Acta Oncologica, 2015; 54: 1574–1581

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ORIGINAL ARTICLE

Evaluation of factors associated with loco-regional failure and survival in limited disease small cell lung cancer patients treated with chemoradiotherapy

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ABSTRACT

Background. Loco-regional failure (LRF) remains a significant problem in limited disease small cell lung cancer (LD-SCLC) patients treated with definitive chemoradiotherapy. Dose-escalation may be a way forward to reduce the failure rate. However, the risk of toxicity rises with increasing doses. Knowledge on factors associated with LRF could aid the selection of patients for more aggressive treatment. Therefore, the aim of this study is to evaluate factors correlated with LRF in a cohort of LD-SCLC patients treated with definitive chemoradiotherapy. Moreover, factors associated with improved survival were investigated.

Material and methods. We included 147 consecutive LD-SCLC patients treated from 2007 to 2013. Radiotherapy was delivered as either 45 Gy in 1.5-Gy fractions twice daily or 46–50 Gy in 2-Gy fractions once daily. Chemotherapy was etoposide combined with either carboplatin or cisplatin given mainly concomitantly with radiotherapy. Pattern of first failure and survival were evaluated retrospectively. Cumulative LRF (CLRF) and overall survival (OS) were calculated by the Kaplan-Meier method. The impact of covariates on LRF and OS was evaluated by using Cox proportional hazards model.

Results. With a median follow-up time of 42.2 months, 37 patients experienced LRF as first failure. Isolated LRF was seen in 16 patients, but no isolated regional failure was seen. The CLRF rate was 22% at 1-year and 43% at 3-years. N3-stage was an independent prognostic factor correlated with LRF development ($p = 0.043$). Median OS was 24.1 months (95% CI 19–29 months) and a three-year survival of 34%. Prognostic factors associated with improved OS were staging including a positron emission tomography (PET) scan ($p = 0.004$) and receiving prophylactic cranial irradiation (PCI) ($p = 0.006$).

Conclusion. N3-stage was an independent prognostic factor for LRF. Receiving a pretreatment PET scan and receiving PCI were prognostic factors for improved OS. Reduction in LRF may be achieved with dose-escalation in patients with N3-stage. This can be evaluated in prospective dose-escalation trials.

Combined chemoradiotherapy (CRT) has been the preferred treatment of small-cell lung cancer (SCLC) patients with limited disease (LD) for several decades [1,2]. Several therapeutic improvements have been introduced. For example, prophylactic cranial irradiation (PCI) has lowered the incidence of brain recurrence [3] and the use of positron emission tomography/computed tomography (PET/CT) scans in the staging procedure has made staging more accurate [4]. The optimal timing of radiotherapy was shown to be concurrent with chemotherapy [5] and accelerated with fractions given twice daily [6]. A more precise target definition has been obtained by using PET/CT scans for delineation of disease [7] and by incorporation of 4D CT-guided planning [8,9]. Furthermore, dose distribution has been increasingly conformal owing to the introduction of intensity-modulated radiotherapy (IMRT) [10]. However, despite all these improvements, recurrence remains

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(Received 15 May 2015; accepted 8 June 2015)

ISSN 0284-186X print/ISSN 1651-226X online © 2015 Informa Healthcare
DOI: 10.3109/0284186X.2015.1062135

a major problem due to the aggressive nature of the disease, and overall survival (OS) remains low.

Consequently, continues work is ongoing to improve treatment of this group of patients. Of particular interest have been a more optimal timing of the dose and the schedule of radiotherapy. Recent work has demonstrated that both 60 Gy (1.5 Gy per fraction, twice daily) [11] and 70 Gy (2 Gy per fraction, once daily) [12] concomitantly with chemotherapy are tolerable regimens and dose-escalation may be one of the clues to achieving higher local control. However, with high-dose regimens introduced in the daily clinical routine, toxicity problems may increase [13]; and proper selection of patients for these regimens will be of utmost importance. Knowledge of prognostic factors associated with the risk of developing loco-regional failure (LRF) could inform this selection. The aim of the present study was therefore to evaluate factors correlated with LRF in a cohort of LD-SCLC patients treated with radical CRT in a routine clinical practice over a seven-year period. A secondary purpose was to evaluate factors associated with longer OS.

