Simultaneous integrated dose reduction intensity-modulated radiotherapy applied to an elective nodal area of limited-stage small-cell lung cancer

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Abstract. The purpose of this study was to evaluate the clinical efficacy and toxicity of simultaneous integrated dose reduction intensity-modulated radiotherapy (SIR-IMRT) applied to an elective nodal area of patients with limited-stage small-cell lung cancer (LS-SCLC). Between January 2010 and March 2013, 52 patients with LS-SCLC that was treated with SIR-IMRT were retrospectively analyzed. A radiation dose of 54 Gy was administered in 30 fractions (1.8 Gy/fraction) to the planning target volume (PTV). Simultaneously, 60 Gy was administered in 30 fractions (2 Gy/fraction) to the planning gross tumor volume. Radiation-related toxicities were estimated according to the Common Terminology Criteria for Adverse Events (version 3.0). Overall survival (OS), locoregional recurrence-free survival and progression-free survival were estimated using the Kaplan-Meier method. By the last follow-up, the median follow-up time was 16.5 months, the median OS was 24.0 months, and 21 (40.4%) patients had experienced treatment failure. Of these patients, 5 (9.6%) patients developed in-field recurrence (within the 95% isodose curve of the PTV) and 1 (1.9%) patient developed an out-of-field recurrence (not a distant metastasis). Grade 3 or higher treatment-related pneumonia was observed in 4/52 (7.6%) patients, and grade 3 radiation-related esophagitis was experienced by 2/52 (3.8%) patients. The results of this preliminary study suggest that SIR-IMRT is safe and effective for patients with LS-SCLC and should be further evaluated in a large prospective clinical trial.

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Introduction

For limited-stage small-cell lung cancer (LS-SCLC), chemo-radiotherapy is a standard treatment and has been shown to improve patient survival (1,2). However, maintenance of local control is not reliably achieved with this treatment approach, which thus contributes to the high morbidity and mortality rates observed for patients with SCLC (3). Over the past several decades, radiation dose and patterns of radiation have been varied to optimize treatment (4-7). Theoretically, the application of higher doses of radiation to a tumor should improve local control rates, and studies have confirmed that there is a positive association between tumor control and higher radiation dose (5). However, in the Radiation Therapy Oncology Group (RTOG)-0617 study of non-small cell lung cancer (NSCLC) (8), the survival time of patients receiving 74 Gy irradiation was found to be shorter than that for patients receiving 60 Gy irradiation. While the reason for this observation remains unclear, it may be due to adverse radiation-induced effects. Thus, research is ongoing to optimize radiation delivery to tumors while sparing surrounding normal structures.

Of particular interest is the application of simultaneous integrated dose reduction intensity-modulated radiotherapy (SIR-IMRT) for the treatment of malignancies (9,10). SIR-IMRT simultaneously delivers a relatively higher dose of radiation to the primary disease, and a relatively lower dose to the subclinical disease or other selected regions. However, the outcome for SIR-IMRT in patients with LS-SCLC remains to be determined.

Therefore, the goal of the present study was to evaluate the feasibility of using SIR-IMRT for the treatment of LS-SCLC, and to provide evidence in support of future clinical studies.

Materials and methods

Patients. This retrospective clinical study was approved by the institutional review board of Tianjin Medical University Cancer Institute and Hospital (Tianjin, China). Between January 2010 and March 2013, patients with LS-SCLC who accepted SIR-IMRT at the hospital were included in this study. Two senior pathologists specializing in lung carcinoma reviewed all biopsy specimens, and pathologic staging was

conducted according to the current American Joint Committee on Cancer (AJCC) criteria for NSCLC (11). All patients were evaluated for hematologic, hepatic and renal function, and also underwent chest computed tomography (CT), neck and abdomen ultrasound, brain magnetic resonance imaging (MRI) and bone scan imaging prior to receiving radiotherapy.

