because this malignant tumor has an unfavorable course in most cases, we reviewed the literature to look for prognostic parameters concerning patients' survival and added another case of a child age 14 years.

MATERIALS AND METHODS

All articles on malignant mesothelioma of the tunica vaginalis were searched in a CD-MEDLINE search of literature from 1966 to June 1997 (CD-MEDLINE is published under license from the National Library of Medicine by Aries Systems Corporation) and by searching the reference lists of the published articles. Knowledge Finder software was used in the search on a Power Macintosh® 6100/60. The parameters used for the literature search were *malignant mesothelioma, tunica vaginalis testis,* and *testis.*

Case Report

A Mediterranean male age 14 years presented with enlargement of the right scrotum, which had developed within the previous 3 months. His general and urologic history were uneventful, with no personal or familial history of asbestos exposure. Urologic examination was normal except for a translucent hydrocele on the right side. Preoperative ultrasonography of the right scrotum (7.5 MHz) revealed a normal testis and a hydrocele. The testis was explored via a midline scrotal incision, with clear fluid aspirated and sent for cytoanalysis. The cytology of the hydrocele fluid showed small cell clusters of regular mesothelial cells with normal nuclear morphology diagnosed as PAP II. Due to the presence of small papillary excrescences of the tunica vaginalis, a frozen section was obtained and reported as benign mesothelioma of the tunica vaginalis. A resection of the hydrocele wall was done, but final histopathology revealed a multifocal malignant mesothelioma of the tunica vaginalis. Inguinal orchiectomy and right hemiscrotectomy was performed 6 days later. For tumor staging, thoracal and abdominal computed tomography (CT) scans were performed, showing enlarged paraaortal and paracaval retroperitoneal lymph nodes with a greatest dimension of 16 mm. The patient underwent a nerve-sparing retroperitoneal lymph node dissection 6 weeks after primary diagnosis. All lymph nodes were free of tumor, but a chronic lymphadenitis was found. The patient has been followed for 12 months and is in complete remission with normal erections and ejaculations.

Etiology and Pathogenesis

Mesotheliomas are tumors arising from the serosal membranes of the coelomic cavities. The tunica vaginalis propria testis is one of these cavities, which is formed by an outpouching of the abdominal peritoneum. Most cases of mesothelioma occur in the pleural or peritoneal cavity, but in rare cases (in less than 5% of all mesotheliomas) these tumors can also arise from the mesothelial cell lining of the tunica vaginalis.[39] Investigations of the worldwide incidence of mesotheliomas reported an overall increase of the disease.[48] The development of malignant mesothelioma has been proven to be related to exposure to asbestos or different asbestos-containing materials.[49] Not only the direct contact to asbestos but also a familiar occupational history significantly increase the risk for developing a malignant mesothelioma. Having a father or spouse employed in an occupation involving exposure to asbestos increased the risk of mesothelioma in the family by a factor of 10.[50] Reviewing the literature on asbestos exposure and mesothelioma of the tunica vaginalis confirmed a positive history for 34.2% of the patients. This confirmed the correlation of asbestos and malignant tunical mesothelioma. However, the real prevalence may have been underestimated, because sufficient information was only given in 51.4% of the reported cases of malignant mesothelioma of the tunica vaginalis.

The pathophysiologic mechanism for the development of malignant mesothelioma in conjunction with asbestos exposure remains unclear. Lew et al. hypothesized a chronic immunosuppression, which was supported by a significantly reduced absolute number of total and T-helper cells in asbestos workers with tumors in comparison to those without mesotheliomas.[51] Furthermore, investigations of the association of the HLA-W27 antigen and asbestos revealed that W27 antigen was three times more common in workers with asbestosis than in normal controls.[52] Because the severity of the disease may be related to W27 antigen, Merchange et al. considered it a marker for increased susceptibility to the pathogenetic effects of asbestos.[52] Although this represents an interesting approach to the search for marker substances in patients exposed to asbestos, there are no reports of an association of the HLA-W27 antigen with malignant mesothelioma of the tunica vaginalis. Furthermore, a direct effect of asbestos fibers on the tunica vaginalis or the deposition of asbestos fibers within the serosa causing chronic irritation of the tissue could be another reason for the development of mesothelioma.[27] Other reports have suggested the appearance of chromosomal abnormalities, such as losses on 1p, 3p, 6q,

