Intraoperative intrathoracic chemotherapy and debulking surgery for pulmonary adenocarcinoma with pleural dissemination and no lymph node metastasis

Yiwang Ye (yyw.ghl@163.com)
Peking University Shenzhen Hospital https://orcid.org/0000-0003-2995-9429
Da Wu
Peking University Shenzhen hospital

Research

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Abstract

Objective: assess the feasibility of intraoperative intrathoracic chemotherapy and debulking surgery for pulmonary adenocarcinoma patients with pleural dissemination and no lymph node metastasis.

Methods: We retrospectively reviewed medical records of 23 pulmonary adenocarcinoma patients with pleural dissemination and no lymph node metastasis underwent debulking surgery. They were divided into intraoperative intrathoracic chemotherapy (IC) group comprising patients who not intraoperative intrathoracic chemotherapy (NIC) group.

Result: There was no significant difference in the adverse reactions of chemotherapy between the two groups. The median progression-free survival (PFS) was 38.0 months (95% CI: 25.6-50.4) in IC group and 24.0months (95% CI: 6.3-41.7) in NIC group, respectively. There was statistical significance between two group (IC vs NIC, p=0.016).The median overall survival (OS) was42.0 months (95% CI: 37.4-46.6) in IC group and was 36.0months (95% CI: 28.4-43.6) in NIC group, respectively. But there were no statistical significance between two groups (p=0.082).

Conclusions: Intraoperative intrathoracic chemotherapy might improve PFS for unexpected pulmonary adenocarcinoma with pleural dissemination and no lymph node metastasis in primary tumor resected patients and with less adverse reactions.

Introduction

Pulmonary adenocarcinoma is the most common Non-small cell lung cancer (NSCLC), which with pleural dissemination was classified as M1a according to the 8th TNM revisions by the International Association for the Study of Lung Cancer (IASLC) and operation is generally contraindicated for this group patients.[1)] Several studies had reported patients get long term survival when underwent debulking surgery in cases of NSCLC with pleural dissemination.[2–4)]

There are also reported that intrathoracic chemotherapy can improves the survival of NSCLC patients with positive pleural lavage cytology.[5,6)] However, there is little available data supported intraoperative intrathoracic chemotherapy could improve the prognosis of pulmonary adenocarcinoma. The aim of this study was to assess the feasibility of intraoperative intrathoracic chemotherapy and debulking surgery for N0 stage (No lymph node metastasis) pulmonary adenocarcinoma patients with pleural dissemination.

Methods

Patients

This study was approved by the ethics committee of the Peking University Shenzhen Hospital. All medical records of patients who underwent surgery for NSCLC between January 2010 and December 2019 in the

Thoracic Surgery Department of Peking University Shenzhen Hospital, China were retrospectively reviewed. All of the patients enrolled in this study underwent thoracotomy or video-assisted thoracoscopic surgery (VATS) and had T1 toT3, N0, M0 or M1a (pleural dissemination), clinic stage disease according to the 8th TNM classification. 23 NSCLC patients with pleural dissemination and no lymph node metastasis were confirmed by pleural biopsy during surgery, and all the patients received debulking surgery. Of the 23 pulmonary adenocarcinoma patients with pleural dissemination , 11 patients with lobectomy and 12paients with sublobectomy (wedge resection or segmentectomy).In all patients with resection of primary tumor, pleural nodules with excised conveniently and larger than 1cm would be excised. The rest of all visible nodules were used electric hook thermal cautery.

Intraoperative intrathoracic chemotherapy

13 patients received intraoperative intrathoracic chemotherapy.150 mg nedaplatin mixed with 50ml of normal saline was intrathoracic injection before suturing incision. Complete distention of lung and clipping chest tube for six hours.

Adjuvant treatment

All of the enrolled patients underwent adjuvant treatment.13 patient with EGFR mutation got targeted therapy (4 patients got gefitinib,6 got ecitinib and 3 got erlotinib) for more than half a year or until relapse and followed by other treatments.1 patient just got 3 cycles platinum-based adjuvant chemotherapies and then stop treatment because of serious adverse reactions of chemotherapy. The rest of patients got four to 6 cycles of platinum-based adjuvant chemotherapies.