Material and methods

Patients

In this retrospective study, we included all consecutive LD-SCLC patients treated with thoracic radiotherapy at the Department of Oncology at Aarhus University Hospital, Denmark between April 2007 and December 2013. The inclusion criteria were a pathologically proven diagnosis of SCLC, a staging confirming LD and initiation of treatment with radiotherapy in curative doses regardless of whether the patient actually completed the treatment or not. Two patients had another malignant disease at the time of diagnosis and were therefore excluded. Data from 79 patients have been reported previously [14].

The diagnostic work-up was performed at three different institutes in Denmark and included complete blood count, bronchoscopy with biopsy and CT imaging of the chest and abdomen. CT or magnetic resonance imaging (MRI) scans of the brain and bones were only performed if clinically indicated. PET/CT scans were gradually incorporated as part of the diagnostic process in 2009.

Data on patient characteristics, treatment and first relapses were obtained from patient records. The date of diagnosis was defined as the date of the first positive biopsy. TNM stage [15] was assigned for each patient if not specified in the patient record according to the 7th edition of the TNM classification.

Chemotherapy

The patients were treated with a standard combination of a platinum derivative and etoposide given every third or fourth week. Dosage of carboplatin was calculated by the Calvert formula (AUC5) and cisplatin dose was 75 mg/m^2; both given on Day 1 of every cycle. Etoposide dose was 120 mg/m^2 i.v. or 240 mg/m^2 orally on Day 1, 2 and 3 of every cycle. Doses were modified on the basic of blood counts, serum chemistry values and toxicity levels.

Radiation therapy

The radiotherapy was given as 45 Gy in 30 fractions, 10 fractions per week. However, 17 patients with large tumours, comorbidity and/or advanced age were treated with a once daily regimen (46–50 Gy in 23–25 fractions, 5 fractions per week) to lower the risk of acute toxicity. Our department policy was to deliver radiotherapy concurrently with chemotherapy; nevertheless, 18 patients received sequential treatment either due to patient-related factors or because chemotherapy was initiated in another department with a different policy.

Before May 2010, a free breathing three-dimensional (3D) CT scan was used for target delineation and treatment planning. After that date, the mid-ventilation phase of a 4D CT scan was used. Since December 2012, all patients were scanned using integrated 4D CT and a PET scan.

The treated volume was planned from a pre-treatment CT scan, and, if available, a PET scan. Nodal involvement was defined as nodes with a diameter >1 cm in the short axis measured on the CT scan. Elective irradiation of uninvolved lymph nodes (ENI) was not performed. A margin of 5 mm was added to the gross tumour volume (GTV) to create the respective clinical target volume (CTV) modified for overlap with bones and major blood vessels in the mediastinum. The CTVs were expanded to the internal target volume (ITV) by adding another 5 mm in all directions. The planning target volume (PTV) was then achieved by adding 5 mm laterally and 8 mm cranio-caudally to the ITV. Dose calculation was performed using the AAA algorithm (Eclipse version 8 to 11, Varian Medical Systems). Patients treated before June 2008 were planned using the PB algorithm. These treatment plans were retrospectively recalculated using AAA. This resulted in decreased target coverage.

The spinal cord, lungs, heart and oesophagus were contoured as organs of risk. The tissue constraints were a maximum dose of 45 Gy to the spinal cord at any point and a maximum of 50 Gy to maximum 20% of the heart. The percentage of the total lung volume receiving 20 Gy (V_{20}) was maximum

40%. In Marts 2011, a maximum mean lung dose of 19 Gy was added as constraint.

Daily cone beam CT (CBCT) for patient setup was incorporated in December 2009 [16]. All patients were set up according to an online bone match. In Marts 2013, daily soft tissue match on the primary tumour was implemented. Before that time, daily bone match using orthogonal kV imaging was performed.

Patients with a performance status (PS) 0–2 at the end of the CR and with no signs of disease progression were offered PCI. The PCI dose given was 25 Gy in 10 fractions, 5 fractions per week.