TABLE 1
Age Distribution of Malignant Mesothelioma of the Tunica Vaginalis Testis (n = 74)

Age (yrs)	Incidence
7–14	4.3%
15–24	5.7%
25–34	7.1%
35–44	11.4%
45–54	8.6%
55–64	27.1%
65–74	20%
75–87	15.7%

9q, and monosomy 22, as a mechanism for the oncogenesis of mesothelioma.[53] In addition, radiation and radiotherapy have also been proposed as causes of malignant mesothelioma.[54] Although malignant mesothelioma rarely presents as a secondary malignancy, regardless of etiology, a causal relation between radiation and the development of malignant mesothelioma has not yet been proven.[55] Correlations of viral infections and malignant mesotheliomas were also reported in patients with pleural mesotheliomas.[54,56] Stenton recently reported a correlation of Simian virus 40 infection with pleural mesothelioma.[56] However, to our knowledge, the development of mesothelioma of the tunica vaginalis has not been reported to be secondary to radiation exposure or radiotherapy or to precede viral infections. A previous testicular trauma or hernial repair were also considered predisposing factors for the development of malignant tunical mesothelioma.[4,5] However, there is no evidence of a correlation of these factors with the development of malignant tunical mesothelioma in the reviewed literature.

Although there are several mechanisms hypothesized for the development of tunical mesothelioma, the exposure to asbestos or asbestos-containing materials remains the only established risk factor.

Age Distribution

The age distribution of patients with malignant mesothelioma of the tunica vaginalis ranged from 7 to 87 years, with the highest incidence between ages 55 and 75 years (47.1%). More than two-thirds of the cases were reported in patients older than 45 years with a median age of 60 years. The tumor frequency in relation to the age is listed in Table 1. The higher incidence of mesothelioma among older patients in related to longer exposure to asbestos, with a latency of 10–40 years.[49] Although malignant mesotheliomas of the tunica vaginalis were commonly reported in older patients, 10% of the cases occurred in patients younger than 25 years.[5,24,25,32,34,42] Unfortunately, especially in this young age group, there were no data on asbestos exposure, familial history of asbestos exposure, or viral studies, nor was any demographic information given; therefore, the reasons for the development of the disease remain unclear in these cases.

Symptoms

The major symptom of patients with malignant mesothelioma was an enlargement of the scrotum, which developed within several months. Reviewing the literature regarding the preoperative suspected diagnosis gave sufficient information in 86.5% of the 74 published cases. In most patients, the preoperative diagnosis was a hydrocele (in 56.3%) or a suspected testicular tumor (in 32.8%). Epididymitis was suspected in 3.2%, a scrotal hernia in 3.2%, a spermatocele in 3.2%, and a posttraumatic testicular lesion in 1.6% of the cases.

In 68.9% of the cases, data concerning the localization of the tumor were given. A malignant mesothelioma of the right tunica vaginalis was found in 48.1% of the patients and a left-sided lesion in 48.1%. The presence of a bilateral malignant mesothelioma of the tunica vaginalis was reported for only 2 patients (3.8%).[34,35]

Primary Therapy

One of the major problems of managing patients with malignant mesothelioma of the tunica vaginalis is the difficulty of diagnosing the disease preoperatively. In only 2 of the 74 published cases (2.7%) was an accurate preoperative diagnosis made of the malignant disease.[12,23] Both of these patients had preoperative cytology of a hydrocele puncture, which led to suspicion of the presence of the tumor. However, cytoanalysis was only performed in 9 of 74 cases, with a negative result in 7 cases, including the current case.[5,7,13,24,37,44] The majority of malignant mesotheliomas of the tunica vaginalis have been determined intraoperatively (97.3%) due to hemorrhagic hydrocele fluid, white-to-yellowish papillary excrescences of the tunica vaginalis, or fibrotic thickening of the tunica vaginalis. Data concerning the first-line surgical approach for patients with malignant mesothelioma of the tunica vaginalis were available in 62 cases (83.8%). An organ-preserving, local excision of the tumor was performed in 1 case (1.6%), a resection of the hydrocele wall in 15 cases (24.2%), orchiectomy in 19 cases (30.6%), inguinal orchiectomy in 26 cases (41.9%), and hemiscrotectomy in 1 case (1.6%). Due to histologically proven malignant mesothelioma of the tunica vaginalis, inguinal orchiectomy was performed as a second procedure in 14 cases (22.6%) and hemi-