Follow up

Patients were followed-up one and three months after surgery, and then at three-month intervals in first two years postoperatively and at six-month intervals after two years postoperatively with: a physical examination; radiological imaging for tumor assessment, including CT of the chest, ultrasound of liver and adrenal gland, ECT scan of Bone and MR scan of brain.

Statistical analysis

Patient characteristics were compared by Chi-squared and Fisher exact probability tests. The variables of post-operation of patients were compared by independent sample t-test. The overall survival time and disease progression-free survival rates were calculated using the Kaplan-Meier method. Survival curves were compared by log-rank test. p values less than 0.05 were accepted to be statistically significant. All statistical analyses were performed using SPSS 22.0software (IBM Corp, Armonk, NY, USA)

Result

The characteristics of the 23 patients comprised 9 men and 14 women, with a mean age of 52.6years (range 36–69years). 14patients with the primary tumor size less than 2cm, 9 patients with larger than

2cm. There no perioperative death in all 23 patients. 13patients with EGFR mutation (19delE746-A750 and 21L858R).There was no significant difference between the two groups in age, gender, tumor location, primary tumor size, EGFR mutation and surgical type (Table 1).

Intrathoracic chemotherapy related reactions

Intrathoracic chemotherapy related reactions after surgery were presented in Table 2. Nausea/vomiting was more common from intrathoracic chemotherapy than not intrathoracic chemotherapy (grade I/II :4 vs 1, grade III/IV: 1 vs 0),but there was no statistical difference(p=0.339).One patient suffered moderate myelosuppression (grade II) with leukopenia 2.5*109/L in 8 days post-operation, and after we treated with G-CSF increased to normal 20 days post-operation. One patient got grade I renal dysfunction and returned to normal in 4 weeks in intrathoracic chemotherapy group. 1 patient got grade I liver dysfunction and returned to normal in 3 weeks in intrathoracic chemotherapy group. 1 patient suffered other adverse drug reaction with mild permanent hearing impairment. There was no difference between the two groups in 1st postoperative drainage, Postoperative extubation time and stay hospital after surgery or other adverse drug reaction.

Survival analysis

The survival analysis is summarized in Table 3,and survival curves are described in Figures 1-2.The median PFS was 38.0 months (95% CI: 25.6-50.4) in IC group and 24.0months (95% CI: 6.3-41.7) in NIC group, respectively. There was statistical significance between two group (IC vs NIC, p=0.016).The median OS was42.0 months (95% CI: 37.4-46.6) in IC group and was 36.0months (95% CI: 28.4-43.6) in NIC group, respectively. But there were no statistical significance between two groups (p=0.082).

Discussion

NSCLC with pleural dissemination was classified as M1a because of the poor prognosis according to the 8th TNM revisions by the International Association for the Study of Lung Cancer (IASLC).[1)] Adenocarcinoma is the most common NSCLC. Several studies had reported patients get long term survival when underwent debulking surgery in cases of NSCLC with pleural dissemination detected during the operation.[7,8,2)] There are also reported that intrathoracic chemotherapy can improves the survival of NSCLC patients with positive pleural lavage cytology. Muraoka M et al reported intrathoracic chemotherapy with cisplatin treatment for lung cancer patients with pleural dissemination can improve prognosis and without causing severe complication.[5)] Kim KW et al prospectively analyzed 40 patients with NSCLC and malignant pleural effusion and found chemotherapy-induced complications were at an acceptable level and had well prognosis.[6)]Zhong LZ et al intrathoracic infusion with nedaplatin compared with cisplatin for management of malignant pleural effusion caused by cancers and found the two drugs had the same efficiency, but nedaplatin had less toxicity in comparison with cisplatin.[9)] In this study, we intrathoracic chemotherapy with nedaplatin expected better chemotherapy tolerance. It needs further study which drug is most suitable for intrathoracic chemotherapy.

