Radiation Therapy in the Treatment of Lung Cancer

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Abstract: Although non-small cell lung cancer (NSCLC) has the potential for cure with surgical resection, unfortunately, less than 15% of all patients and less than 25% of those who present with intrathoracic localized disease are candidates for curative surgical resection. Elderly patients, even if they have resectable disease, often have medical contraindications to surgery, such as cardiovascular diseases and pulmonary dysfunction. For inoperable or unresectable NSCLC, radiation therapy (RT) is widely used as either curative or palliative treatment. There is increasing evidence that RT may improve the survival rate for patients with locally advanced unresectable NSCLC when combined with cisplatin-based chemotherapy or administered by altered fractionation. In limited-stage small cell lung cancer, the addition of thoracic RT and prophylactic cranial irradiation to systemic chemotherapy has also improved disease control. In patients with more advanced disease, RT has provided relief of symptoms. Newer radiotherapeutic methods are promising for increasing the dose targeted to the tumor while sparing healthy tissue. In addition, heavy ion charged particle therapy, brachytherapy, stereotactic irradiation, and multi-daily fractionation have shown promise in the treatment of lung cancer. Furthermore, there have been advances in the technology for treatment delivery, especially three-dimensional treatment planning systems, patient fixation tools, and respiratory synchronous system for RT.

Key words: Lung cancer; Radiotherapy; Chemotherapy

Introduction

Radiotherapy for lung cancer has been practiced as (1) curative treatment for unresectable non-small cell lung cancer (NSCLC); (2) pre-operative and postoperative irradiation; (3) thoracic irradiation for small cell lung cancer (SCLC); (4) prophylactic cranial irradiation (PCI) for brain metastasis of SCLC; and (5) palliative treatment for respiratory symptoms.
superior vena cava syndrome, and bone and brain metastases. Although the treatment outcome is still poor, survival rates have been improved gradually through the development of radiotherapy techniques, as well as the advancement of combined chemoradiotherapy. This article discusses the role of radiotherapy in the treatment of lung cancer and reviews recent advances of radiotherapy, including combined therapies.

Curative Radiotherapy for Non-Small Cell Lung Cancer (NSCLC)

Curative radiotherapy is indicated for locally advanced NSCLC patients in the clinical stage of Bulky N2 IIIA and IIIB excluding the cases with malignant pleural effusion, as well as early-stage NSCLC in patients who are considered too old to be operable or who have other complications such as cardiopulmonary dysfunction.

1. Tumor size and local control

Because radiotherapy induces stochastic death of cancer cells according to the dose of radiation, the possibility of tumor control depends on the amount of cancer cells. In addition, larger tumors have higher proportions of hypoxic cells, which are less sensitive to radiation. Thus, patients with smaller tumors have a better chance of cure. It is generally considered that curative radiotherapy is indicated for tumors of sizes up to about 5 cm. Using the standard fractionated irradiation of 2 Gy once daily, the dose needed for tumor control is 40 to 50 Gy for microscopic tumors and over 60 Gy for macroscopic residual tumors. The tumor control probability is 80% for T1 tumors at the dose level of 70 to 75 Gy, and 50% to 70% for T2 tumors with diameters of 5 cm or less at 75 Gy or more.

2. Histological types and irradiation to nodal metastasis

Different histological types of lung cancer show different trends in lymph node metastasis. Observation in surgical cases indicates that squamous cell carcinoma metastasizes continuously from the pulmonary hilum to the mediastinum, while adenocarcinoma tends to spread discontinuously. Some cases of squamous cell carcinoma have no distant metastasis even when there are mediastinal lymph node metastasis. On the other hand, mediastinal lymph node metastasis of adenocarcinoma and large cell carcinoma often accompanies distant metastasis. As a result, long-term survivors treated with radiotherapy include a high percentage of cases with squamous cell carcinoma, in which local control of disease has improved long-term survival. If the primary tumor is located in the upper lobe or the superior segment of the lower lobe, both the primary tumor and nodal metastasis can be irradiated within a relatively small field of irradiation. Better long-term survival can be expected in these cases as compared with cases having primary sites in other locations.