TABLE 2
Local Invasion of Malignant Mesothelioma of the Tunica Vaginalis Testis (n = 30)

Site of invasion	% of patients
Subtunical connective tissue	25.8%
Testis	19.4%
Vascular infiltration	9.7%
Scrotal skin	9.7%
Epididymis	6.5%
Other (spermatic funicle, neural infiltration, lymphatic infiltration)	9.6%

scrotectomy in 12 cases (19.6%). In addition, inguinal lymphadenectomy was performed in 5 cases (8.1%), an iliac lymph node dissection in 4 cases (6.5%), and a retroperitoneal lymphadenectomy in 8 cases (12.9%). Histopathology of the resected lymph nodes showed metastasis in 11 cases (64.7%), whereas negative histology was found in 6 cases (35.3%).

Histology and Invasion

Microscopic analysis of malignant mesotheliomas of the tunica vaginalis testis may show considerable variation in the morphologic appearance of the tumors. Due to their different histopathologies, malignant mesotheliomas have been subclassified into three groups: the epithelial type, most often seen in the peritoneal cavity and the tunica vaginalis; the mesenchymal or sarcomatous type, commonly found in the pleural cavity; and the biphasic or mixed type, which occurs in serosal membranes.[15] Histomorphologic data were available in 51 (68.9%) of 74 cases. Epithelial type was found in 31 cases (60.8%) and biphasic type in 19 cases (37.3%). These results are different from those of the study by Antman et al., who reported an incidence of epithelium like tumors in 75% and biphasic tumors in 25% of 24 reviewed cases.[5] To our knowledge, there was only 1 case of a pure sarcomatous mesothelioma of the tunica vaginalis (1.9%), reported by Eimoto and Inoue.[15]

Most of the malignant mesotheliomas presented as papillary, exophytic excrescences of the tunica vaginalis, but subtunical infiltration of adjacent structures was commonly found. Data concerning local invasion were given in 25 patients (33.7%), with infiltration of the subtunical connective tissue (25.8%) and invasion of the adjacent testicular parenchyma (19.4%) most frequently reported. A list of the incidence and site of infiltration is given in Table 2. Malignant mesothelioma of the tunica vaginalis has an expansive and infiltrative growth pattern; therefore, a local organ-preserving excision of the tumor must be considered with caution.

Because the primary treatment might be related to the development of local tumor recurrence, we reviewed the available data concerning the primary surgical approach to treating patients with local recurrence. In cases of resection of the hydrocele wall (15 patients), local recurrence was seen in 35.7%. In comparison, locally recurrent malignant mesothelioma was found in 10.5% after scrotal orchiectomy (19 patients) and in 11.5% after inguinal orchiectomy (26 patients). Because tunical mesotheliomas have the potential for local invasion and development of metastasis, long term survival is a major concern. There was a wide range in the duration of follow-up reported (2–192 months), with a median follow-up of 23 months. Information regarding patients' disease course was given in 59 cases. After primary surgery, complete remission was reported in 28 patients (47.5%) for a median follow-up of 12 months (range, 3–180 months). Tumor recurrence was observed in 31 patients (52.5%), including 14 cases (23.7%) with local recurrence. A local recurrence without the development of metastasis was seen in only 5 patients (16.1%). All other patients with recurrent disease finally experienced disseminated tumor progression (83.9%). The median time to tumor recurrence was 10.5 months (range, 2–180 months). More than 60% of recurrences developed within the first 2 postoperative years. An early recurrence within the first 6 months was seen in 26.7%, with a recurrence rate of 53.4% after 12 months of follow-up. Overall, 92.9% of the patients with recurrence experienced it within the first 5 years of follow-up. However, there were 2 late recurrences reported after 10 and 15 years, respectively.[5,25] The frequency of tumor recurrence in relation to the follow-up period is shown in Figure 1.

