Isolated nodal failure after chemo-radiotherapy in limited disease small cell lung cancer (LD-SCLC)

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ABSTRACT

BACKGROUND: The irradiation volume for treatment of limited disease small cell lung cancer (LD-SCLC), are still controversial. One of the aspects of radiation volume is the use of elective nodal irradiation (ENI), which has never been subjected to randomized study in SCLC patients.

AIM: To review retrospectively patterns of failure in relation to the radiation field after chemoradiotherapy (CHT-RT) in patients with limited disease small cell lung cancer (LD-SCLC).

MATERIAL AND METHODS: Between 1997 and 2006, 117 consecutive patients with LD-SCLC received chemotherapy with sequential radiotherapy (70%) and concurrent or alternating CHT-RT (30%). All but one case had predefined elective nodal irradiation (ENI) without inclusion of supraclavicular regions. Prophylactic cranial irradiation (PCI) was administered to 39% of patients.

RESULTS: The median follow-up for the 20 living patients was 33 months. The overall survival at 2 years was 36% (median survival: 18 months). In-field locoregional progression was observed in 42 patients (36%). Distant metastases occurred in 71 patients (61%). Five patients (4%) developed isolated nodal failure (INF) without local progression in the supraclavicular region. Patients with INF had N3 disease more often than those without INF (60% vs 21%, p = 0.04). There was 5% RTOG grade 3 or higher early radiation toxicity.

CONCLUSIONS: INF failures are rare; however, the need for extension of ENI to supraclavicular areas may be reconsidered in N3 patients.

KEY WORDS: small-cell lung cancer, limited disease, radiotherapy, elective nodal irradiation, isolated nodal failure

BACKGROUND

The benefit of using radiotherapy (RT) for limited disease small cell lung cancer (LD-SCLC) was shown by two meta-analyses [1, 2] in 1992 and its use has not raised major controversies since then. However, many topics related to RT for LD-SCLC, such as the timing of its use in relation to chemotherapy (CHT), fractionation schedule, total dose, and irradiation volumes, are still controversial and involve unresolved issues. Since timing, fractionation, and dose have been subject to many prospective trials, we can draw a number of conclusions from these studies and guide our clinical practice by the results of these trials, even if there is still some debate on these issues. On the other hand, radiation target volume has not been evaluated in prospective studies, apart from one pre-CT-era study in which patients with partial response after CHT were randomized to treatment by the use of portals including pre-CHT or post-CHT images on chest X-rays. Although there was no difference in the rate of local recurrences in the respective treatment arms according to pre- and post-CHT volumes [3], we probably cannot rely on the findings of a study based on, from a contemporary point of view, poor imaging. The other aspect of radiation volume

is the use of elective nodal irradiation (ENI), which has never been subjected to randomized study in SCLC patients. Despite the lack of evidence on the safety and/or benefit of the omission of ENI, the two current randomized trials on RT in LD-SCLC (one in its final approval stage by a major North American collaborative group and one recently launched by EORTC) do not allow for any form of ENI [4]. As our departmental policy has always been to use some ENI for LD-SCLC, the question has arisen as to whether we should also limit the radiation portals to the involved fields.

AIM

To review retrospectively patterns of failure in relation to the radiation field after chemoradiotherapy (CHT-RT) in patients with limited disease small cell lung cancer (LD-SCLC).

PATIENTS AND METHODS

Patients

A review of the database in the Department of Radiation Oncology of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw identified 117 consecutive patients who completed radical thoracic radiotherapy as part of initial treatment for LD-SCLC between 1997 and 2006. Medical records of all patients were available for review. The characteristics of the group are given in Table 1.

The departmental policy was to perform bronchoscopy, chest CT with inclusion of upper abdomen, brain CT or MRI and bone scan as obligatory components of initial staging for establishing a diagnosis of LD-SCLC. Bone marrow aspiration/biopsy was not mandatory in the later part of the period of interest. Despite these guidelines, the chart review showed that 20% of patients had no brain imaging, 35% had no bone scan, and 70% had no bone marrow aspiration/biopsy done for initial staging.