3. Combination with chemotherapy (chemoradiotherapy)

The standard treatment for unresectable locally advanced NSCLC now consists of combinations of radiotherapy and chemotherapy intended to control microscopic metastases and enhance the local effect of radiation. The timing of the combined use of these therapies is crucially important in chemoradiotherapy. There are 3 different timings of the combined use: (1) sequential chemoradiotherapy in which neoadjuvant (induction) chemotherapy is followed by radiotherapy, (2) alternating chemoradiotherapy in which the two therapies are performed, and (3) concurrent chemoradiotherapy in which antineoplastic agents are used during radiotherapy. Sequential chemoradiotherapy is the least toxic and used widely in routine clinical practice. However, it has been reported that sequential chemoradiotherapy did not show clear benefit in the survival of patients with squamous cell carcinoma, although
it was effective in non-squamous cell carcinoma,\textsuperscript{5}) and it does not improve the overall rate of local relapse. For these reasons, the preference is moving towards concurrent chemoradiotherapy aiming at the improvement of local control rate.\textsuperscript{4) Alternating chemoradiotherapy is not commonly used, since this protocol involves split course of radiotherapy. Chemoradiotherapy for elderly patients is still controversial because of the problems of toxicity.\textsuperscript{5)}

4. Advancement of radiotherapy techniques

The basic principle of radiotherapy is to improve the local control rate through administration of as large doses as possible to target lesions while limiting the effect on surrounding normal tissues within the limit of tolerance. Several irradiation methods have been developed to maximize dose concentration to lesions, including 3-dimensional conformal radiotherapy,\textsuperscript{6)} heavy ion (charged particle) therapy, stereotactic irradiation, and brachytherapy. Apart from brachytherapy, external radiotherapy methods are further reinforced by the development of techniques such as respiration synchronous irradiation and dynamic tracking systems, which counteract the respiratory movement of tumors. These techniques have been reported to achieve good local control of inoperable peripheral lung cancer in the early stage. While early-stage squamous cell carcinoma in the pulmonary hilum region is showing a tendency to increase, the most effective therapy for this cancer is endobronchial brachytherapy. This treatment is reported to achieve a cure rate of over 80\%.\textsuperscript{7)}

While standard radiotherapy uses once daily fractionated irradiation at 1.8–2 Gy, 5 times per week, multi-daily fractionation may be performed for the purpose of expanding the difference between the effect on normal tissues and the therapeutic effect on tumors. The benefit of increasing doses in multi-daily fractionation is reported to be more marked in cases with squamous cell carcinoma.

Combination with Surgery

Because surgery and radiotherapy are both local therapies, a combination of these two modalities can be used only to a limited extent. The timing of combined use can be preoperative irradiation intended to improve resectability and prevent intraoperative metastasis and postoperative irradiation for the main purpose of controlling residual tumors and microscopic mediastinal lymph node metastasis. While the effectiveness of preoperative irradiation has not been reported except for the reports on Pancoast tumor, recent progress of chemotherapy has promoted clinical studies on the use of preoperative chemoradiotherapy. On the other hand, postoperative irradiation is generally considered to offer no benefit in survival, although it contributes to the improvement of the local control rate. However, radiotherapy after non-curative resection has been reported to achieve a 5-year survival rate of over 40\%,\textsuperscript{1)} suggesting the significance of postoperative irradiation in cases with residual tumors. Future study is needed to evaluate postoperative mediastinal irradiation in patients with pN 2 to 3 tumors intended for control microscopic residual tumors.\textsuperscript{8)}

Radiotherapy for Small Cell Lung Cancer (SCLC)

1. Thoracic radiotherapy

While SCLC is more sensitive than NSCLC to both radiation and many antineoplastic

Note: LD refers to the lesions that are limited to the hemi-thorax, including the ipsilateral pulmonary hilum, the bilateral mediastinal lymph nodes and supraclavicular fossa (or ipsilateral pleural effusion). Advanced cases beyond the above-mentioned limits are referred to as ED (ipsilateral malignant pleural effusion is usually included in ED).
agents, it proliferates aggressively and the majority of patients show locally advanced disease or distant metastasis at the time of diagnosis. For this reason, clinical stages are generally classified into limited disease (LD) and extensive disease (ED).\textsuperscript{Note} Although SCLC is treated mainly with chemotherapy, standard therapy for LD disease includes the addition of thoracic irradiation to systemic chemotherapy, because it reduces local progression rate. The timing of radiotherapy is best when it is used concurrently with chemotherapy early after the beginning of treatment, and a 5-year survival rate of about 20\% has been reported for LD cases.\textsuperscript{9} Recommended dose and fractionation is 45 Gy delivered as twice daily 1.5 Gy fractions over 3 weeks (accelerated hyperfractionation).