Tumor progression with the development of lymphatic or distant tumor metastases has been reported several times.[4,5,9,11–14,18,19,21,22,27,28,37,38,40,43,45] Reviewing the available data for the 74 cases determined an incidence of primary disseminated disease in 14.9% (11 cases). All of these patients were older than 40 years, with a median age of 58 years. In cases of primary metastatic disease, retroperitoneal lymph nodes were most often involved (5 cases), followed by inguinal lymph nodes in 3 cases and iliac lymph nodes in 2 cases. Primarily disseminated disease with organ metastasis was only reported in 4 cases, with lesions of the thoracal and lumbal vertebrae in 2 cases and of the omentum and the lung in 1 case each.[5,10,33] From the given data, primary metastatic mesothelioma occurs rarely but should be considered and carefully looked for at the initial diagnosis.

In cases of disease progression, organ metastasis besides lymph node metastasis were reported in 19 of

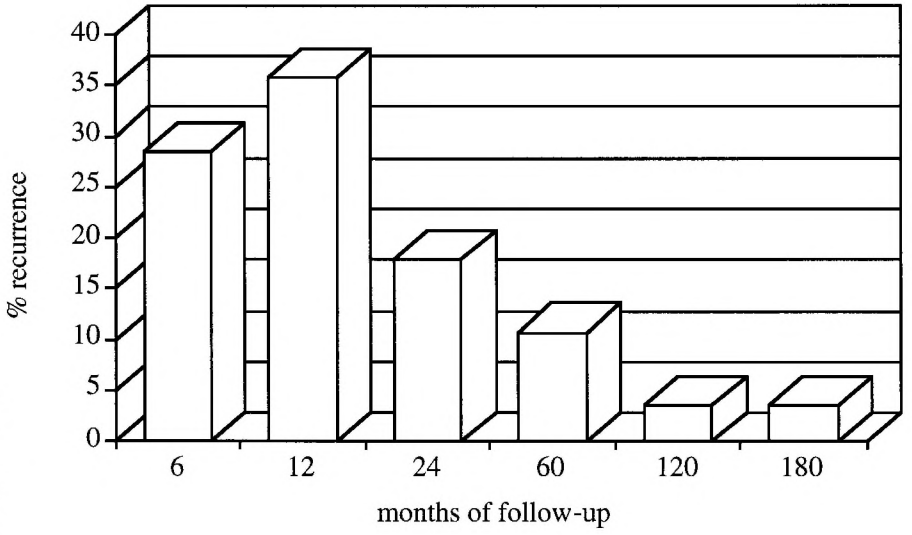


FIGURE 1. The frequency of tumor recurrence is shown in relation to the follow-up period. More than 60% of recurrences developed within 2 years of follow-up, over 90% developed within 5 years, and 2 late recurrences were observed.

TABLE 3
Development of Metastasis in Malignant Mesothelioma of the Tunica Vaginalis Testis

Site of metastasis	% of patients
Local recurrence	23.7%
Lymph nodes	13.8%
Lung	9.7%
Liver	4.2%
Pleura	2.7%
Omentum	2.7%
Other (colon, spleen, mesentery, mediastinum)	5.6%

the 31 cases (61.3%). The location and frequency of metastasis are listed in Table 3. Finally, 22 patients (37.9%) died of disease progression after a median survival of 24 months (range, 2–64 months).

Adjuvant Therapeutic Strategies

Some patients with disseminated malignant mesothelioma underwent adjuvant therapy, except for patients in poor physical condition. Adjuvant treatment regimes consisted of 3 different strategies: chemotherapy (for 10 patients), radiotherapy (for 10 patients), and combined chemotherapy and radiotherapy (for 6 patients).[4,5,10–12,14,16,20,22,27–29,33,35,37,38,40,46,47] Adjuvant immunonucleotide and radionucleotide therapy were given to 1 patient each.[5,9] None of the patients who achieved complete remission after adjuvant therapy had a follow-up period of longer than 12 months. Due to the heterogenity of the therapeutic regimes and the small caseload, only a descriptive analysis of the results was performed.