Follow-up

Patients were evaluated with CT imaging of chest and abdomen and clinical evaluation every third to fourth month in the first year and every sixth month in the following years. Imaging of brain and bones was performed only if clinically indicated. CT scans were evaluated according to RECIST 1.0 criteria [17]. All relapses were confirmed by a biopsy. However, a few patients progressed clinically in such a way that a biopsy became unnecessary. Date of relapse was defined as the date of a positive CT scan. All patients received all follow-up scans and no patients were lost to follow-up.

Local failure was defined as recurrence within the radiation field. Regional relapse was defined as recurrence within the regional lymph nodes of the mediastinum or supraclavicular region outside of the original PTV. Distant metastases were metastases anywhere else than mentioned above. All radiotherapy treatment plans were evaluated to define the LRF. In patients with LRF and available CBCT scans, all CBCT scans were retrospectively evaluated. Deviations between GTV on the planning CT and the daily CBCT scans were scored. In-field, marginal and partly out-of-field deviations were defined as misalignment of the GTV at the CBCT scans < 5 mm, between 5 and 10 mm and > 10 mm, respectively. Only observation of more than 5 fractions with deviations above 5 or 10 mm was scored as marginal or out-of-field failure.

Statistical analysis

OS was determined as the time from diagnosis until death or last follow-up date. Disease-free survival (DFS) was defined as the time from diagnosis until recurrence of disease or death and cumulative LRF (CLRF) as the time from diagnosis until recurrence of LRF. Patients still alive at the last follow-up date (15 May 2014) were censored at that day. Estimates of median DFS and OS were calculated using the Kaplan-Meier method and analysed by the log-rank test. Univariate and multivariate hazard ratios (HR) were determined using Cox proportional hazards model. Variables that tended to be associated in the univariate analysis were inserted into the multivariate analysis with respect to the number of events. The median values were used to define the cut-off point for the four variables; age, time from start of chemotherapy to end of radiotherapy (SER) and the GTV and PTV. As cut-off point for the variable "coverage of GTV" 98% was used (mean value). Follow-up time was calculated by reverse Kaplan-Meier estimate. All tests were two-sided, and p-values less than 0.05 were considered to be statistically significant. Statistics analyses were performed using SPSS statistics version 20.0 for windows (IBM SPSS Statistics, Chicago, IL, USA).

Results

Patient characteristics

We included a total of 147 patients. Patient characteristics and treatment are summarised in Table I. The majority of patients received hyperfractionated radiotherapy, concurrently with carboplatin and etoposide, and received PCI. Five patients did not receive all planned radiotherapy fractions due to patient-related issues.

Pattern of failure

After a median follow-up time of 42.2 months [95% confidence interval (CI) 37–48 months], recurrence was observed in 90 patients (61%). The median DFS was 13.9 months (95% CI 11–17 months) with a one-year DFS of 53% (95% CI 58–49%), a two-year DFS of 36% (95% CI 40–32%) and a three-year DFS of 31% (95% CI 35–26%).

The sites of first failure are shown in Table II. As can be seen, LRF was found in 37 patients (25%) and no isolated regional failure was identified. The CLRF rate was 22% (95% CI 18–26%) at one-year, 35% (95% CI 30–40%) at two-years, and 43% (95% CI 37–49%) at three-years. Distant metastases were seen in 74 patients (50%) and the most common sites were liver (n = 29), brain (n = 20), bones (n = 14) and opposite lung (n = 14).

Factors associated with LRF

Factors associated with the risk of LRF development are shown in Table III. Harbouring T3-T4 stage, N3-stage and a coverage of GTV below 98% were significant factors associated with LRF in the univariate analysis, but only N3-stage remained an indepen-

Table I. Patient characteristics (N = 147).

