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Background: To study the intra-thoracic failure pattern, clinical target volume (CTV) and survival status following 3D conformal radiotherapy (3DCRT) boost for non-small cell lung cancer (NSCLC).

Methods: From May 1994 through June 1998, 33 patients (26 male, seven female) with NSCLC were treated with a complete course of radiotherapy (RT) in our institute. Group A included 10 patients receiving radical operation and adjuvant postoperative RT. The other 23 patients (groups B and C) received definitive radiotherapy as local treatment. Among them there were seven cases as group B (stage I–II) and 16 cases as group C (stage III). Fifteen (15/33) patients received chemotherapy. The radiotherapy strategy constituted conventional AP/PA radiotherapy (RT) 19.8–45 Gy (median 39.6 Gy) plus 3DCRT boost 6–34.2 Gy (median 20 Gy). The median total tumor dose was 59.6 Gy (ranging from 39.8 to 64.8 Gy). Patients were followed up regularly (6/33) or until their death (27/33). Nineteen patients received follow-up chest computed tomography (CT). The relationship between intra-thoracic failure found by chest CT and the initial RT and boost RT fields was analyzed. Local failure was defined as one of the following: clinical disease progression, CXR progression or relapse noted by CT. The overall survival (OS) and local failure free survival (LFF) were obtained using the Kaplan–Meier method.

Results: Sixteen intra-thoracic failures were noted in 15 follow-up chest CT examinations, which included nine in-field relapses, three partial in-field relapses and four out-field relapses. The 2-year OS and LFF for groups A, B and C were 78.8/59.2, 14.2/16.7 and 6.2/7.1% respectively. RTOG grade III/IV complications included one pneumothorax (RTOG grade III).

Conclusion: Our retrospective study showed that selective omission of contralateral mediastinal lymph node station irradiation may be appropriate in RT for NSCLC. Chest wall and pleural relapses may not be a negligible cause of intra-thoracic failure after RT for NSCLC.

Key words: non-small cell lung carcinoma – conformal radiotherapy – neoplasm local recurrence

INTRODUCTION

Radiotherapy (RT) is an important modality in the treatment of non-small cell lung cancer (NSCLC) (1–3). In the era of 3D conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT), clear delineation of the clinical target volume (CTV) (4) on computed tomography (CT) is an important step in the practice of modern radiotherapy (1,5–7).
Local failure pattern and survival rate in 3DCRT for NSCLC

Analysis of failure patterns is helpful in delineation of CTV. However, there have been few studies focusing on the relationship of intra-thoracic failure with the initial irradiated volume (8–10) and it was not clearly mentioned that they were all based on chest CT studies. Therefore, we performed this retrospective analysis to review the survival status and the local failure pattern of 33 patients with NSCLC treated with a complete course of RT with 3DCRT boost in our institute from 1994 to 1998.

MATERIALS AND METHODS

PATIENTS’ CHARACTERISTICS

From May 1994 through June 1998, a total of 33 patients (26 male, seven female) with non-metastatic NSCLC were treated with complete courses of radiotherapy in our institute. The median age at the initiation of radiotherapy was 68.8 years (range 44.4–82.9 years). No specific occupation history was noted. Patients’ characteristics are shown in Table 1. All patients were uniformly staged by complete medical history and imaging finding. Pathological TNM (pTNM) staging was based on the operative finding and pathological records in 11 patients. Clinical TNM (cTNM) staging was based mainly on chest CT for the other 22 patients. Mediastinum lymph node was considered to be pathologically significant only when the diameter of the short axis of a lymph node was more than 1 cm (11). Bronchoscopy, bone scan, abdominal sonography and brain CT were performed when they were indicated clinically. The TNM staging was obtained according to the American Joint Committee on Cancer (AJCC), 5th edition, 1997 (12). All patients were classified into three groups. Group A included those patients who received radical operation. Group B included stage I–II patients who received definitive radiation therapy alone as local treatment. Group C included stage III patients who received definitive RT as local treatment (Table 2).

TREATMENT

Ten patients received radical operations (tumor excision and mediastinum lymph node dissection) and adjuvant postoperative RT. One patient received partial open-and-close surgery for advanced disease (stage IIIB). Twenty-three patients received RT as definitive local treatment.