Concerning chemotherapy, 17 different substances with varying treatment regimes were applied, with doxorubicin and cyclophosphamide given most frequently. Partial remission, defined as stable disease or reduction of tumor volume, was reported in 2 of 10 cases (20%). No improvement in symptoms or tumor size was seen in 6 patients (60%), and none of the patients experienced complete remission after chemotherapy. In 2 cases insufficient information on the outcome of chemotherapy was given. Although some patients with malignant mesothelioma of the tunica vaginalis experienced partial remission, 8 of 10 finally died of disease progression.

The results of radiotherapy for the treatment of systemic disease were also very heterogeneous. Again, therapeutic regimes varied significantly, with a difference in the applied intensities (40–60 gray) and the duration of therapies. A complete remission was reported in 5 (50%) of 10 cases for a maximum follow-up of 12 months, and 1 patient (10%) experienced partial remission for 3 months. No reduction of tumor size or symptomatic improvement was seen in 2 patients (20%) after radiotherapy. Again, two cases could not be evaluated due to the lack of survival data. Although an effect of adjuvant radiotherapy was reported in 60% of the cases, 4 patients (40%) died of disease progression.

Combined chemotherapy and radiotherapy were given to 6 patients with disseminated malignant mesothelioma. Complete remission was not reported, but partial remission was seen in 3 patients, including 1 who had had stable disease for 16 years. No response to chemotherapy and radiotherapy was observed in three patients. Finally, four patients died due to progressive disease after combination therapy.

In addition, interferon-α and radionucleotide P32

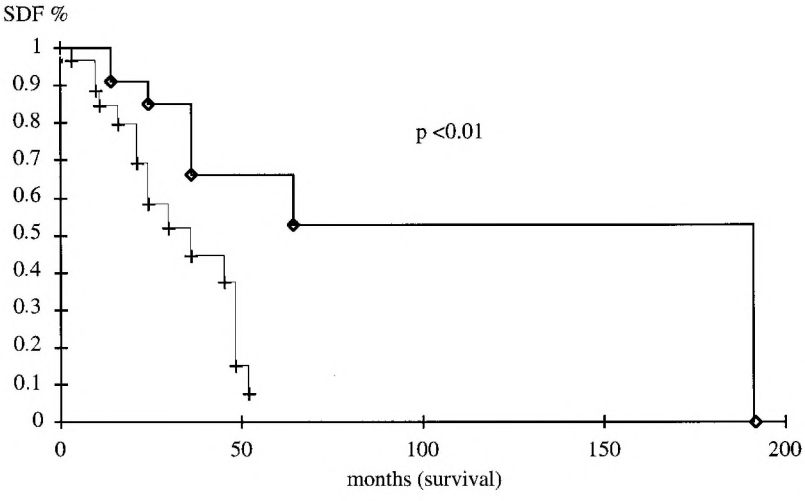


FIGURE 2. The survival distribution function (SDF) of the influence of patient's age on survival is shown. Because most mesotheliomas occurred between ages 55 and 75 years, patients were differentiated into age <60 years (n = 29; bold line) and age ≥60 years (n = 29; fine line).

were given to two patients as adjuvant therapy.[5,9] There were no therapeutic protocols or improvements reported; therefore, these treatments must be considered investigational and must not be used outside of clinical trials.

Prognostic Parameters

Because there were no tumor markers or prognostic parameters reported for patients with malignant mesothelioma of the tunica vaginalis testis, we investigated the influence of a patient's age, history of asbestos exposure, tumor histology, primary therapeutic approach, and the presence of metastasis at diagnosis on survival. Due to the incompleteness of the reported data, further parameters could not be evaluated. For the assessment of prognostic variables, all reported data were included in a univariate and multivariate Cox regression model (PROC LIFEREG). All correlations were performed with the SAS software package (SAS Institute Inc., Cary, NC).

The univariate analysis revealed a significant correlation of age with survival ($P < 0.01$), emphasizing longer survival for younger patients (<60 years) than for older patients (≥60 years) (Fig. 2). A significant correlation was also found between the presence of primary metastatic disease and survival ($P < 0.05$) (Fig. 3). Patients with metastatic disease at diagnosis had a significantly shorter survival time than patients with organ-confined disease. Concerning the development of local recurrence, patients with a positive history of asbestos exposure had a significantly shorter interval before tumor recurrence than patients with no history ($P < 0.05$) (Fig. 4). However, this must be interpreted cautiously, because only 9 patients were enrolled in that analysis.

