International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: http://www.tandfonline.com/loi/ihyt20

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To cite this article: Kiran K. Turaga, Marcello Deraco & H. Richard Alexander (2017) Current management strategies for peritoneal mesothelioma, International Journal of Hyperthermia, 33:5, 579-581, DOI: 10.1080/02656736.2017.1320591

To link to this article: http://dx.doi.org/10.1080/02656736.2017.1320591

Published online: 30 Jun 2017.

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INTERNATIONAL JOURNAL OF HYPERTHERMIA, 2017
VOL. 33, NO. 5, 579–581
https://doi.org/10.1080/02656736.2017.1320591

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Current management strategies for peritoneal mesothelioma

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ABSTRACT

Mesothelioma of the peritoneum is a distinct entity that requires multidisciplinary care to improve oncological outcomes. In this article, we review the current management strategies discussed at the PSOGI meeting in Washington DC 2016 and provide evidence based recommendations for diagnosis and management of this disease.

ARTICLE HISTORY
Received 16 March 2017
Revised 14 April 2017
Accepted 14 April 2017
Published online 6 June 2017

KEYWORDS
Mesothelioma; HIPEC; peritoneal

Mesothelioma of the peritoneum is a distinct entity from mesothelioma of the pleura in its etiopathogenesis and pathophysiology. While relatively infrequent with an estimated incidence of 500–800 new cases per year in the United States, it can be debilitating for patients due to development of bowel obstructions, inanition and death [1]. At the recent peritoneal surface oncology group international (PSOGI) meeting held in Washington D.C. 2016, a roundtable was held and this article summarises some of the strategies in the management of peritoneal mesothelioma.

Recommendation 1

- Antecedent exposure factors including asbestos exposure, previous radiation and smoking should be ascertained in addition to a thorough history.
- BAP-1 germline testing should be considered for families with clustering of disease.

Causative factors for peritoneal mesothelioma remain elusive although the effects on asbestos exposure in causation of this disease has been established previously. Increasing asbestos exposure has been linked to higher rates of peritoneal mesothelioma (2.2 fold increased risk per kg per year) [2]. However, not all patients with peritoneal mesothelioma report an antecedent history of exposure. In addition, detection of asbestos fibres in the peritoneal cavity is not always consistent with electron microscopy.

Genetic association of peritoneal mesothelioma with BRCA-1 associated protein (BAP-1) has been suggested in small studies [3]. While deletions of BAP-1 region are found in several peritoneal mesothelioma tissue samples, these are not always germ-line mutations. Potentiation of the carcinogenic effect of asbestos has been suggested in families with germline BAP-1 deletions and may play a role in the etiopathogenesis of this disease.

Recommendation 2

- Histological diagnosis of a peritoneal mesothelioma must be reviewed by an expert pathologist.
- Synoptic reporting on histological subtype (well differentiated papillary, multicystic, epithelioid, biphasic and sarcomatoid), invasiveness (necrosis, Ki-67, mitotic rate) and nodal status (if available) is recommended.

The diagnosis of peritoneal mesothelioma is often made incidentally during abdominal operations in patients with indolent disease. Patients with aggressive variants can present with ascites, bowel obstructions, inguinal masses and cancer cachexia. While cross sectional imaging such as CT scans and MRIs can suggest the presence of peritoneal mesothelioma, establishing a diagnosis based on imaging alone is difficult.

Pathological examination of a mesothelioma is essential for diagnosis and characterisation. Laparoscopic or percutaneous biopsy provides adequate tissue in most cases. Immunohistochemistry is essential to confirm diagnosis. Histological differentiation into papillary, multicystic (benign variants) and epithelioid, biphasic and sarcomatoid is critical for decision making. Synoptic reporting including necrosis, grade and mitotic count can also help with prognostication. Ki-67 has been shown to be a prognostic marker for outcomes for patients undergoing surgery and may be considered [4,5].

Recommendation 3

- Serum tumour markers such as CA-125, CA-19-9, CA 15.3, fibulin-3 and Mesothelin may be obtained to detect disease and therapy course.

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Tumour markers such as fibulin and mesothelin have been shown to incredibly specific for mesothelioma although its relevance in clinical practice is still unknown [6,7]. Variable elevations of the protein biomarkers have been reported in many studies.

Recommendation 4

- High quality cross sectional imaging modalities such as multi-slice CT scan, and/or diffusion weighted MRI must be obtained to assess burden of disease.

Cross sectional imaging provides valuable information about distribution of disease, presence of bicavitary disease, nodal metastases and negative prognostic factors such as mesenteric foreshortening and peri-portal disease. Interpretation of such images must occur in conjunction with the peritoneal surgeon in order to assess accurately the burden of disease. While several patients have a "wet" phenotype, and this may make assessment of disease burden difficult, this may not preclude patients from receiving cytoreductive surgery.