Follow-up visits started one month after treatment completion, and then were performed every three months. These visits involved clinical examinations, chest X-rays, and basic blood examinations; chest CT scans were performed one and six months after RT and thereafter annually or more frequently if disease progression was suspected. Other examinations were performed if metastases were clinically suspected. Bronchoscopy and pulmonary function tests were performed when needed for clinical purposes.

Table 1. Characteristics of patients

Characteristics	Number (%) unless otherwise stated
Sex	
Male	73 (62%)
Female	44 (38%)
Age	Median: 57 (Range: 43 – 78)
WHO Performance status	
0	87 (74%)
I	29 (25%)
II	1 (1%)
Weight loss (%)	
0	96 (82%)
1-5	11 (9%)
6-10	7 (6%)
>10	3 (3%)
Tumor Main Site	
Upper lobe	50 (43%)
Middle or lower lobe	67 (57%)
Nodal involvement	
N0	20 (17%)
N1	11 (9%)
N2	51 (44%)
N3	24 (21%)
No exact data	11 (9%)
Presence of Bulky Mediastinal Disease	70 (60%)
Upper mediastinum involvement	23 (20%)

Treatment characteristics

Chemotherapy consisted of 2–6 (median: 4) courses of cisplatin and etoposide (PE) every 21 days; however 18 (15%) patients received another type of CHT due to toxicity or other reasons, as listed in Table 2. Sequential treatment was given to 82 (70%) patients. The total dose of sequential RT varied from 44 Gy to 60 Gy (median: 56 Gy), with 2 Gy per fraction. Seventeen (15%) patients were treated with a concurrent schedule with hyperfractionation,

Table 2. Chemotherapy schedules used

Regimen	Number of patients (%)
PE cisplatin with etoposide	100 (85%)
KE karboplatin with etoposide	6 (5%)
CAV (Cyclofosfamide, Doxorubicin, Vincristine)	1 (1%)
Other (mostly combinations of above)	10 (9%)

with a regimen of 30 x 1.5 Gy twice daily given with the first of four cycles of PE. The alternating schedule was used in 18 (15%) patients and consisted of a combination of four courses of PE divided by three courses of RT of 20 Gy, 20 Gy, and 16 Gy, respectively, with 2 Gy per fraction. The assignment to the type of CHT-RT combination reflected changes in departmental treatment policy over time, but as a rule, patients who were fitter and with smaller tumour volumes were given concurrent treatment. Prophylactic cranial irradiation (PCI) was administered to 39% of patients. The total dose of PCI varied between 10 Gy (one patient) and 30 Gy (median: 25 Gy) with a dose per fraction of 1.8 to 3 Gy (median 2.5 Gy).

For 52% of patients, the elective fields were 2D planned using anterior–posterior/posterior–anterior (AP/PA) fields and treated up to 44 Gy in the conventional fractionation group, and up to 30 Gy in the hyperfractionated schedule. The oblique fields were consecutively 3D planned for boost and treated up to a median of 56 Gy in the conventional arm and 45 Gy in the cases treated twice daily. For the remaining 48% of patients, the total course of radiotherapy (elective and boost fields) was 3D planned. Two-D techniques were used before routine introduction of the entire 3D planning for lung cancer patients in our department. The boost volumes were defined as macroscopic tumour and pathologic mediastinal/hilar (rarely, supraclavicular) lymph nodes (with short axis diameter larger than 1 cm in CT) with a 1–2 cm margin. The elective area encompassed the bilateral mediastinal and ipsilateral hilar lymph nodes. Supraclavicular regions were not electively treated, except in one case. The superior border of the elective field was set at the sternal notch. The inferior border was set 5 cm under the carina for upper lobe tumours and at the diaphragm for lower/middle lobe tumours. The lateral borders were set at 1 cm from the mediastinal shadow. 3D-planned elective fields were mainly also AP/PA-oriented and their borders did not vary significantly from the 2D-planned fields, as attention was paid to keeping the same anatomical landmarks as for the borders in 2D-planned ENI fields. The general departmental policy was to include in the radiation field the pre-CHT involved lymph node stations regardless of the CHT response, and decisions regarding inclusion in the field of pre-CHT volumes of tumours located within the pulmonary parenchyma were left to the discretion of the treating physician. In cases of massive initial lung involvement and/or poor pulmonary function, the radiation volume did not include the entire pre-CHT involved lung.