Calculations of the correlation between previous asbestos exposure, tumor histology, or primary therapy and survival did not reveal any significant findings in univariate analysis. Although the incidence of local recurrence was higher after resection of the hydrocele wall alone (35.7%) than after scrotal (10.5%) or inguinal orchiectomy (11.5%), a significant survival benefit was not observed after radical orchiectomy as compared with hydrocele wall resection.

The performance of a multivariate Cox regression model for the parameters mentioned with survival did not determine any significant findings.

DISCUSSION

Malignant mesothelioma of the tunica vaginalis is a rare disease, with less than 80 cases reported within the last 30 years. Approximately 15% of tunical mesotheliomas are malignant, with an overall frequency of 5% of all mesotheliomas developing in the tunica vaginalis.[29,39] However, a worldwide increase of mesotheliomas has been observed.[48] More than 60% of cases have developed in patients older than 45 years, with the highest incidence during the fifth to seventh decades of life. Malignant mesotheliomas of the tunica vaginalis have also been reported in younger patients, but the reasons for the development of the disease have remained unclear in those cases.

Exposure to asbestos or asbestos-containing materials has been demonstrated to be a risk factor for the development of mesothelioma. A positive history of asbestos exposure was found in 34.2% of patients with mesotheliomas of the tunica vaginalis. These results were consistent with those described by Jones et al., who reported a positive occupational history in 41% of 27 reviewed cases.[25] Furthermore, the frequency of asbestos exposure among patients with mesotheliomas of the tunica vaginalis is comparable to

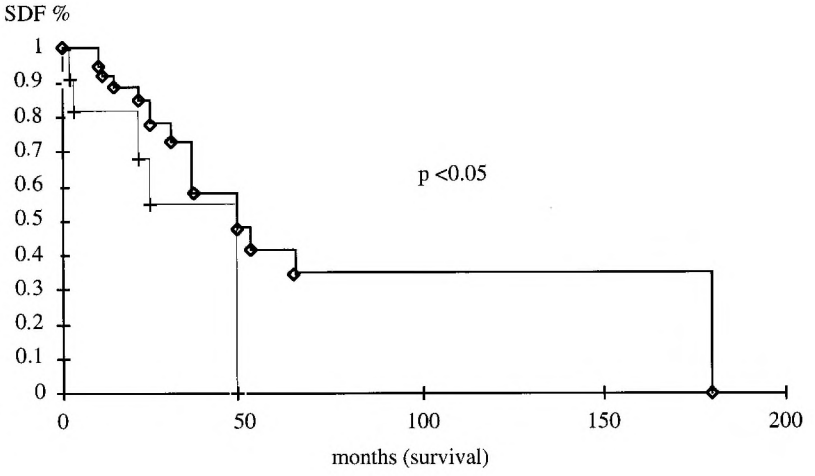


FIGURE 3. The survival distribution function (SDF) of the prognostic relevance of primary disseminated mesothelioma to survival is shown. Patients with metastatic disease (n = 11; fine line) at diagnosis had significantly worse prognoses than patients with organ-confined disease (n = 46; bold line).