In this study, 23patients received intrathoracic chemotherapy with nedaplatin, the PFS were longer in the intrathoracic chemotherapy patients, indicating a better prognosis. But the OS between two group was not reach to the statistical difference (p = 0.082), and the reason may be the sample we adopted was small. As adverse reaction of intrathoracic chemotherapy, Grade I/II nausea/vomiting was more common from intrathoracic chemotherapy than not intrathoracic chemotherapy, but there was no statistical difference. One patient suffered moderate myelosuppression. So we should monitoring chemotherapy adverse reactions if the patients received intraoperative intrathoracic chemotherapy.

Conclusion

Intraoperative intrathoracic chemotherapy and debulking surgery might lead to the development of a better therapeutic strategy for pulmonary adenocarcinoma with pleural dissemination and no lymph node metastasis.

Declarations

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none.

Disclosure Statement

Yiwang Ye and Da Wu have no conflict of interest.

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Availability of data and material

All data are fully available without restriction.

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Tables

Table 1. Patient characteristics of the two study groups of pulmonary adenocarcinoma patients.

Characteristic		IC (n=13)	NIC(n=10)	p
Age(years)	<60	7	5	1.000
	≥60	6	5	
Gender	Female	8	6	1.000
	Male	5	4	
Tumor location	Upper lobe	3	4	0.352
	Middle lobe	3	0	
	Low lobe	7	6	
Primary tumor size	<2cm	8	6	1.000
	≥2cm	5	4	
EGFR mutation	Yes	8	5	0.685
	No	5	5	
Surgical type	sublobectomy	5	7	0.214
	lobectomy	8	3	

IC：introperative introthoracic chemotherapy.NIC:not intraoperative intrathoracic chemotherapy.

Table 2.Comparisons of post-operation conditions of patients with two groups

Characteristic		IC (n=13)	NIC(n=10)	p
Nausea and vomiting	0	8	9	0.339
	I/II	4	1	
	III/IV	1	0	
Myelosuppression	0	12	10	1.000
	I/II	1	0	
	III/IV	0	0	
Renal dysfunction	0	12	10	1.000
	I/II	1	0	
	III/IV	0	0	
Liver dysfunction	0	12	9	1.000
	I/II	1	1	
	III/IV	0	0	
Other adverse drug reaction	0	12	10	1.000
	I/II	1	0	
	III/IV	0	0	
1st postoperative drainage		199.2±45.0	167.5±96.8	0.356
Postoperative extubation time		5.2±1.9	5.0±1.2	0.818
Stay Hospital after surgery		8.4±2.7	7.4±2.1	0.341

Table 3. Univariate and multivariate analysis of clinical variables in relation with OS and PFS for pulmonary adenocarcinoma patients.

Characteristic	PFS				OS	
	Univariate analysis		Multivariate analysis		Univariate analysis	
	Hazard ratio(95%CI)	p	Hazard ratio(95%CI)	p	Hazard ratio(95% CI)	p
Intraoperative chemotherapy(Yes vs No)	0.233(0.066-0.827)	0.024	0.233(0.058-0.932)	0.039	0.346(0.096-1.250)	0. 105
EGFR mutation (Yes vs No)	0.191(0.054-0.679)	0.011	0.190(0.050-0.723)	0.015	0.282(0.079-1.002)	0.050
Tumor size (<2cm vs≥2cm)	0.789□0.263 2.372□	0.674			0.529(0.160-1.753)	0..298
Ag(<60years vs 60≥years)	0.940(0.315-2.808)	0.912			0.865(0.260-2.880)	0..814
Gender(Female vs Male)	0.633(0.205-1.956)	0.427			0.351(0.097-1.267)	0.110
Tumor location(Upper lobe vs Middle lobe vs Low lobe)	0.816(0.421-1.583)	0.548		.	1.034(0.513-2.083)	0.925
Surgical type(sublobectomy vs lobectomy)	0.6680(0.223-1.996)	0.470			1.519(0.444-5.198)	0.505

