



# Does cytoreduction surgery and hyperthermic intrathoracic chemotherapy prolong survival in patients with N0–N1 nonsmall cell lung cancer and malignant pleural effusion?

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**Patients with pleural effusion and lung cancer have a poor survival (3–12 months). Debulking surgery and HITHOC shows 62% survival at 1 year and 28.5% at 2 years. Evaluation of this promising novel therapeutic approach in the form of an RCT is mandatory.** <http://bit.ly/2WPbCXS>

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## ABSTRACT

**Introduction:** Debulking surgery and hyperthermic intrathoracic chemotherapy (HITHOC) has been successfully used in the treatment of thoracic tumours. Few authors report on the feasibility of its use in patients with lung cancer and malignant pleural effusion. The aim of this study was to evaluate the efficacy and results of debulking surgery and HITHOC in the treatment of selected patients with nonsmall cell lung cancer (NSCLC) and malignant pleural effusion.

**Methods:** A systematic review was conducted in MEDLINE in accordance with PRISMA guidelines. The word search included: “hyperthermic intrathoracic chemotherapy and/or HITHOC or hyperthermic intrapleural”. Inclusion criteria were only those studies reporting a sufficient amount of data on HITHOC and surgery for lung cancer. Single case reports and review articles were excluded.

**Results:** 20 articles were selected as they related to the topic of HITHOC and lung cancer. Most were from China (n=8) and Japan (n=6). Only four out of the 20 articles had sufficient data for this review. In total, data for 21 patients were collected. Debulking surgery ranged from wedge resection to pneumonectomy and pleurectomy. Mean survival was 27 months and median survival was 18 months (range 1–74 months). 13 patients out of 21 (62%) were alive at 1 year and six (28.5%) were alive at 2 years. 10 patients were still alive at the time of the respective publication in the 21 patients included. Systemic toxicity and treatment-related mortality were nil. There were insufficient data to perform a meta-analysis.

**Conclusion:** Although reported survival in this systematic review is encouraging, available evidence concerning debulking surgery and HITHOC in N0–N1 NSCLC with malignant pleural effusion is weak. Better evidence in the form of a randomised controlled trial is mandatory.

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## Introduction

Although more than 100 years have elapsed since the first reports on lung cancer [1], recent studies confirm that long-term survival in patients with nonsmall cell lung cancer (NSCLC) is still unsatisfactory. This is mainly due to the late diagnosis and dismal survival of inoperable patients with advanced disease, who represent 70–75% of the entire group of lung cancer patients.

Surgery has the main role only in early-stage NSCLC, while nonsurgical treatments are recommended in patients with stage IV. We believe that in order to prolong survival of the entire group of patients affected by NSCLC, great efforts should be made to prolong survival in the inoperable patients.

For this reason, on the basis of our recent experience with cytoreductive surgery and hyperthermic intrathoracic chemotherapy (HITHOC) for mesothelioma and malignant pleural effusion [2, 3], and some recent publications reporting good survival in selected patients with stage IVA lung cancer [4–6], we strongly believe that not all patients with stage IVA (M1a) NSCLC are the same and that longer survival can be obtained in those with disease confined in the hemithorax, and therefore a “new” form of precision (individualised) surgery should be explored as part of a multidisciplinary treatment modality. ZHOU *et al.* [7] performed a meta-analysis on the effect of debulking surgery and HITHOC on malignant pleural effusion for various primary cancers. They showed that patients who received HITHOC had a significantly longer survival. ZHOU *et al.* [7] concluded that HITHOC is safe, effective and increases the survival rate.

We performed a systematic review with the aim to evaluate the efficacy and preliminary results of debulking surgery and HITHOC in the treatment of patients with malignant pleural effusion (M1a) and NSCLC confined in the hemithorax (N0–N1).

