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^{18}FDG-PET/CT Is a Useful Tool in Staging Procedure before Chemo-Radiotherapy in Patients with Limited Disease Small-Cell Lung Cancer. Pattern of Failure and Survival Is Analyzed

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ABSTRACT

Background: The purpose of this study was to evaluate the use of ^{18}FDG-PET/CT in staging procedure, the pattern of failure and survival in patients with small-cell lung cancer limited disease (LD-SCLC) undergoing chemo-radiotherapy. **Methods:** A total of 79 LD-SCLC patients were treated with a combination of chemotherapy and chest radiotherapy. Radiotherapy of the tumour and the pathological lymph nodes was performed either as 45 Gy twice-daily or 46 - 50 Gy once-daily. ^{18}Fluro-2-deoxy-D-glucose (^{18}FDG)-PET/CT was performed in 35 patients as part of the staging procedure. **Results:** With a median follow-up time of 17 months 6% developed isolated loco-regional failures while 57% developed distant metastases. No isolated regional failures were seen. Median overall survival was 22 months. Patients staged with a ^{18}FDG-PET/CT had a significantly lower incidence of distant failures and a significantly improved overall survival compared with patients only staged with a CT scan ($p = 0.03$) (median overall survival of 34 versus 17 months, respectively). **Conclusion:** The pattern of failure showed a high risk of distant metastases but a low incidence of isolated loco-regional failures. Patients staged with an ^{18}FDG-PET/CT had a significantly lower incidence of distant failures and better overall survival, indicating that ^{18}FDG-PET could be beneficial in patients with LD-SCLC before deciding on treatment regimen.

Keywords: Small-Cell Lung Cancer; Limited Disease; Thoracic Radiotherapy; Positron Emission Tomography; Pattern of Failure

1. Introduction

Small-cell lung cancer (SCLC) accounts for about 12% - 15% of all lung cancers. It is an aggressive disease with a rapid doubling time and a considerable potential for early development of metastases. Only 20% - 30% of SCLC patients have limited disease (LD) at diagnosis and hence considered potentially curable. SCLC has a high sensitivity to chemotherapy (CT) and radiotherapy (RT), and an improvement in overall survival was achieved when CT and RT were combined [1,2]. Optimal dose, timing and fractionation of RT have been investigated previously but results are conflicting [3-5]. Despite the high sensitivity to treatment, most patients experience a relapse of disease, particularly with distant metastases, but also in the form of local and regional failures, and overall survival rate is always low. Optimal treatment strategies should partly be based on an understanding of patterns of failure in standard therapies. Moreover, accurate staging is of utmost importance in the management of SCLC. During the last decade, ^{18}FDG-PET scans have been incorporated in the staging procedure in some institutes, but the documentation for its usefulness is not as robust as in non-small-cell lung carcinoma (NSCLC) [6].

The aim of this study was to present the treatment results of consecutively enrolled LD-SCLC patients undergoing radical CT and RT over a four-year period particularly focusing on pattern of failure and effect of PET/CT.

2. Materials and Methods

2.1. Patient Population

All consecutive LD-SCLC patients treated with chest RT at the Department of Oncology at Aarhus University Hospital, Denmark between 2007 and 2010 were included. The inclusion criteria were: a pathologically proven diagnosis of SCLC, a staging confirming LD and

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initiation of treatment with RT in curative doses regardless of whether the patient actually completed the treatment.

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/MR scans of the brain and bones were only performed if clinically indicated in accordance with clinical guidelines at our department at the time of study. [18]FDG-PET/CT scans were gradually incorporated as part of the diagnostic process during the study period.

Data on patient characteristics, treatment and relapses were obtained from patient records. The date of diagnosis was defined as the date of the first positive biopsy. The clinical staging by the TNM system was retrospectively determined by reviewing the CT- and PET-scans and done by the authors. The date of death was documented in our electronic patient file system. If follow-up was in another department the patient record and scans were retrieved. Two patients had another malignant disease at the time of diagnosis and were thus excluded from the analysis.

2.2. 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 AUC5 and cisplatin dose was 75 mg/m^2; both given on day one 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.

2.3. Radiation Therapy

The RT was given twice-daily with 45 Gy in 30 F, 10 F per week and either concomitant with or sequential to CT (**Table 1**). A few patients with large tumours, comorbidity and advanced age were treated once-daily regime (46 - 50 Gy in 23 - 25 F, 5 F per week) to lower the risk of acute toxicity.

The treated volume was planned from a pre-treatment CT scan and a PET/CT scan if available. Elective irradiation of uninvolved lymph nodes (ENI) was not performed. The gross target volume (GTV) for the primary tumour (GTVt) and pathological lymph nodes (GTVn) was delineated on the planning 3D-CT scans by two clinical oncologists assisted by a radiologist using both lung window and mediastinal window and guided by the visual interpretation of the PET/CT scan. Nodal involvement was defined as nodes > 1 cm in the short axis. A margin of 0.5 cm was added to the GTVt and GTVn to create respective Clinical Target Volumes (CTV) modified for overlap with bones and major blood vessels in the mediastinum. The CTV volumes were expanded to the Internal Target Volume (ITV) by adding another 0.5 cm in all directions. The Planning Target Volume (PTV) was then achieved by adding 0.5 mm laterally and 0.8 mm cranio-caudally to the ITV.