Characteristics	Number of patients (%)
Age (years)	
Median (range)	64 (40–80)
Sex	
Male	69 (47)
Female	78 (53)
Performance status, ECOG[a]:	
0	72 (49)
1	71(48)
2	4 (3)
T-stage (TNM)	
T1	18 (12)
T2	37 (25)
T3	33 (23)
T4	54 (37)
Tx	5 (3)
N-stage (TNM)	
N0	15 (10)
N1	11 (7)
N2	63 (43)
N3	58 (40)
Year for initiation of radiotherapy	
2007–2009	62 (42)
2010–2013	85 (58)
Pretreatment PET scan	
Yes	102 (69)
No	45 (31)
Chemotherapy	
Carboplatin and etoposide	97 (66)
Cisplatin and etoposide	49 (34)
Cycles of chemotherapy	
Mean, cycles, (range)	4 (2–7)
Dose of radiotherapy	
45 Gy (1.5 Gy per fraction, twice-daily)	130 (88)
46 Gy or 50 Gy (2 Gy per fraction, once-daily)	17 (12)
Schedule of radiotherapy	
Concomitant	129 (88)
Sequential	18 (12)
Full dose of radiotherapy	
Yes	142 (97)
No	5 (3)
SER (days)	
Median (range)	51 (25–240)
PCI (25 Gy in 10 fractions)	
Yes	122 (84)
No	23 (16)
GTV (cm^3)	
Median (range)	85 (2–509)
GTV coverage (%)[b]	
Mean (range)	98 (53–100)

ECOG, Eastern Cooperative Oncology Group; GTV, gross tumour volume; PCI, prophylactic cranial irradiation; PET, position emission tomography; SER, time from start of chemotherapy to end of radiotherapy.

[a] Performance status was evaluated at the beginning of treatment with chemotherapy; [b] Patients treated before June 2008 were planned using the PB algorithm. These treatment plans were retrospectively recalculated using AAA. This resulted in decreased target coverage. Volume covered by 95% of the prescribed dose.

Table II. Pattern of failure of first failure (N = 147).

Recurrence	Number of patients (%)
None	57 (39)
Local failure	31 (21)
Local failure + distant failure	15 (10)
Isolated local failure	14 (10)
Isolated local + regional failure	2 (1)
Regional failure	10 (7)
Regional failure + distant failure	8 (5)
Isolated regional failure	0 (0)
Distant failure	74 (50)
Distant failure + local/regional failure	21 (14)
Isolated distant failure	53 (36)

dent predictive factor in the multivariate analysis (adjusted HR of 2.07; 95% CI 1.02–4.20). Coverage of GTV below 98% showed a trend towards a correlation in the multivariate analysis (p = 0.086). The CLRF according to N-stage is illustrated in Figure 1A.

Distribution of loco-regional failure

CBCT scans were available in 20 of the 37 patients with LRF. Of these 20 patients, 15 had local failure, three had regional failure and two had both local and regional failure. In 14 patients, the GTV was in-field during radiotherapy treatment as scored from the daily CBCT scans. In four patients, the GTV was marginally covered and in two patients the GTV was partly out-of-field for several fractions. One of the patients with GTV partly out-of-field during treatment received only 18 of the 30 planned fractions. All other patients received full dose. In 19 of these 20 patients, the target definition had been defined using a PET scan and 4D CT for treatment planning. Hyperfractionated radiotherapy had been given in 17 patients, and the radiotherapy had been given concomitantly with chemotherapy in 16 patients.

Survival

On the last follow-up day, 86 patients (59%) had died. Among these patients, 17 (20%) had died without relapse. Four patients died of treatment related courses (one patient of febrile neutropenia, three patients of radiation pneumonitis). Two patients died of heart disease few weeks after completing treatment, and this could be related to the treatment. Three patients died while relapse of disease was suspected. The last eight patients died of causes unrelated to the treatment or to lung cancer.

The median OS for all patients was 24.1 months (95% CI 19–29 months) with a one-year survival of 74% (95% CI 70–78%), a two-year survival of 52%

Table III. Univariate and multivariate analysis of loco-regional failure.