Therapy. The primary tumor was delineated using a lung window, while mediastinal windows were used to delineate the medial border of centrally located primary tumors, involved lymph nodes and adjacent normal organs. Gross tumor volume (GTV) was defined as any visible primary lesion present on CT simulations. All lymph nodes with a diameter ≥1 cm along their short axis were also included. The planning gross tumor volume (PTV_G) was established by including a 0.5-cm margin around the GTV. Clinical target volume (CTV) was defined as the high-risk lymph nodal regions, including adjacent regions of involved lymph nodes and the ipsilateral hilar [in accordance with the new lymph node map of the International Association for the Study of Lung Cancer (12)], including the GTV with a 0.5-cm margin. Another 0.5-cm margin was added to establish the planning target volume (PTV). The prescribed radiation dose, 60 Gy to the PTV_G at 2 Gy/day and 54 Gy to the PTV at 1.8 Gy/day, was delivered to ≥95% of the PTV_G or PTV, respectively. The representative dose distribution using SIR-IMRT is shown in Fig. 1. Each treatment plan consisted of five static fields with the following normal tissue constraints: i) total lung, $V_{lung}5$ (i.e., the percentage of lung volume receiving ≥5 Gy) was ≤60% and $V_{lung}20$ was ≤35%; ii) $V_{lung}40$ was ≤30%; iii) $V_{esophagus}50$ was ≤50%, $V_{esophagus}$ maximum was ≤60 Gy; and iv) $V_{spinal\ cord}$ maximum was ≤45 Gy. The definitive dose volume parameter for the organ at risk (OAR) parameter for each subject is listed in Table I. For patients who achieved a complete response (CR) following thoracic radiotherapy, prophylactic cranial irradiation (PCI) was recommended, with a dose of 25 Gy administered over 10 fractions.

Follow-up. Patient follow-up started after the radiation treatment was completed. Initially, patients were monitored 1 month and 3 months after irradiation; they were monitored every 3 months thereafter. Follow-up appointments included a chest X-ray or CT scan and a color Doppler ultrasound of the abdomen. Cranial CT/MRI and bone scans were also performed if necessary. However, regardless of follow-up stage, any symptoms that developed were immediately examined. By November 30, 2013, the follow-up rate for this cohort was 100%, and the median follow-up period was 16.5 months (range, 7-42 months).

Response assessments and toxicity. Radiation-related toxicities for lung and esophagus were assessed by two senior radiation therapists according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (13). Response to radiation was first assessed 3 months after the completion of radiation based on new guidelines designed to evaluate the treatment response of solid tumors (14). These guidelines include considerations of CR, partial response (PR), stable disease (SD) and progressive disease (PD). Local recurrence was classified as in-field relapse or out-of-field relapse. The former was defined as recurrence within the 95% isodose curve of PTV. Correspondingly, PTV_G, GTV, CTV, and PTV recurrence were defined as being within the 95% isodose curve of each, respectively. Regarding out-of-field recurrences, these were defined as lesions outside of the 95% isodose curve of the PTV target area that were confined to the lung, pulmonary, mediastinal and supraclavicular regions without distant metastasis (DM). Recurrences beyond these areas were considered DM events.

Statistical analysis. Statistical analyses were performed using SPSS software, version 17.0 (SPSS, Inc., Chicago, IL, USA). Using the Kaplan-Meier method, OS, locoregional recurrence-free survival (LRFS) and progression-free survival (PFS) were calculated using the pathological diagnosis date as the starting point. The endpoint for OS was the date of mortality or the date of the last follow-up; the endpoint for LRFS was the date of primary tumor detection, the date of

Table I. Dose volume parameter of organ at risk (OAR; n=52).

OAR	Dose volume
MLD, cGy	1,479.06±188.53
$V_{lung}5$, %	49.33±7.08
$V_{lung}20$, %	28.85±3.29
$V_{lung}30$, %	20.17±3.13
Esophagus D_{max}, cGy	6,052.50±355.46
$V_{esophagus}50$, %	42.98±14.88
Cord D_{max}, cGy	4,451.93±343.43

MLD, mean lung dose; $V_{lung}5$, percentage of lung volume receiving ≥5 Gy; $V_{lung}20$, percentage of lung volume receiving ≥20 Gy; $V_{lung}30$, percentage of lung volume receiving ≥30 Gy; D_{max}, maximum dose; $V_{esophagus}50$, percentage of esophagus volume receiving ≥50 Gy.

