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RESEARCH ARTICLE

Management of Patients with Malignant Peritoneal Mesothelioma: The Evolving Role of Surgery and Immunotherapy

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ABSTRACT

Malignant peritoneal mesothelioma, a neoplastic process that arises from the peritoneal membranes and presents as a diffuse malignant process, has an incidence of approximately 400-600 new cases annually in the United States. Systemic chemotherapy regimens, like the combination of cisplatin and pemetrexed, have response rates of approximately 25% in peritoneal mesothelioma. Due to chemotherapy's poor response rates, the first line approach to treating malignant peritoneal mesothelioma over the last 30 years has been surgical resection with regional intra-peritoneal chemotherapy in appropriately selected patients. Hyperthermic intraoperative intraperitoneal perfusion with chemotherapy with cisplatin or mitomycin c for 90 to 120 minutes is the most commonly reported type of regional chemotherapy that is administered during surgical cytoreduction. Favorable prognostic factors for patient outcomes after cytoreduction and hyperthermic intraperitoneal perfusion with chemotherapy tend to be favorable operative characteristics (lower peritoneal cancer index, better complete cytoreduction score), less aggressive tumor characteristics (epithelioid histology, low Ki-67, well-differentiated), and other patient characteristics (young, female, fewer comorbidities). Recently, there has been considerable interest in the utility of immune checkpoint inhibitors either alone or in combination with chemotherapy for patients with mesothelioma. Data demonstrate that programmed death-ligand 1 may be highly expressed in a large proportion of malignant peritoneal mesothelioma tumors and therefore the evaluation of checkpoint blockade in this patient population is a high clinical priority.

Introduction

Malignant mesothelioma is a neoplastic process that typically arises from the pleural or peritoneal membranes and presents as a diffuse malignant process with a tendency for local regional progression. Malignant peritoneal mesothelioma (MPM) represents about 20% of all new mesothelioma diagnoses which translates into approximately 400-600 new cases annually in the United States.[1] While the two conditions are histologically similar, there are many distinctive clinical characteristics of each. In contrast to malignant pleural mesothelioma, which is far more common in older males, MPM afflicts both genders equally and presents at a slightly earlier age. Although both conditions are known to evolve from asbestos exposure, the association between asbestos and MPM is not as strongly established as for its pleural counterpart. In approximately 10% of patients, MPM is a manifestation of a familial cancer syndrome in which there is an associated germline BAP-1 mutation.[2] This review will discuss the historical background behind our current understanding of MPM and its tumor biology and review the current data regarding the utility of cytoreduction with hyperthermic intraperitoneal chemotherapy in this patient population. In addition, the evolving concepts around the use of checkpoint blockade as a potential novel treatment for patients with MPM will be presented.

Just over 100 years ago, a case of a 32-year-old male with a diffuse malignant abdominal condition was reported in literature and was subsequently confirmed to be the first documented case of MPM.[3] Fifty years later a review of the literature described 12 cases of this diffuse malignant abdominal malignancy which was described for the first time as malignant peritoneal mesothelioma.[4] In 1965, Selikoff et al published a seminal observation unequivocally demonstrating a strong association between asbestos exposure and the development of both pleural and peritoneal mesothelioma.[5] He followed almost 18,000 asbestos insulation workers and observed a much higher than expected incidence of both pleural and peritoneal mesothelioma with a latency period of decades. After Moertel at al published a detailed description of the MPM disease entity including its clinical and pathologic features as well as its natural history in 1972, the number of reported cases in the literature increased significantly.[6] In 1980 the first report of a multi-modal therapy specifically for the treatment of patients with MPM was published by Antman et al.[7]