Characteristics	HR[a] (95% CI)	p-Value	Adjusted HR [a] (95% CI)	p-Value
Age[b]				
<64 years vs. ≥ 64 years	1.24 (0.65–2.36)	0.520		
Sex				
Female vs. male	0.53 (0.28–1.03)	0.060		
Performance status, ECOG[c]:				
0 vs. 1–2	0.76 (0.39–1.45)	0.397		
T-stage (TNM)				
T1–2 vs. T3–4	0.33 (0.14–0.76)	0.009	0.50 (0.21–1.21)	0.125
N-stage (TNM)				
N3 vs. N0–2	2.53 (1.13–4.87)	0.005	2.07 (1.02–4.20)	0.043
Year for initiation of radiotherapy				
2007–2009 vs. 2010–2013	0.89 (0.47–1.69)	0.716		
Pretreatment PET scan				
Yes vs. no	0.68 (0.35–1.35)	0.272		
Chemotherapy				
Cisplatin vs. carboplatin	0.69 (0.33–1.42)	0.307		
Dose of radiotherapy				
45 Gy vs. 46 Gy or 50 Gy	1.02 (0.54–1.93)	0.942		
Planning CT scan				
4D vs. 3D	0.97 (0.50–1.90)	0.574		
SER[b]				
<51 days vs. ≥ 51 days	0.61 (0.32–1.18)	0.140		
Size of GTV[b]				
<85 cm^3 vs. ≥ 85 cm^3	1.05 (0.55–2.03)	0.875		
Size of PTV[b]				
<527 cm^3 vs. ≥ 527 cm^3	0.65 (0.34–1.25)	0.195		
Coverage of GTV[d]				
$\geq 98\%$ vs. $<98\%$	0.40 (0.17–0.92)	0.025	0.47 (0.20–1.11)	0.086

CI, confidence interval; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumour volume; HR, hazard ratio; PET, position emission tomography; PTV, planning target volume; SER, time from start of chemotherapy to end of radiotherapy.
[a]HR was calculated with the Cox proportional hazard model; [b]Cut-off value are defined by the median value of the variable; [c]Performance status was evaluated at the beginning of treatment with chemotherapy; [d]Cut-off value are defined by the mean value of the variable.

(95% CI 47–56%) and a three-year survival of 34% (95% CI 29–38%) (Figure 1B).

Factors associated with overall survival

Factors affecting the OS were evaluated in a Cox proportional hazards model (Table IV). As can be seen in the univariate analysis, an initial staging process including a PET/CT scan and administration of cisplatin instead of carboplatin were factors significantly correlated with longer OS. However, in the multivariate analysis, staging including a pretreatment PET/CT scan [adjusted HR 0.39 (0.21 – 0.74)] and receiving PCI [adjusted HR 0.43 (0.24 – 0.78)] were the only two independent factors significantly prolonging OS.

Discussion

In the present study, we evaluated factors correlated with development of LRF and survival in a consecutive cohort of LD-SCLC patients treated with definitive CRT over a seven-year period. Our main finding is that harbouring N3-stage disease is an independent risk factor for LRF with a two times higher risk. As far as we know, we are the first to evaluate T- and N-stage as potential predictors of LRF in LD-SCLC patients. Wzietek et al. [18] evaluated factors affecting LRF in 409 LD-SCLC patients and found male gender, long SER and pleural effusion to be independent prognostic factors. However, they did not include TNM stage in their analysis. Our result indicates that initial local control is lacking in patients with N3-stage disease and that a more aggressive local treatment in these patients could be a promising strategy forward leading to a decrease in the rate of LRF. The optimal dose fractionation of radiotherapy is a much debated issue. The standard accelerated radiotherapy (45 Gy in 1.5 Gy twice daily fractions) is recommended based on the only phase III study on this topic [6] which showed improved survival compared with a once daily regimen (45 Gy in 1.8 Gy once daily fraction). However, the superiority of the accelerated regimen has been

Table IV. Univariate and multivariate analysis for overall survival.