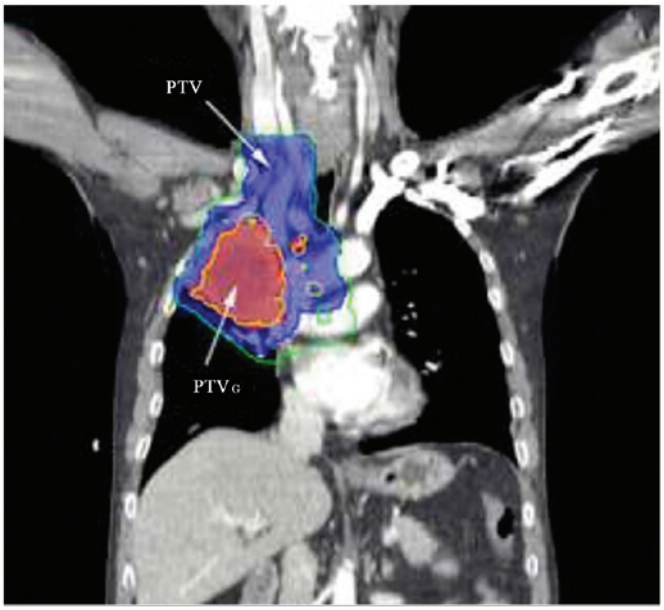

Figure 1. Representative image of simultaneous integrated dose reduction intensity-modulated radiotherapy with 60 Gy to the planning gross tumor volume (PTV_G). The colored lines indicate: Red, PTV_G; blue, planning tumor volume (PTV); yellow, field receiving 6,000 cGy; green, field receiving 5,400 cGy.

Table II. Patient characteristics (n=52).

Characteristics	No. (%)
Age (years)	
Median	59
Range	41-71
Site	
Left lung	19 (36.5)
Right lung	33 (63.5)
Type	
Peripheral	6 (11.5)
Central	46 (88.5)
Gender	
Male	35 (67.3)
Female	17 (32.7)
Clinical T stage	
T1	5 (9.6)
T2	29 (55.8)
T3	13 (25.0)
T4	5 (9.6)
Clinical N stage	
N0	1 (1.9)
N1	0 (0.0)
N2	28 (53.9)
N3	23 (44.2)
Clinical stage	
IIa	1 (1.9)
IIIa	25 (48.1)
IIIb	26 (50.0)
Induction chemotherapy	
Yes	51 (98.1)
No	1 (1.9)
Adjuvant chemotherapy	
Yes	37 (71.2)
No	15 (28.8)
Concurrent radiation with chemotherapy	
Yes	27 (51.9)
No	25 (48.1)
Prophylactic cranial irradiation	
Yes	25 (48.1)
No	27 (51.9)

regional lymph recurrence or the last follow-up date; and the endpoint for PFS was the date that disease progression was detected or the date of the last follow-up.

Results

Patients. Fifty-two LS-SCLC patients who received SIR-IMRT were enrolled in the present study. Patient characteristics are listed in Table II. All patients completed thoracic radiotherapy. The chemotherapy regimens that were administered included platinum-based doublets that were combined with either etoposide (72%) or teniposide (28%). A total of 42 patients accepted 2-4 cycles of induction chemotherapy before SIR-IMRT was performed, while 9 patients accepted radiotherapy after receiving 5-6 cycles of induction chemotherapy. In addition, 37 patients received chemotherapy after SIR-IMRT and 27 patients received concurrent chemo-radiotherapy. The 25 patients (83.3%) who achieved a CR after thoracic radiotherapy underwent PCI.

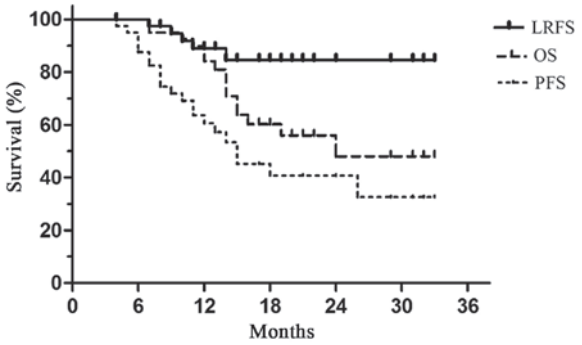

Figure 2. Overall survival (OS), locoregional recurrence-free survival (LRFS) and progression-free survival (PFS) curves for patients who received simultaneous integrated dose reduction intensity-modulated radiotherapy.

