Commentary

The factors affecting local tumor control after stereotactic body radiotherapy for non-small cell lung cancer

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Stereotactic body radiotherapy (SBRT), also called stereotactic ablative radiotherapy (SABR), has been widely used as an effective treatment for early-stage lung cancer, especially in medically inoperable cases (1,2). The local control (LC) rates after SBRT for early-stage non-small cell lung cancer (NSCLC) have been reported to be 85-98% (1). Although the treatment results seem to be favorable, several risk factors for local tumor progression have been reported. Here, we would like to summarize and discuss about reported factors that affect local tumor control after SBRT.

Tumor stage

Tumor stage is one of the most well recognized risk factor for local tumor progression after SBRT. Onimaru *et al*. analyzed the treatment results of 41 patients with stage I NSCLC (25 with T1 and 16 with T2 tumor) treated by SBRT (3). The dose fractionation schedule of SBRT was 40 or 48 Gy in 4 fractions within 1 week. They reported that T stage was a significant factor for LC in multivariate analysis. Dunlap *et al*. compared the LC rates of 40 patients with peripheral T1 and T2 NSCLC treated with SBRT (4). SBRT was delivered at a median dose of 60 Gy in 3 or 5 fractions. Increasing tumor size correlated with worse LC. LC at 2 years was 90% and 70% in T1 and T2 tumors, respectively (P=0.03). Matsuo *et al*. investigated the factors that influence clinical outcomes after SBRT for NSCLC (5). A total of 101 patients underwent SBRT with 48 Gy in 4 fractions were evaluated. Factors including age, maximum tumor diameter, sex, performance status, operability, histology, and overall treatment time were evaluated. Tumor diameter was the only significant factor for local progression in a Cox proportional hazards model. Shirata *et al*. investigated the prognostic factors for LC of stage I NSCLC in SBRT (6). Eighty patients (81 lesions) treated with 3 dose levels, 48 Gy in 4 fractions, 60 Gy in 8 fractions and 60 Gy in 15 fractions were evaluated. The 3-year LC rates were 89.0% with T1 tumors and 64.8% in those with T 2 tumors (log-rank P=0.001) and T factor was shown to be a significant factor for LC with a Cox proportional hazard model analysis (P=0.013).

These findings indicate that T2 tumor, compared with T1 tumor, is the risk factor for local progression after SBRT for early-stage NSCLC.

The maximum standardized uptake value (SUVmax) on F18-fluorodeoxyglucose positron emission tomography (FDG-PET)

Pre-treatment SUVmax of primary tumor on FDG-PET is also described predictive factor for LC after SBRT in several reports. Takeda *et al*. evaluated the relationship between SUVmax on FDG-PET of 95 patients with 97 tumors and local recurrence (7). By multivariate analysis, the SUVmax of a primary tumor was the only predictive factor for local recurrence (P=0.002). Two-year LC rates for lower SUV-max (less than 6.0) and higher SUV-max (6.0 or more) were 93% and 42%, respectively. Clarke

et al. investigated if SUVmax on pre-treatment FDG-PET would predict clinical outcome after SBRT for early-stage NSCLC (8). Eighty two patients who were evaluated with FDG-PET before SBRT were analyzed. On univariate analysis SUVmax predicted for local failure (P=0.044). Na *et al*. reported a meta-analysis of prediction value of SUVmax for the outcome in NSCLC receiving radiotherapy (9). In the analysis of SBRT group, hazard ratio for LC was reported to be 1.11 (95% confidence interval, 1.06-1.18) for SUVmax of pre-treatment FDG-PET.

Although the optimal cut-off value of SUVmax is still controversial, "high" primary tumor SUVmax seemed to be a risk factor for local tumor progression.

Overall treatment time of SBRT

Kestin *et al*. investigated the factors that affect the clinical outcome for lung SBRT (10). Five hundred five tumors in 483 patients with clinical stage T1-T2N0 NSCLC treated with SBRT at 5 institutions were evaluated. In their analysis, overall treatment time of SBRT correlated to 2-year local recurrence. Two-year local tumor progression rates for longer overall treatment time of SBRT (11 or more elapsed days) and shorter overall treatment time (less than 10 days) were 14% and 4%, respectively (P<0.01). The longer overall treatment time might have a negative effect on the outcome after SBRT.

