Revista Argentina de Clínica Psicológica
2021, Vol. XXX, N°1, 302-312
DOI: 10.24205/03276716.2020.2026

Short-term efficacy of surgery combined with intrapleural perfusion with hyperthermic chemotherapy in NSCLC patients with MPE

Fan Chen, Zhilin Luo, Hong Zhang, Tianhu Wang*

Abstract

Backgrounds: To investigate the short-term efficacy and safety of surgery combined with intrapleural perfusion with hyperthermic chemotherapy (IPHC) in non-small-cell lung cancer (NSCLC) patients with malignant pleural effusion (MPE).

Methods: A total of 54 NSCLC patients with MPE were enrolled(26 in treatment group vs 28 in the control group). The patients in the treatment group underwent surgery combined with 3 IPHC for 60 minutes each time. The control group was treated with traditional intrathoracic perfusion.

Results: The control rate of pleural effusion at 4 weeks, 2 months and 3 months in the treatment group was 92.31%, 84.21% and 83.33%; the rate in the control group was 42.86%, 50.00% and 38.89% (P<0.05). The improvement rate of karnofsky performance status (KPS) score in the treatment group(80.77%) was higher than that in the control group(46.43%) (P < 0.05).

Conclusions: The short-term effect of surgery combined with IPHC is effective and safe in the treatment of NSCLC patients with MPE.

Keywords: intrapleural perfusion with hyperthermic chemotherapy; video-assisted thoracoscopy surgery; lung cancer; malignant pleural effusion

1. Introduction

Malignant pleural effusion (MPE) is a common clinical issue in patients with primary chest malignancy and thoracic metastatic malignancies. MPE is one of symptoms in multiple cancer sites such as lung cancer (LC), breast cancer, and lymphoma[1]. At present, LC has become the third leading cause of death in China, following stroke and ischemic heart disease[2] and it is also the most common cause of cancer-related deaths worldwide[3]. Although most LC patients without obvious symptoms could be found using physical examination, some patients with LC lost the best time of surgery because it turns out to be mid or late stage at the time of first visit[4]. The advanced LC patients are often accompanied with MPE, which is often manifested in progressively worsened dyspnea, chest pain, and dry cough, even leading to the end-sitting breathing and cyanosis, which seriously affect the quality of life and survival time of patients. The prognosis of these patients is extremely poor, with a median survival of only a few months [5], and adenocarcinoma is the most common pathological types in these patients[6]. Thus, people pay more attention to the treatment of LC with MPE. The effective control of MPE can alleviate the clinical symptoms of patients, improve the quality of life of patients, and prolong the survival period of patients.

Hyperthermia combined with chemotherapy has a synergistic sensitization effect, which has a more significant clinical effect on MPE than chemotherapy alone and hyperthermia alone. It is now used for the treatment of malignant tumors, such as malignant pleural diseases, malignant ascites, ovarian cancer, advanced gastric cancer, bladder cancer, etc[7-10]. This retrospective study will provide practical evidence for the short-term efficacy and safety of uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC in NSCLC patients with MPE.

2. Materials and Methods

2.1 Patients' general information

The clinical data of 54 NSCLC patients with MPE from May 2016 to December 2019 were retrospectively analyzed. The patients were all from

Department of Thoracic Surgery, The Third Affiliated Hospital of Chongqing Medical University, Chongqing, China , 401120
**Corresponding Author: Tianhu Wang*
Email: wtianhu@hospital.cqmu.edu.cn

the electronic medical record system of the Third Affiliated Hospital of Chongqing Medical University(Gener Hospital) and Yiduyun system (222.180.236.22). The IPHC treatment protocol was reviewed and approved by the Ethics Committee of The Third Affiliated Hospital of Chongqing Medical University, and all patients signed surgery and IPHC informed consent prior to treatment and were performed by the same surgical team. Inclusion criteria were as follows: (1) patients with MPE of NSCLC were diagnosed by pathological/histological/cytological confirmation; (2) sufficient blood routine, liver function, renal function and cardiorespiratory function; (3) karnofsky performance status (KPS) more than 60(these patients with good physical condition to tolerance treatment). Exclusion criteria were as follows: (1)except for malignant lung lesions, tumor lesions in other organs throughout the body [11];(2) patients with severe pleural adhesions on the affected side of the chest;(3) patients with bleeding disorders and bleeding tendency. According to different treatment plans, 54 patients included were divided into two groups (26 in treatment group *vs* 28 in control group). There was no significant difference between the two groups in age, gender, pathological type and other general data ($P > 0.05$) (Table 1).

2.2 Treatment method

2.2.1 Treatment group

All patients underwent uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC after they underwent an effective and complete pre-treatment assessment, including the chest and abdomen computed tomography, pulmonary function tests, electrocardiogram, the brain magnetic resonance imaging.