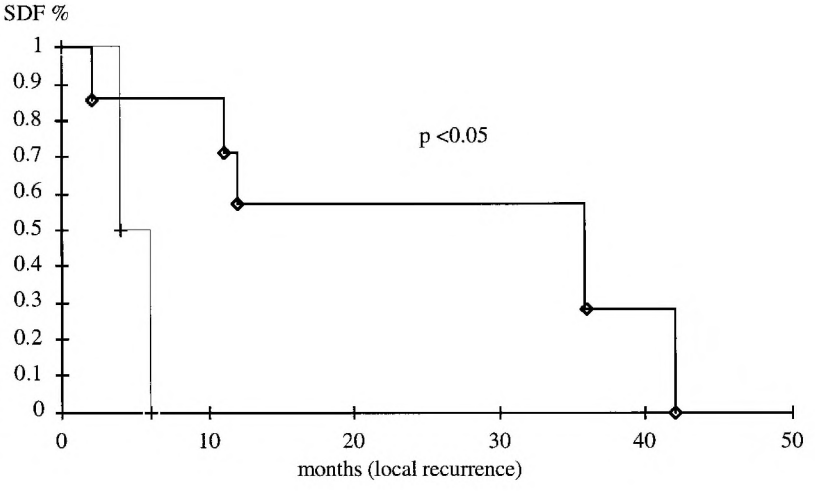


FIGURE 4. Univariate analysis of the development of local tumor recurrence in relation to asbestos exposure is shown. Those patients with an asbestos history (n = 2; fine line) had a significantly shorter interval until tumor recurrence than patients with no history (n = 7; bold line). Because there were only 9 patients with sufficient data given for univariate analysis, the significance ($P < 0.01$) of these results must be interpreted cautiously. SDF: survival distribution function.

that among patients with pleural mesotheliomas.[57] Therefore, patients known to be exposed to asbestos or asbestos-containing materials (shipyard workers, car brake workers, and engineering and building maintenance workers) are at risk for the development of a tunical disease and should be monitored.

One of the major difficulties in managing malignant mesothelioma of the tunica vaginalis is making an accurate preoperative diagnosis. Because there are no characteristic clinical symptoms or tumor markers available, the majority of the cases (97.3%) were diagnosed intraoperatively. A correct preoperative diagnosis was available in only 2 cases (2.7%). Most frequently, a rapidly growing hydrocele (56.3%) or suspected testicular tumor (32.8%) were reported as indications for surgery. Rapid growth of the scrotum should be suspicious for the presence of a tunical or testicular disease. Ultrasonography of the scrotum can provide further information for use in the determination of tumor excrescences of the tunica vaginalis, although there are limitations. Because papillary lesions can be smaller than 0.5 cm, it may be difficult to identify these lesions, even with the use of a high-resolution ultrasound probe (7.5MHz).[13] In addition, mesotheliomas can be solitary or multifocal and, especially in case of a solitary lesion, may be missed during sonography. However, preoperative ultrasound can give substantial information for the determination of inhomogenous hydrocele fluid, hypoechogenecity of the fluid, or exophytic tumors. In case of suspicion, cytoanalysis of the hydrocele fluid can be diagnostic and is therefore recommended. By immunohistochemical staining methods, the presence of malignant mesothelioma may be determined, which is a major therapeutic advantage prior to surgical intervention.[58]

In case of suspected mesothelioma of the tunica vaginalis, exploration of the testis should be performed through an inguinal incision. If a tumor is found intraoperatively, resection of the hydrocele wall is not adequate due to the increased risk of local

recurrence, which was found to be three times higher in patients after hydrocele wall resection than in patients undergoing radical orchiectomy. A reason for the worse outcome after mere resection of the tunica may be the implantation of tumor cells at the incision site or an incomplete resection due to invasive tumor growth.[23] These cells may be the origin of local recurrence or tumor dissemination. Although local recurrence was seen more often after hydrocele wall resection than after radical orchiectomy, no significant difference in the effect of the primary treatment on patients' survival could be determined. In accordance with others, radical orchiectomy via an inguinal incision should be the first-line therapy.[5,9,44]

Because mesotheliomas of the tunica vaginalis were mostly found intraoperatively or at final pathology, as in our case, incomplete resection of the tunica vaginalis was commonly reported as the primary therapy. A radical approach could not have been taken due to the lack of informed consent by the patients. To diminish the risk of local recurrence in these cases, a hemiscrotectomy within due course and safe cut margins should be performed as second-line therapy.

Besides the importance of primary orchiectomy, the necessity for inguinal or iliac lymph node dissection as primary therapy is still under discussion. The presence of primary metastasis was reported in 15% of cases, and dissemination to the retroperitoneal lymph nodes was most often seen (in 8.5% of cases). Positive inguinal or iliac lymph nodes were found in 5.1% and 3.4% at diagnosis. The presence of positive lymph nodes at diagnosis were significantly correlated with shorter survival. However, 35.3% of these patients underwent staging lymphadenectomy without any tumor found. Retroperitoneal lymph nodes are the first station of lymphatic drainage in testicular diseases, but 8.5% of the cases had metastatic disease to the inguinal and/or iliac lymph nodes. The lymphatic drainage of the scrotum is to the horizontal tract of the superficial inguinal lymph nodes. Depending on the localization of the mesothelioma on the serosa (the parietal or visceral layer of the tunica vaginalis), the site of infiltration of the subtunical tissue and/or the scrotal skin which was seen in more than 35% of cases, the presence of positive inguinal or iliac lymph nodes may be possible. Staging by thoracal and abdominal CT scan should be performed after orchiectomy, and a limited lymph node dissection of the suspected region is recommended in cases of suspected dissemination. If there is no suspicion of metastasis, staging lymphadenectomy is not supported due to the low risk of positive lymph nodes.