Analysis of sites of failure

The sites of failure were defined based on medical record review. If doubt on the occurrence or location of relapse arose, the radiological imaging and radiation planning data were reviewed. Locoregional relapse was defined as progression of the primary tumour or initially involved lymph nodes, whichever occurred first. Isolated nodal failure (INF) was defined as a regional nodal failure occurring without locoregional progression. Whether or not the location of the INF was included in a radiation field was recorded.

Statistical analysis

The overall survival and disease-free survival were assessed using the Kaplan–Meier method. The log-rank test was used to find any relationships between outcomes and treatment parameters. For the occurrence of INF, the influence of tumour-related parameters such as the location of the tumour, the N stage, the involvement of the upper mediastinum and the presence of bulky mediastinal disease (BMD) were sought by proportion comparisons using the chi-square test in a 2 x 2 contingency table format. BMD was defined as the initial involvement of at least three lymph node stations within the mediastinum and/or an increase in the size of a single lymph node to at least 3 cm. SPSS software (Statistical Package for the Social Sciences) for Windows (version

14; SPSS, Chicago Illinois, USA) was used for statistical analysis.

RESULTS

Median follow-up for the 20 censored patients was 33 months. The overall survival rates at 2 and 3 years were 36% and 26%, respectively, and median survival was 18 months. The disease-free survival rates at 2 and 3 years were 17% and 15%, respectively. The overall survival at 2 years was 29% for patients treated with sequential treatment and 49% for those with concurrent and alternating schedules ($p = 0.28$). There was no difference in 2-year overall survival with respect to PCI use (41% PCI vs 33% without PCI, $p = 0.23$). There was no difference in 2-year overall survival with respect to the technique of radiotherapy used (29% for 2D technique vs 43% for 3D technique, $p = 0.14$).

Locoregional progression was observed in 42 (36%) patients. Distant recurrence occurred in 71 patients (61%). It is noteworthy that 41 (35%) had brain metastases, 21 (18%) with isolated brain metastases. Only five (11%) patients developed isolated brain metastases in the PCI group. There was a statistically significant difference in the cumulative incidence of brain metastases with respect to PCI use (50% vs 16% at 2 years for no PCI vs PCI, $p = 0.003$).

Five (4%) patients developed INF. All detected cases of INF were localized in the supraclavicular region and were out-of-field failures. The nodal stages of this selected group with occurrence of INF were N1 – one patient, N2 – one patient, and N3 – three patients. Patients with an N3 nodal stage accounted for 60% of the five patients with INF, compared with 21% of 101 without INF with known N stage ($p = 0.04$). Four of five cases (80%) with INF had BMD at the initial staging in comparison with 66 (59%) in the remainder ($p = 0.34$). Two of five patients (40%) with INF had the primary tumour localized in the upper lobe, in comparison with 48 (43%) in the remainder ($p = 0.90$). Two (40%) of the INF cases had initial involvement of the upper mediastinum in comparison with 21 (19%) patients without occurrence of INF ($p = 0.24$). Median time to INF occurrence was 9.5 months (range: 8–17 months). Median survival of patients from the diagnosis of INF was 4 months (range 2–50 months).

The retrospectively evaluated toxicity was mild, with only 5% RTOG grade 3 or higher radiation-induced toxicity (one toxicity-related death).