Surgery procedure

We performed a uniportal(shown in supplementary Fig.1.) video-assisted thoracoscopy cytoreductive surgery which underwent under general anesthesia and were ventilated by double-lumen endotracheal tubes in the operating room. The basic vital signs such as blood pressure, breathing, pulse, oxygen saturation and the urine volume were continuously monitored during the operation. The patient was in a lateral position. An 3cm-5cm incision which protected by the incision protective sheath was made in the 4th or 5th intercostal level between the anterior iliac crest and the midline of the axillary. Video-assisted thoracoscopic thoracic exploration was carried out along this port, such as the degree of pleural adhesion and the degree of tumor involvement, as far as possible to separate the pleural adhesions and peel off the pulmonary surface fiberboard, and then removed the primary lesion by wedge resections or lobectomies , and removed pleural metastases by pleurectomy as much as possible. All the thoracoscopic instruments were removed after thoracoscopic exploration was confirmed no active hemorrhage and pulmonary air leakage, then two 26F thoracic drainage tubes were placed in the pleural cavity via the port(shown in supplementary Fig.2.). One tube was placed at the coastal diaphragm angle and the other at the top of the pleura(shown in supplementary Fig.3.) so that the in-vivo hyperthermic perfusion treatment system(BR-TRG-I) could be connected with the two drainage tubes to implement IPHC postoperatively. The thoracic drainage tubes were fixed on the chest wall with 7 silk thread and connected to a water-sealed bottle respectively.

IPHC

We performed the BR-TRG-I developed by Guangzhou Baorui Medical Technology Co., Ltd. The patients underwent IPHC in the special room for IPHC from the 1st postoperative day with the patient awake. Before IPHC, oxygen inhalation, ECG and oxygen saturation were monitored. Meanwhile, sedation and analgesia treatment were given. Connected the two red ports of the treatment pipeline to the inlet and blue ports to the outlet. The storage bag was reached 1000 ml by the liquid, then preheating was started at the fastest speed of 600 ml/min, and the air in the heat exchanger was exhausted. When the preheating temperature reached 40 ℃, the treatment began. At the end of the perfusion, the fluid in the pleural cavity was discharged as completely as possible. IPHC treatment was performed 3 times. The temperature during the treatment was controlled at 46℃—48℃. The time of each treatment was 60 minutes and the interval was 24 hours. Chemotherapeutic drugs were administered according to intravenous chemotherapy dosage, and the isotonic saline was used in an amount of 3000 ml (adjusted according to the specific conditions). IPHC medication regimen: isotonic saline + cisplatin (75 mg/m^2 [12])/ gemcitabine (1250 mg/m^2, squamous cell carcinoma[13]) / docetaxel (75mg/m^2, adenocarcinoma[13]) (Platinum is used interchangeably with gemcitabine/docetaxel).

2.2.2 Control group

The group was only treated with traditional

intrathoracic perfusion. After B-ultrasound localization, closed thoracic drainage was performed to completely drain the pleural effusion, and cisplatin was injected into the chest cavity. Instruct the patient to change position frequently.

2.3 Evaluation index

2.3.1 MPE control rate

The changes of MPE in patients at 4 weeks, 2 months and 3 months after treatment were evaluated by chest CT. (1) complete response (CR): the effusion disappeared completely, the symptoms disappeared, no fluid accumulated and stabilized for more than 4 weeks; (2) partial response (PR): effusion reduction more than 50%, symptom improvement, no growth of residual effusion for 4 weeks; (3) stable disease(SD): less than 50% reduction in fluid accumulation; (4) progression disease(PD): increased MPE or worsening symptoms. MPE control rate = { (CR+PR)/ number of patients in each group }× 100%[14].

2.3.2 The improvement rate of KPS score

The physical condition of the patients was evaluated 4 weeks after treatment. According to the KPS score standard[15], the score increased more than 20 points compared with before treatment was significantly effective, the score increased more than 10 points was effective, the score increased less than 10 points or no change was stable, and the decreased score was invalid. The improvement rate of KPS score = {(significantly effective + effective)/ (number of patients in each group)} × 100%.

2.3.3 Serum carcinoembryonic antigen (CEA) level

The changes of serum CEA in the treatment group were compared between 4 weeks after treatment and before treatment (The CEA level was significantly higher in metastatic of NSCLC patients[16]).

2.3.4 Adverse reactions

(1) in the course of IPHC, whether patients in the treatment group suffered from discomfort including decreased oxygen saturation, higher body temperature, chest pain and chest tightness; (2) whether there were harmful effects on blood routine, liver and kidney function before and after treatment in the treatment group; (3) whether there were pulmonary interstitial changes in two groups; (4) whether patients suffered from nausea and vomiting after IPHC in in two groups.

