Journal of Cancer Research and Treatment, 2014, Vol. 2, No. 1, 1-5
Available online at http://pubs.sciepub.com/jcrt/2/1/1

DOI:10.12691/jcrt-2-1-1

Effect of Cytoreductive Surgery Combined with Intraoperative Intra-Thoracic Hyperthermic Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer

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Received November 17, 2013; Revised December 11, 2013; Accepted December 25, 2013

Abstract Patients with non-small cell lung cancer and malignant pleural effusion have high morbidity and mortality rates. In order to improve patients' survival rate and the quality of life, various methods of treatment are investigated, but the existing method of treatment efficacy is not satisfactory. According to the literatures of effect of cytoreductive surgery with intrathoracic hyperthermic chemotherapy in patients with advanced non-small cell lung cancer, the results showed that it improves the patient survival rate and reduce the patient mortality rate. On conclusion, cytoreductive surgery combined with intraoperative intrathoracic hyperthermic chemotherapy is a better choice for the patients with advanced non-small cell lung cancer.

Keywords: *cytoreductive, chemotherapy, non-small cell lung cancer, intra-operative, intra-thoracic, hyperthermic*

Cite This Article: Myat Aung Kyaw, and Weidong Hu, "Effect of Cytoreductive Surgery combined with Intraoperative Intra-thoracic Hyperthermic Chemotherapy in patients with advanced Non-small Cell Lung Cancer." *Journal of Cancer Research and Treatment* 2, no. 1 (2014): 1-5. doi: 10.12691/jcrt-2-1-1.

1. Introduction

Non-small cell lung cancer (NSCLC) is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histologic variants. Patients with resectable disease may be cured by surgery or surgery followed by chemotherapy. Local control can be achieved with radiation therapy in a large number of patients with unresectable disease, but cure is seen only in a small number of patients. Non-small cell lung cancer with malignant pleural effusion and pleural dissemination has a very poor prognosis, and many attempts to treat the disease including the surgery have not met with success. Therefore, surgical therapy alone is generally not recommended [1]. In order to improve prognosis, more extensive surgical procedures, such as pleuropneumonectomy and adjuvant chemotherapy, have been attempted, but no 'gold standard' for therapy has yet been established [2,3]. In recent years, thoracic surgery has investigated and adopted some of this research for use and treatment of thoracic cancers, in a procedure known as hyperthermic intra-thoracic chemotherapy (HITHOC). In thoracic surgery, intra-thoracic (inside the chest) administration of heated chemotherapy in the operating room has been used primarily to treat malignant thymoma and malignant pleural mesothelioma [4]. Results of recent studies have been mixed – with the best results occurring in patients with malignant pleural effusion. In patients with NSCLC, prognosis is dependent on stage. Recently, one study reported good results using a combination of intrapleural hyperthermic chemotherapy and lung resection in patients in whom pleural dissemination without malignant effusion was first detected at thoracotomy.

2. What is Cytoreductive Surgery?

Cytoreductive surgery or debulking surgery is the surgical removal of part of a malignant tumor which cannot be completely excised, so as to enhance the effectiveness of radiation or chemotherapy. It is used only in specific malignancies, as generally partial removal of a tumor is not considered a worthwhile intervention.

With the patient in a lateral position, under general and thoracic epidural anesthesia and with a double-lumen endotracheal tube, a posterolateral thoracotomy through the fifth intercostal space was performed. Extrapleural dissection, between chest wall, diaphragm and mediastinum on one side and parietal pleura on the other side, was continued until the hilar structures were free. Subsequently, the thickened pleural sheets were removed from underlying healthy tissue, either visceral pleura or

pulmonary parenchyma. After this decortication, the viability of the remaining lung was assessed. When the damage to the lung was too extensive, a pneumonectomy was performed. Small tumor nodules on the diaphragm and pericardium were evaporated by coagulation, while larger or invasive deposits required partial resection of the diaphragm and pericardium. When the diaphragm was accidentally opened or after limited diaphragmatic resection, the defect was left open to permit exposure of its margins and the subphrenic area to the chemotherapeutic agent.

3. Effect of Cytoreductive Surgery

According to one study of accessing effectiveness and influencing factors of debulking operation for NSCLC, the 1, 3, 5-year cumulative survival of patients treated with debulking operation was 56.9%, 20.6%, 17.5% respectively while that received thoracotomy was 41.1%, 7.8%, 5.3% respectively (debulking Vs thoracotomy, Breslow = 27.55, $P < 0.0001$) [5]. Multivariate analysis showed that the debulking operation or thoracotomy ($B = -0.4600$, $P < 0.0001$) and post-operative adjuvant therapies ($B = -0.1059$, $P = 0.0216$) were the most important influencing factors on the cumulative survival.

