Open Journal of Surgery

Review Article

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

***Address for Correspondence:** Gregor J Kocher, Division of General Thoracic Surgery, University Hospital Bern, CH – 3010 Bern, Switzerland, Tel: +413-163-223-30; Fax +413-163-223-27; E-mail: gregor.kocher@insel.ch

Submitted: 16 February 2018; **Approved:** 13 March 2018; **Published:** 15 March 2018

Cite this article: Tudor AA, Schmid RA, Kocher GJ. Does Hyperthermic Intrathoracic Chemotherapy Prolong Survival in Patients with Pleural Thymoma? - a Systematic Review of the Literature. Open J Surg. 2018;2(1): 001-004.

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 extrapleural pleuropneumonectomy) 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 IVa thymoma, compared to surgical resection alone.

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

INTRODUCTION

Stage Masaoka-Koga IVa thymoma 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 a 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 complied 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 [8,9].

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 anhydrosis. Intraoperatively 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 IVa 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 (chylothorax 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. 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

Table 1: Best Evidence Papers.

Author, date and country, Study type (level of Evidence	1. Patient group	Outcomes	Key results	Comments
Ambrogi MC, Korasidis S, Lucchi M, Fanucchi O, Giarratana S, Melfi F, et al. 2016; Eur J Cardiothorac Surg. [1] Retrospective (level 3 evidence)	13 patients with pleural relapse; EPP and HITHOsC	Survival (months)	Mean 58, Median 64	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.
		Recurrence free interval (months)	Median 64 months	
		morbidity	5 cases (38%) (2 haemorrhage, 1 nerve damage, 1 persistent air leak, 1 anaemia)	
		Mortality	None postoperatively	
Ried M, Neu R, Schalke B, Sziklavari Z, Hofmann HS. 2013; Zentralbl Chir. [2] Prospective cohort study	11 patients with primary Masaoka stage IVa or pleural relapse; radical pleurectomy and HITHOC	Survival (months	Median 27	No specifications as to why this surgical procedure was chosen. Mean follow-up 27 months.
		Mortalit	None postoperatively	
de Bree E, van Ruth S, Baas P, Rutgers EJ, van Zandwijk N, Witkamp AJ, et al. 2002; Chest. [3]* Prospective cohort study	3 patients: 2 with Masaoka IVa and 1 with IVb thymoma; cytoreductive surgery and HITHOC	Survival (months)	Complete during follow-up (mean/ median 18, range 5-31)	Extremely limited number of patients warrants no conclusion. The surgical procedure is not described. Mean follow-up 18 months.
		Recurrence (months)	2 patients (at 13 and 20)	
		Morbidity	2 cases (1 nephrotoxicity, 1 wound dehiscence)	
Refaely Y, Simansky DA, Paley M, Gottfried M, Yellin A. 2001; Ann Thorac Surg. [4] Retrospective cohort study	10 patients with Masaoka IVa thymoma ; cytoreductive surgery and HITHOC	Survival (months)	80% during follow-up (median 34 months)	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.
		Morbidit	4 early, 2 late complications	
		Mortality	2 cases at 7, 36 months resp.	
		Recurrence	1 case	
Yellin A, Simansky DA, Ben Avi R, Perelman M, Zeitlin N, Refaely Y, et al. 2013; J Thorac Cardiovasc Surg. [5] Retrospective cohort study	31 patients; cytoreductive surgery and HITHOC	Overall survival 5-years 10-years 15-years	Masaoka IVa 80% 72% 58%	Relapse 66% 55% 27%	The extent of resection (R0 vs. R1) predicted disease-free survival ($p < .001$). Surgical procedure not specified. Mean follow-up 62 months.
		Progression-free survival 5-year 10-year	60% 43%	47% 17%	
		90-day mortality	2.5%	
		Morbidity: Major Minor	12% 12%	
Ried M, Potzger T, Sziklavari Z, Diez C, Neu R, Schalke B, et al. 2014; Thorac Cardiovasc Surg. [6] Retrospective cohort study	9 patients with Masaoka IVa; radical pleurectomy and HITHOC	Overall survival	Median 20 months; 89% (without signs of relapse)	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.
		morbidity	no individual data available on HITHOC treated patients	
		Mortality (postoperative)	0%	
Yu L, Jing Y, Ma S, Li F, Zhang YF, 2013; OncoTargets and Therapy. [7] Retrospective cohort study	4 patients with Masaoka IVa; cytoreductive surgery and HITHOC	Perioperative mortality 4-year survival	0% 75%	Very small patient group and no exact information about surgical procedure. Mean follow-up 2.25 years.

EPP: Extrapleural Pleuropneumonectomy; HITHOC: Hyperthermic Intrathoracic Chemotherapy.

Table 2: HITHOC protocols used.