The use of PET scan in detecting nodal disease has been described but is not routinely indicated [8].

Recommendation 5

- All patient with peritoneal mesothelioma must be evaluated at a peritoneal malignancy specialty centre with access to peritoneal surgeons experienced in the techniques of cytoreductive surgery and medical oncologists with access to clinical trials.

High volume centres have been shown to reduce peri-operative mortality and morbidity and considering the steep learning curve in the performance of cytoreductive surgeries and HIPEC, we strongly recommend evaluation by an experienced centre [9].

Recommendation 6

- Patients with malignant epithelioid mesothelioma that are resectable should be offered cytoreductive surgery and HIPEC.

The effectiveness of cytoreductive surgery and HIPEC has been demonstrated previously in patients with malignant epithelioid mesothelioma with a median survival of 40–90 months [10,11]. Principles of surgery include peritonectomy procedures to complete visible cytoreduction although the controversy between selective parietal peritonectomy vs. complete parietal peritonectomy have not been resolved. Visceral preservation is preferred unless absolutely necessary to complete cytoreduction. Sampling of retroperitoneal lymph-nodes should be done systematically. Burden of peritoneal disease must be documented using one of the validated peritoneal staging scoring systems such as the PCI score. Completeness of cytoreduction (CC) must be documented by the CC or the R-score [12]. The objective of maximal surgical effort, known as optimal cytoreduction, is defined as CC-0 or CC-1, which means residual disease measuring less than 2.5 mm.

HIPEC with platinum based agents such as cisplatin, and carboplatin either alone or in combination with doxorubicin, pemetrexed, ifosfoamide and mitomycin have been used [13]. Single agent mitomycin has also been used with similar efficacy although slightly inferior survival outcomes. Normothermic intraperitoneal chemotherapy with pemetrexed and other agents have also been considered demonstrating significantly improved survival in patients [14]. HIPEC has been independently correlated with improved survival even in the setting of an incomplete cytoreduction, and to control malignant ascites [15].

Recommendation 7

Patients with well differentiated papillary and multicystic mesothelioma may be offered observation, cytoreduction only, or cytoreduction with HIPEC depending on disease course.

The disease biology of both these histologies is considered relatively indolent and can generally be safely observed unless the disease course, imaging characteristics or symptoms of a patient suggest otherwise [16]. The incremental benefit of HIPEC in this setting is unknown.

Recommendation 8

Patients with biphasic, sarcomatoid or unresectable disease may be considered for systemic chemotherapy, clinical trials or cytoreductive surgery and HIPEC after a careful multidisciplinary fashion.

Patients with biphasic and sarcomatoid histology perform rather poorly with surgery although a small subset of patients benefit from cytoreductive surgery and HIPEC as well [15]. Such patients are best served in clinical trials with novel agents. The association of high Ki67 and high PCI defined a subset of patients with unsatisfactory results after CRS HIPEC [4]. In patients with unresectable disease, the use of systemic therapy with a neoadjuvant intent has not been shown to improve survival but anecdotally has been shown to lead to clinical responses that might then lead to a more complete cytoreduction [17]. While such a strategy has been used often in practice, evidence supporting the same needs to be accrued.

Recommendation 9

- The effectiveness of adjuvant chemotherapy for patients with malignant peritoneal mesothelioma is currently unknown and may be used after careful multidisciplinary consideration.

While the overall response rates of systemic chemotherapy for malignant epithelioid mesothelioma are around 20%, the use of therapy in the adjuvant setting is extrapolated from pleural mesothelioma data [18]. Agents used in this setting can include pemetrexed, carboplatin, cisplatin and bevacizumab. Duration, frequency and end points are ill defined in published data. Recently reported long-term adjuvant

combined intraperitoneal and systemic chemotherapy has shown promise at a single institution [14].

Recommendation 10

- All patients with peritoneal mesothelioma must be considered for inclusion in clinical trials, registries or both.

Given the infrequency of disease, it is imperative for oncologists treating patients with mesothelioma to ensure participation of patients with peritoneal mesothelioma in clinical trials. Novel agents such as anti-mesothelin antibody (anetumumab), anti PDL-1 (pembrozilumab), CAR T cells, Listeria based immunotherapy construct among others are currently ongoing and might offer survival benefit to patients with this disease. In addition, registry efforts including those of the peritoneal surface group international (PSOGI), are suitable venues for pooled analysis of data and for outcomes based research, including patient reported outcomes.

In summary, we recommend multidisciplinary management for patients with peritoneal mesotheliomas that may offer such patients improved oncological and patient reported outcomes.

Disclosure statement

Dr. Kiran Turaga has received honoraria from CARIS Biosciences and CASTLE Biosciences.

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