4. Hyperthermic Intrathoracic Chemotherapy (HITHOC)

As a class, NSCLCs are relatively insensitive to chemotherapy and radiation therapy compared with SCLC. Patients with locally advanced disease may expect to achieve long-term survival with cytoreductive surgery combined with hyperthermic chemotherapy. Human neoplastic tissues are vulnerable to the heat from 41°C to 43°C (increased thermosensitivity), while are tolerated by normal cells. Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. [4] By killing cancer cells and damaging proteins and structures within cells, hyperthermia may shrink tumors.

Many of these studies, but not all, have shown a significant reduction in tumor size when hyperthermia is combined with other treatments. [6,7,8,9] However, not all of these studies have shown increased survival in patients receiving the combined treatments. [7,9,10] Combining the local effect of intrapleural chemotherapy with hyperthermia may offer an additional benefit: the effect of heat on cytotoxicity, demonstrated in vitro at temperature over 42.5°C [11]; the synergistic effect of heat and chemotherapy on certain drugs like mitomycin and cisplatin [12].

Current theories about the effectiveness of hyperthermic intra-thoracic chemotherapy (HITHOC) suggest that the heat of the chemotherapy allows the drugs to penetrate more deeply into the tissues compared to application of systemic chemotherapy. Additional advantages of HITHOC are a better response to chemotherapeutic agents and synergistic antineoplastic effects. Several investigators have shown that hyperthermia can either sensitize cancer cells to subsequent chemotherapy or may enhance the cytotoxic effect of these interventions.

Cancer cells when exposed to hyperthermia show a selectively induced apoptosis during the S-phase in lung cancer cells, but, the exact mechanism is unknown. Some study reported that hyperthermia ranging from 39°C up to 48°C induces transgene expression, representing a promising strategy could be particularly beneficial, which augment the effects of hyperthermia at both cellular and systemic level [13]. And, another study demonstrates that hyperthermia induces apoptosis in lung cancer cells by activation of cell-death membrane receptors of the tumor-necrosis-factor family or extrinsic pathway.

The success of heat-responsive gene therapy greatly depends on whether hyperthermia can be applied efficiently and in a controlled manner to the desired tissue. It is an essential requirement that applied heat has the temperature level, timely defined duration and spatial control to activate efficiently the heat-responsive vector. To achieve this, already clinically used hyperthermia systems could be employed for local, regional or whole body application of hyperthermia. In analogy to these clinically established technologies, similar and also novel approaches are used for controlled hyperthermic activation of heat-responsive vectors [14]. The first clinical applications of hyperthermia (between 39.5°C and 43°C) were performed for treatment of superficious tumor lesions, showing some efficacy [15].

Improvement in clinical outcome has been shown for tumors of the head and neck, pleural cavity, breast, brain, bladder, cervix, rectum, esophagus and for melanoma. In these trials, combination of hyperthermia with radio- or chemotherapy generated best results, due to the sensitizing activity of the applied hyperthermia [16]. One study suggests that median survival rate is 19.4 months in patients treated with cytoreductive surgery and intraoperative intra-thoracic hyperthermic therapy (IIH) and 41 months in patients treated with cytoreductive surgery and intraoperative intra-thoracic hyperthermo chermotherapy (IIHC) compared to 25 months in patients treated with surgery only [17]. Moreover, not only a simple IIHC but also a simple IIH might be beneficial to quality of life (QOL) or prevention of pleural effusion instead of improvement in prognosis.

5. Method of HITHOC

After completion of cytoreductive surgery, the perfusion system was set up. One Tenckhoff inflow catheter (Curl Cath; Quinton; Bothell, WA) was placed centrally in the thoracic cavity, and three silicone outflow catheters (Dura-Sil; Biometrix Ltd; Jerusalem, Israel) were placed in the pleural cavity top, posterior diaphragm sinus, and anterior diaphragm sinus, respectively. Temperature sensors (Mon-a-therm; Mallinckrodt Medical; St. Louis, MO) were attached to the inflow and outflow catheters and to the pump system, immediate after the heat exchanger. The core temperature was measured by a probe in the proximal esophagus. The outflow catheters were connected through connection tubes containing filters (blood transfusion filters; Pall Corporation; East Hills, NY) to a reservoir with filter (Safe II Filtered Cardiotomy Reservoir; Polystran; Copenhagen, Denmark). The

reservoir was connected to a roller pump (Polystan) and subsequently to a heat exchanger (Baxter; Uden, the Netherlands), from where the perfusate returned back to the patient through the inflow catheter. Afterwards, a watertight continuous locking suture leaving at the highest point a small opening for the introduction of the catheters closed the skin.