2.4 Statistics

Continuous variable data were expressed as mean ± standard deviation ($\bar{\chi}\pm$ SD). If the normal distribution was consistent, the data was compared with the *t*-test of the paired sample. If the normal distribution was not met, the non-parametric test was used. The categorical variables were expressed in terms of frequency and percentage, and the Pearson χ^2 test was used for comparison between groups. Statistical analysis was performed using SPSS 24 (IBM SPSS Statistics for Windows, version 24.0; IBM Corp., Armonk, NY, USA). $P<0.05$ indicates that the difference was statistically significant.

3. Results

3.1 MPE control rate

The MPE control rate was 92.31%(24/26)in the treatment group at 4 weeks after treatment(shown in supplementary Fig.4,5.). In the treatment group, 19 patients survived for more than 3 months, except 3 patients who lost the follow-up and 2 patients whose follow-up time was less than 2 months, and the MPE control rate was 84.21%(16/19)at 2 months after treatment. The MPE control rate was 83.33%(15/18)at 3 months after treatment except 1 patients whose follow-up time was less than 3 months. The MPE control rate was 42.86%(12/28) in the control group at 4 weeks after treatment. In the control group, 18 patients survived for more than 3 months, except 6 patients who lost the follow-up and 1 patients whose follow-up time was less than 2 months, and the MPE control rate was 50.00%((9/18)) at 2 months after treatment. The MPE control rate was 38.89%(7/18) in the control group at 3 months after treatment. There was significant difference in the MPE control rate between the two groups at 4 weeks, 2 months and 3 months after treatment ($P < 0.05$) (Table 2).

3.2 The improvement rate of KPS score

The improvement rate of KPS score in the treatment group was 80.77% (21/26), which was significantly higher than that in the control group 46.43% (13/28). The difference was statistically significant (P <0.05) (Table 3).

3.3 Serum CEA level

The serum CEA level in the treatment group before treatment was 75.57±148.71 ng/ml, and it decreased to 43.19±82.46 ng/ml after 4 weeks followed with treatment (P<0.05).

3.4 Adverse reactions

In the treatment group, 78 times of IPHC were performed. During the IPHC process, the number of

adverse reactions such as increased body temperature, decreased oxygen saturation, chest pain and chest tightness was 10, with an incidence of 12.82% (Table 4). There were some changes in the blood routine, liver, and kidney function between before and after treatment. The difference of WBC and Cr were statistically significant (Table 5). There were 3 cases with pulmonary interstitial changes in the treatment group and 0 cases in the control group(P<0.05). And 3 cases of gastrointestinal reaction occurred in the treatment group and 10 occurred in the control group (P<0.05) (Table 6).

4. Discussion

The innovations of this study are as follows: first, uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC is a relatively new treatment model, which can reduce intrathoracic tumors in a minimally invasive manner, and control the toxicity and side effects of chemotherapy drugs in the lowest possible range; second, this mode can improve the control efficiency of pleural effusion in NSCLC patients with MPE, improve the quality of life of patients, and provide opportunities for subsequent comprehensive treatment; third, it may provide more effective treatment for more NSCLC patients with MPE.

The development of MPE is mainly related to the following mechanisms: (1) Malignant tumors undergo extensive pleural metastasis, which destroys the walls of pleural capillaries and increases pleural effusion; (2) Obstruction of lymphatic ducts and metastasis of the mediastinal lymph nodes cause obstruction to the return of exudate; (3) Tumor cells decompose in the thoracic cavity to produce a large amount of protein, which increases the colloid osmotic pressure in the pleural cavity, thereby increasing the exudation of pleural effusion; (4) The invasion of the pleura by a malignant tumor causes an inflammatory response to the pleura, which increases the permeability of the capillary. NSCLC patients with MPE or pleural metastasis are classified as stage IV LC (M1a) and have lost the opportunity for surgical treatment. The median survival time is only about 4 months, and more than 80% are adenocarcinoma[17]. At present, the main clinical methods are thoracentesis drainage to relieve symptoms, pleural fixation, intraperitoneal injection of chemotherapeutic drugs or biological immune agents, pleurotomy and other treatment methods. Studies have shown that the effective rate of pleural fluid control by sclerosing agent, cisplatin, interleukin-2, bevacizumab, etc. into the chest cavity is 52% to 80%[18-21]. A meta analysis has shown that Endostar could be an effective agent for controlling MPE[22]. Most do not achieve the desired effectiveness of MPE control rate. IPHC combines hyperthermia on the basis of simple intracavitary chemotherapy, which greatly improves the efficacy of chemotherapy alone and controls the MPE more effectively. Normal human tissue cells can withstand 60 minutes at 47℃, however, tumor cells can be killed at the temperature of 43℃ for 60 minutes. Hyperthermia increases the concentration of intracavitary chemotherapy drugs[23], improve the toxicity and efficacy of chemotherapy and drug penetration[24-25]. Intracavitary hyperthermic perfusion chemotherapy allows the local high dose of drugs and less systemic toxicity [26]. The BR-TRG-I achieves the perfect integration of temperature control, temperature measurement and flow control. The accuracy of temperature measurement and temperature control of the system is ±0.1℃ and ±0.2 ℃ respectively. The residual cancer cells in the cavity can be washed and filtered mechanically.