2. Prophylactic cranial irradiation (PCI)

Central nervous tissues are not sufficiently sensitive to the effect of chemotherapy because of the presence of the blood-brain barrier. Hence, prophylactic cranial irradiation PCI has long been used for the purpose of controlling microscopic brain metastases in the treatment of SCLC. Although PCI reduced the relapse rate of brain metastasis, few reports had documented the improvement of survival rate, and the propriety of this procedure is controversial. Recent results of meta-analysis, however, demonstrated that PCI also improves survival rate in patients showing clinically complete remission (CR) after initial treatment. As a result, PCI is gradually being incorporated into the standard therapy for patients showing CR after initial treatment. Recommended doses for PCI are 25 to 30 Gy in 10 to 15 fractions.\textsuperscript{10}

**Palliative Radiotherapy**

Even if extensively advanced stage of cancer prohibits the expectation of cure, patients with advanced cancer have multiple symptoms that impair function and quality of life. Various symptoms of lung cancer can be palliated by a slight reduction of the tumor volume in the infiltration sites causing symptoms. Hence, radiotherapy is also widely used as palliative treatment. Indications for palliative irradiation include (1) cancer pain, (2) symptoms due to tumor compression on organs, and (3) hemorrhage from tumors.\textsuperscript{21} More specifically, such treatment is considered for symptoms such as pain from chest wall infiltration and bone metastasis, disturbance of motor function and consciousness due to brain metastasis, superior vena cava syndrome, airway obstruction, and hemoptysis. All these symptoms are improved by irradiation in 80 to 95\% of the patients. Doses of 20 Gy or less are sufficient for the purpose of relieving subjective symptoms. Unlike narcotics, irradiation for pain can achieve not only pain relief but also the control of metastatic foci. The ability of radiotherapy to facilitate rehabilitation of patients is an important advantage.

**Adverse Events Associated with Radiotherapy and Precautions**\textsuperscript{21}

Because the effect of radiation on normal tissues is limited to the irradiated volume, radiotherapy usually does not cause significant systemic adverse reactions such as leukopenia, vomiting, and immunodeficiency, unless anticancer drugs are used concurrently. One of the acute reactions observed frequently during thoracic radiotherapy is radiation esophagitis associated with mediastinal irradiation. In some patients treated with multi-daily irradiation or the concurrent use of chemotherapy, radiation esophagitis may cause severe swallowing difficulty that would require interruption of treatment. In most patients, however, esophagitis is transient and resolves naturally after a few weeks from the completion of treatment. Alcohol ingestion during radiotherapy must be strictly prohibited.

Adverse reactions occurring after treatment include radiation pneumonitis and pulmonary fibrosis. Lung tissues receiving irradiation de-
velop inflammatory changes a few months after treatment and might eventually develop fibrosis. Although this condition is usually limited to the field of irradiation, serious pneumonitis extending beyond the radiation field may occur occasionally after chemoradiotherapy.

Among delayed adverse reactions after radiotherapy, the most important one that requires the greatest caution is the effect on the spinal cord. However, radiation myelopathy can be avoided if sufficient precautions are taken in the treatment plannings.

**Conclusion**

Radiotherapy plays important roles in the local control of lung cancer. Radiotherapy for inoperable or unresectable NSCLC provides a greater chance of cure when the tumor is smaller in diameter. The success of the treatment for locally advanced NSCLC depends on the locations of primary tumors and lymph node metastases. Recent advances of therapeutic techniques have enabled us to deliver large doses to the targets and improve local control rate. An important theme for future study is development of optimal regimens for the combined use of chemotherapy and radiotherapy aiming to improve local control rate and prevent distant metastases.

While clinical results of the treatment for SCLC has been improved substantially by the introduction of platinum agents, thoracic radiotherapy also plays a major role and PCI has been gradually incorporated into the standard therapy.

**REFERENCES**