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Research Article

Surgical Therapy for Non-small Cell Lung Cancer in Japan

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Abstract

Despite recent advances in surgical and multimodality treatments, lung cancer is still the leading cause of death due to malignant disease worldwide. In Japan, the number of surgical procedures for lung cancer has been steadily increasing (31,303 in 2009; 32,801 in 2010), totaling 33,878 in 2011. Lobectomy is a standard operating procedure commonly performed worldwide, which is recommended as the first choice of treatment for operable patients with clinical stage I or II non-small cell lung cancer. The proportion of Video-Assisted Thoracic Surgery (VATS) procedures increasing from 59.6% in 2010 to 62.9% in 2011. However, the treatment of choice varies depending on the extent of N2 lymph node involvement. Adjuvant therapy is generally administered to improve these outcomes, although its long-term effectiveness has not yet been demonstrated in lung cancer patients. Accordingly, there are great expectations regarding the potential of induction therapy and neo-adjuvant therapy. Nevertheless, the increased risk associated with surgery following induction therapy is a concern, attributable to possible surgical complications, especially after combined chemo-radiation therapy, and surgery-related death. Therefore, accurate mediastinal lymph node staging is one of the most important factors that can affect the patient outcome, as it not only determines the prognosis but also dictates the most suitable treatment strategy. We report on the status of surgical therapy and postoperative adjuvant chemotherapy for lung cancer patients in Japan. It is important to carefully select the most appropriate therapy on the basis of reliable evidence after considering the advantages as well as the potential therapeutic to improve the prognosis of each patient.

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- Non-small cell lung cancer
- Surgical therapy
- Postoperative chemotherapy
- Effect predictor

ABBREVIATIONS

VATS: Video-Assisted Thoracic Surgery; EBUS: Endbronchial Ultrasound; CTCs: Circulating Tumor Cells; EBUS-TBNA: Endobronchial Ultrasound-guided Transbroncheal Needle Aspiration; EGFR: Epidermal growth factor receptor; EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor; UFT: Tegafur-uracil

INTRODUCTION

Lung cancer is associated with high mortality in developed countries. In Japan, it is the most common cause of cancer-related death in men, whereas it is second only to colorectal cancer in women. Undoubtedly, early detection and rapid treatment have a decisive influence on the prognosis of all types of cancer. With regards to lung cancer, the therapeutic strategies differ substantially between clinical stage IA and IIIB tumors, with surgical treatment being the universally recommended first choice for operable patients with clinical stage I or II non-small cell lung cancer [1]. Although lobectomy is commonly performed worldwide as the standard operating procedure, a more limited operation using video-assisted thoracic surgery is becoming popular [2]. However, even in patients with clinical stage I lung cancer with localized tumors, the 5-year survival rate is only 70% [3,4]. Thus, the use of postoperative adjuvant chemotherapy and optimal therapeutic strategies lung cancer remain matters of debate.

Present surgical therapy options

The primary purpose of surgical treatment in lung cancer patients is tumor resection. However, for tailoring of chemotherapy according to the biological characteristics of each case, collection of tumor specimens and gene analysis are indispensable for effective anticancer drug therapy. Accordingly, procedures such as exploratory thoracotomy and thoracoscopic tumor biopsy have come to play key roles, even in patients who are preoperatively suspected to have clinical stage IIIB or IV cancer. In Japan, the number of surgical procedures for

lung cancer has been steadily increasing (31, 303, 2009; 32, 801, 2010), totaling 33,878 in 2011 [5], with the proportion of Video-Assisted Thoracic Surgery (VATS) procedures increasing from 59.6% in 2010 to 62.9% in 2011. The definition of VATS varies among institutions. At our institution, both pure VATS, (in which the surgery is exclusively performed using a monitoring device), and hybrid VATS, (in which VATS is combined with other surgical procedures performed under direct vision using a small open chest wound, 4 -7 cm in size), are considered as VATS procedures [6]. The 30-day mortality for lung cancer patients undergoing a lobectomy is as low as 0.3% (0.4%, 2010), whereas pneumonectomy performed in 596 patients was reported to be associated with an in-hospital death rate of 1.8% (1.8%, 2010) [5]. Interstitial pneumonia was the most frequent cause of death after lung cancer surgery, affecting 67 patients in Japan in 2011.

Clinical stage I and II lung cancer

The standard operating procedure for clinical stage I lung cancer is lobectomy, although several studies on limited operations for lung cancer with tumor diameters < 2cm have been reported [7-9]. Moreover, lung cancer with extensive ground-glass opacity on thoracic computed tomography has been reported to be pathologically noninvasive [10], and some studies have reported that a limited operation is indicated for such cases [11,12]. Conversely, there is insufficient evidence supporting the use of segmentectomy as a standard procedure. However a prospective randomized controlled study is in progress and the results are anticipated to provide important information with respect to this issue.

