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Stereotactic body radiotherapy for lung cancer patients with idiopathic interstitial pneumonias.

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Summary

We compared toxicity and survival after stereotactic body radiotherapy (SBRT) between lung cancer patients with or without idiopathic interstitial pneumonias (IIPs), and investigated the potential value of SBRT for the patients. SBRT achieved excellent local control with acceptable pulmonary toxicity in lung cancer patients with IIPs: the 2-year local recurrence rate was 3.4%, incidence of grade $\geq$ 3 radiation pneumonitis was 12%. SBRT can be a reasonable option for early lung cancer patients with IIPs.

Introduction

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of non-neoplastic disorders resulting from damage to the lung parenchyma, with varying patterns of inflammation and fibrosis. The median survival of patients with idiopathic pulmonary fibrosis (IPF), the most common subtype of IIPs, is only 2–3 years on the whole; however, some patients with stable disease survive relatively longer. Various comorbidities, such as cardiovascular disease, and lung cancer, can occur during the course of IIPs. The incidence of lung cancer is markedly increased among patients with IIPs, ranging from 6% to 17%. Treatment decision-making for lung cancer patients with IIPs is difficult. Treatments for lung cancer in the patients,

including resection, chemotherapy, and radiotherapy, are often contraindicated due to poor pulmonary function prior to treatment and may trigger severe pulmonary toxicities, such as acute exacerbation (AE) or radiation pneumonitis (RP). The optimal treatment should be determined with consideration of potential disease progression of IIPs and lung cancer and the balance between treatment benefit and toxicity.

Stereotactic body radiotherapy (SBRT) is a high-precision conformal external-beam radiation technique that delivers high-dose radiation, showing excellent local control rates with minimal toxicity in patients with medically inoperable stage I non-small cell lung cancer (NSCLC). We performed SBRT for lung cancer patients with IIPs after deliberate multidisciplinary discussion and informed consent in scant data regarding the role of SBRT for the patients. We retrospectively investigated the tolerability of SBRT for lung cancer patients with IIPs comparing toxicity and survival after SBRT for them to those for patients without IIPs.

Discussion

The treatment of lung cancer patients with IIPs requires careful decision-making not only because such patients commonly have a poor prognosis but also because therapeutic interventions for lung cancer may provoke AE of IIPs. In an analysis of resection cases from multiple institutions in Japan, AE occurred in 164 patients (9%), with a mortality rate of 44%, and was the leading cause of 30-day mortality (72%) among patients with ILD (n=1763). Those results suggested that the 30-day rate of grade ≥ 3 pulmonary toxicity was 9% or greater, and that the 30-day rate of grade 5 toxicity was 4%. In addition, they found that the risk of AE gradually increased with the volume of the lung removed.

SBRT is less toxic than resection especially during the acute phase, although historically, radiotherapy has been considered unsuitable for patients with IIPs. Following conventional radiation therapy for patients with IIPs, the frequency of AE is reported to be approximately 25% in Japan. Therefore, IPF is often considered a contraindication to conventional radiation. Based on the evidence from those studies, previous prospective SBRT studies also excluded patients with IIPs. In this study, the rate of grade ≥ 3 RP was 12%, and that of grade 5 RP was 2% (one patient) in the IIPs group. Grade ≥ 3 RP did not occur within 30 days. These rates of RP were equivalent to those of previous studies in patients following SBRT (grade ≥ 3 RP rate of 10–39%) and proton beam therapy (grade ≥ 3 RP rate of 12.5%). The range of grade 5 RP rates was 0–21%; however, no grade 5 toxicities within 30 days have been reported.

Several medications to mitigate RP have been evaluated, including corticosteroids, amifostine and angiotensin-converting enzyme inhibitors. However, the efficacy of those medications remains to be determined. Recently, some studies reported that angiotensin-converting enzyme inhibitors decreased the risk of RP after radiotherapy. We have used clarithromycin to treat RP in some high-risk patients because of its immunomodulatory and anti-inflammatory effects. This drug was effective for treatment of inflammatory pulmonary diseases including diffuse panbronchiolitis, cystic fibrosis and chronic obstructive pulmonary disease. It was also reported to be effective for radiation-related organizing pneumonia, although its efficacy is uncertain.

This study also suggested that severe RP may occur more frequently in patients with UIP. This may be because patients with non-UIP commonly have nonspecific interstitial pneumonia (NSIP), which has a favorable

prognosis and is less frequently associated with AE compared with IPF. We found that grade ≥ 3 RP was observed only in patients with UIP alone or CPFE within the IIPs group. This is consistent with findings from surgical studies in which patients with UIP had a higher risk of developing postoperative AE than did those without UIP. According to the abovementioned multi-institutional analysis of resection cases in Japan, the incidence of AE in patients with UIP was significantly higher than that of those with non-UIP (10.3% vs. 6.5%, $p=0.01$; OR, 0.59). Further evaluation of the relationship between severe RP and these risk factors in patients with IIPs is required.