Presentation, Diagnosis, and Staging

In any patient who presents with signs and symptoms of a diffuse malignant process within the abdominal cavity, MPM must be in the differential diagnosis. Most patients with MPM present with vague, non-specific, and gradually progressive symptoms including abdominal bloating, early satiety, abdominal discomfort, and weight loss. Radiographically, the disease is most commonly associated with ascites, an omental mass, and evidence of other peritoneal based lesions (Figure 1). In some patients the disease manifests as a more

solid and infiltrative process diffusely involving the viscera (Figure 2). Serum cancer antigen (CA)-125 is often elevated; however, this marker alone is not specific for MPM and is best used during surveillance after diagnosis and treatment.[8,9] If the serum cancer antigen (CA)–125 is elevated in a female patient, the condition can masquerade as ovarian cancer. Colonoscopy and upper endoscopy are often used to exclude a colonic or gastric primary tumor and cross-sectional imaging will exclude a primary pancreatic or biliary system malignancy.

A definitive diagnosis is made based on image guided or laparoscopic biopsy of representative intra-abdominal tissue with appropriate histopathologic studies. Based on NIH consensus guidelines, two or more markers associated with MPM should be positive to establish a definitive diagnosis.[10] The antibodies that typically stain positive for MPM and most commonly used in the clinical setting include calretinin, cytokeratin 5/6, and Wilms Tumor (WT)–1. Antibodies typically used for diagnosis of epithelial malignancies such as CEA, MOC–31, and Ber–EP 4 are negative. Histologically, there are several well described subtypes of MPM. Epithelioid MPM comprises 70 to 80% of cases and has a somewhat favorable tumor biology. The sarcomatoid or biphasic histologic subtype (includes features of both epithelioid and sarcomatoid) constitutes approximately 10% of diagnoses and is associated with a very aggressive biological behavior. Lastly, a tubulopapillary variant of epithelioid mesothelioma is diagnosed in approximately 5 to 10% of patients and is associated with a very favorable and often indolent biologic behavior. A BAP-1 mutation is observed in approximately over 60% of MPM tumors.[11]

General Treatment Approaches for Patients with Peritoneal Mesothelioma

Over the past 30 years a large number of retrospective reports both single center and multicenter in nature, have been published that have characterized the long-term outcomes of MPM patients undergoing surgical exploration with cytoreduction with some form of regional intraperitoneal chemotherapy. Based on these data, it has largely been accepted that surgical treatment with regional intra-peritoneal chemotherapy in appropriately selected patients should be considered the first line approach in MPM patients. Hyperthermic intraoperative intraperitoneal perfusion with chemotherapy (HIPEC) with cisplatin or mitomycin c for 90 to 120 minutes is the most commonly reported type of regional chemotherapy and is administered during surgical cytoreduction. With respect to systemic treatments, about twenty years ago the combination of cisplatin and pemetrexed was approved as first line systemic therapy for patient with MPM based upon the results of single arm prospective clinical trials that demonstrated overall response rates of approximately 25%, a disease control rate of 71%, and a median survival of 13.1 months.[12] The couplet of gemcitabine and pemetrexed is also approved for use but because of its more severe toxicity profile is not as commonly used.[13]

Recently, there has been considerable interest in the utility of immune checkpoint inhibitors either alone or in combination with chemotherapy for patients with mesothelioma. Unfortunately, the number of patients with MPM that have been included in existing clinical studies evaluating anti-PDL-1 therapies have been very limited and so the relevance of the available data to MPM patients specifically is not known. However, as discussed in detail below, recent data demonstrate that PD-L1 may be highly expressed in a large proportion of MPM tumors and therefore the evaluation of checkpoint blockade in this patient population is a high clinical priority.

Factors Influencing Outcomes in Malignant Peritoneal Mesothelioma Patients

Several studies analyzing large databases, such as the Surveillance, Epidemiology and End Results (SEER) Database and the National Cancer Database (NCDB), have agglomerated treatment protocols, survival outcomes, and prognostic factors for MPM patients [Table 1]. These studies have demonstrated that over the last 50 years, more patients with MPM were treated with chemotherapy alone than with surgery or a combination of the two. Miura et al showed that the use of surgery has not increased much in treatment of MPM patients over the years with 33% of patients undergoing surgery prior to 1991 compared to 40% between 1991 and 2010.[14] In general, large database analyses have found that longer 5-year survival and median overall survival were associated with patients who underwent any type of surgical resection as part of treatment.[14-20] While patient selection was most likely a major factor, one study demonstrated an increase in median overall survival from 11 months with chemotherapy alone to 57 months with surgical intervention.[19] Verma et al reported that the use of surgery in MPM patients was associated with prolonged survival and survival rates were further prolonged when surgery was combined with systemic or intraperitoneal chemotherapy (median survival 17-21 months versus 52-61 months).[18] All database studies have demonstrated that any surgical intervention is a favorable prognostic factor in MPM survival.[14-20]

