Current Advances in Radiotherapy for Non-Small-Cell Lung Cancer: from Conventional Radiotherapy to Carbon-Ion Radiotherapy

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EDITORIAL

The prevalence of and mortality due to lung cancer have been steadily increasing worldwide. Based on differences in treatment strategies, lung cancer can be classified as non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC mainly consists of adenocarcinoma and squamous cell carcinoma, comprising about 80% of the total lung cancer cases. The treatment strategy for NSCLC is determined based on the TNM classification of cancer. I will briefly summarize the current advances in radiotherapy for NSCLC.

Surgery is the standard treatment for clinical stage I or II NSCLC. Radiation therapy is the mainstay for the treatment of medically inoperable cases. Especially, in stage I NSCLC, treatment outcomes following stereotactic body radiotherapy (SBRT) were as good as those of surgery. SBRT is a type of external radiation therapy in which multiple focused beams are aimed at the tumor volume from different angles. SBRT is the standard treatment for medically inoperable stage I NSCLC. SBRT is performed using several hypo-fractionation schedules which are 48 Gy in 4 fractions and 45-60 Gy in 3 fractions, etc. The local control rate following SBRT is about 90% [1]. A matched-pair-analysis of overall survival after surgery or SBRT showed no difference for elderly stage I NSCLC [2]. On the other hand, stage III NSCLC is still intractable. Surgery is indicated when stage IIIA carcinoma is resectable. Some studies reported the results of neoadjuvant chemoradiotherapy [3]. However, cases of operable stage III NSCLC are rare. Inoperable stage III NSCLC patients are treated with radiotherapy. Conventional radiotherapy alone resulted in median survival time of 10 months and 5-year survival rates of 5%. This result led to the clinical trial comparing conventional radiotherapy and chemoradiotherapy. RT0G 8808 showed that sequential chemoradiotherapy was statistically superior to conventional radiotherapy [4]. Chemoradiotherapy combined with platinum-containing drugs is the standard treatment for stage III NSCLC patients in whom chemotheraphy can be combined [5]. As for the combination of chemotherapy and radiotherapy, Furuse [6] showed that concurrent chemoradiotherapy was superior to sequential chemoradiotherapy in survival. A meta-analysis demonstrated that, compared to sequential chemoradiotherapy, concurrent chemoradiotherapy can significantly improve overall survival [7]. The 5-year survival rate improved by 4.5%. Although there were more acute toxicity cases, including esophagitis, during concurrent chemoradiotherapy, pulmonary toxicity did not increase. Advances in the development of systemic chemotherapeutic agents coupled with those in radiotherapy have contributed in the treatment of NSCLC. Since both primary and mediastinal lymph node lesions should be irradiated in radiotherapy for NSCLC, conventional fractionated radiotherapy is a treatment of choice. The standard dose in chemoradiotherapy is 60 Gy in 30 fractions. Conventional radiotherapy dose (60 Gy in 30 fractions) for patients with unresectable locally advanced NSCLC (stage IIIA, IIIB) was established by RT0G 7301 [8]. A favorable combination of chemotherapy demonstrated in phase III studies is cisplatin and second-generation anticancer drugs. Most of third-generation anticancer drugs show increased toxicity when combined with radiotherapy. As such, it is difficult to administer full-dose of third-generation anticancer drugs in combination with radiotherapy. OLC0G 0007 resulted that no significant efficacy difference was observed between Cisplatin/Docetaxel and Mitomycin/ Vindesine/ Cisplatin combined with radiotherapy [9]. To date, it has been difficult to achieve more than a 20% 5-year survival rate with chemoradiotherapy. About two-thirds of patients had either local recurrence or local recurrence and distant metastasis. Although initial studies of concurrent chemoradiotherapy using cisplatin and docetaxel suggested favorable outcomes, compared to conventional second-generation anticancer drugs, these agents did not lead to a significant improvement of outcomes in chemoradiotherapy.