This study investigated the short-term efficacy and safety of uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC in the treatment of NSCLC patients with MPE. The surgery procedures were finished under thoracoscopy through only one 30mm-50mm port incision, which minimized the trauma of surgery to the patient. Through thoracoscopy surgery, pleural effusion elimination and fiberboard exfoliation are achieved to promote lung recruitment, thereby improving the pulmonary functions. Combined with IPHC after surgery, the thermal effect and the penetration ability of chemotherapeutic drugs are used to maximize the removal of residual cancer cells in the thoracic cavity, so as to improve the efficiency of pleural fluid control, improve the quality of life of patients, and provide opportunities for follow-up intravenous chemotherapy, targeting and other comprehensive treatment.

The results of this study showed that MPE control rate at 4 weeks, 2 months, and 3 months and the improvement rate of KPS in the treatment group were significantly higher than those in the control group (P <0.05). In the treatment group, the incidence of adverse reactions such as increased body temperature and elevated blood pressure during the IPHC was 12.82%. There were statistically significant differences in WBC and Cr before and after treatment in the treatment group. The increase of white blood cells after treatment

was considered caused by post-operative stress. The Cr after treatment was lower than that before treatment, indicating that uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC did not increase the Cr in patients. There were no statistically significant differences in PLT, ALT, AST and BUN, indicating that uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC had no significant effect on patients' bone marrow suppression and liver and kidney function. The incidence of nausea and vomiting after the IPHC in the treatment group(3 patients) was less than that in the control group(10 patients) which caused by chemotherapeutic drugs were considered, but all of them were mild and relieved by the treatment of metoclopramide, Ondansetron and Omeprazole. The incidence of interstitial lung changes with the controllable condition is 11.54% which we considered that it was caused by IPHC in the lungs of patients with a slight air leak after the operation. After treatment with methylprednisolone in time, the interstitial changes in the lungs of the patients were effectively controlled. Our present study shows that the short-term effect of uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC has a reliable inhibitory effect on NSCLC patients with MPE and it is relatively safe.

Limitations of this study: (1) The potential source of selection bias may cause different result; (2)At present, due to the small number of cases, it is not possible to compare groupings such as pathological types. It is still necessary to continue to increase the sample size for further analysis. (3) Due to the short follow-up time of most patients, the three-year and five-year survival rate is currently lacking and the follow-up is still needed. But the short-term effect of uniportal video-assisted thoracoscopy cytoreductive surgery combined with IPHC in the treatment of NSCLC patients with MPE is accurate and has certain clinical application value.

Statements

Acknowledgments

Part of the suggestion on the submission of the article was provided by Dr.Jie Tian(Department of Thoracic Surgery, The Third Affiliated Hospital of Chongqing Medical University(Gener Hospital), Chongqing, China).

Conflicts of interest

The authors declare that they have no competing interests.

Funding Sources

None.

Author Contributions

(I) Conception and design: Fan Chen, Zhilin Luo, Hong Zhang
(II) Administrative support: Tianhu Wang
(III) Provision of study materials or patients: Fan Chen
(IV) Collection and assembly of data: Fan Chen
(V) Data analysis and interpretation: Fan Chen, Zhilin Luo, Hong Zhang
(VI) Manuscript writing and Final approval: All authors

References

[1] Sahn SA. Pleural diseases related to metastatic malignancies. Eur Respir J 1997;10:1907-1913.
[2] Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;394:1145-1158. DOI:10.1016/S0140-6736(19)30427-1
[3] Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ, Wu YL, et al. Lung cancer: current therapies and new targeted treatments. Lancet 2017;389:299-311. DOI:10.1016/S0140-6736(16)30958-8
[4] Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-289. DOI:10.3322/caac.21349
[5] Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51. DOI:10.1016/j.jtho.2015.09.009
[6] Gomez-Fernandez C, Jorda M, Delgado PI. Thyroid transcription factor 1: a marker for lung adenoarinoma in body cavity fluids. Cancer 2002;96:289-293. DOI:10.1002/cncr.10743
[7] Migliore M, Calvo D, Criscione A, Viola C, Privitera G, Spatola C, et al. Cytoreductive surgery and hyperthermic intrapleural chemotherapy for malignant pleural diseases: preliminary experience. Future Oncol 2015;11:47-52. DOI:10.2217/fon.14.256
[8] Zhang T, Pan Q, Xiao S, Li L, Xue M. Docetaxel combined with intraperitoneal hyperthermic perfusion chemotherapy and hyperthermia in the treatment of advanced ovarian cancer. Oncol Lett 2016;11:3287-3292.