As to tumor characteristics, sarcomatoid and biphasic histology, advanced tumor stage, and distant metastases all serve as poor prognostic factors, while epithelioid histology bears a favorable prognosis.[14-20] Age, sex, race, and insurance status are also associated with differences in MPM patient survival. Medicaid or lack of insurance was found to be a poor prognostic factor.[16,18] Female sex and younger age have been reported to be favorable prognostic factors in all studies; however, the data were discordant regarding race. Ullah et al reported that Caucasian race was a poor prognostic factor while Shavelle et al found the opposite.[15,20] Although both studies used the SEER database, Ullah et al analyzed five additional years of data (2011-2016), suggesting that any relationship between race and outcomes needs further study.

Table 1. Results of SEER and NCDB Analyses of Patients with Malignant Peritoneal Mesothelioma

Study	N	Survival	5-yr OS	Median OS (mos)	Treatment Type		Poor Prognostic Factors	
Ullah 2022		Overall	20%		Surgical rxn alone	30%	Poor differentiation Tumor size > 4cm	CTX or RT without surgery
(1975–2016)	1998	Any surgery Any CTX	43% 19%		CTX alone	51%	Distant metastases Caucasian race	
SEER		Any RT	26%		RT alone	2%		
Pan 2022					Surgery (adult)	48%	Poor differentiation	No CTX
		Adult (<65y)	30%	19	Surgery (elderly)	33%	Sarcomatoid type	No cancer-directed surgery
(1975 - 2016)	1492						Distant metastases	
		Elderly (>65y)	13%	6	CTX (adult)	60%	Male sex	
SEER					CTX (elderly)	44%	Uninsured	
Bijelic 2020					No/Limited surgery	66%	Fibrous/biphasic type	No CTX
					Radical surgery	34%	Younger age	No surgical intervention
(2003-2014)	2062		33% at 3 years	16	CTX/Surgery	27%	Male sex	
					CTX	60%	High comorbidity score	
NCDB					RT	1%		
Verma 2018		CRS/HIPEC	52%	61	CRS/HIPEC	14%	Male sex	CRS, CTX, observation vs
		CRS/CTX	43%	52	CRS/CTX	23%	Advanced age	CRS/CTX or CRS/HIPEC
(2004-2013)	1514	CRS	22%	21	CRS	13%	Uninsured	Sarcomatoid/biphasic type
		CTX	22%	17	CTX	24%	Medicaid	
NCDB		Observation	9%	6	Observation	25%		

Table 1. Results of SEER and NCDB Analyses of Patients with Malignant Peritoneal Mesothelioma

Study	N	Survival	5-yr OS	Median OS (mos)	Treatment Type		Poor Prognostic Factors	
Naffouje 2018		No treatment		4	No treatment	35%	Distant metastasis	No treatment
		CTX		11	CTX	39%	Nodal metastasis	CTX only
(2004-2014)	2664	Surgery	58%	57	Surgery	10%	High Charlson score	Sarcomatoid/biphasic type
NCDB		CTX/Surgery	53%	54	CTX/Surgery	16%	Male sex	
Shavelle 2017		Overall	18%		Cancer-directed surgery	42%	Distant metastasis	RT only
					Surgery only	40%	Fibrous/biphasic type	
	1634			N/A				
(1973-2011)		Localized disease	26%		No RT or Surgery	52%	Male sex	
		Regional disease	19%		RT/Surgery	3%	Non-caucasian race	
SEER		Distant disease	11%		RT	3%		
Muira 2014		Overall		9	Limited surgery	12%	Biphasic type	No surgical rxn
					Radical surgery	18%	Advanced stage	
(1973-2010)	1591	Disease extent	N/A		No surgery	62%	Increasing age	
		Localized		21			Female sex	
SEER		Distant		7				