Characteristics	HR[a] (95% CI)	p-Value	Adjusted HR[a] (95% CI)	p-Value
Age[b]				
<64 years vs. ≥ 64 years	0.96 (0.63–1.47)	0.841		
Sex				
Female vs. male	0.77 (0.50–1.18)	0.223		
Performance status, ECOG[c]:				
0 vs. 1–2	1.17 (0.77–1.79)	0.464		
T-stage (TNM)				
T1–2 vs. T3–4	0.64 (0.40–1.02)	0.059	0.76 (0.46–1.25)	0.278
N-stage (TNM)				
N3 vs. N0–2	1.50 (0.98–2.30)	0.064	1.38 (0.86–2.22)	0.117
Year for initiation of radiotherapy				
2007–2009 vs. 2010–2013	1.48 (0.96–2.28)	0.078	1.60 (0.84–3.07)	0.154
Pretreatment PET scan				
Yes vs. no	0.51 (0.33–0.78)	0.002	0.39 (0.21–0.74)	0.004
Pretreatment MRI or CT scan of the brain				
Yes vs. no	1.30 (0.73–2.30)	0.376		
Chemotherapy				
Cisplatin vs. carboplatin	0.53 (0.31–0.89)	0.016	0.69 (0.38–1.27)	0.232
Cycles of chemotherapy				
4–6 cycles vs. 1–3 cycles	1.04 (0.48–2.27)	0.914		
Dose of radiotherapy				
45 Gy vs. 46 Gy or 50 Gy	0.98 (0.53–1.81)	0.956		
Schedule of radiotherapy				
Concomitant vs. sequential	0.92 (0.50–1.69)	0.783		
SER[b]				
<51 days vs. ≥ 51 days	0.84 (0.55–1.29)	0.434		
PCI				
Yes vs. no	0.59 (0.34–1.02)	0.057	0.43 (0.24–0.78)	0.006

CI, confidence interval; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; PET, position emission tomography; SER, time from start of chemotherapy to end of radiotherapy.
[a] Hazard ratios was calculated with the Cox proportional hazard model; [b] Cut-off value are defined by the median value of the variable; [c] Performance status was evaluated at the beginning of treatment with chemotherapy.

questioned since it was compared with a conventional regimen with a biologically inferior dose. Daily fractionation regimens, such as 60–70 Gy in 1.8–2 Gy daily fractions may serve as reasonable alternatives, and two phase-III randomized trials are currently ongoing in an attempt to determine the optimum combination of dose, fractionation and treatment duration (http://www.cancer.gov/clinicaltrials/). CALGB 30610 is a two-arm study comparing standard accelerated radiotherapy (45 Gy in 1.5 Gy twice-daily fractions) with 70 Gy (2 Gy fractions once-daily) while CONVERT is comparing the standard accelerated regimen (45 Gy in 1.5 Gy fractions) with 66 Gy (2 Gy fractions once daily). However, the introduction of high dose regimens may raise concerns concerning toxicity due to increased dose intensity [19]. Bearing our result in mind, a promising strategy forward may be to consider a more differentiated treatment based on the TNM staging and to reserve the more aggressive local treatment for patients with N3-stage disease. This would spare other patients with lower risk of recurrence having to suffer from unnecessary toxicity.

Although the presence of distant metastases was the primary pattern of first failure in our cohort, LRF remained a significant problem with an incidence rate of 25%. This result is in agreement with results reported in other previous studies evaluating LD-SCLC patients treated with CRT in the routine clinical setting [20–22] (between 26% and 30%). However, the LRF rates vary much in retrospective studies; from 12% [23] to 45% [24]. The size of this range is probably due to lack of uniformity in the treatment, especially as far as radiotherapy is concerned, and to variations in the follow-up time which hamper comparison.

We were able to evaluate the position of the GTV during treatment from daily CBCT scans in 20 patients with LRF. In 70% of the patients, the GTV was in-field while only 10% was partly out-of-field. This observation indicates that inadequate target coverage was not the primary problem in our patients, and the observation supports a strategy of