## Materials and methods

A systematic review of the literature was conducted in accordance with PRISMA guidelines and the review was registered in the PROSPERO registry of systematic reviews with identifier CRD42018102155. An effort was made to find all publications reporting patients who underwent debulking surgery (pleurectomy, decortications and lung resection), in combination with HITHOC, for advanced stage NSCLC. The search was performed in MEDLINE up to April 30, 2018. As HITHOC is not a common procedure, the key words used in the search were necessarily varied, and included: “hyperthermic intrathoracic chemotherapy and/or HITHOC or hyperthermic intrapleural” in the title and in the abstract.

After screening for duplicates, only articles in English reporting the type of tumour, type of approach, type of resection, survival in months for every single patient and clinical results were included. Unpublished material, congress abstracts and proceedings were not considered. Reviews were also excluded.

The results of the search were screened and reviewed by both of the current authors individually and the results were compared. There were no disagreements between the two authors. Due to the small number of patients and the different outcomes measured, a meta-analysis of the data could not be performed, and therefore this review is limited to the description of the included studies and their results.

## Results

The PRISMA flowchart of the final article selection process is shown in figure 1. In the title, the words “hyperthermic intrapleural” were present in 168 articles, “hyperthermic intrathoracic chemotherapy” in 85 articles and “HITHOC” in 20 articles.

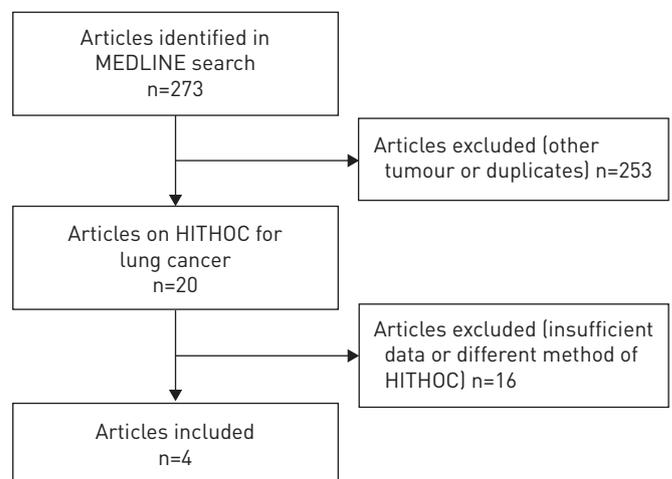


FIGURE 1 PRISMA flowchart of article selection. HITHOC: hyperthermic intrathoracic chemotherapy.

TABLE 1 Evidence table: histopathology, type of surgery and survival data in 21 patients who underwent cytoreductive surgery and hyperthermic intrathoracic chemotherapy (HITHOC)