DOI:10.3892/ol.2016.4414
[9] Ni X, Wu P, Wu J, Ji M, Tian B, Jiang Z, et al. Hyperthermic intraperitoneal perfusion chemotherapy and response evaluation in patients with gastric cancer and malignant ascites. Oncol Lett 2017;14:1691-1696. DOI:10.3892/ol.2017.6342
[10] Liem EI, Crezee H, de la Rosette JJ, de Reijke TM. Chemohyperthermia in non-muscle-invasive bladder cancer: An overview of the literature and recommendations. Int J Hyperthermia 2016;32:363-373. DOI:10.3109/02656736.2016.1155760
[11] Feng X, Zhu L, Xiong X, Jiang H, Wu Z, Meng W, et al. Therapeutical effect of intrapleural perfusion with hyperthermic chemotherapy on malignant pleural effusion under video-assisted thoracoscopic surgery. Int J Hyperthermia 2018;34:479-485. DOI:10.1080/02656736.2017.1340676
[12] Pérol M, Chouaid C, Pérol D, Barlési F, Gervais R, Westeel V, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524. DOI:10.1200/JCO.2011.39.9782
[13] Fossella F,Pereira JR,von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024.DOI:10.1200/JCO.2003.12.046
[14] Yildirim H, Metintas M, Ak G, Metintas S, Erginel S. Predictors of talc pleurodesis outcome in patients with malignant pleural effusions[J]. Lung cancer (Amsterdam, Netherlands),2008,62(1):139-144. DOI:10.1016/j.lungcan.2008.02.017
[15] Péus D, Newcomb N. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. BMC Med Inform Decis Mak 2013;13:72. DOI:10.1186/1472-6947-13-72
[16] Dogan I, Karyagar S, Karyagar SS, Kahraman C, Alver A. Relationship between pretreatment levels of serum Cyfra 21.1, CEA and PET metabolic parameters in NSCLC. Ann Nucl Med 2014;28:829-835. DOI:10.1007/s12149-014-0877-y
[17] Kasapoglu US, Arınç S, Gungor S, Irmak I, Guney P, Aksoy F, et al. Prognostic factors affecting survival in non-small cell lung carcinoma patients with malignant pleural effusions. Clin Respir J 2016;10:791-799. DOI:10.1111/crj.12292
[18] Lee YG, Jung I, Koo DH, Kang DY, Oh TY, Oh S, et al. Efficacy and safety of Viscum album extract (Helixor-M) to treat malignant pleural effusion in patients with lung cancer. Support Care Cancer 2019;27:1945-1949. DOI:10.1007/s00520-018-4455-z
[19] Zhong LZ, Xu HY, Zhao ZM, Zhang GM, Lin FW. Comparison of efficacy and toxicity between nedaplatin and cisplatin in treating malignant pleural effusion. Onco Targets Ther 2018;11:5509-5512. DOI:10.2147/OTT.S168391
[20] Masotti A, Fumagalli L. Intrapleural administration of recombinant interleukin-2 in non-small cell lung cancer with neoplastic pleural effusion. Monaldi Arch Chest Dis 1997;52:225-228.
[21] Nie K, Zhang Z, You Y, Zhuang X, Zhang C, Ji Y. A randomized clinical study to compare intrapleural infusion with intravenous infusion of bevacizumab in the management of malignant pleural effusion in patients with non-small-cell lung cancer. Thorac Cancer 2020;11:8-14. DOI:10.1111/1759-7714.13238
[22] Biaoxue R, Xiguang C, Hua L, Wenlong G, Shuanying Y. Thoracic perfusion of recombinant human endostatin (Endostar) combined with chemotherapeutic agents versus chemotherapeutic agents alone for treating malignant pleural effusions: a systematic evaluation and meta-analysis. BMC Cancer 2016;16:888. DOI:10.1186/s12885-016-2935-4
[23] Sakaguchi H, Ishida H, Nitanda H, Yamazaki N, Kaneko K, Kobayashi K, et al. Pharmacokinetic evaluation of intrapleural perfusion with hyperthermic chemotherapy using cisplatin in patients with malignant pleural effusion. Lung Cancer 2017;104:70-74. DOI:10.1016/j.lungcan.2016.12.015
[24] Storm FK. Clinical hyperthermia and chemotherapy. Radiol Clin North Am 1989;27:621-627.
[25] Matsuzaki Y, Shibata K, Yoshioka M, Inoue M, Sekiya R, Onitsuka T, et al. Intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion. Ann Thorac Surg 1995;59:127-131. DOI:10.1016/0003-4975(94)00614-D
[26] Rusch VW, Niedzwiecki D, Tao Y, Menendez-

Botet C, Dnistrian A, Kelsen D, et al. Intrapleural cisplatin and mitomycin for malignant mesothelioma following pleurectomy: pharmacokinetic studies. J Clin Oncol 1992;10:1001-1006.