SEER Grade: Well-differentiated (Grade 1), moderately differentiated (Grade 2), poorly differentiated (Grade 3), Undifferentiated, anaplastic (Grade 4).
SEER Staging: Localized, Regional, Distant, Unstaged
NAC: Neoadjuvant chemotherapy AC: Adjuvant chemotherapy CTX: Chemotherapy
CRS: Cytoreductive Surgery HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Surgical Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy

As cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is considered the current standard of surgical treatment for selected patients with MPM, several multi-center database studies have analyzed outcomes for patients who underwent this treatment [Table 2]. All studies found that a higher peritoneal cancer index (PCI) and incomplete cytoreduction were poor prognostic factors for survival.[21-24] Deraco and Kepenekian reported that the use of neoadjuant chemotherapy was associated with a worse prognosis.[23,24] In a retrospective and uncontrolled study, Malgras et al reported that using a combination of two chemotherapy drugs intraoperatively, most commonly cisplatin and mitomycin-C or cisplatin and doxorubicin was favorable for survival.[22]

Consistent with the studies analyzing national databases, large single-center and multi-center reports analyzing results of cytoreductive surgery generally show higher five-year survival rates than studies that include patients who did not undergo surgery. Single-center studies have reported diverse operative characteristics [Table 3]. For example, while the median PCI was relatively low at most centers (range: 15-23), the percentage of patients who had a complete cytoreduction (CCR0/1) varied greatly (36-86%).[25-29] Most centers employed the use of HIPEC only, however in one single arm study by Sugarbaker et al assessed the use of an ambitious regimen which included prolonged administration of intraperitoneal chemotherapy (NIPEC) after early postoperative chemotherapy (EPIC) and HIPEC. Although the study was uncontrolled, the data showed that EPIC was associated with a slightly improved survival while a protracted course of post-CRS intraperitoneal therapy (EPIC and NIPEC) was associated with a more prolonged survival.[25] All single-center reports found that a better CCR score (0 or1) and a lower PCI (generally less than 20) were associated with better prognoses.[25-29] As to preoperative biomarkers, Li and Deraco both reported that preoperative thrombocytosis was associated with worse outcomes, while Schaub reported that a low preoperative CA-125 tends to be a favorable prognostic factor.[26,28,29] Multi-center studies found that the majority of MPM is epithelial in histology (79-94%), which tends to have a favorable prognosis. Congruent with national database studies, both single-center and multi-center studies identified epithelial histology, negative lymph nodes, and a low Ki-67 as favorable in overall survival.[30-33] In a multicenter retrospective study, Alexander et al showed that the use of cisplatin versus mitomycin-C during HIPEC was associated with favorable outcomes while Yan et al showed that the addition of HIPEC to surgery has a survival benefit as well.[30,31]

Table 2. Results of Multi-Center Database Analyses of Patients with Malignant Peritoneal Mesothelioma who Underwent CRS/HIPEC

Study	N	5-yr OS	Median OS (months)	Treatment Type	Prognostic Factors
Roife 2020 (2000-2017) US HIPEC Col.	174	N/A	Overall 86 No organ rxn 130 Organ rxn 75	 No organ rxn 54% Organ rxn 23%	<u>Poor prognostic factors:</u> Distant metastases CCR 3/4 Higher PCI Male sex Increasing age
Deraco 2019 (1997-2014) PSOGI	45	80% (all well-differentiated mesothellioma)	N/A	NAC 18% AC 4.5%	<u>Poor prognostic factors:</u> Higher PCI Preop CTX
Malgras 2018 (1989-2014) RENAPE	249	N/A	N/A	Preop CTX 41% Intraop CTX Single agent 35% Couplet therapy 65%	<u>Favorable prognostic factors:</u> Two vs one CTX drugs
Kepenekain 2016 1991-2014 RENAPE	126	Overall 53% NAC 40% AC 67% CRS/HIPEC 57% CTX/CRS/HIPEC 62%	Overall 61 NAC 37 AC 83 CRS/HIPEC 71	 NAC 33% AC 13% CRS/HIPEC 38% CTX/CRS/HIPEC 13%	<u>Favorable prognostic factors:</u> PCI <30 CCR 0/1 No NAC