DISCUSSION

We have identified distant metastases as the most common type of failure after combined treatment of LD-SCLC, with 35% local relapses, which is in agreement with other data [5, 6]. The frequency of isolated nodal failure following thoracic radiotherapy for this disease has rarely been the subject of investigation. Studies from the pre-CT era suggested that violations in protocols related to incomplete coverage of the predefined large elective area, including the bilateral mediastinum and hila, as well as the bilateral supraclavicular regions, led to excessive locoregional relapse rates and shortened survival [7]. However, such findings must be interpreted with reference to the inadequate diagnostic techniques and the high probability of the geographic mistargeting of gross disease. In the CT era, Tada et al. [8] have shown a 16% rate of marginal (at the edge and out-of-field) failure in 117 patients managed with RT-CHT. When we exclude from the marginal failures three cervical metastases and five others in the peripheral lung, we obtain 11 "true" marginal nodal failures, which gives a 9% isolated nodal failure rate. This is more than in our retrospective study; however, our approach to elective treatment was stricter, rendering our elective fields more extensive than in the study by Tada et al. [8]. We have adopted a field design as described by Turrisi et al. [9], treating the bilateral mediastinum and ipsilateral hilum, without supraclavicular nodes if not involved, following what was a quite general policy in most trials beginning in the 1990s [4]. Our policy resulted in a 4% isolated nodal failure rate, all in the supraclavicular area and outside the radiation field. This is less than in the study of Tada et al., which did not have a strict approach to elective field design, and less than the 11% supraclavicular nodal failures seen in the short follow-up period of a prospective phase II study with the omission of ENI for LD-SCLC [10]. In contrast to those

findings, Baas et al. [11] did not observe any isolated nodal failures in 37 patients treated with concurrent CHT-RT without ENI. The observed difference in the rate of isolated nodal failures localized to the supraclavicular region between these studies with omission of ENI may be related to very meticulous patient staging before treatment in the study of Baas et al. [11], in contrast to the study of De Ruysscher et al. [10], which was based on evaluation of the supraclavicular areas by CT only. As indicated by Belderbos [12], in comparison with CT alone, the evaluation of the supraclavicular area with at least ultrasound, in the absence of PET, may improve the diagnosis of supraclavicular nodes. Improved staging may improve radiation planning for LD-SCLC; however, the role of tools such as 18FDG-PET is still under investigation in this disease and requires more data before their routine implementation [4, 13, 14].

The low rate of isolated nodal failures reported after RT for LD-SCLC, with an approximately 30%–50% rate of local relapse [5], prompted some investigators to shift to a higher radiation dose to the involved fields or more aggressive chemotherapy (without ENI), in view of improvements in the therapeutic ratio [4]. However, the failure rate of about 5% is not negligible, as all isolated nodal failures ultimately failed salvage therapy, as shown in our study. This led to the worsening of outcome in about 5%, equal to the benefit resulting from the use of thoracic therapy or PCI, which was a reason for the common implementation of these treatment strategies. We have no evidence that the omission of ENI in LD-SCLC may reduce toxicity, since in the two prospective studies with omission of ENI, the toxicity was quite high and was not reduced in comparison with historical series [10, 11]. We observed an exceptionally low rate of early toxicity in our study, but this was related to the mostly sequential schedule of delivering CHT-RT and very careful selection of patients for the concurrent combination. The retrospective character of the study may also underestimate the incidence of toxic events.

We tried to define the characteristics of patients with isolated nodal failures. Tada et al. [8] found that a higher nodal stage was related to a higher risk of isolated nodal failure. A similar observation was made for non-small cell lung cancer (NSCLC) in the study of Kepka et al. [15]. Therefore, we looked for any relationship between initial nodal characteristics and the risk of isolated nodal failures. The small number of events may compromise any statistical considerations; however, N3 disease reached statistical significance, as it did in the study of Tada et al. [8]. The presence of bulky mediastinal disease as well as the involvement of the upper mediastinum may also influence the incidence of supraclavicular failures in the absence of irradiation of this area. As the toxicity of ENI is not proven in clinical studies, enlargement of the radiation field to the supraclavicular region is unlikely to increase toxicity, especially if large portals for upper mediastinum involvement and/or treatment of bulky mediastinum are already employed. Taking into account the results of this study and our previous work on the risk of out-of-field failure for NSCLC [15], we have started a planning study to examine the influence of enlargement of the field to the supraclavicular area on doses to critical structures, especially the oesophagus and lung, in cases of extensive nodal involvement in terms of stage, number, and/or location.

CONCLUSIONS

INF failures are rare; however, the need for extension of ENI to supraclavicular areas may be reconsidered in a more advanced nodal stage.

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