Does Hyperthermic Intrathoracic Chemotherapy Prolong Survival in Patients with Pleural Thymoma? – A Systematic Review of the Literature

Alecsandra A. Tudor, Ralph A. Schmid and Gregor J. Kocher*
Division of General Thoracic Surgery, Bern University Hospital, University of Bern, Switzerland

ARTICLE INFO
Article history:
Received: 11 October 2017
Accepted: 16 January 2018
Published: 31 January 2018

Keywords:
Thymoma;
Advanced;
HITHOC;
Hyperthermic;
Chemoperfusion;
Thermochemotherapy

Copyright: © 2018 Kocher GJ et al., Lung Pulm Respir Res J
This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.


ABSTRACT

Introduction: Thymoma with pleural spread, whether de novo or in form of pleural relapse after surgical resection, is a difficult to treat disease. Hyperthermic intrathoracic chemotherapy (HITHOC) has recently been increasingly discussed as a possible beneficial adjunct to cytoreductive surgery with the aim of reducing pleural recurrence and prolonging survival in these patients.

Methods: We searched the PubMed interface in order to present a comprehensive review on the topic.

Results: More than 1600 papers were found using the reported search, of which 7 presented the best evidence to answer the clinical question whether HITHOC in combination with surgery might prolong survival in patients with pleural thymoma. Most patients included in these 7 studies were younger than 65 years, had only minor or no comorbidities and presented in good general condition. With these premises, surgical resection (both radical pleurectomy and extrapleuralpleuropneumonectomy) combined with HITHOC seemed to have the potential to improve survival, as well as recurrence free interval compared to an approach without HITHOC. Furthermore, despite the addition of HITHOC, only minimal postoperative mortality and morbidity were reported.

Conclusion: All the relevant papers on this topic are only small descriptive cohort studies, nevertheless HITHOC seems to have the potential to prolong recurrence free interval in a multimodality approach of Masaoka-Koga Stage IVthymoma, compared to surgical resection alone.

Introduction
Stage Masaoka-Koga IV athymoma with pleural spread is a therapeutical dilemma, and yet there is no consensus on a standard of treatment. The combination of HITHOC and cytoreductive surgery used in a curative intent has gained more attention in the treatment of thymoma with pleural seedings (relapse as well as de novo) in recent years. Yet the scarcity of this condition, and subsequently also of the abovementioned treatment options creates a major hurdle when deciding whether or not to use such multimodality approach.
In this review we intend to summarise the results of all papers reporting on the experience with HITHOC in the treatment of thymoma with the aim of helping clinicians to better understand this therapeutic option when deciding which strategy to choose for their patients. It has to be noted that there are no results from any comparative studies available to date, all reviewed papers are small descriptive cohort studies.

Methods

We systematically searched the PubMed database from 1950 until October 2017 using the keywords “thymoma”, “HITHOC”, “chemoperfusion”, “thermochemotherapy”, “hyperthermic chemotherapy” and “intrathoracic” and compiled all the relevant papers in form of a comprehensive review.

Results

More than 1600 papers were found using the reported search. From these, 7 papers were identified to correspond with all of the criteria, i.e. pleural spread of thymoma and association of cytoreductive surgery with HITHOC in a curative intent. A summary of these selected papers can be found in table 1. Two additional papers were chosen as a comparison reference for the surgery-only treatment.

Ambrogi et al. [1] retrospectively analysed 13 cases with pleural relapse, to primarily assess the safety of HITHOC, and secondarily, to observe the oncological outcomes. They observed no postoperative mortality, and a 38% morbidity rate (5 patients) with moderate complications such as persistent air leak, persistent bleeding and ipsilateral an hydrosis. Intra operatively no technical problems were noted. The mean survival was 58 months with a mean follow-up of 64.6 months and a median recurrence-free interval of 64 months. Notably, none of the patients had any severe comorbidities and the mean age of the included patient population was only 46 years.

A prospective study by Ried et al. [2] comprising 11 patients, 8 with pleural relapse and 3 with primary Masaoka stage IV a thymoma who all underwent radical resection combined with HITHOC, yielded a 82% survival rate after a mean follow-up of 23 months. Relapse was noted in 3 patients, with no mentioning of the exact disease-free interval. In 2 cases a re-intervention was necessary due to surgical complications (chylotorax and hemothorax) including one patient that also needed haemodialysis for acute kidney failure. No postoperative mortality was noted. The authors concluded that HITHOC does not add substantial risk to the surgical outcome compared to surgery alone, and patients had a good quality of life during the follow-up.