MOR0: No multi organ resection MOR1: Single organ resection MOR2: >1 organ Resection
NAC: Neoadjuvant chemotherapy AC: Adjuvant chemotherapy CT: Chemotherapy
CRS: Cytoreductive Surgery HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Table 3. Results of Cytoreduction and Regional Therapy – Large Single Center Reports

Study	N	5-yr OS	Median OS (months)	Operative Characteristics	Treatment Characteristics	Prognostic Factors
Sugarbaker 2017	129	CRS/HIPEC 44% +EPIC 52% +EPIC/NIPEC 74%	N/A	PCI 10-30 68% CCR 0/1 36% Positive LN 9%	HIPEC 33% +EPIC 45% +EPIC/NIPEC 22%	Poor prognostic factors: No NIPEC CCR 2/3
Li 2017	100	36	Overall 33 Thrombocytosis 13 Platelets wnl 58	Mean PCI 23 CCR 0/1 80%		Poor prognostic factors: CCR>1 PCI>20 Thrombocytosis
Deraco 2013	116	49%	N/A	Median PCI 21 CCR 0/1 86%	NAC 52% Platinum/pemetrexed 48% Other 51%	Poor prognostic factors: CCR 2/3 Thrombocytosis Biphasic/sarcomatoid type High preop morbidity score
Baratti 2013	108	52%	63.2	Median PCI 17 CCR 0/1 49% Low CA-125 43%	NAC 45%	Favorable prognostic factors: Epithelial hist Negative LN Ki-67<10%
Schaub 2012	104	46%	52	Median PCI 15 CCR 0/1 66% Repeat CRS/HIPEC 12%	EPIC 66%	Favorable prognostic factors: Epithelial hist Low PCI Low preop CA-125

CRS: Cytoreductive Surgery HIPEC: Hyperthermic Intraperitoneal Chemotherapy NIPEC: Normothermic Intraperitoneal Chemotherapy EPIC: Postoperative Intraperitoneal Chemotherapy NAC: Neoadjuvant chemotherapy AC: Adjuvant chemotherapy CTX: Chemotherapy
CCR: Completeness of cytoreduction LN: lymph nodes

Among studies describing the association of various treatments and outcomes of MPM, there is a consensus that surgical intervention is associated with clinical benefit in selected patients. Certain operative characteristics, like a low peritoneal cancer index and a complete cytoreduction are associated with longer survival. While the use of HIPEC specifically has not been proven to be beneficial, addition of some mode of chemotherapy to surgery is associated with in better outcomes.

Checkpoint Blockade in Malignant Peritoneal Mesothelioma Patients

The JAVELIN study was a phase 1b trial of the PD-L1 inhibitor, avelumab, in patients with previously treated pleural and peritoneal mesothelioma. Although the objective response rate was only 9%, the median duration of response was relatively long at just over 15 months. Interestingly, the JAVELIN study found that the response rate was three-fold higher in patients with tumors with high (>5%) PD-L1 expression[34].

Checkmate-743 was a random assignment study comparing dual checkpoint blockade consisting of nivolumab plus ipilimumab to systemic chemotherapy (cisplatin-pemetrexed) in patients with unresectable pleural mesothelioma. The study showed a statistically significant benefit for patients treated with dual checkpoint blockade with a 2-year survival of 41% in the immunotherapy group versus 27% in the chemotherapy group [35]. Since Checkmate-743, several other trials investigating immune checkpoint blockade have been conducted. Agents such as tremelimumab plus durvalumab, nivolumab, abemaciclib and others are currently being investigated, with preliminary results indicating similar findings to Checkmate-743 [36,37]. Based on this body of literature, dual checkpoint blockade was approved by the FDA as therapy for patients with pleural mesothelioma in October of 2020.