In patients who were administered postoperative adjuvant therapy, the 5-year survival rate increased by 2.5% in patients with clinical stage I adenocarcinoma (85.4% for the surgery-only group vs. 87.9% for the combined tegafur-uracil [UFT] group), as a direct result of the adjuvant UFT therapy. Notably, postoperative chemotherapy has been suggested to be effective in patients with stage IB disease (stage IA: 5-year survival of 89.0% for both groups, p=0.886; stage IB: 5-year survival of 73.5% for the surgery-only group vs. 84.9% for the combined UFT group) [13].

Clinical stage IIIA lung cancer

The prognosis of patients with stage IIIA N2 disease with mediastinal lymph node metastasis is poor. Even in patients with complete tumor resection, the postoperative 5-year survival rate is only 20 -30%. Adjuvant therapy is generally administered to improve these outcomes, although its long-term effectiveness has not yet been demonstrated in lung cancer patients. Accordingly, there are great expectations regarding the potential of induction therapy and neo-adjuvant therapy [14,15]. With induction therapy, a sufficient dose of the drug can be administered with good compliance by administration at a stage when patient has a favorable preoperative performance status. This is an important advantage of induction therapy as compared to postoperative adjuvant therapy. Nevertheless, the increased risk associated with surgery following induction therapy is a concern, attributable to possible surgical complications, especially after combined chemo-radiation therapy, and surgery-related death [14]. Presently, there are no standard criteria for operative indications in cN2 patients or for optimal treatment as induction therapy. Therefore we have been attempting to accurately classify disease stages since 2005.

In patients with suspected cN2, we aggressively perform endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); when cN2 is indeterminable, additional mediastinoscopy is performed to confirm cytopathological N2 (cpN2). In contrast, when cpN0-1 is confirmed, treatment with surgery is possible. For patients with confirmed cpN2, we aggressively perform induction therapy followed by surgery after reevaluation of the mediastinum. Initial mediastinal lymph node staging using EBUS-TBNA allows mediastinoscopy to be reserved for re-staging after induction therapy [16, 17]. We believe that surgical procedures should only be performed when the benefits are obvious, and always by a team of experts, including thoracic surgeons, medical and radiation oncologists, and pulmonologists.

Individualization of postoperative chemotherapy

Among the available biomarkers for predicting the effects of chemotherapy for lung cancer, the Epidermal Growth Factor Receptor (EGFR) gene abnormality is the most practical in clinical settings for its association with the effects of EGFR tyrosine kinase inhibitors (EGFR-TKI). In the IPASS trial of Asian lung cancer patients, the results of an exploratory analysis suggested that the effects of EGFR-TKI varied greatly according to the presence of EGFR gene mutations [18]. Moreover, the EGFR gene might serve as a prognostic factor for stage I lung cancer patients [19]. Furthermore, we have been studying Circulating Tumor Cells (CTCs) in peripheral blood as possible surrogate marker of microscopic metastasis.

We conducted a series of prospective studies on lung cancer patients using the CellSearch system (Veridex LLC, Raritan, NJ), to assess the clinical significance of CTCs. CTCs were detected in the peripheral blood of 30.6% patients and were shown to be significantly associated with clinically detectable distant metastasis [20]. In our subsequent study, we found that CTC test findings had significant prognostic value for small cell lung cancer patients [21]. Along with prospective studies on CTCs in the peripheral blood of lung cancer patients, we initiated a prospective study on CTCs in pulmonary venous blood, as tumor cells that may be shed by the primary tumor might circulate after passing through the drainage pulmonary vein [22]. We first showed direct evidence of a significant increase in the number of tumor cells in the drainage pulmonary venous blood during lobectomy for lung cancer, which suggested spillage of tumor cells due to surgical manipulation [23]. Based on these findings, we speculate that CTCs are important biomarkers for lung cancer. Recently, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATA/ERA) proposed a new classification system for lung adenocarcinoma [24]; therefore, Woo and colleagues reevaluated 179 adenocarcinoma patients according to the new criteria. Their results showed that high histological grade was the only prognostic factor for postoperative recurrence [25]. Therefore, we hope that there will be progress in the research efforts for individualized surgical procedures according to the biological characteristics of each case.

CONCLUSION

In this review, we report on the status of surgical therapy and postoperative adjuvant chemotherapy for lung cancer patients in Japan. Effective treatment can be accomplished using only surgery in patients with stage IA lung cancer, whereas postoperative adjuvant chemotherapy is necessary for patients with stage IB or more advanced lung cancer. However, these findings have not been fully confirmed in Japanese patients, and further studies are required to confirm these findings. Therefore, it is important to carefully select the most appropriate therapy on the basis of reliable evidence after considering the advantages as well as the potential therapeutic to improve the prognosis of each patient.

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