A feasibility study was published in 2002 by de Bree et al [3], in which 3 patients with Masaoka stage IVa and 11 patients with malignant pleural mesothelioma underwent radical resection accompanied by HITHOC. All patient survived during a mean follow-up of 18 months, however 2 of the thymoma patients developed recurrence, 1 presented nephrotoxicity and 1 wound dehiscence. Due to the small number of patients this study is however inconclusive.

Rafaely et al [4] studied the early and midterm results of an aggressive surgical therapy coupled with HITHOC in 10 patients with thymoma with pleural relapse. After a mean follow-up of 37.5 months, 8 patients were alive and one patient presented suspicion for contralateral recurrence. 40% early, and 20% late postoperative morbidity was reported. Technically, the HITHOC procedure was unproblematic. Noteworthy is that the resection type varied between cases (1 patient received an extrapleural pneumonectomy while 4 others underwent radical pleurectomy and 5 patients received only tumor resection).

Yellin et al [5] compared the long term outcomes of lung sparing surgery and HITHOC in a population of 31 patients presenting with stage IVA thymoma, de novo as well as pleural relapse. The median follow-up was 62 months and the median survival was 184 months (de novo) and 140 months (relapse), respectively. Five-year overall survival rates were 81% for de novo and 67% for relapse, respectively. The 5-year recurrence-free intervals of 68% (de novo) and 48% (relapse) were improved corresponding to the extent of resection (p<0.001). No toxicity related to HITHOC was recorded and morbidity for minor and major complications was
12% each. All the patients recruited for the study had no major comorbidities.

A second study by Ried et al [6] analysed the effects of radical resection combined with HITHOC in patients with de novo thymoma.

### Table 1: Best Evidence Papers.

<table>
<thead>
<tr>
<th>Author, date and country, Study type (level of Evidence)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrogi et al, 2016 Eur J CardiothoracSurg [1] Retrospective (level 3 evidence)</td>
<td>13 patients with pleural relapse; EPP and HITHOC</td>
<td>Survival (months)</td>
<td>Mean 58, Median 64</td>
<td>Limitations include small sample size and relapse heterogeneity (patients present 1-10 pleural foci), also, no details were given as to why this surgical procedure was chosen. Mean follow-up period 64.6 months.</td>
</tr>
<tr>
<td>Ried et al, 2013 ZentralblChir [2] Prospective cohort study</td>
<td>11 patients with primary Masaoka stage IVA or pleural relapse; radical pleurectomy and HITHOC</td>
<td>Survival (months)</td>
<td>Median 27</td>
<td>No specifications as to why this surgical procedure was chosen. Mean follow-up 27 months.</td>
</tr>
<tr>
<td>De Bree et al, 2002 Chest [3]* Prospective cohortstudy</td>
<td>3 patients: 2 with Masaoka IVA and 1 with IVbthymoma; cytoreductive surgery and HITHOC</td>
<td>Survival (months)</td>
<td>Complete during follow-up (mean/median 18, range 5-31)</td>
<td>Extremely limited number of patients warrants no conclusion. The surgical procedure is not described. Mean follow-up 18 months.</td>
</tr>
<tr>
<td>Rafaely et al, 2001 Ann Thorac Surg. [4] Retrospective cohort study</td>
<td>10 patients with MasaokaIVathymoma ; cytoreductive surgery and HITHOC</td>
<td>Survival (months)</td>
<td>80% during follow-up (median 34 months)</td>
<td>Limitations include small sample size and the different resection strategies (4 tumor resections with and 5 without pleurectomy;1 EPP), without specifying why. Mean follow-up 37.5 months.</td>
</tr>
<tr>
<td>Yellin et al, 2013 J ThoracCardiovascSurg. [5] Retrospective cohort study</td>
<td>31 patients; cytoreductive surgery and HITHOC</td>
<td>Overall survival 5-years</td>
<td>Masaoka IVA 80%</td>
<td>The extent of resection (R0 vs. R1) predicted disease-free survival (p&lt;.001). Surgical procedure not specified. Mean follow-up 62 months.</td>
</tr>
<tr>
<td>Ried et al, 2014 ThoracCardiovasc Surg. [6] Retrospective cohort study</td>
<td>9 patients with MasaokaIva; radical pleurectomy and HITHOC</td>
<td>Overall survival</td>
<td>Median 20 months; 89% (without signs of relapse)</td>
<td>Locoregional recurrence is the most common cause of death in this patient group. Mean follow-up period 29.3 months. Mean Age was 55 years.</td>
</tr>
<tr>
<td>Yu et al, 2013 OncoTargets and Therapy [7] Retrospective cohort study</td>
<td>4 patients with MasaokaIva; cytoreductive surgery and HITHOC</td>
<td>Perioperative mortality 4-year survival</td>
<td>0%</td>
<td>Very small patient group and no exact information about surgical procedure. Mean follow-up 2.25 years.</td>
</tr>
</tbody>
</table>