Paper	Drug dosage	Temperature and perfusion time
Ambrogi MC, Korasidis S, Lucchi M, Fanucchi O, Giarratana S, Melfi F, et al. 2016 Eur J Cardiothorac Surg. [1]	Cisplatin (80 mg/m^2) and Doxorubicin (25 mg/m^2).	42.5°C for 60 min
Ried M, Neu R, Schalke B, Sziklavari Z, Hofmann HS. 2013; Zentralbl Chir. [2]	Cisplatin (100 mg/m^2 n = 7; 150 mg/m^2 n = 4)	42°C for 60 min
de Bree E, van Ruth S, Baas P, Rutgers EJ, van Zandwijk N, Witkamp AJ, et al. 2002; Chest. [3]	Adriamycin (15 to 25 mg/m^2) and Cisplatin (80 mg/m^2; 50 mg/m^2 in one case)	40.9-42.5°C for 90 min
Refaely Y, Simansky DA, Paley M, Gottfried M, Yellin A. 2001; Ann Thorac Surg. [4]	Cisplatin (100 mg/m^2)	40.3-43°C for 60 min
Yellin A, Simansky DA, Ben Avi R, Perelman M, Zeitlin N, Refaely Y, et al. 2013; J Thorac Cardiovasc Surg. [5]	Cisplatin (100 mg/m^2) and Doxorubicin* (50-60 mg total)	45°C for 60 min
Ried M, Potzger T, Sziklavari Z, Diez C, Neu R, Schalke B, et al. 2014; Thorac Cardiovasc Surg. [6]	Cisplatin (100-150 mg/m^2)	42°C for 60 min
Yu L, Jing Y, Ma S, Li F, Zhang YF, 2013; OncoTargets and Therapy	Cisplatin (100 mg/m^2)	43-44°C for 120 min

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

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) of all the available series so far. When comparing their 5-year survival rates of 8081% 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% [9] and 87.2% [8]. It has to be noted that multidisciplinary treatments varied significantly between the abovementioned three studies. While Yellin et al. [5] report that neoadjuvant chemotherapy was administered in 42% (13/31) of thymoma patients and adjuvant radiation therapy in 25% (8/31), Moser et al. [8] report administration of neoadjuvant chemo - in 62.6% (67/107) and adjuvant radiotherapy in 59% (63/107) - in 14 of these patients even combined with chemotherapy. Okuda et al. [9] on the other hand did not use any kind of neoadjuvant treatment, but rather adjuvant chemotherapy 31.6% (43/136), adjuvant radiotherapy 45% (61/136) or a combination of both 11.8% (16/136).

However, what all of the aforementioned studies show in common is the fact that survival rates are best in case of macroscopic complete resection.

In summary in can be stated that not only is there limited evidence whether HITCOC in combination with surgery may improve survival in thymoma with pleural spread, but also multimodality treatment regimens vary significantly between all reported studies on the treatment of this disease in the international literature.

Clearly worldwide randomized controlled multicenter studies are needed to answer the question which treatment is best for patients with pleural thymoma disease.

REFERENCES

1. Ambrogi MC, Korasidis S, Lucchi M, Fanucchi O, Giarratana S, Melfi F, et al. Pleural recurrence of thymoma: surgical resection followed by hyperthermic intrathoracic perfusion chemotherapy. Eur J Cardiothorac Surg. 2016; 49: 321-326. https://goo.gl/QU3Pr8
2. Ried M, Neu R, Schalke B, Sziklavari Z, Hofmann HS. Radical pleurectomy and hyperthermic intrathoracic chemotherapy for treatment of thymoma with pleural spread. Zentralbl Chir. 2013; 138: 52-57. https://goo.gl/QBW5oZ
3. de Bree E, van Ruth S, Baas P, Rutgers EJ, van Zandwijk N, Witkamp AJ, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. Chest. 2002; 121: 480-487. https://goo.gl/Vm3jf9
4. Refaely Y, Simansky DA, Paley M, Gottfried M, Yellin A. Resection and perfusion thermochemotherapy: a new approach for the treatment of thymic malignancies with pleural spread. Ann Thorac Surg. 2001; 72: 366-370. https://goo.gl/QYXFKh
5. Yellin A, Simansky DA, Ben Avi R, Perelman M, Zeitlin N, Refaely Y, et al. Resection and heated pleural chemoperfusion in patients with thymic epithelial malignant disease and pleural spread: a single-institution experience. J Thorac Cardiovasc Surg. 2013; 145: 83-87; discussion 87-89. https://goo.gl/TYzmnf
6. Ried M, Potzger T, Sziklavari Z, Diez C, Neu R, Schalke B, et al. Extended surgical resections of advanced thymoma Masaoka stages III and IVa facilitate outcome. Thorac Cardiovasc Surg. 2014; 62: 161-168. https://goo.gl/Sk1uPP
7. Yu L, Jing Y, Ma S, Li F, Zhang YF. Cytoreductive surgery combined with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination. Onco Targets Ther. 2013; 6: 517-521. https://goo.gl/Ugvukd
8. Moser B, Fadel E, Fabre D, Keshavjee S, de Perrot M, Thomas P, et al. Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group Project. Eur J Cardiothorac Surg. 2017; 52: 346-355. https://goo.gl/AmnyK2
10. Okuda K, Yano M, Yoshino I, Okumura M, Higashiyama M, Suzuki K, et al. Thymoma patients with pleural dissemination: nationwide retrospective study of 136 cases in Japan. Ann Thorac Surg. 2014; 97: 1743-1748. https://goo.gl/7kGByy