The thoracic cavity was perfused at a speed of approximately 1 L/min with isotonic dialysis fluid (Dianeal PD1; Baxter). During perfusion, the contralateral lung was separately ventilated. The ipsilateral lung, when left in situ, was inflated at a pressure of 15 cm H2O with oxygen, keeping the lung semi-inflated. This allowed sufficient space between parietal and visceral pleura for adequate perfusion, but limited possible toxicity of cytostatic drugs to lung parenchyma. After stabilization of the system with homogenous intra-thoracic temperature distribution of 40°C to 41°C, chemotherapeutic agents were added to the system. Perfusion was continued for 90 min. At the completion of perfusion, the inflow and outflow catheters and temperature probes were removed.

One study suggested that the volume needed to fill the perfusion circuit varied from 2-5L, while the thoracic cavity contained 1.1 to 4.5L of this perfusate. The highest volume had to be administered after pneumonectomy, although thoracic cavities with a partially collapsed lung harbored up to 3.6L of perfusate [4]. After an average of 19min (variation, 10 to 30 min) the perfusate was adequately warmed up (> 40'C) to administer the chemotherapeutic agents. This period tended to be shorter after pneumonectomy. During perfusion chemotherapy, the maximal temperatures of the perfusate immediate after passing the heat exchanger, at the inflow and at the outflow catheters, were 41.0 to 42.6'C, 40.9 to 42.5'C and 40.6 to 41.8'C, respectively. The maximal core temperature varied between 38.0'C and 39.4'C.

One study described that there were partial response to intra-thoracic chemotherapy in malignant pleural mesothelioma (27.3%), SD (54.5%), PD (18.3%) but there was no complete response [18]. Hyperthermia combined with intra-thoracic chemotherapy using cisplatinum or carboplatinum may be tolerable.

6. Chemotherapeutic Agents Used in HITHOC

Although several studies have reported the effect of intraoperative intra-thoracic chemotherapy in lung cancer, there is no definitive agent for intra-thoracic therapy. A pilot study reported that HITHOC with cisplatin was feasible to provide a possibility for safe and effective radical local tumor control for patients of lung cancer with advanced carcinomatous pleuritis [19]. In another study, they used cisplatin (CDDP) for seven patients, carboplatinum (CBDCA) for three patients and both CDDP and CBDCA for one patient [6]. Complete response was not achieved in any of the 11 patients. Partial response was achieved in three of 11 patients (27.3%), SD in six patients (54.5%) and PD in two patients (18.2%).

7. Complication or Side-Effect of Intra-thoracic Hyperthermic Therapy

Most normal tissues are not damaged during hyperthermia if the temperature remains under 111'F. However, due to regional differences in tissue characteristics, higher temperatures may occur in various spots. This can result in burns, blisters, discomfort, or pain [6,9,10]. Perfusion techniques can cause tissue swelling, blood clots, bleeding, and other damage to the normal tissue in the perfused area; however, most of these side effects are temporary.

One study reported that no haematological toxicity was observed. One case of sinus tachycardia, one case of atrial fibrillation and one case of nephrotoxicity were noted as complications [4]. The degree of post-operative nausea and vomiting was comparable to that observed after major thoracic surgery without synchronous chemotherapy. The 30-day post-HITHOC complication rate was 47% [4]. Furthermore, Ruth reported that three patients had a complication; one late empyema, one gastric herniation and one late empyema with broncho-pleural fistula [Table 1]. A median survival of 15-months was reported [20].

Table 1. Complications of hyperthermic intrathoracic chemortherapy

	Ruth[20] (n=20)	Bree[4] (n=14)	Shigemura[19] (n=5)
Diaphragmatic rupture	2	2	-
Chylous effusion	1	1	-
Bronchopleural fistula	4	-	-
Thoracic air leakage	2	-	-
Pulmonary emboli	2	-	1
Pneumothorax	2	-	-
Cardiac temponade	1	-	-
Atrial fibrillation	-	1	-
Sinus tachycardia/arrhythmia	-	1	2
Nephron toxicity	-	1	-
Late haemorrhage	1	-	-
n = number			

One study reported that the single operative mortality (hospital 30-days mortality) was related to complications secondary to major thoracic air leaks, and six additional patients had surgical complications: an aeric leak in one patient; pleural clotting occurred in two patients; wound abscesses occurred in two patients without necessitating new surgery; one patient presented a prolonged hyperthermia syndrome without bacteriological standpoint documentation [21].