Survival. Three months after completing the radiation treatment, 30/52 (57.7%) patients and 20/52 (38.5%) patients experienced CR and PR, respectively. The median OS for the population was 24.0 months, and the median PFS was 18.0 months. Furthermore, the 1- and 2-year OS rates were 86.2 and 54.8%, the 1- and 2-year LRFS rates were 91.6 and 83.0%, and the 1- and 2-year PFS rates were 68.2 and 46.4%, respectively in each case (Fig. 2).

Patterns of failure. By the last follow-up, 21 (40.4%) patients experienced treatment failure. Of these, locoregional recurrence (LRR) developed in 6 (11.5%) patients, DM events at various sites were detected in 18 (34.6%) patients, and 3 (5.8%) patients experienced both LRR and DM. For the patients who developed LRR, 5 (9.6%) had in-field recurrences [4 (7.7%) within the GTV and 1 (1.9%) within the CTV], and 1 (1.9%) case involved an out-of-field recurrence. Regarding the latter case, the cervical lymph nodes were <1 cm in diameter prior to treatment. A clear diagnosis was not obtained, and therefore, prophylactic neck irradiation was not administered. Detailed data regarding DM events are listed in Table III.

Treatment-related toxicity. Various grades of treatment-related toxicity were observed in this study (detailed results are provided in Table IV). Grade 3 or higher treatment-related pneumonia (TRP) was observed in 4/52 (7.6%) patients, and grade 3 radiation-related esophagitis was experienced by 2/52 (3.8%) of patients. In particular, 2/52 (3.8%) patients experienced grade 5 TRP. Of these two patients, one succumbed due to infectious pneumonia combined with TRP 69 days after completing radiotherapy and the other patient succumbed to TRP that was contracted 33 days after radiotherapy was completed. While the first patient accepted six cycles of induced chemotherapy prior to radiation therapy, the second

Table III. Patterns of failure for first recurrence (n=52).

Recurrence	No. (%)
Total	21 (40.4)
Local regional recurrence	6 (11.5)
In-field	5 (9.6)
GTV	4 (7.7)
CTV	1 (1.9)
Out-of-field	1 (1.9)
Distant metastasis	18 (34.6)
Bone	2 (3.8)
Liver	5 (9.6)
Celiac lymph nodes	4 (7.7)
Brain	9 (17.3)
Adrenal gland	2 (3.8)
Heart	1 (1.9)
Pancreas	1 (1.9)
Local regional recurrence and distant metastasis	3 (5.8)

GTV, gross tumor volume; CTV, clinical target volume.

Table IV. Treatment-related toxicity (n=52).

	CTCAE 3.0 grade, n (%)				
Site	0-1	2	3	4	5
Lung	36 (69.3)	12 (23.1)	2 (3.8)	0 (0.0)	2 (3.8)
Esophagus	31 (59.7)	19 (36.5)	2 (3.8)	0 (0.0)	0 (0.0)

CTCAE 3.0, Common Terminology Criteria for Adverse Events, version 3.0.

patient accepted two cycles of induced chemotherapy with two cycles of synchronous chemotherapy.