Dose-response relationship

The applicability of biologically equivalent dose (BED) employing a large dose per fraction is criticized by the likelihood overestimating the BED (11). However many clinicians often use the linear-quadratic (LQ) model and BED to estimate the effects of various radiation schedules. It has been also reported that the LQ model fits the radiation response of epithelial tissues <23 Gy per fraction (12). Onishi *et al*. reported multicenter retrospective study of SBRT for stage I NSCLC (13). Two hundred fifty five patients were analyzed and the median BED 10 was 111 Gy (range, 57-180 Gy). The local tumor progression rate was 8.4% for a BED of 100 Gy or more compared with 42.9% for less than 100 Gy (P<0.001). Kestin *et al*. examined dose-response relationships with various NSCLC SBRT fraction regimens (10). Five hundred five tumors in 483 patients with clinical stage T1-T2N0 NSCLC treated with SBRT at 5 institutions were evaluated. Median prescription BED 10 was 132 Gy (50.4-180). Two-year local recurrence rates were 4% and 15% for BED10 >105 Gy and BED <105 Gy, respectively (P<0.01). According to these findings, BED 100 Gy or more generally seemed to be necessary for SBRT in order to achieve a more than 90% LC rate.

Dose-escalation

Although the LC rate of small tumor after SBRT seemed to be excellent, that of larger tumor, such as T2 tumor, is not still unsatisfied. Davis *et al*. reported the clinical outcome of patients with T1-T2N0M0 and treated with SBRT. The RSSearch® Patient Registry was screened for 723 patients (517 with T1 and 244 with T2) (14). Median SBRT dose was 54 Gy (range, 10-80 Gy) delivered in a median of 3 fractions (range, 1-5), and median BED10 was 151.2 Gy (range, 20-240 Gy). LC was associated with higher BED10 for T2 tumors. Seventeen-month LC rate for T2 tumors treated with BED10 <105 Gy, BED10 105-149, and BED10 150 or more was 43%, 74%, and 95% respectively (P=0.011). On the other hand, there was not significant association between higher BED10 and T1 tumors. These results indicate that dose-escalation in SBRT might be beneficial for the treatment of larger tumor. On the other hand, Mehta *et al*. reported that dose-escalation beyond a BED10 of 159 Gy likely translates to a clinically insignificant gain in tumor control probability but may result in clinically significant toxicity (15). Zhang *et al*. reported a meta-analysis of SBRT for stage I NSCLC (16). BED was divided into four groups: low (<83.2 Gy), medium (83.2-106 Gy), medium to high (106-146 Gy), high (>146 Gy) and the treatment outcome was evaluated. The overall survival for the medium or medium to high BED groups was higher than those for the low or high BED groups. Therefore medium or medium to high BED (range, 83.2-146 Gy) was indicated to be more beneficial and reasonable BED. Thus, careful attention should be paid in case of dose-escalation of SBRT for early-stage NSCLC.

Recently, the results of JCOG0702 trial (multicenter phase I study of SBRT for T2N0M0 NSCLC with planning target volume <100 cc) were reported (17). The dose of SBRT was prescribed at D95 of the PTV. The recommend dose was determined to be 55 Gy in 4 fractions in the study. Further prospective studies are needed to determine whether dose-escalated SBRT improve clinical outcomes.

Centrally located tumor

Timmerman *et al*. reported a phase II study of SBRT for

medically inoperable stage I NSCLC (18). SBRT treatment dose was 60 to 66 Gy total in 3 fractions. In their study, SBRT for central tumors was associated with a greater than 10-fold increase risk of high grade toxicity or death. According to the results, SBRT with high dose for centrally located tumor has been considered to be risky. On the other hand, several investigators have reported favorable outcomes and toxicity profiles with moderate dose of SBRT (19).

Recently, Davis *et al*. reported treatment patterns and outcomes of SBRT for centrally located NSCLC or lung metastases from the RSSearch® (20). One hundred eleven patients with 114 centrally located lung tumors (48 T1-T2N M0 NSCLC) were evaluated. Median dose to centrally located NSCLC was 48 Gy and median BED10 was 105.6 Gy. Two-year LC rate was 76.4% and toxicity was low with no grade 3 or higher acute or late toxicities.

JROSG10-1 and RTOG0813 are dose escalation studies of SBRT for centrally located stage I NSCLC. Data from these trials will provide prospective date to determine the feasibility and optimal dose fractionation of SBRT for these tumors.

In summary, SBRT has been considered as highly effective treatment for early-stage NSCLC. However, there are still many unsolved issues, such as optimal dose fractionation or tolerable dose of normal organs. Further studies are warranted to provide the optimal treatment.

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