8. Effect of Hyperthermic Intra-Thoracic Chemotherapy

The reported study confirms that the combination of surgery and ITCH is feasible and relatively safe with mortality and morbidity rates, which did not exceed 4 and 25%. Recently, The Netherlands Cancer Institute reported mortality and morbidity rates of 0 and 47%, respectively,

after treatment of 14 patients with pleural malignancies by cytoreductive surgery and ITCH with CDDP and Adriamycin [4]. Moreover, in a previously published study of 26 patients treated with the same combined treatment (CDDP alone for ITCH), the mortality and morbidity rate did not reached 4 and 31%, respectively [22].

In the Institutional report of Thoracic oncologic, the study suggested that despite intraoperative intra-thoracic hyperthermic therapy (IIH) or intraoperative intra-thoracic hyperthermic chemotherapy (IIHC), there were no significant differences in body temperature or duration of thoracic drainage between the three groups: patients received IIH after surgery (group A), patients received IIHC after surgery (group B) and patients underwent surgery only (group C) [23]. In terms of overall survival, there was no death during the follow-up period (9–35 months, median 19.4 months) in the group A. The median survival time was 41 months in the group B and 25 months in the group C. However, there were no significant differences in overall survival rate between the groups [21]. With regard to freedom from pleural effusion, the group A was completely free from pleural effusion during the follow-up period. Only one patient in the group B suffered from pleural effusion 26 months after surgery. On the other hand, four patients in the group C had pleural effusion within three months after surgery and the median term of freedom from pleural effusion was three months in the group C. There was a significant difference between the group A and group C, however, there was no significant difference between the groups A and group B [23].

In one study, they reported that combined regional hyperthermia with intrapleural chemotherapy could control the malignant pleural effusion effectively with mild toxicity [24]. Compared HICT to ICT, the overall response rates of the whole group, breast cancers and lung cancers were 80.8% vs 54% ($P < 0.01$), 86.7% vs 56.3% ($P > 0.05$) and 78.4% vs 52.9% ($P < 0.05$) respectively. The ratios of CD4+, CD4+/CD8+ and NK cells increased and the concentration of VEGF decreased more significantly after HICT.

In another trial of intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion, the pleural effusion was well controlled in 100% of patients [25]. The median survival time in the 12 patients with pleural disseminated lesions who were treated with intrapleural perfusion hyperthermo-chemotherapy was 20 months. On the other hands, the median survival time in 7 patients with similar lesions who did not receive IPHC was only 6 months [25].

One study also suggested that the local hyperthermo-chemotherapy is useful to control pleural effusion and can improve the quality of life of patients with pleural carcinomatosis [26]. Fourteen cases (87.5%) of complete or partial response according to the criteria of the Japan Lung Cancer Society were obtained. There were 2 cases of no change and one case that were impossible to evaluate. In one case, the disappearance of pleural disseminated lesions was confirmed by flexible thoracoscopy after the procedure.

9. Conclusion

The treatment strategy for disseminated non-small cell lung cancer with malignant pleural effusion but no distant metastases is often perplexing and remains controversial but the major challenge for the thoracic surgeons. Surgical cytoreduction and HITHOC seems to be an attractive approach to locally advanced NSCLC with malignant pleural effusion and is associated with an acceptable morbidity rate. Recently cytoreductive surgery of primary and secondary pleural tumors has been combined with hyperthermic intra-thoracic chemotherapy perfusion (HITHOC) for better local tumor control. In comparison to simple instillation of chemotherapeutic agents into the pleural cavity, the combination of surgical resection of pleural tumors and simultaneous HITHOC seems to be a more effective treatment. Intra-operative perfusion allows an improved distribution of the drugs in the pleural space and a higher local concentration of the chemotherapeutic agents in contrast to systemic chemotherapy. Additional advantages of HITHOC are a better response to chemotherapeutic agents and synergistic antineoplastic effects. A prerequisite for safe application of HITHOC is compliance with safety regulations. Due to the reduction in morbidity and mortality this new concept is a valuable alternative for selected patients who do not undergo radical resection (e.g. extrapleural pneumonectomy). HITHOC is an additional therapeutic option in the multimodal treatment of patients with non-small lung cancer with pleural effusion.

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