Discussion

This study appears to be one of only a few clinical reports to describe the treatment outcome for LS-SCLC following SIR-IMRT. For LS-SCLC, chemo-radiation therapy is a standard treatment. In 2013, the National Comprehensive Cancer Network (NCCN) recommended that chemo-radiotherapy should include 1-2 cycles of chemotherapy followed by radiation therapy (15). The latter could include a 1.5 Gy dose twice a day for a total dose of 45 Gy, or a 2 Gy dose once a day for a total dose of 60-70 Gy. Currently, the optimal radiation dose for SCLC remains unknown. However, certain studies suggest that an appropriate increase in total dose may improve local control and prolong OS. Correspondingly, in the RTOG 97-12 trial for SCLC (5), the total doses were 50.4, 54.0, 57.6, 61.2 and 64.8 Gy, respectively, and the maximum tolerated dose was 61.2 Gy. Furthermore, 54/62 (87%) patients achieved a CR (68%) or PR (19%), and 61.2 Gy irradiation versus 50.4 Gy irradiation was found to improve 18- month OS rates (82% vs. 25%, respectively). In another phase II study (16), the efficacy and feasibility of accelerated radiotherapy involving a total dose of 61.2 Gy concurrent with chemotherapy for SCLC was investigated. The median survival period was 19.0 months, the 2-year OS rate was 46.4%, the 2-year PFS rate was 19.7%, and the median PFS period was 9.9 months. However, the results of the RTOG-0617 clinical trial showed that a higher radiation dose did not improve the survival of NSCLC patients compared to a traditional dose (8). While the reason for the latter unexpected result remains unclear, treatment-related toxicities associated with the high dose delivered to the PTV may play a role. Correspondingly, the safe application and escalation of radiation doses to a target while sparing and minimizing doses to adjacent healthy organs may be key to improving the therapeutic outcome for SCLC. At our institution, IMRT for SCLC patients includes a total dose of 60 Gy applied to the PTV_G and 54 Gy applied to the PTV. Using this approach, the 2-year OS, LPFS, and PFS rates for the present study were 54.8, 83.0 and 46.4%, respectively, and these are consistent with the RTOG 9311 study (16). It should also be noted that the present study achieved good results with a lower radiation dose, and yet the LRR for the present study did not increase compared with that observed in other studies, even though a relative lower total dose (54 Gy) was delivered to an elective nodal area. Based on these results, it appears that this dose of SIR-IMRT could benefit the LRFS and OS of LS-SCLC patients.

Some studies have found that three-dimensional conformal radiotherapy (3D-CRT) can result in a low elective nodal failure rate. This may be due to incidental radiation received by clinically uninvolved nodal regions (17,18). Moreover, the amount of incidental radiation delivered to non-targeted elective nodes may differ with IMRT, and thus, may be a factor in the rate of elective nodal failure. Furthermore, it has been observed that regional recurrence continues to occur in low-dose areas (18). In the present study, elective nodal regions received radiation therapy as a preventative measure, while healthy adjacent organs were exposed to tolerable doses. Elective nodal radiation of selected high risk regions is standard for IMRT performed at our medical center. Moreover, when elective nodal irradiation was applied, elective nodal failure in the PTV occurred in only 6 patients. This suggests that relatively lower doses of radiation delivered to elective nodal regions can be sufficient to control subclinical lesions when SIR-IMRT is used. Moreover, the overall results of the present study confirm that treatment of SCLC with SIR-IMRT deserves further consideration.

The toxic side-effects reported in the present study were encouraging compared with those noted in other studies, although IMRT has been associated with fewer side-effects (19,20). In the present study, 4/52 (7.7%) cases involved TRP of grade 3 or greater, and this is consistent with previous results (21). Moreover, in a recent study of IMRT for NSCLC and SCLC, the incidence of acute esophagitis and acute TRP (grade 3) ranged from 18-23% and from 7-11%, respectively (22). In addition, only 3.8% of patients experienced grade 3 or higher radiation-related esophagitis, and this is a lower incidence rate than that previously published (20). The use of the SIR-IMRT technique also resulted in the application of a dose gradient to the PTVG and PTV. This had the benefit of ensuring tumor dose and providing

protection for proximal normal organs. Correspondingly, in a recent meta-analysis, symptomatic pneumonitis increased 3% when lung V_{20} increased by 1% (23). In addition, predictors of fatal pneumonitis were found to include a daily radiation dose >2 Gy, V_{20} and the location of a tumor in the lower lobe (11).

This study had limitations. First, because the patients were not prospectively followed, selection bias and loss to follow-up may have contributed to underestimates of tumor recurrence and mortality rates. Second, four-dimensional CT examinations were not performed in this study, and this may have influenced the clinical outcomes. However, most of the primary tumors were located in the upper or middle lobes, or were central type tumors. Despite these limitations, however, the results of the present study indicate that SIR-IMRT improves patient survival and reduces toxic side-effects for patients with LS-SCLC, and also provides an intriguing justification for future studies of SCLC treatment involving SIR-IMRT.

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