Hyperthermic intrathoracic chemotherapy (HITHOC) should be included in the guidelines for malignant pleural mesothelioma

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While reading the last guidelines of the task force of the ERS/EACTS/ESTS/ESCRO on treatment of malignant pleural mesothelioma (MPM) (1) we noted that hyperthermic intrathoracic chemotherapy (HITHOC) as adjunct to surgery in MPM has not been even discussed or cited. Being curious about what the other guidelines suggest we read also the guidelines published by other Societies (2-4), and surprisingly even those guidelines do not report about the use of HITHOC as adjuvant treatment. However, although not clearly reported, the ASCO guidelines (3) cite at least 3 papers reporting experience on HITHOC for MPM that have been included in the references list (ref. 61, 118, 171 of the ASCO guidelines 2018).

To prolong survival, one of primary aims in mesothelioma surgical treatment is to improve the local tumor control within a multimodality treatment protocol after surgery such as lung-sparing extended pleurectomy/decortication (P/D) (3-5). Since P/D, known often as surgical cytoreduction, is not expected to achieve an R0 resection, multimodality therapy should always be administered after surgery, and HITHOC is just another type of adjuvant local treatment but performed in the operating room immediately after surgery. Therefore, to improve local tumour control additional local therapy could be useful, and for which reason the effects of intracavitary chemotherapy are now under investigations since the last years (6).

HITHOC is a high concentrated dose of chemotherapy (usually cisplatin) infused in 3-4 liters of normal saline solution (according to the chest size), warmed at 38–43°, introduced and circulated in the chest for 60 minutes after the surgical pleurectomy/decortication, but also after extrapleural pneumonectomy (8-14) (Table 1). The HITHOC acts with a double action: chemotherapeutic drug has a local and direct effect on the tumor cells while hyperthermia enhances the impact of chemotherapy by increasing its penetration into the tissue (14). Furthermore, although many experiences and studies have been reported to date, there is no standardized protocol for HITHOC (15).

HITHOC shows promising value after many studies, such as prospective phase I-II trials and robust retrospective series on MPM patients, which have shown good quality of life and prolonged survival up to 35 months median survival without increasing morbidity or mortality (5).

Although guidelines are written after a rigorous systemic review of the literature and based mainly on randomized phase II or III clinical trials, guidelines have demonstrated that most treatments for mesothelioma are “weak”, and therefore it sounds unclear why the results of systematic review and metanalysis (6,7) and the published data obtained with surgery and HITHOC as shown in evidence Table 1, should not be included or at least cited in the guidelines. Moreover, the absence of HITHOC in the guidelines could create confusion to our patients as they could erroneously think that the procedure is still experimental, while the reality says that HITHOC is at least 20 years old but it is only less used. Nonetheless, the procedure is still viewed...
with some suspicion based mainly by discrepancies in the methods and significant toxicities such as acute renal injury that have been only rarely reported by HITHOC (18).

As uncertainty still exists in the treatment of MPM, it is evident that the gold standard treatment remains a moon shot, and for this reason new ideas, and innovations based on a strong scientific background should be always welcomed. Academic centers should take responsibility on a global scale to perform more pilot studies (19), and multicenter large randomized controlled trials (20) to confirm or perform new treatments.

Writers of future guidelines on MPM should therefore be encouraged to discuss and/or include HITHOC as a type of “adjuvant” treatment to be considered after debulking surgery for MPM.

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**Table 1** Evidence table showing results of surgical procedures associated with HITHOC for malignant pleural mesothelioma

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Surgical procedure associated with HITHOC</th>
<th>No. pts.</th>
<th>Survival median/mean - months</th>
<th>Clinical message</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Bree E et al. 2002</td>
<td>EPP n=4; Debulking n=4</td>
<td>8</td>
<td>9 out 11 alive mean follow-up 7.4 m</td>
<td>Feasible in early stage MPM with acceptable morbidity rates. Phase II study will be conducted.</td>
</tr>
<tr>
<td>Sugarbaker et al. 2013</td>
<td>EPP 74%; pleurectomy decortication 26%</td>
<td>72</td>
<td>Overall survival 35.3 vs. 22.8 months</td>
<td>A favorable outcome and minimal incremental morbidity support the incorporation of hyperthermic intraoperative cisplatin chemotherapy into multimodality treatment strategies for patients with low-risk epithelial malignant pleural mesothelioma.</td>
</tr>
<tr>
<td>Ried et al. 2013</td>
<td>Pleurectomy/decortication</td>
<td>8</td>
<td>Median survival 18 months</td>
<td>Early clinical results may encourage the use of this surgical option to provide better local tumour control in a multimodality treatment setting.</td>
</tr>
<tr>
<td>Migliore et al. 2015–2020°</td>
<td>VATS pleurectomy decortication</td>
<td>19</td>
<td>Median survival 27 months</td>
<td>Pleurectomy/decortication and HITHOC are a good therapeutic option in the multimodality treatment of MPM. A randomized controlled trial is necessary.</td>
</tr>
<tr>
<td>Burt et al. 2018</td>
<td>EPP n=59; PD n=41</td>
<td>104</td>
<td>Median survival 20.3 months</td>
<td>Heated intraoperative chemotherapy can be administered safely and feasibly in the context of complete surgical resection of malignant pleural mesothelioma.</td>
</tr>
<tr>
<td>Ambrogi et al. 2018</td>
<td>Lung–diaphragm–pericardium-sparing pleurectomy</td>
<td>49</td>
<td>Median survival 22 months</td>
<td>Feasible and safe, with no mortality and low morbidity. Preserving lung and diaphragmatic function might warrant an acceptable long-term outcome.</td>
</tr>
<tr>
<td>Klotz et al. 2019</td>
<td>Pleurectomy decortication</td>
<td>61</td>
<td>Median survival 42.2 months in the P/D group vs. 22.4 months for EPP alone</td>
<td>P/D and HITHOC appears safe in mesothelioma patients with increased overall survival compared to EPP within a trimodal treatment approach.</td>
</tr>
</tbody>
</table>

°, in the present manuscript the number of operated patients in Catania has been updated from 6 in 2015 to 2019.
Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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