The development of tumor recurrence was frequently observed, with more than 60% developing within the first 2 years. There were also late recurrences after 10 and 15 years of follow-up. Thus, clinical examinations and CT scan or retroperitoneal ultrasound should be performed every 3 months for the first 2 years. Later on, patients should be controlled on a yearly basis until 5 years of follow-up have been provided. In accordance with Eden et al., chest radiology should be performed for pulmonary symptoms or in cases of recurrent disease.[13] Due to the possibility of late tumor recurrence reported in 2.7%, lifelong follow-up can be recommended and should be offered to the patient.

Although organ metastasis was rarely reported, adjuvant therapy may be useful for some patients. However, these treatments should be considered investigational, because the efficacy of adjuvant treatments has not yet been established due to the limited number of reported cases. Most of the patients with disseminated mesothelioma received chemotherapy, radiotherapy, or combined radiotherapy and chemotherapy, although malignant mesotheliomas are considered rather chemoresistant.[59]

Patients undergoing adjuvant chemotherapy had a reduction in tumor volume of 20%, but no complete remission was reported. Although there were some reports of symptomatic improvement, 80% of the patients died of disease progression after chemotherapy. Recently, Ong and Vogelzang reviewed the results of chemotherapeutic trials involving patients with malignant pleural mesotheliomas.[59] These data must be interpreted cautiously, because pleural mesotheliomas are commonly sarcomatous or biphasic in comparison to the mostly epithelial mesothelioma of the tunica vaginalis. However, the response rates of either single or combined chemotherapy did not reach more than 30% in pleural tumors. Promising results were reported only for methotrexate and edatrexate, although these data need further confirmation.[59] Due to the limited experience with chemotherapy for tunical mesothelioma, conclusions regarding the effect of chemotherapy must be drawn with caution. However, the given data seem to support that chemotherapy should not be recommended as primary adjuvant therapy for disseminated malignant mesothelioma of the tunica vaginalis.

Similarly, the efficacy of adjuvant radiotherapy has not yet been clearly determined. Complete remission for 12 months was reported in 50% of cases and transient partial remission in 10% of cases (1 patient). Finally, 40% of patients died due to disease progression after radiotherapy. Because of the small number of treated patients, the efficacy of the treatment must be interpreted cautiously, but radiotherapy was more effective than chemotherapy. We believe that the in-

dication for adjuvant radiotherapy should be considered for patients with locally extended mesothelioma after resection of the tumor with safe cut margins, and also for patients with disseminated disease who are in good physical condition.

There has also been limited experience with combined chemotherapy and radiotherapy in the treatment of malignant mesothelioma of the tunica vaginalis. There were only 6 patients reported with no complete remission achieved after combination therapy, but 2 survivals for 4.5 and 13 years. This may present a major improvement in survival as compared with a median survival of less than 2 years. However, in cases of pleural mesothelioma, no significant difference in survival was seen with radiotherapy alone compared with combined therapy.[60] This suggests that combined chemotherapy and radiotherapy may be effective in treating disseminated disease, although the numbers are too small for any final conclusions to be drawn.

CONCLUSIONS

Malignant mesothelioma of the tunica vaginalis is a rare disease of the testis with potentially aggressive behavior. Due to the lack of tumor markers and characteristic symptoms, correct preoperative diagnosis is extremely difficult. Radical surgical treatment is of major importance to the survival of the patients. Investigations of prognostic parameters reported better survival for patients younger than 60 years and worse outcomes in cases of primary metastatic disease. Lifelong follow-up should be offered to patients with malignant mesothelioma of the tunica vaginalis because of its metastatic potential.

ADDENDUM

Since the completion of this study, an additional case has been reported by Khan et al.[61]

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