The radiotherapy strategy constituted external beam RT (EBRT) via AP/PA two portals (13), 19.8–45 Gy (median 39.6 Gy) as first-stage RT, followed by 3DCRT boost 6–34.2 Gy (median 20 Gy) as second-stage RT. The median total tumor dose was 59.6 Gy (range 39.8–64.8 Gy). The CTV1 in first-stage RT included tumor site (in non-operated cases) or risky tumor bed (in operated cases), ipsilateral hilum, whole mediastinum and bilateral supraclavicular fossa (SCF) lymphatics when indicated (such as upper lobe tumor or enlarged SCF lymph node). The CTV2 in second-stage RT generally included the tumor site or risky tumor bed with/without elective nodal irradiation (ENI). For ENI, American Thoracic Society (ATS) station 6 (anterior mediastinum nodes) were generally excluded and ATS station 5 (aortopulmonary nodes) were generally excluded for right lung cancer (12). The margin between planned target volume (PTV) and CTV is generally about 1–2 cm. For 3DCRT, a plastic immobilizer with metallic wire marker was used for each patient. Chest CT was then performed in the same position with a 5–8 mm slice thickness. After CTV contouring slice by slice made by radiation oncologists (S. W. Chen, J. A. Liang, S. N. Yang), treatment planning was carried out by physicists with Nucleatran PLATO 2.0. The actual dose delivery was calculated without lung density correction. The portal number in 3DCRT was 2.9 on average (range 2–4). In most cases three coplanar portals were used. An

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Total No. of patients</td>
<td>33 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>26 (79)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Smokers</td>
<td>23 (70)</td>
</tr>
<tr>
<td>SCC</td>
<td>20 (61)</td>
</tr>
<tr>
<td>AC</td>
<td>12 (36)</td>
</tr>
<tr>
<td>NS</td>
<td>1 (4)</td>
</tr>
<tr>
<td>RUL</td>
<td>6 (18)</td>
</tr>
<tr>
<td>RML</td>
<td>5 (15)</td>
</tr>
<tr>
<td>RLL</td>
<td>9 (28)</td>
</tr>
<tr>
<td>LUL</td>
<td>7 (21)</td>
</tr>
<tr>
<td>LLL</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma; AC, adenocarcinoma; NS, non-specified non-small cell lung cancer; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe.

### Table 2. Patient grouping and staging (patient number)

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
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<tbody>
<tr>
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<td>3</td>
<td>5</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>II A</td>
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</tr>
<tr>
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<td>9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

Group A, 10 patients receiving radical operation; group B, seven stage III patients receiving definitive radiotherapy (RT) as local therapy; group C, 16 stage III patients receiving definitive radiotherapy (RT) as local therapy; IA–IIIB, TNM staging.
example is shown in Fig. 1. Wedges were used to improve the dose homogeneity as necessary. The main constraint was to keep the cumulative spinal dose <50 Gy. The irradiated lung volume was to be kept as small as possible. The EBRT was generated from linear accelerators (Siemens, MEVATRON KDS-2) and shaped by custom-fabricated blocks. Radiotherapy was given in a period of 37–84 days (median 57 days) except for one case in 136 days.

Fifteen patients also received chemotherapy (C/T). Generally, C/T was applied to those with a relatively good general condition and patient acceptance. The time sequence of C/T included pre-definitive RT C/T in two cases, adjuvant concurrent chemo-radiation therapy (CCRT) in two operated cases, definitive CCRT in four non-operated cases, adjuvant C/T following radical operation and RT in five cases and adjuvant C/T following definitive RT in six cases. Before mid-1997, MFL (Mitomycin C + Floral + Leucovorin) was the main C/T regimen. After mid-1997, the C/T regimen was Taxotel- and Gemzar-based C/T (two patients) or Cisplatin-based C/T (three patients).

FOLLOW-UP

After completion of treatment, all patients were followed up until their death. Three of them died of early clinical disease progression before follow-up CXR was done. Follow-up chest CT had been performed in 19 cases. Since it is often difficult to differentiate post-radiation and/or post-operative change from disease progression, CXR were used to evaluate disease progression only. CXR progression was defined as a progressive change in follow-up CXR. Intra-thoracic failure was defined as obviously enhancing soft tissue mass or progressive change noted in follow-up chest CT. When there were one or more intra-thoracic failures noted in the chest CT, local regional relapse chest CT (LRR-CT) was recorded. The location of the failure and its geographic relationship with CTV1 and CTV2 were documented. Relapse in CTV2 was defined as ‘in-field’ relapse, while relapse only in CTV1 was defined as ‘partial in-field’ relapse and relapse outside the CTV1 was defined as ‘out-field’ relapse. The lymph node location was documented according to AJCC, 5th edition, 1997 (12,14). ‘Local failure’ was defined as one of the following: clinical disease progression, CXR progression or LRR-CT. Brain CT, bone scan and abdominal sonography were performed only when distant metastasis was suspected.