Table 1. **Clinical data of two groups of patients**

Characteristics	Treatment group（n=26）	Control group（n=28）
Sex		
Male	19	16
Female	7	12
Age	61.23±11.10	63.18±10.22
Pathological type		
Squamous cell carcinoma	1	2
Adenocarcinoma	25	26
Smoking history		
Yes	13	15
No	13	13
KPS score		
100	0	0
90	2	4
80	14	18
70	5	5
60	5	1

Table 2. **The MPE control in two groups[n(%)]**

Groups	Time	CR	PR	SD	PD	Control rate	*P*
Treatment group (n=26)	4 weeks	8(30.77)	16(61.54)	0(0.00)	2(7.69)	24(92.31)	0.000
Control group (n=28)		1(3.57)	11(39.29)	6(21.43)	10(35.71)	12(42.86)	
Treatment group (n=26)	2 months	4(21.05)	12(63.16)	0(0.00)	3(15.79)	16(84.21)	0.033
Control group (n=28)		1(5.56)	8(44.44)	4(22.22)	5(27.78)	9(50.00)	
Treatment group (n=26)	3 months	4(22.22)	11(61.11)	0(0.00)	3(16.67)	15(83.33)	0.025
Control group (n=28)		1(5.56)	6(33.33)	4(22.22)	5(27.78)	7(38.89)	

Table 3. **The improvement of KPS score in 4 weeks in two groups[n(%)]**

Groups	Significantly effective	Effective	Stable	Invalid	Improvement rate	*P*
Treatment group (n=26)	6(23.08)	15(57.69)	3(11.54)	2(7.69)	21(80.77)	0.003
Control group (n=28)	0(0.00)	13(46.43)	6(21.43)	9(32.14)	13(46.43)	

Table 4. **Adverse reactions during IPHC treatment in the treatment group**

Adverse reactions	Persons	Incidence rate（100%）
Increased body temperature	1	1.28
Decreased oxygen saturation	5	6.41
Chest pain	2	2.56
Chest tightness	2	2.56
Total	10	12.82

Table 5. **Blood routine, liver and kidney functions of patients in the treatment group before and after treatment**

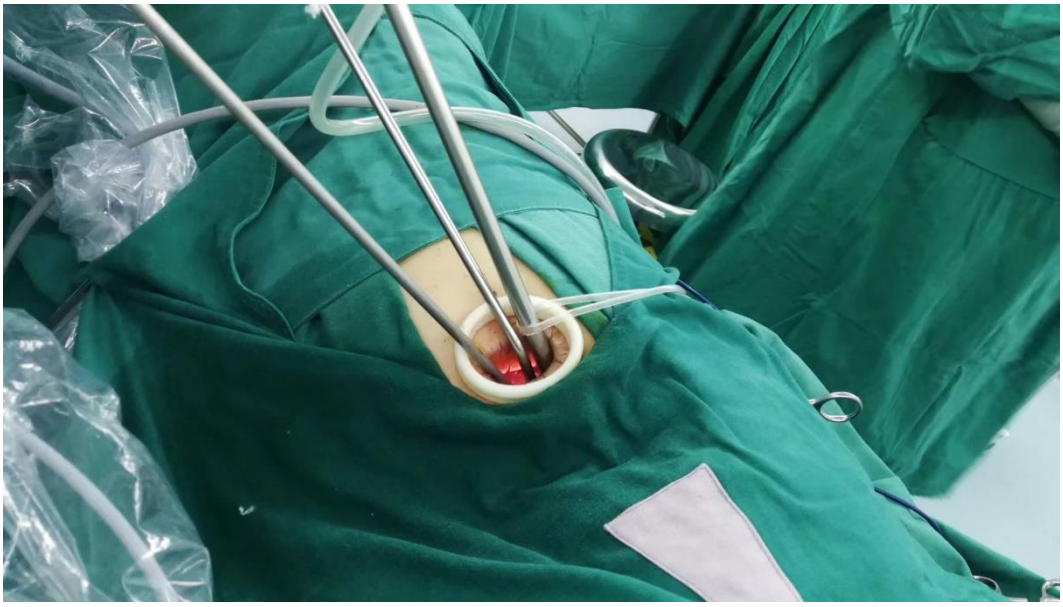
Index	Treatment group (n=26) Before treatment	After treatment	*P*
WBC($\times10^9$/L)	8.30±4.16	10.03±3.41	0.004
PLT($\times10^9$/L)	266.96±99.88	282.96±127.85	0.218
ALT(u/L)	31.65±26.79	35.27±27.22	0.286
AST(u/L)	25.65±11.28	27.54±13.28	0.909
BUN(mmol/L)	4.90±1.35	5.50±2.13	0.071
Cr(mmol/L)	66.77±21.25	60.46±25.74	0.011

