



Minimally invasive lobectomy with neoadjuvant targeted therapy: the Zhejiang Cancer Hospital experience

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Introduction

Non-small cell lung carcinoma (NSCLC) is a growing threat worldwide. The management of NSCLC is suggested to be systematic, which means the collaboration of multiple departments. For some NSCLC patients, neoadjuvant treatment is necessary for better prognosis. The role of neoadjuvant chemotherapy is well accepted. Targeted therapy is prior than chemotherapy for stage IV NSCLC patients, whether it shows an advantage in neoadjuvant management is unknown. Our team at Zhejiang Cancer Hospital reported a case treated with neoadjuvant targeted therapy, followed with radical resection, and try to provide some information to standardize the management of NSCLC.

Clinical vignette

A 63-year-old woman was referred to our hospital because of a lung mass found by routine medical examination half a year ago. A local hospital treated her with antibiotics, but there was little effect. She was asymptomatic, and her medical history was clean. Physical examination did not find any positive signs, and the Karnofsky was 100. Computed tomography (CT) showed a mass in her left superior lung. Positron emission tomography (PET) CT showed an elevated FDG metabolic of the mass, suggested the possibility of malignancy; PET-CT also found several hilar (bilateral) and mediastinal lymph nodes had elevated standardized uptake values (SUV), which suggested lymphatic metastasis. CT-guiding biopsy confirmed the mass was adenocarcinoma with EGFR 19 exon mutation. Clinical staging was T2aN3M0, stage IIIB. With fully communicating with the patient, chemotherapy (pemetrexed

0.8 g d1 + cisplatin 40 mg d1–3) were performed. After two cycles of chemotherapy, the size of lung mass and lymph nodes remained the same. Therapeutic effect evaluation was stable disease (SD). Then we changed our strategy, gave the patient gefitinib 250 mg once a day instead of chemotherapy agents. One month later, the lung mass was significantly smaller, all the hilar and mediastinal lymph nodes did not show any change. So, we considered the result of PET-CT might be false positive, clinical stage was modified to T2aN0M0, stage IB. We proceeded onto surgical resection. Postoperative pathological examination showed the tumor size was 2.7 cm × 1.1 cm × 0.8 cm, and all the lymph nodes were negative. According to the curative effect of neoadjuvant treatment and her pathological staging, gefitinib 250 mg once a day was continued.

Surgical techniques

Exposition

The patient lied on her right side. Both surgeons stood on the front of the patient when the assistant stood on the right. We performed video-assisted thoracic surgery with only one incision, which was about 3 cm, located in the anterior axillary line, between the fourth and fifth rib. We adopted bronchial occlude to achieve one-lung ventilation.

Operation (Figure 1)

We opened the chest through the single incision and found the interlobular fissure was hypogenetic, which means it is difficult to expose the pulmonary arterial trunk through the interlobular fissure. Therefore, we decided to perform a thorascopic lobectomy in a single direction. We started



Figure 1 The procedure of operation was shown in the clipped video. Minimally invasive lobectomy of the left superior lung was performed, with hilar and mediastinal lymph node dissected (1). Available online: <http://www.asvide.com/article/view/29634>

the dissociation from anterior superior pulmonary hilum, remove hilar lymph nodes, so to reveal pulmonary arterial trunk. We dissociated along the artery until the anterior segmental artery was emitted. The anterior segmental artery was firstly disconnected, and then was the two branches of apical and posterior segments. Afterward, we turned to the anterior hilum, dissociated and then disconnected left superior pulmonary vein with a stapler. In this step, identifying and protecting the inferior vein was the primary point, as, on some occasions, superior vein and inferior vein divided out of the pericardium looks like they belong to one vein. After the vein was disconnected, both superior and inferior lobar bronchus were exposed.

Then, we began to dissociate along the superior lobar bronchus, in the meantime remove the twelfth sets of lymph nodes. In many cases, lobar bronchus was left to be the last to disconnect. In the single-direction thoracoscopic lobectomy of the left superior lung; however, lobar bronchus must be disconnected ahead of schedule, only in this way we can see lingual artery. Also, on this occasion, a stapler may not be suitable because lobar bronchus was not dissociated enough yet. Once the superior lobar bronchus was cut, and the superior lung was lifted, the lingual arteries can be seen just in the back of lobar bronchus. The interlobular fissure was the last thing to be disconnected, and the superior lung could be removed. What's left was sewing on the bronchial stump and remove mediastinal lymph nodes.