From the perspective of radiology, it is important to evaluate whether local effects are improved by dose escalation, and whether such an improvement contributes to better outcomes. In the 1980s, the Radiation Therapy Oncology Group (RT0G)
conducted a series of randomized clinical trials of radiation dose escalation. RTOG 8311 showed the dose escalation group of hyperfractionated 69.6 Gy produced a significant increase in survival compared with the group of conventional 60 Gy [10]. However, there was no survival increase in the group of more than 70 Gy. In the early 1990s, treatment planning has evolved from 2- to 3-dimensional planning in clinical study, enabling us to irradiate target lesions more accurately. Graham [11] and Tsujino [12] reported there was the relationship between clinical radiation pneumonitis and dose-volume histograms of radiotherapy. They concluded that the volume of normal lung receiving ≥ 20 Gy was strongly associated with the radiation pneumonitis. Local control was actually better with the treatment of 3-dimensional conformal radiotherapy than that of conventional 2-dimensional radiotherapy, suggesting the advantage of the use of computed tomography (CT) for tumor delineation and treatment planning. To improve the local control and survival rate, several phase II studies of dose-escalation radiotherapy have been performed for patients with inoperable stage III NSCLC [13,14]. Yuan carried out a phase III clinical study to compare a 68 to 74-Gy of total dose with involved field radiotherapy (IFRT) planning using a conventional fractionation technique with a 60 to 64-Gy total dose with elective nodal irradiation (ENI) planning [15]. There were more cases of radiation pneumonitis in the ENI group, and 2-year survival was significantly favorable in the IFRT group. However, in the RTOG 0617 study, a phase III comparison study of a standard dose (60 Gy) versus high dose (74 Gy), the high-dose group had a poor result [16]. Based on an interim analysis, RTOG 0617 was discontinued prematurely. Even though the toxicity rate was no difference between standard dose group and high dose group, a multivariate analysis of factors contributing to survival demonstrated that increased V5 to the heart (cardiac volume receiving more than 5 Gy) might be considered to lead to a poor result. In 3-dimensional radiotherapy and high-dose radiotherapy with an intensity-modulated radiotherapy (IMRT) design, a low dose of irradiation to adjacent lung areas may cause adverse events. Therefore, in lung cancer radiotherapy, the dose concentration should be improved to deliver a higher dose to the gross tumor volume (GTV), and decrease the dose to the surrounding normal radiation-sensitive pulmonary tissue.

In order to achieve improved treatment effects, it is necessary to improve the dose concentration to the target volume. In this regard, particle therapy is considered to be promising.

A major characteristic of carbon-ion radiotherapy is its high physical and biological effectiveness. Carbon-ion beams have a high linear energy transfer (LET), because carbon-ions decelerate rapidly in the body and release the maximum energy at the end of energy-dependent range [17]. This phenomenon is known as the Bragg peak. This property enables us to limit the dose to normal tissue while improving the dose concentration to the target volume. Therefore, carbon-ion radiotherapy offers superior dose conformity in the treatment of deep-seated tumors compared with conventional X-ray radiotherapy [18]. Proton beams also have similar physical properties. Several treatment planning studies have clearly demonstrated that proton radiotherapy and carbon-ion radiotherapy offer a superior dose distribution, and reduced dose to adjacent normal tissues and organ at risk, compared with conventional radiotherapy and 3D-conformal radiotherapy. On the other hand, there is not a sufficient discussion for proven clinical effectiveness of proton therapy for locally advanced NSCLC at the present time.

A major difference between carbon ion and proton beams is the biological effect. The relative biological effectiveness (RBE) of different forms of radiation can be compared, for example, by determining the doses of various forms that reduce the survival fraction to 10% in vitro. The RBE of X-ray and proton beam are 1.0 and 1.1, respectively and that of carbon-ion beam is 2.5 to 3. Thus, carbon ion beams are even effective for a large tumor containing radioresistant hypoxic cells. A clinical trial was conducted by the National Institute of Radiological Sciences (Chiba, Japan). The study evaluated the clinical effectiveness of carbon-ion beam radiotherapy in patients with stage I NSCLC (peripheral type). Favorable local control were reported: The 5-year local control rate was 90%, and 5-year overall survival rate was 50% [19]. In addition, no severe pulmonary adverse effect (grade 3 or more) was reported. Carbon-ion radiotherapy was safe even in the elderly (80 years or older). Many phase I/II studies for various tumor sites have been carried out at NIRS since 1994 [20]. A favorable local control rate of as high as 80 to 90% has been achieved in the treatment results obtained so far [21]. Future research will clarify the effectiveness and safety of proton beam and carbon-ion therapies in patients with locally advanced stage III NSCLC. At present, phase I clinical trial of carbon-ion radiotherapy alone for unresectable stage III NSCLC in Gunma University Heavy Ion Medical Center (GHMC) (Maebashi, Japan) has been started. High local control rate can be achieved by carbon-ion radiotherapy, but the control of metastases outside the irradiated field pose a problem when linking this local control effect with an improvement in overall survival rate. At NIRS and GHMC, mucosal malignant melanoma and pancreatic cancer are treated by a concurrent combination of carbon-ion radiotherapy and chemotherapy. For the future, clinical study of chemoradiotherapy using carbon-ion radiotherapy for locally advanced NSCLC will be planned to achieve a good survival result.

Current dose escalation studies have not yield strong evidence for improved outcomes with higher doses. Future studies of precise radiotherapy including particle therapy (carbon-ion therapy and proton therapy) will provide such evidence. In addition, a study of new chemotherapeutic agents and molecular-targeted drugs combined with radiotherapy will yield important findings.

REFERENCES