Table 6. **The occurrence of nausea , vomiting and pulmonary interstitial changes in two groups after treatment[n(%)]**

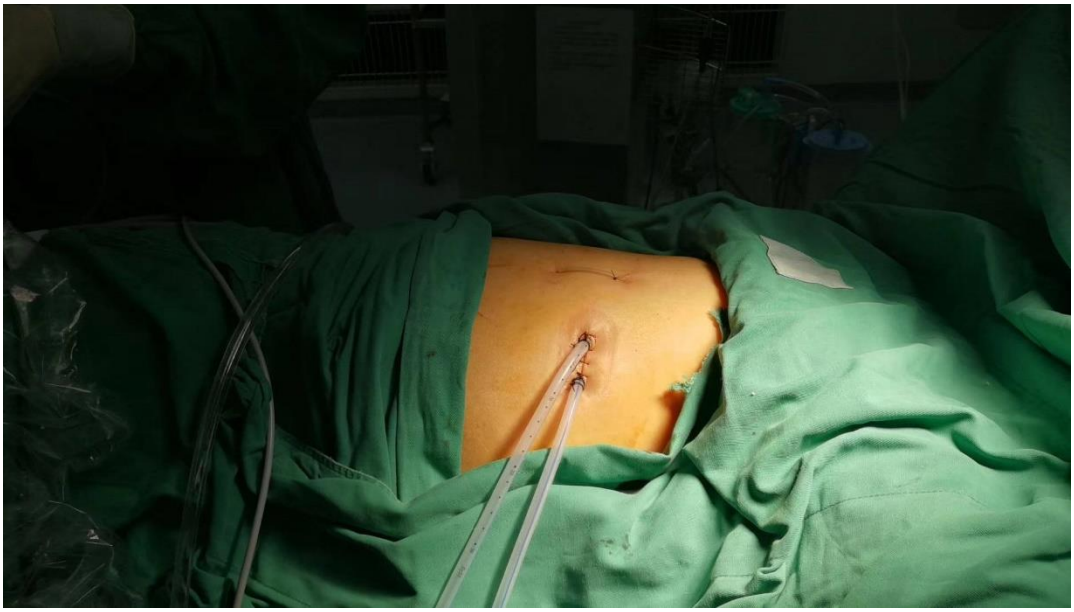
Groups	nausea and vomiting	*P*	Pulmonary interstitial changes	*P*
Treatment group (n=26)	3(11.54)	0.038	3(11.54)	0.032
Control group (n=28)	10(35.71)		0(0.00)	

Figure Legends

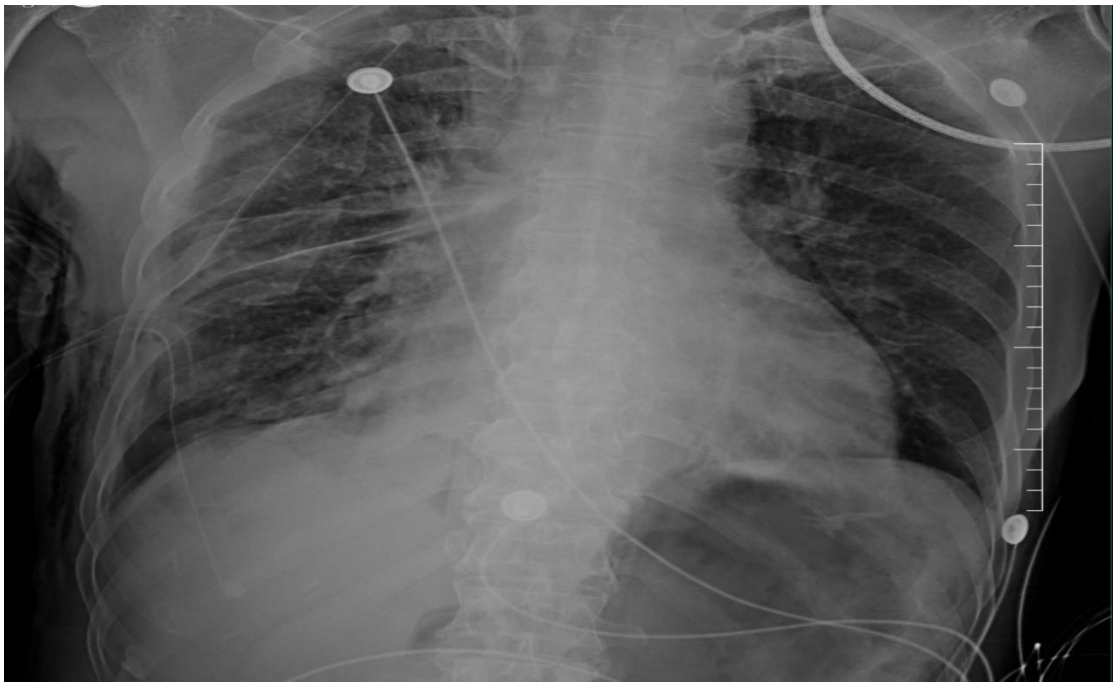
Supplementary Fig. 1. The uniportal video-assisted thoracoscopy minimally invasive cytoreductive surgery
Supplementary Fig. 2 . Thoracic drainage tubes fixed at one port
Supplementary Fig. 3. Placement of the two thoracic drainage tubes in the thoracic cavity
Supplementary Fig. 4,5. The chest CT of patient in the treatment group before and after treatment