| Patient number | Year [ref.]           | Sex    | Age years | Type of tumour | Approach          | Type of surgery  | Survival months |
|----------------|-----------------------|--------|-----------|----------------|-------------------|--|-----------------|
| 1              | 2013 [8]              |        |           | Adenocarcinoma | Right thoracotomy | Pleurectomy  | 8 (deceased)    |
| 2              |                       |        |           | Adenocarcinoma | Right thoracotomy | Pleurectomy/decortication  | 1 (deceased)    |
| 3              |                       |        |           | Adenocarcinoma | Right VATS        | Pleurectomy/decortication  | 27 (deceased)   |
| 4              |                       |        |           | Adenocarcinoma | Left thoracotomy  | Pleurectomy/decortication  | 3 (deceased)    |
| 5              |                       |        |           | Adenocarcinoma | Right thoracotomy | Pleurectomy/decortication  | 16 (deceased)   |
| 6              |                       |        |           | Adeno-squamous | Left thoracotomy  | Pleurectomy/decortication  | 30 (alive)      |
| 7              |                       |        |           | Adenocarcinoma | Left thoracotomy  | Pleurectomy/decortication  | 22 (alive)      |
| 8              |                       |        |           | Adenocarcinoma | Right thoracotomy | Wedge upper lobectomy+<br>pleurectomy/decortication                          | 18 (alive)      |
| 9              | 2003 [9]              |        |           | Adenocarcinoma | Left thoracotomy  | Pneumonectomy+pleurectomy  | 18 (alive)      |
| 10             |                       |        |           | Adenocarcinoma | Right thoracotomy | Lower lobectomy+<br>pleurectomy/decortication                                | 8 (alive)       |
| 11             |                       |        |           | Adenocarcinoma | Left thoracotomy  | Pleurectomy/decortication  | 7 (alive)       |
| 12             |                       | Male   | 55        | Adenocarcinoma | Thoracotomy       | HITHOC (first)+<br>panpleuropneumonectomy                                    | 32 (alive)      |
| 13             |                       | Female | 65        | Adenocarcinoma | Thoracotomy       | HITHOC+<br>panpleuropneumonectomy  | 24 (alive)      |
| 14             |                       | Male   | 67        | Adeno-squamous | Thoracotomy       | HITHOC+<br>panpleuropneumonectomy  | 8 (deceased)    |
| 15             |                       | Male   | 50        | Adenocarcinoma | Thoracotomy       | HITHOC+<br>panpleuropneumonectomy  | 18 (alive)      |
| 16             |                       | Female | 55        | Adenocarcinoma | Thoracotomy       | HITHOC+<br>panpleuropneumonectomy  | 12 (alive)      |
| 17             |                       | Male   | 42        | Adenocarcinoma | Thoracotomy       | Pleurectomy  | 74 (deceased)   |
| 18             |                       | Male   | 49        | Adenocarcinoma | Thoracotomy       | Pleurectomy  | 20 (deceased)   |
| 19             |                       | Male   | 65        | Adenocarcinoma | Thoracotomy       | Wedge+pleurectomy  | 6 (deceased)    |
| 20             | 2015 [3] <sup>#</sup> | Female | 53        | Adenocarcinoma | Right VATS        | Wedge upper lobectomy+<br>pleurectomy/decortication                          | 36 (deceased)   |
| 21             |                       | Male   | 54        | Adenocarcinoma | Right thoracotomy | Wedge upper lobectomy+<br>chest wall resection+<br>pleurectomy/decortication | 7 (deceased)    |

VATS: video-assisted thoracoscopic surgery. <sup>#</sup>: our experience updated from [7].

As shown in figure 1, 20 out of 273 articles were selected as they related to the topic of HITHOC and lung cancer: n=8 from China, n=6 from Japan, n=2 from Korea, n=1 from France, n=1 from Italy, n=1 from Israel and n=1 from Turkey. Of these 20 articles, only four articles with a total of 21 patients had sufficient data for this review (table 1) [3, 8–10]. All 21 patients had undergone debulking surgery and HITHOC. Data was available on age and sex in 10 patients: seven males and three females with a mean age of 55.5 years (range 42–67 years). In the case of positron emission tomography (PET)-positive N2 or N3, endobronchial ultrasound (EBUS) and/or video-mediastinoscopy was performed to guarantee that no patient was denied surgery because of a false-positive computed tomography (CT) or PET scan. Debulking surgery ranged from wedge resection to pneumonectomy and pleurectomy. HITHOC was performed in all patients for 1 h.

Mean survival was 27 months and median survival was 18 months (range 1–74 months). 13 out of the 21 patients (62%) were alive at 1 year. Six patients (28.5%) were alive at 2 years. 10 patients were still alive at the time of the respective publication in the 21 patients included (figure 2). Systemic toxicity and treatment-related mortality were nil. There were insufficient data to perform a meta-analysis.

### Discussion

It is known that drug infusion into the pleural cavity leads to direct exposure of tumour cells lining the surface of the pleural cavity. Systemic absorption from the pleural cavity is lower when compared with absorption from the peritoneal cavity during intraperitoneal hyperthermic chemotherapy procedures [11]. The hyperthermia itself has a toxic effect on malignant cells [12] and modifies the toxicity of the chemotherapeutic agent [13]. However, systemic concentrations remain below toxic levels due to the limited absorption of the drug from the cavity. By attempting to “sterilise” the microscopic residual disease