Completion

After inflating the lung and confirm the bronchial stump

was closed, a tube was placed within the chest cavity. The port site was closed in standard fashion, and the patient was revived in the Postanesthesia Care Unit. The tube was removed two days post operation, and the patient was discharged from the hospital to their home, five days post operation.

Comments

Surgical resection was regarded as the first choice for patients of NSCLC, though there were only less than half of the patients may be the candidates of surgery (2). However, even after complete resection, many patients will undergo recurrence, which suggested the existence of micrometastatic disease at the time of surgical resection (3). Many clinical trials about adjuvant chemotherapy have been conducted, and its benefits have been well recognized (4). The curative effect of adjuvant chemotherapy has reached its ceiling, however, and the postoperative morbidity may increase because of the side effects of chemotherapeutics (5,6).

In recent years, targeted therapy has become the focus of attention in the treatment of NSCLC. For patients who are at stage IV, a targeted therapy could achieve better results than traditional chemotherapy, when the side effects are less (7-9). The edema, fibrosis of the tissue of patients, underwent neoadjuvant chemotherapy often means unclear anatomic layer and the adhesive vessel wall, which increase the difficulty of dissociating and risk of bleeding (10). Meanwhile, targeted agents act mainly on the tumor tissue, with little effect on the healthy tissue, which does not increase the difficulty of operation. Some scholars also raised the opinion that targeted therapy should be considered as an alternative option when conventional chemotherapy fails (11), as downstaging is considered as the main purpose for neoadjuvant treatment (12).

However, there is insufficient evidence about the role of targeted therapy in neoadjuvant management. A clinical trial published in 2012 was believed to be one of the pioneer studies that focus on the effect of neoadjuvant targeted therapy (13). After 28 days of gefitinib pretreatment, the researchers found statistically noticeable downstaging. Another clinical trial containing 86 cases of stage IIIA EGFR-mutant lung adenocarcinoma showed targeted adjuvant therapy had a higher complete/partial response rate, higher histological efficacy and lower hematological toxicity (4). A study including 60 patients who received preoperative erlotinib demonstrated that neoadjuvant targeted therapy would not increase the risk of postoperative

complications, though the response rate may not be as high as patients of stage IV (14).

A clinical trial named CTONG1103 is a national, multicenter, randomized, open-level, phase II trial of erlotinib *vs.* the combination of gemcitabine plus cisplatin as neoadjuvant treatment in stage IIIA-N2 NSCLC with sensitizing EGFR mutation in exon 19 or 21. This study recruited patients with stage IIIA-N2 EGFR activating mutation NSCLC confirmed preoperatively by PET/CT, endobronchial ultrasound (EBUS) or mediastinoscopy and evaluate efficacy and safety of erlotinib *vs.* GC as neoadjuvant therapy (15). We hope this study could explore a brand-new treatment strategy for this subsetting.

In the management of lung cancer, PET-CT plays an important role. Malignant tumors are often highly metabolically active, with increased glucose metabolism and consequently FDG uptake, and can be detected as 'hot spots' with higher SUV. A meta-analysis concluded that FDG-PET could diagnose malignant pulmonary lesions with an estimated sensitivity of 94.2% and specificity of 83.3% (16). Staging is another common function of PET-CT. PET-CT is helpful in the evaluation of involvement of mediastinal lymph nodes (17).

Further assessment is necessary, however. If the PET-CT scan is positive for mediastinal nodes, the lymph node status needs histological confirmation in order to stage the patient accurately (18). In this case, the size of mediastinal lymph nodes stayed the same when the volume of tumor reduced obviously, which suggested the PET-CT showed a false positive result. Histological examination is essential.

Currently, the value of neoadjuvant targeted therapy still needs to be proven, but it is promising. Neoadjuvant targeted therapy followed by radical resection will be an essential part of the systemic management of NSCLC.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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