STATISTICAL ANALYSIS

The Kaplan–Meier method was used in the calculation of overall survival (OS) and local failure free (LFF). The period of LFF was from the first day of RT to the first day of local failure or the last day of imaging study with stationary finding. The period of OS was from the first day of RT to the day of the last follow-up, the day of a telephone visit or death. The log rank test and Cox regression method were used for univariate and multivariate analysis.

RESULTS

For group A patients, there were four patients living without disease, three patients died of local failure, two patients died of both local failure and distant metastasis and one patient died of distant metastasis. The 1 and 2 year OS/LFF were 80/80 and 50/45%, respectively.

For group B patients, there was one patient living without disease, five patients died of local failure and one patient died of both local failure and distant metastasis. The 1 and 2 year OS/LFF were 57.4/50 and 14.2/16.7%, respectively.

For group C patients, there was one patient living without disease, 11 patients died of local failure, three patients died of both local failure and distant metastasis and one patient died of distant metastasis. The 1 and 2 year OS/LFF were 43.7/7.1 and 6.2/7.1%, respectively.

The 2 year OS of all patients for smoker/non-smoker, operated (OP)/non-operated (nonOP) and chemotherapy/non-chemotherapy were 21.7/20, 50/8.7 and 20/22.2%, respectively. In univariate analysis, the only statistical significance was found in OP/nonOP (p = 0.006). The same was found in multivariate analysis (p = 0.021). The 2 year LFF of patients receiving an RT dose of >60 Gy was inferior to those receiving an RT dose of <60 Gy (8/17%) without statistical significance.

Seven patients in group A received follow-up chest CT; five LRR-CT were found in four of the seven patients (follow-up CT in one patient showed two local regional relapses). The relapse pattern included three ‘in-field’ relapses, one ‘partial in-field’ relapse and one ‘out-field’ relapse. Twelve patients in groups B and C received follow-up CT; 11 LRR-CT were found in 11 of the 12 patients. The relapse pattern included six ‘in-field’ relapses, two ‘partial in-field’ relapses and three...
"out-field" relapses (Table 3). For the nine cases of "in-field relapse", the median total RT dose was 60 Gy (range 46–64.6 Gy). For the three cases of "partial in-field relapse", the RT dose to relapse site was 45, 49.6 and 53.1 Gy, respectively. All the sixteen LRR-CT were first failure site except in one case in which LRR-CT was found 1 month later after distant metastasis was found. A representative diagram showing the distribution of the LRR-CT is shown in Fig. 2.

Extra-thoracic metastases were noted in eight cases (bone metastases in four cases, liver metastases in two cases and brain metastases in two cases). Isolated extra-thoracic metastasis was noted in two cases (brain and bone). Three extra-thoracic metastases were found within 2 months after the evidence of local failure and the other three extra-thoracic metastases were found within 2 months before evidence of local failure. The only RTOG grade III/IV complication was one pneumothorax (RTOG grade III), which was noted in one case in group C during the course of RT.

DISCUSSION

The optimum area of CTV for NSCLC is still not well established (15–17). The ratio of the largest to smallest contoured volume had been reported to be within the range 1.6–2 among different radiation oncologists (RO), independent of the experience of the RO (17). According to ICRU Report 62 (4), CTV included CTV-T and CTV-N. So it is better to have information about the lymphatic drainage of the lung and the relapse pattern to assess what should be included in CTV-N and CTV-T.

With regard to CTV-N, the lymphatic drainage of lung cancer is mainly ipsilateral and cephalad irrespective of the primary site (18). It seems that there is a tendency to reduce the volume of CTV, although skip metastasis was found in 20–80% of pN2 patients (19,20). Emami et al. suggested a strategy to include high-risk area, ipsilateral hilum, mediastinum and selective ipsilateral supraclavicular fossa for post-operative RT to NSCLC (21). Armstrong and Ginbey suggested that it may be appropriate to ignore subclinical extensions when designing CTV (5,22). McGibney et al. suggests omission of ENI and 3DCRT to achieve dose escalation (23). Armstrong et al. suggested a strategy to exclude ENI after 50 Gy for dose escalation (median dose 70.2 Gy) for a better survival rate (32% 2 year OS for inoperable NSCLC) (24). For clinical stage I cases, only 13% pathological N2 metastasis had been reported (25) and Hayakawa et al. reported similar results.