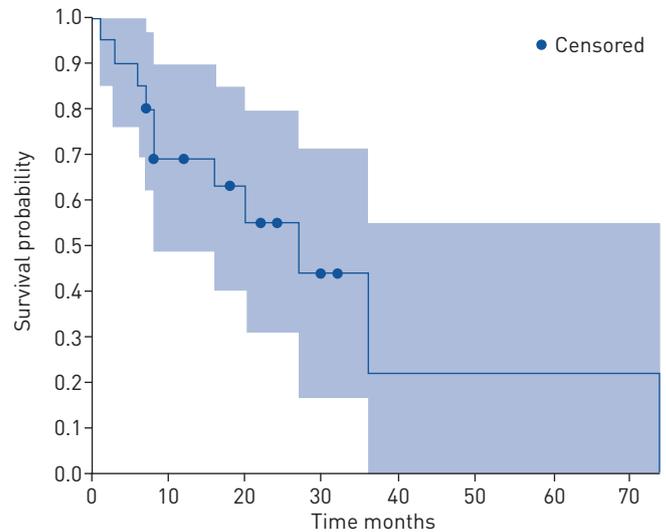


FIGURE 2 Kaplan–Meier survival curve with 95% confidence intervals (shaded area) for stage IVA (M1a) pleural effusion.

after surgical resection, HITHOC has been successfully used in the treatment of some thoracic tumours such as malignant pleural mesothelioma and thymomas [14–16]. Moreover, a recent well-designed study demonstrated that hyperthermia together with cisplatin is an effective treatment for epidermal growth factor receptor (EGFR) kinase domain mutation-positive lung cancer patients [17]. The authors of the study confirmed that hyperthermia and cisplatin, synergistically, downregulated the EGFR protein level, leading to quenching of the signal from EGFR and induction of apoptosis.

For the same reasons, the hypothesis that cytoreductive surgery and HITHOC could improve local pleural control and overall survival for selected patients with advanced NSCLC confined in the chest seems based on a good rationale. It is therefore fascinating that our systematic review, on the possible role of debulking surgery and HITHOC for selected stage IV NSCLC, confirms that something “new” should and could be done to prolong survival. A mean survival of 27 months, with 13 out of 21 (62%) patients alive at 1 year and 10 patients still alive at the time of the respective publication in the 21 patients included (table 1) are positive results for those who, on the basis of the present literature, have a poor prognosis, with a median overall survival of just 4 months, and 1- and 5-year survival rates of less than 16% and 2%, respectively [18]. Although we did not look at perioperative complications, there was no systemic toxicity or treatment-related mortality.

Of note, all 21 patients included in our systematic review had adenocarcinoma of the lung and all of them had also been treated with chemotherapy. Certainly, the appropriate indications for this type of surgery are mandatory to obtain longer survival. Surgical indications in this group of patients could be proposed as summarised in table 2. The exclusion of N2 and N3 patients is mandatory, and therefore correct histology of mediastinal nodes prior to surgery is obligatory. In the case of PET-positive N2 or N3, the standard protocol must include EBUS and/or video-mediastinoscopy to guarantee that no patient is denied surgery because of a false-positive PET scan or enlarged nodes on CT [19].

In 2003, SHIGEMURA *et al.* [9] published a pilot study on HITHOC and panpleuropneumonectomy for patients with advanced carcinomatous pleuritis caused by lung cancer. Surgery was performed after HITHOC. The mean survival time was 19 months. IŞIK *et al.* [8] performed cytoreduction and HITHOC in 19 patients overall. The 1-year survival rate was 54.7% in the HITHOC group, while it was 0.6% and 0.8% in the two historical control groups ( $p < 0.01$  and  $p < 0.05$ , respectively). Both of our patients who underwent this procedure were reported in 2015 [3], but have since died. The first died after 7 months

TABLE 2 Proposed indications for debulking surgery and hyperthermic intrathoracic chemotherapy for stage IVA (M1a) nonsmall cell lung cancer

**Good performance status**  
**Disease confined in the hemithorax**  
**Parietal pleural invasion**  
**Presence or not of pleural effusion**  
**Resectable lung cancer(s)**  
**Histologically proven N0–N1**