Figures

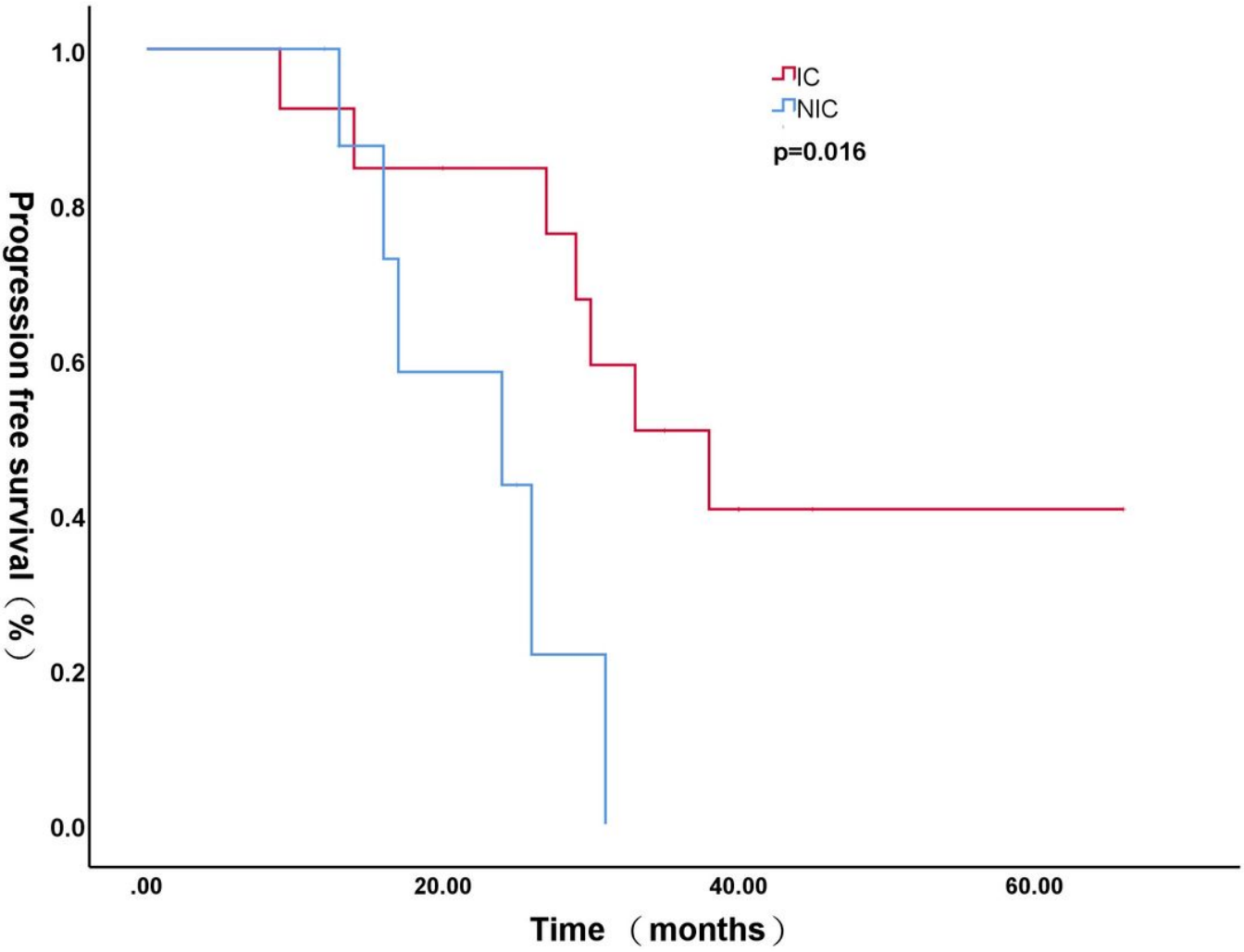

Figure 1

Kaplan–Meier survival curves of progression-free survival in intraoperative intrathoracic group (IC,n = 13) and not intraoperative intrathoracic group (NIC,n = 10).