<table>
<thead>
<tr>
<th>Location</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Total</th>
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</thead>
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<td>1</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Chest wall</td>
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<tr>
<td>iLN</td>
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</tr>
<tr>
<td>Pleural nodules</td>
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<tr>
<td>Pleural nodules</td>
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<tr>
<td>Total</td>
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<td>4</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

Group A, 10 patients receiving radical operation; group B, seven stage I/II patients receiving definitive radiotherapy (RT) as local therapy; group C, 16 stage III patients receiving definitive radiotherapy (RT) as local therapy; "in-field" relapse, relapse in initial RT volume and boost volume; "out-field" relapse, relapse outside initial RT volume; iLN, ipsilateral mediastinum lymph node; iPE, malignant ipsilateral pleural effusion without obvious mass; cPE, contralateral malignant pleural effusion without obvious mass.
for either omission of ENI or not (5 year OS: ENI/non-ENI 39/40%) (26) and Slotman et al. also reported a good result (76% 3 year disease specific survival) with omission of ENI (27). Of the 16 LRR-CT in our study, there were two ipsilateral mediastinal lymph nodes (ATS LN stations 4 and 5). Hence it may be reasonable to exclude contralateral mediastinum lymph node stations from the CTV and even to exclude ENI from the beginning for stage I cases.

Concerning CTV-T, the intra-thoracic recurrence rate for stage I/II cases had been reported to be 5–22% and even higher in more advanced stages (3). However, the problem depends on how we detect local relapse. The earlier study used chest X-ray as a major tool (28,29). Chest CT has an important role in detecting local relapse. In one study, 75% of tumor recurrence was recognizable only by CT (30). Positron emission tomography (PET) scanning has a better sensitivity/specificity (100%/92%) to detect recurrent/residual lung cancer than does chest CT (sensitivity/specificity 71/95%) (31). With regard to the relationship between intra-thoracic relapse and the initial RT field, Perez et al. reported 35% local relapse (diagnosed by chest X-ray) in irradiated lung and 30% local relapse in non-irradiated lung (19% in both fields) for inoperable NSCLC patients receiving an RT dose of 60 Gy (8). Byhardt et al. (9) reported an intra-thoracic failure rate of ~41–50% after definitive RT for stage I–IIIB NSCLC, which is composed of five Radiation Therapy Oncology Group (RTOG) studies (32–36). However, it was not clearly mentioned in these studies whether the failure pattern was based only on chest CT studies or not, except in the report by Byhardt et al. (32). Whether 3DCRT is used in these studies was also not mentioned. Further, the failure pattern in this study was only documented as ‘primary’, ‘thorax’ or ‘both’. The failure rate of primary, thorax and both were 17–22, 16–18 and 5–9%, respectively. Of the 16 LRR-CT in our study, nine were found to be totally in our RT field. Another three were partially in our field. On the other hand, eight of the 16 LRR-CT were chest wall metastasis (three), pleural nodules (three) and malignant pleural effusion (two). These were not easily included in the ordinary idea of CTV (risky tumor bed/site plus regional lymphatics) (3,5,6,15). How to define the optimal ‘margin’ for CTV-T to include the risky pleurae/chest wall deserves further studies. Recent meta-analysis showed the effect of C/T in the treatment of NSCLC (37). Perhaps systemic chemotherapy will help in this situation.

The RT dose also influenced the local results. Perez et al. had suggested that a higher dose of irradiation would be necessary in order to improve the intra-thoracic tumor control (the failure rate within the irradiated lung was 38% for a tumor dose of 50 Gy and 27% for a tumor dose of 60 Gy) (8). The current tendency also showed that a high dose was favored (median dose ranging from 66 to 70.2 Gy) (1,2,27). In our study, local failure was noted in 25 cases (75%). This may be due to the high (7/16) non-‘in-field’ relapse rate or the RT dose in our study was not effectively high enough (maximum 64.8 Gy). The optimum RT dose for NSCLC deserves further study.

After the disclosure of the human genome, the genetics of cancer may be better understood in the future. Perhaps molecular staging can help us in assessing the risk of lymph node metastasis (38) and the concept of biological target volume (BTV) (39) can further help us in defining the optimum volume of RT for NSCLC in the future.

CONCLUSION

Our preliminary retrospective study showed that most of the intra-thoracic relapses were within the initial large RT field. LN failure as first failure site was noted in only 12.5% LRR-CT. Also, there was a high percentage (43%) of ‘out-field’ or ‘partial in-field’ relapses. Chest wall/pleural relapses may be contributory to the intra-thoracic failure after RT for NSCLC. Selective omission of the ENI region (especially contralateral mediastinum lymph node region) from the RT field may be appropriate.

Acknowledgments

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References

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