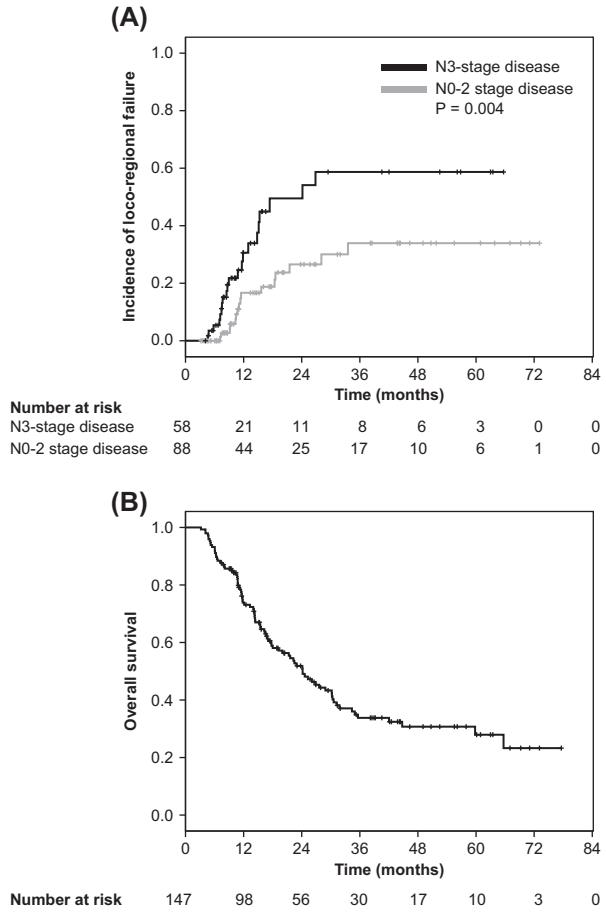

Figure 1. Kaplan-Meier curves for (A) Cumulative loco-regional failure rate stratified by N-stage (N0-2 stage disease vs. N3-stage disease). The p-value was calculated by the log-rank test. (B) Overall survival. (N = 147).

dose escalation. Our observation is in line with results published by Watkins et al. [20] who retrospectively analysed patterns of failure in 52 LD-SCLC patients treated with platinum-based chemotherapy concomitantly with hyperfractionated radiotherapy delivered without elective nodal irradiation (ENI). They found 50% of the LRF to be in-field, 29% to be out-of-field; and the remaining 21% failures were both in-field and out-of-field. The majority of these patients (87%) had undergone a pre-treatment PET scanning. Inversely, Giuliani et al. [21] observed out-of-field and marginal failures to be the predominant pattern of LRF in their cohort of 227 patients treated with platinum-based chemotherapy concomitantly with a radiation regimen of 40 Gy in 2 Gy fractions. None of these patients were staged with a PET scan. Like in Watkins study, the majority of our patients (95%) had undergone a pre-treatment PET scan which was used for the target definition. A more precise target definition based on the PET scan may explain the difference in result compared with Giuliani.

Lastly, we found that undergoing PCI and staging including a pretreatment PET/CT scan was associated with an improved survival independently of other clinical factors. These results are not surprisingly. The positive effect of PCI in LD-SCLC patients was stated in a large meta-analysis in 1999 [3]. This effect has subsequent been confirmed several times [25,26].

PET/CT scans have a high sensitivity for detection of primary tumours in SCLC patients owing to their high metabolic activity. The use of PET/CT scans in initial staging has been studied in several papers. A recent review stated that the cumulative staging concordance between PET/CT and conventional CT imaging was only 84% and that PET/CT overall seems to improve the accuracy of staging [4]. The impact of PET/CT staging on survival has been addressed in one previous retrospective study which included 54 LD-SCLC patients treated with definitive CRT [27]. In line with our result, they found a markedly improved survival in the PET-stage patients with an adjusted HR of 0.24.

The present study has some limitations. Firstly, it is a retrospective study with variations in the diagnostic work-up and the treatment delivered to patients, which could result in unknown selection bias. Furthermore, unmeasured confounders may exist. However, our population is consecutive and no patients were lost to follow-up. Second, the radiotherapy planning and technique have improved throughout the study period which has made it difficult to compare patterns of failure between patients treated in different time periods. However, we have chosen to incorporate the time period as a factor in our analysis in an attempt to take this problem into account and no significant difference was found.

In conclusion, our data indicates that LRF remains a significant concern in LD-SCLC patients undergoing definitive CRT in the daily clinical setting. N3-stage was an independent prognostic factor for development of LRF and in-field failures was found to be the predominantly pattern of recurrence. Undergoing PCI and a staging with PET/CT scan were independent prognostic factors for improved OS. In patients with N3-stage disease, dose-escalation may have a positive impact on the LRF rate. This can be evaluated in a prospective dose-escalation trial.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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