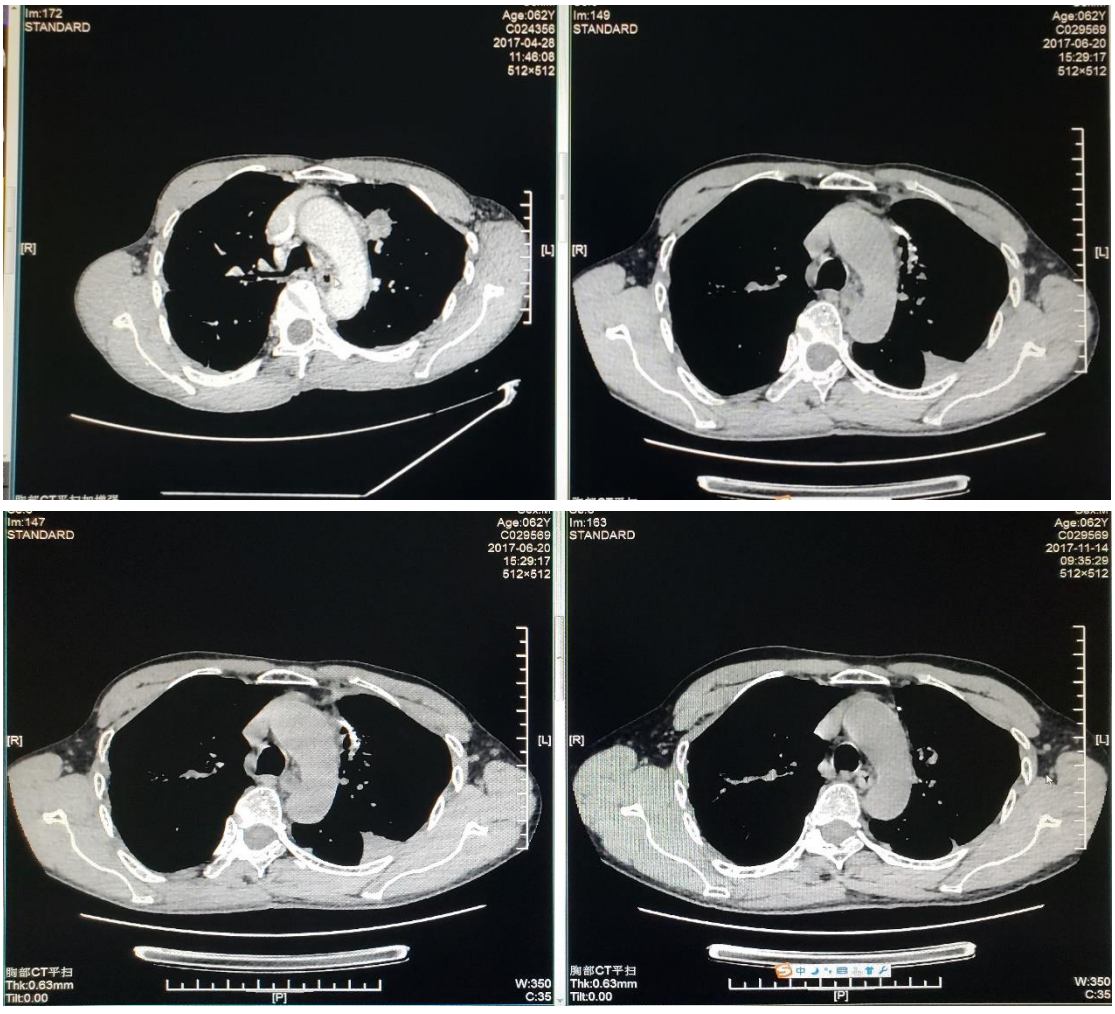
Supplementary Fig.1. **The uniportal video-assisted thoracoscopy minimally invasive cytoreductive surgery**



Supplementary Fig.2. **Thoracic drainage tubes fixed at one port**



Supplementary Figure 3. **Placement of the two thoracic drainage tubes in the thoracic cavity**



Supplementary Figure 4,5. **The chest CT of patient in the treatment group before and after treatment**