Most recently, the CONFIRM study, a random assignment trial compared nivolumab to placebo in patients with relapsed pleural and peritoneal mesothelioma, found a statistically significant improved median overall survival for the biologic therapy arm of the trial. The median overall survival in patients who received nivolumab was 10.2 months, compared to 6.9 months in the placebo group. In discordance with the JAVELIN trial however, the level of PD-L1 expression was not found to be predictive of response to treatment for overall survival or progression-free survival [38].

The vast majority of patients enrolled in the aforementioned studies had predominantly pleural mesothelioma and little is known to date about the efficacy of PD-L1 inhibitors in MPM patients. It appears that the proportion of MPM tumors expressing PD-L1 is higher than pleural mesothelioma and is associated with more aggressive tumor biology[39,40 41]. If PD-L1 expression is in fact related to tumor response and biologic agents prove to be efficacious in MPM patients, this may result in a shift away from traditional chemotherapy [42].

Due to the better understanding of the biology of MPM, there has been an increase in studies focusing on MPM patients specifically. A 2021 cohort study conducted at MD Anderson, demonstrated encouraging clinical activity of dual inhibition with nivolumab plus ipilimumab or single immune checkpoint inhibition in patients with advanced MPM. The objective response rate was 19% and the median progression free survival was 5.5 months. Prior chemotherapy did not affect disease response rates and the safety profile for the drugs was non-inferior to standard chemotherapy treatment[40]. A phase 2 study of atezolizumab in combination of bevacizumab in patients with MPM previously treated with chemotherapy showed an objective response rate of 40%. The response rates were durable, progression-free survival was found to be 61% and overall survival was 85% [43].

The investigation into immune checkpoint blockades continues, as there are several ongoing phase II trials investigating nivolumab, ipilimumab, atelizumab and other biologics in patients with MPM[44-46]. In addition, there is an ongoing phase II clinical trial, the MESOPEC trial, which is investigating adjuvant dendritic cell-based immunotherapy in patients with MPM who have undergone a cytoreductive operation with hyperthermic intraperitoneal chemotherapy[47]. Dendritic cell therapy in other types of malignancies has been well-documented, however recently a murine model demonstrated a significant survival benefit in mice with peritoneal mesothelioma injected with dendritic cell therapy, providing a strong basis for the MESOPEC trial question[48].

Further clinical studies evaluating the role of checkpoint blockade as neoadjuvant therapy prior to surgical cytoreduction or as prophylactic therapy in high-risk patients after surgical cytoreduction are a high clinical priority.

Conclusion

Malignant peritoneal mesothelioma is a rare primary cancer of the serosa of the peritoneum, the diagnosis of which is often difficult due to the varied presentation. The first line approach for malignant peritoneal mesothelioma over the last 30 years has been surgical treatment with regional intra-peritoneal chemotherapy, as this regimen significantly prolongs survival. However, recently, several studies have demonstrated the potential use of immune checkpoint inhibitors, either alone or in combination with traditional chemotherapy, in MPM. Specifically, inhibition of PD-L1 is of interest, as peritoneal mesothelioma tumors tend to have high PD-L1 expression. The specific role of immune checkpoint blockade agents, as neoadjuvant or post-operative therapy, is yet to be established and further research is necessary to elucidate the utility of such agents.