TABLE 3 Experiences with surgery and hyperthermic intrathoracic chemotherapy not included in the systematic review

| First author [ref.] | Patients n | Associated procedure | Median survival time months | Survival rate            |
|---------------------|------------|----------------------|-----------------------------|--------------------------|
| KIMURA [20]         | 7          | Debulking            |                             | 0 deaths after 35 months |
| MATSUZAKI [21]      | 11         | Debulking            | 20                          |                          |
| HU [22]             | 54         | VATS pleural biopsy  | 21.7                        | 74.1% at 1 year          |
| YI [23]             | 23         | Debulking            |                             | 24.3% at 3 years         |
| KODAMA [24]         | 101        | Debulking            |                             | 37.4% at 5 years         |

VATS: video-assisted thoracoscopic surgery.

because of sepsis following spinal surgery and the second died after 3 years because of tumour spread in the abdomen (the chest had minimal uptake on PET-CT).

Nevertheless, some other relevant publications not included in the systematic review (figure 1) confirmed a better survival of the study groups (table 3). KIMURA *et al.* [20] demonstrated absence of death during a follow-up period of 9–35 months in seven patients who underwent HITHOC and debulking surgery for disseminated malignant pleural effusion for lung cancer. MATSUZAKI *et al.* [21] performed HITHOC following resection of the lung primary tumour (no pleurectomy) in 11 consecutive patients with primary pulmonary adenocarcinoma and pleural effusions containing tumour cells but without distant metastasis. The median survival time for the patients receiving perfusion treatment was 20 months, while the median survival time for the control group was only 6 months [16]. HU *et al.* [22] performed video-assisted thoracoscopic surgery pleural biopsy and HITHOC in 54 patients with malignant pleural effusion caused by lung carcinoma with a median survival of 21.7 months and a 1-year survival rate of 74.1%. YI *et al.* [23] performed an interesting study on 23 patients with advanced lung adenocarcinoma who underwent debulking surgery alone *versus* debulking surgery with HITHOC, which was continued for only 30 min (compared with 60 min in our technique). The complication rate was 34.8% *versus* 40%, while the 3-year survival rate was 24.3% *versus* 0% ( $p=0.045$ ), respectively. KODAMA *et al.* [24] performed debulking surgery and HITHOC in 101 patients with pleural surface malignancy, obtaining a 37.4% survival rate at 5 years.

Of note, because all of the patients in our systematic review had adenocarcinoma, which presents high heterogeneity, other factors such as molecular biology indicators, classification and degree of infiltration could have had an impact on the therapeutic effect with a possible influence on long-term follow-up results [25]. Furthermore, on the basis of the survival obtained in our systematic review, which showed a mean survival of 27 months and a median survival of 18 months, we believe that there is a subgroup of lung cancer and pleural effusion/nodules confined in the chest that does not have the proper allocation in the tumour, node and metastasis classification. These tumours may be better downstaged to stage IIIB, and this is supported by the International Association for the Study of Lung Cancer Lung Cancer Staging Project that reported the survival for pathological stage IIIC and pathological stage IVA is about the same, with no statistically significant differences [26].

Furthermore, although the recent results of a prospective randomised study on the use of “solo” HITHOC or chemical talc pleurodesis in patients diagnosed with NSCLC and metastatic malignant pleural effusion have shown a dismal survival of only 8 months [27], the good results of our systematic review suggest that debulking surgery and HITHOC need to be investigated thoroughly with the intention to give hope, but not false hope, to the group of patients with advanced stage lung cancer.

In conclusion, although this systematic review shows that some encouraging evidence exists, the quality of evidence available concerning debulking surgery and HITHOC is still weak in order to confirm the effectiveness of this procedure for selected patients with advanced lung cancer. Therefore, better evidence, preferably in the form of randomised controlled trials, is necessary to evaluate clearly the benefit of this novel therapeutic approach. Setting standardised criteria for surgery is also mandatory. The positive results obtained in this systematic review can contribute to generating interest in this form of surgery for selected patients with stage IV lung cancer. This new interest could also drive further evidence supporting the prolongation of survival time while maintaining a good quality of life.

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