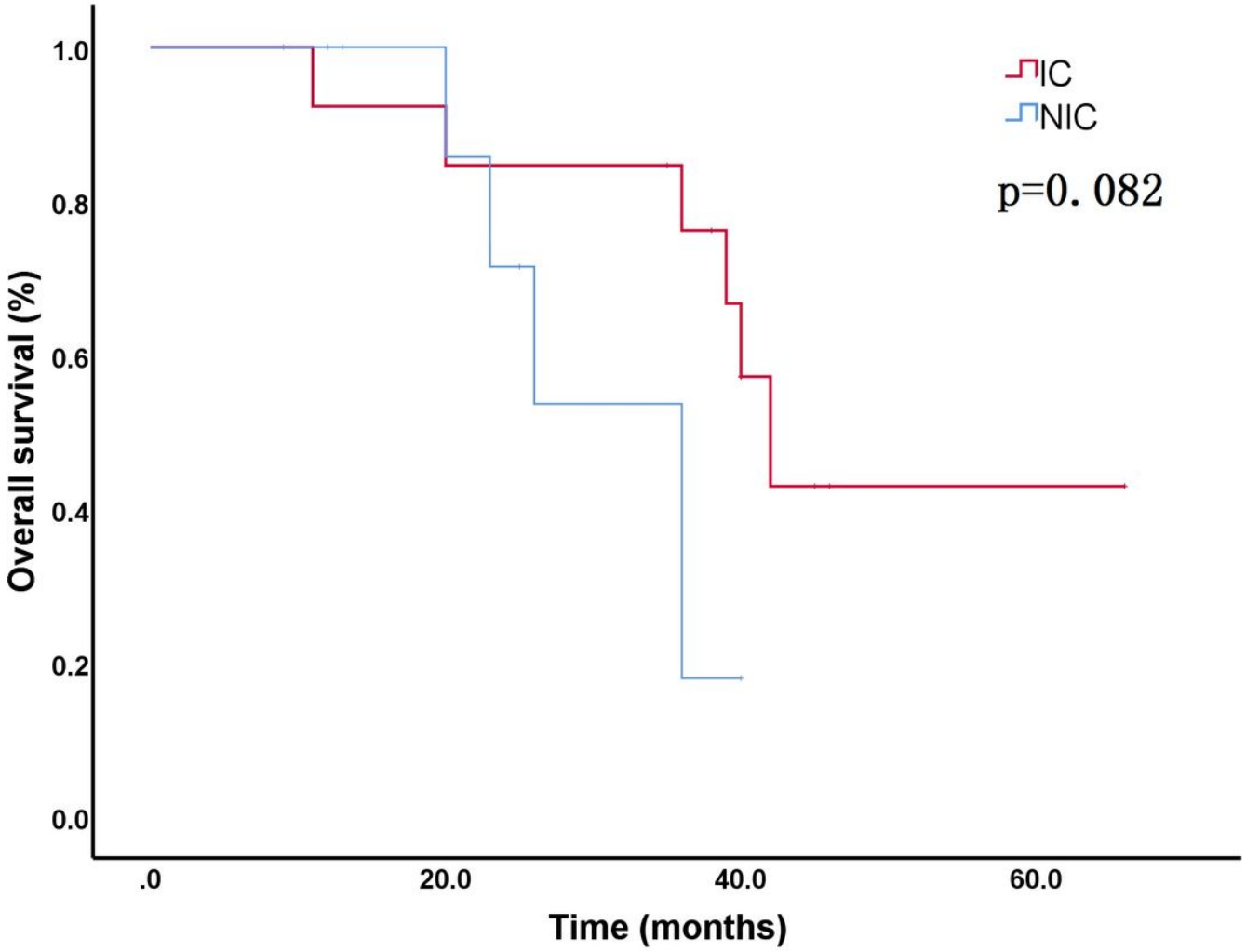

Figure 2

Kaplan–Meier survival curves of overall survival in intraoperative intrathoracic group (IC,n = 13) and not intraoperative intrathoracic group (NIC,n = 10).