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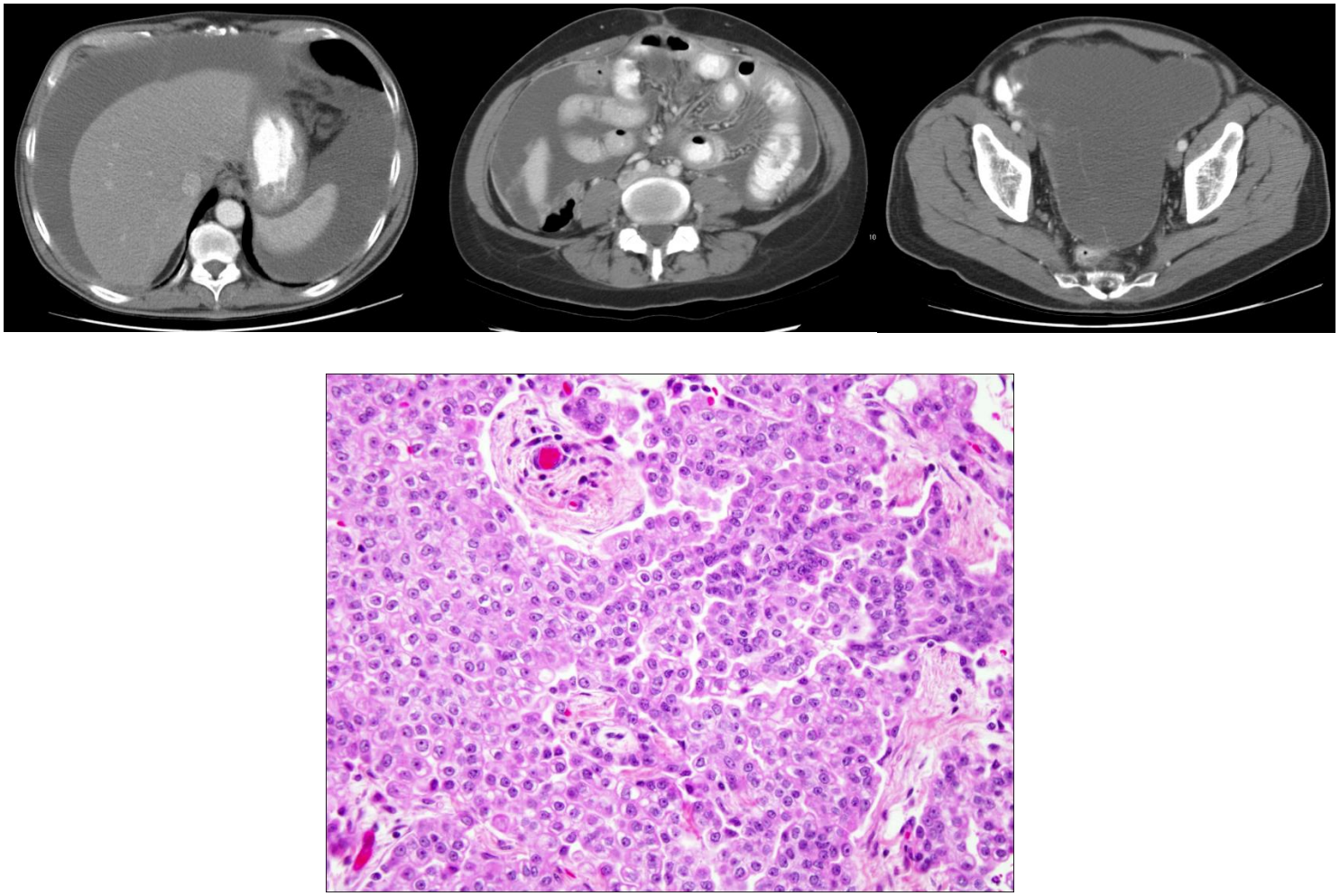

Figure 1.

Figure 1. Computed tomography scan of a patient with MPM manifested primarily by ascites (top panels). The patient had a complete cytoreduction and the final histology showed typical features of epithelioid MPM (bottom panel) on hematoxylin and eosin staining (400x).