The prognosis of lung cancer patients with IIPs is poor. It remains controversial as to which local treatment, resection or SBRT, is suitable for such patients. According to the abovementioned analysis of resection cases from multiple institutions in Japan, the 5-year OS rates of NSCLC patients with ILD ($n=1763$) staged as IA, IB, or IIA were 59%, 42%, or 43%, respectively. These OS rates were substantially lower than those of the NSCLC patient population overall reported by the Japanese Joint Committee for Lung Cancer Registration (87%, 74% and 62% for stage IA, IB and IIA patients, respectively). The outcomes after SBRT were also poorer compared with those of patients without IIPs. The 2-year OS rates in stage I lung cancer patients with ILD were 44.4–70% in previous studies and 42.2% in this study. Those outcomes after resection and SBRT are associated with substantial selection bias.

Outcomes of lung cancer treatment have been extremely poor regardless of the tumor stage or severity of IPF. Such poor prognoses may be because of not only the separate effects of the individual diseases, IIPs and lung cancer, but also their synergistic effects. The multi-institutional

resection analysis in Japan suggested that patients with ILD have a high incidence of cancer recurrence. Even among patients with pathologic stage IA NSCLC, the rate of cancer-related death was significantly higher in patients with IPF than in those without IPF (17.9% vs. 3.7%, $p=0.001$). Also in this study, early death from lung cancer occurred more frequently in the IIPs group, which was due to distant metastases, despite that ^{18}F -FDG PET/CT staging was performed in the majority of patients (83.8%), and local recurrence was rare (2-year local recurrence rate of 3.4%). Stella et al. suggested similar molecular biological behaviors between IPF and cancer. According to a pathogenic perspective, the aberrant proliferative events in IPF resemble those occurring in malignant transformation. Receptor tyrosine kinases (RTKs) are key players in cancer onset, spread and metastasis. The expression of certain RTK family members, e.g., the MET proto-oncogene, is also activated in IPF to enhance organ regeneration as a reaction to inappropriate persistent lung damage. Although the biological significance of RTK activation may differ between the two diseases, their common aberrant activation may induce synergistically poor outcomes.

We consider that IIPs is not an absolute contraindication for SBRT but rather a poor prognostic factor, in light of acceptable pulmonary toxicities: grade ≥ 3 RP rate of 12%, grade 5 RP rate of 2% and 30-day mortality rate of 0%. We believe that the decision to perform SBRT should be discussed on a per-patient basis as well as among multidisciplinary teams for the following reasons. First, SBRT itself may reduce survival duration due to severe toxicities. Second, IIPs is a heterogeneous disorder in terms of its clinical course. Some patients deteriorate rapidly, and others survive relatively longer with stable disease. Third, there is no other treatment option for lung cancer in most patients who are not candidates for SBRT. Fourth,

the natural course of stage I NSCLC is poor even in patients without IIPs. The median survival of patients with untreated stage I NSCLC was reported to be 14–27 months.

Although predicting the natural history is difficult, we have evidence regarding the prognosis of such patients. The prognosis depends on the subtype of IIPs. The overall prognosis and response to therapy of NSIP, the second most common type of chronic IIPs, is favorable compared with those of IPF. Some clinical variables have been shown to predict mortality in patients with IPF (e.g., number of comorbidities, older age and weak pulmonary function). In addition, we compare the progression of between cancer and IIPs by referring to serial images, additionally estimate which disease is more likely to diminish quality of life and be cause of death. If IIPs'-related symptoms and prognosis are likely to be more critical, we can take course observation for cancer. Taking these clinical features and SBRT-induced benefits and toxicities into account, clinicians should have adequate information for discussing the treatment course with their patients.

SBRT can be a reasonable option for early lung cancer with IIPs. A propensity score matching analysis suggested that oncologic outcomes are comparable between patients treated with limited resection and those treated with SBRT plus lymph node evaluation. Moreover, quality of life could be maintained after SBRT in contrast to after pulmonary resection. We showed excellent local control and acceptable pulmonary toxicities. These outcomes suggest that SBRT has comparable outcomes to those of resection, with less toxicity, especially during the acute phase.

Despite this being the largest study involving SBRT for patients with IIPs to our knowledge, the sample size of patients with IIPs and events of severe toxicities (grade 3-5 RP) might still be too small to generalize our

findings in terms of survival, incidence of RP and outcomes of IIPs subtypes.

In conclusion, we showed that SBRT achieved excellent local control with acceptable pulmonary toxicity in lung cancer patients with IIPs. SBRT provides a reasonable option for early lung cancer with IIPs. Clinicians should deliberately discuss the treatment course for individual lung cancer patients with IIPs via multidisciplinary teams, taking these clinical features and SBRT-induced benefits and toxicities into account.