

Debulking surgery and hyperthermic intrathoracic chemotherapy (HITHOC) for lung cancer

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Keywords: Lung cancer; NSCLC; advanced stage; cytoreduction; hyperthermic intraoperative intrapleural chemotherapy

Submitted Sep 05, 2017. Accepted for publication Nov 02, 2017.

doi: 10.21147/j.issn.1000-9604.2017.06.07

View this article at: <https://doi.org/10.21147/j.issn.1000-9604.2017.06.07>

One hundred years ago, the first patients with lung cancer have been reported (1). Since then long term survival in patients with lung cancer remains disappointing, and this is not only due to the delayed diagnosis but also to the dismal survival of the 70%–75% inoperable patients.

Hyperthermic intrathoracic chemotherapy (HITHOC) has been successfully used alone in the treatment of malignant pleural effusion (2,3) or associated with debulking surgery in the treatment of some thoracic tumors such as malignant pleural mesothelioma (MPM) and thymomas (4-6). We know that hyperthermia has toxic effect on malignant cells (7), and modifies toxicity of the chemotherapeutic agent (8) as the infusion of the agent into the pleural cavity leads to direct exposure of tumor cells adjacent to its surface. Another study proved that under *ex vivo* hyperthermic conditions, cisplatin diffused into human lung tissue with a median penetration depth of approximately 3–4 mm. The penetration of cisplatin into lung tissue may affect the local therapy of residual tumor cells on the lung surface using HITHOC perfusion in patients with malignant pleural tumors (9).

For the above mentioned reasons, the hypothesis that cytoreductive surgery and HITHOC could improve local pleural control and overall survival for selected patients with advanced non-small-cell lung cancer (NSCLC) confined in the chest seems to be based on an excellent rationale.

Already in 2003, Shigemura *et al.* (10) published a pilot study on HITHOC and panpleuropneumonectomy for

advanced patients with carcinomatous pleuritis caused by lung cancer. Surgery was performed after HITHOC, and the mean survival time was 19 months. Recently Zhou *et al.* (11) 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 longer survival $P < 0.001$. Işık *et al.* (12) performed cytoreduction and HITHOC in 19 patients. The 1-year survival was 54.7% in the HITHOC group 1 while it was 0.6% and 0.8% in the other groups, respectively ($P < 0.01$ and $P < 0.05$). Yi *et al.* (4) performed an interesting study on 23 patients with advanced lung adenocarcinoma who underwent debulking surgery alone vs. debulking surgery with HITHOC performed for 30 min. Complications rate was 34.8% vs. 40.0% while 3 years survival was 24.3% vs. 0% ($P = 0.045$), respectively. Moreover, we have recently demonstrated in a systematic review a survival of 27 months in 21 collected patients with advanced lung adenocarcinoma (13) after debulking surgery and HITHOC; the fact that 10 patients were still alive at the time of the respective publication suggests that survival could be longer than 27 months.

In the Department of Surgery, University of Catania, the indications for debulking surgery and HITHOC for NSCLC are very strict as follows: good performance status, a disease confined in the hemithorax with parietal and/or visceral invasion, resectable lung tumor(s) in presence or not of pleural effusion, and finally absence of N2 or N3 disease. Although at the beginning this kind of surgery was

performed through a thoracotomy, nowadays the operation could be performed via a uniportal or single incision technique reducing the postoperative complication due to the thoracotomy.

In conclusion, the evidence of more than a “few” successful experiences seems to confirm that new operations could be offered to prolong survival in selected patients with advanced stage lung cancer, and therefore it is fantastic to consider the possible role of debulking surgery and HITHOC for selected stage IV NSCLC. Caution is necessary, and therefore randomized controlled trials are mandatory to evaluate the real benefit of this promising novel therapeutic approach.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Migliore M. Debulking surgery and hyperthermic intrathoracic chemotherapy (HITHOC) for lung cancer. *Chin J Cancer Res* 2017;29(6):533-534. doi: 10.21147/j.issn.1000-9604.2017.06.07