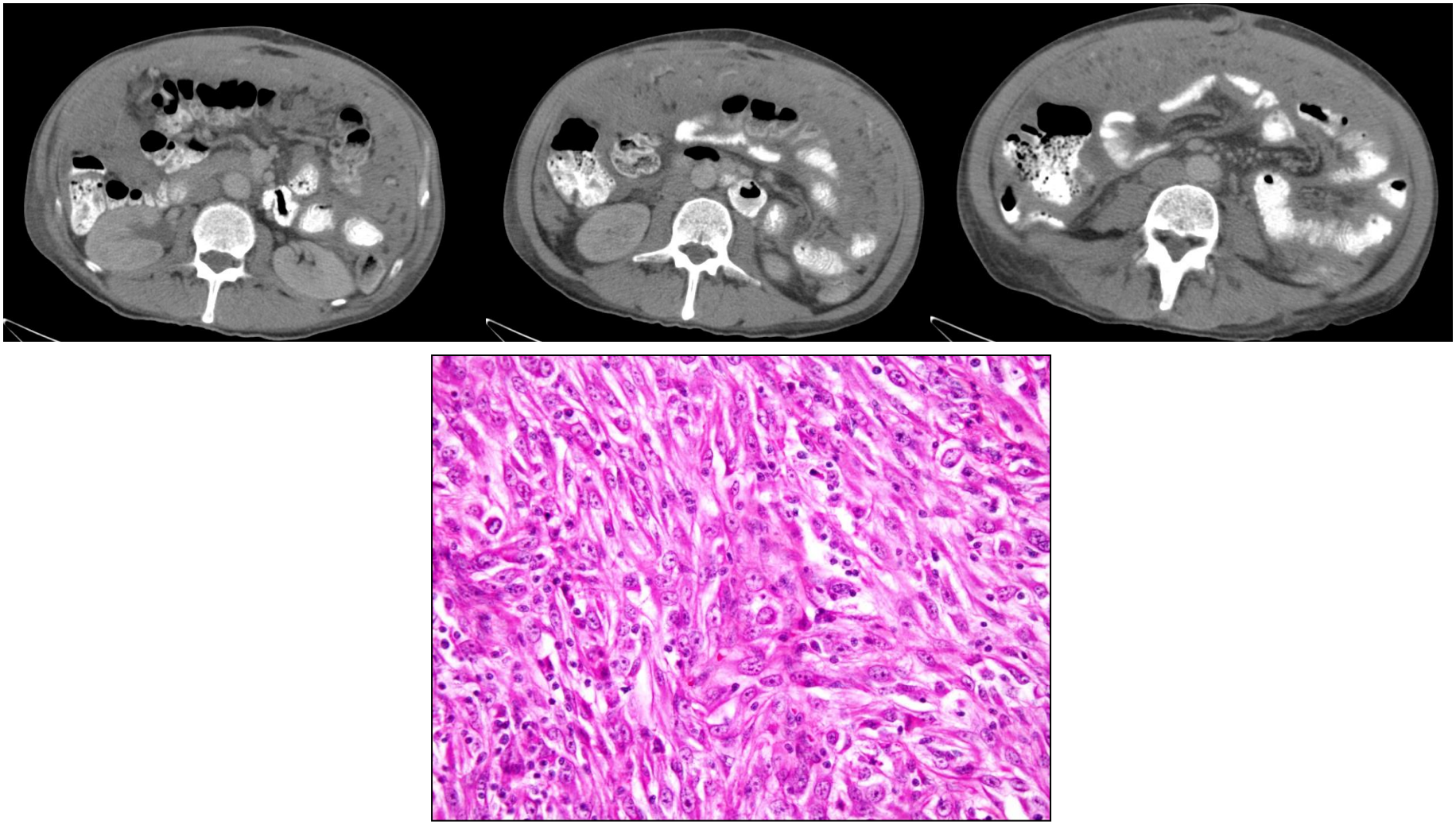

Figure 2.

Figure 2. Computed tomography scan of a patient with MPM manifested by a solid and more infiltrative pattern (top panels). The patient had unresectable disease and incisional biopsy show typical features of sarcomatoid MPM with spindle shaped cells and nuclear atypia on hematoxylin and eosins staining (400x).

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