EPP: Extrapleural pleuropneumonectomy; HITHOC: Hyperthermic Intrathoracic Chemotherapy
Out of 22 patients, 9 received a pleurectomy combined with HITHOC in Masaoka-Koaga stage IVa, the remaining patients had stage III disease. However, the paper does not stratify the patient groups, such that the cited outcomes cannot be traced back to these 9 patients. The only clear result is that locoregional recurrence accounts for most cases of death in this patient group.

Yu et al [7] report 4 cases of pleural thymoma spread, 2 de novo and 2 recurrences, where HITHOC was used after cytoreductive surgery (exact details on the type of resection are not mentioned). Mean patient age was 59 years and no details are given about comorbidities. The sole complication cited is 1 case of pneumonia, where the patient died 1 year postoperatively (no further specifications are given). The case series however has no statistical significance with such a small number of patients and only a vague characterization of their treatment and outcome.

Discussion

All cited studies present a relatively small number of patients and none compare the proposed therapy, i.e. cytoreductive surgery combined with HITHOC directly with other options, such as surgery, chemotherapy, radiotherapy, alone, or in other combinations. Also the differences in tumor characteristics are considerable, making it difficult to come to a solid conclusion. With regard to the perfusion protocol, the procedures are comparable in all papers (Table 2), but the surgical therapy varies widely. Only Yellin et al. [5] changed their chemoperfusion protocol during their study period in that way, that they added doxorubicin to the regimen after 2002, however due to the small number of treated patients no conclusion can be made whether the addition of doxorubicin had a beneficial effect or not.

Most authors agree that this therapeutic approach has no, or few perioperative complications in their population of relatively young and otherwise healthy patients, it does not pose a technical challenge and the recurrence free interval (see also table 1) may be higher than in regimens not including HITHOC. One last key aspect is the limited length of the follow-up period, which in only 2 of the selected papers exceeds 5 years, therefore no clear statement about long-term survival benefits can be made.

Overall the most significant study on surgery and HITHOC for thymoma with pleural spread was definitely published by Yellin et al. [5], comprising the largest cohort of patients (n=31). When comparing their 5-year survival rates of 80% for de novo pleural disease, the results are however similar to those described by the two largest studies investigating surgery w/o chemotherapy and w/o radiotherapy (no HITHOC), reporting 5-year survival rates ranging between 83.5% [8] and 87.2% [9].

Clearly worldwide randomized controlled multicentre studies are needed to answer the question which

### Table 2: HITHOC protocols used.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Drug dosage</th>
<th>Temperature and perfusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrogi et al, 2016 Eur J CardiothoracSurg [1]</td>
<td>Cisplatin (80 mg/m²) and Doxorubicin (25 mg/m²).</td>
<td>42.5°C for 60 min</td>
</tr>
<tr>
<td>Ried et al, 2013 Zentralbl Chir [2]</td>
<td>Cisplatin (100 mg/m²) n = 7; 150 mg/m² n = 4</td>
<td>42°C for 60 min</td>
</tr>
<tr>
<td>De Bree et al, 2002 Chest [3]</td>
<td>Adriamycin (15 to 25 mg/m²) and Cisplatin (80 mg/m²; 50 mg/m² in one case)</td>
<td>40.9-42.5°C for 90 min</td>
</tr>
<tr>
<td>Rafaely et al, 2001 Ann Thorac Surg. [4]</td>
<td>Cisplatin (100 mg/m²)</td>
<td>40.3-43°C for 60 min</td>
</tr>
<tr>
<td>De Bree et al, 2002 Chest [3]</td>
<td>Cisplatin (100 mg/m²) and Doxorubicin* (50-60 mg total)</td>
<td>45°C for 60 min</td>
</tr>
<tr>
<td>Yu et al, 2013 Oncotargets and Therapy [7]</td>
<td>Cisplatin (100-150 mg/m²)</td>
<td>42°C for 60 min</td>
</tr>
<tr>
<td>Ried et al, 2014 Thorac Cardiovasc Surg. [6]</td>
<td>Cisplatin (100 mg/m²)</td>
<td>43.4-44°C for 120 min</td>
</tr>
</tbody>
</table>

*In patients treated since 2002 Doxorubicin was added to the regimen

Treatment is best for patients with pleural thymoma disease.

References