Table 1. Treatment and patient characteristics.

Patient characteristics	No. patients
Median age in years (range)	64 (44 - 78)
Gender: male/female	34/45
PS: 0/1/2	37/40/2
Stage (TMN): IB/IIA/IIB/IIIA/IIIB	2/2/2 27/46
RT total dose in Gy: 45/46/50	66/3/10
Timing of RT: concurrent/sequential	70/9
Series of chemotherapy: 2/3/4/5/6/7	2/2/37/3/34/1
PCI: yes/no	69/10

PS: ECOG Performance Status; RT: radiotherapy; PCI: prophylactic cerebral irradiation.

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%. Mean lung dose (MLD) was maximum 19 Gy.

Patients with a good performance (PS = 0 - 1) at the end of the CT-RT and with no signs of disease progression were offered prophylactic cranial irradiation (PCI). The PCI dose given was 25 Gy in 10 F, 5 F per week.

2.4. Follow-Up

After completion of treatment, patients were followed with CT imaging of chest and abdomen and clinical evaluation every third to fourth months in the first year and every sixth months in the following years. Imaging of brain and bones was only performed if clinically indicated. If there was sign of relapse, the CT scan was evaluated by a multidisciplinary tumour board to confirm the evidence of radiological tumour progression. If relapse was considered likely, a biopsy was performed. If a biopsy was not possible, a PET scan would be used to confirm the diagnosis of relapse, except in patients with metastases in the brain. A few patients, however, progressed clinically in such a way that a biopsy became unnecessary. Date of relapse was defined as the date of a positive CT scan, even if a biopsy or a PET-scan was subsequently carried out to confirm the recurrence. All patients received all follow-up scans and no were lost to follow-up.

Local relapse was defined as recurrence in the radiation field, and regional relapse as recurrence in the

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regional lymph nodes of the mediastinum or supraclavicular region outside of the original PTV. Distant metastases were defined as metastases anywhere else than mentioned above. All RT treatment plans were evaluated by the authors to define the loco-regional relapses.

2.5. Statistical Analysis

The statistical analyses were performed using SPSS 18.0 for windows. The survival functions were calculated from the time of diagnosis for the endpoints and overall survival by the methods of Kaplan and Meier. The incidence of local, regional and distant relapse was calculated from the time of diagnosis. Patients were censored from the date of last follow-up. The log rank test was used for comparison of groups.

3. Results

3.1. Patient Characteristics

The median follow-up time was 17 months (range, 3 - 48 months) for all patients and 28.5 months (range, 14 - 48 months) for patients still alive at the time of analysis. Treatment and patient characteristics are summarized in **Table 1**. Ten patients (13%) were diagnosed in 2007, 23 patients (29%) in 2008, 30 patients (38%) in 2009 and 16 patients (20%) in 2010. During the diagnostic process, all patients had a CT scan of the chest and abdomen, but only 8 patients (10%) had a CT/MR scan of the brain. Thirty-five patients (44%) underwent a FDG-PET scan as part of the diagnostic process, and this was mainly patients diagnosed in 2009 and 2010. The frequency of PET scans in patients diagnosed in 2007 was 20%, 17% in 2008, 50% in 2009 and 88% in 2010.

The median follow-up time for patients still alive at the time of analysis was in the PET-staged group 25 months (range, 14 - 48 months) and 33.5 months (range, 17 - 48 months) in the CT-staged group. Sixty-two patients (78%) received carboplatin and 17 patients (22%) cisplatin. All patients received the planned dose of RT. For patients receiving RT concomitant with CT the median time from CT to start of RT was 29 days. The size of the chest radiation fields varied considerably. One patient had a pathological lymph node in the supraclavicular region as the only disease manifestation and RT was only performed in the affected supraclavicular region resulting in a very small radiation field.

The GTV of the primary lung tumour and the pathological lymph nodes had a median value of 93 cm^3 (range, 3 - 494 cm^3); PTV 581 cm^3 (range, 86 - 2055 cm^3). The median V_{20} was 29% (range, 10% - 52%) and the MLD was 14 Gy (range, 6 - 24 Gy). Four patients had a V_{20} exciding the tissue constraints of maximum 40% (41%, 42%, 44% and 52%, respectively) because of special circumstances specified in the patients records.

Prophylactic cerebral irradiation (PCI) was given median 19 days (range, 0 - 138 days) after the patient had finished chemotherapy. The most common reason not to receive (PCI) was deterioration of the patient's general condition.

3.2. Pattern of Tumour Recurrence

At the end of analysis 50 of the 79 patients (63%) had a recurrence of disease.

Figure 1 illustrates pattern of first failure. Seventeen patients (22%) had a local relapse and five patients (6%) a regional relapse. No patients had isolated regional failure. Forty-five patients (57%) developed distant metastases and 15 of these patients (33%) had synchronously loco-regional relapse.

The most common sites to develop the first distant metastases were the liver (n = 18), bones (n = 11) opposite lung (n = 10) and the brain (n = 8). **Figure 2** shows the incidence of distant relapse is significantly different between the PET/CT-staged patients and the CT-staged patients (p = 0.03). Fifteen of the 35 PET/CT-staged patients (43%) developed distant failure compared with 30 of the 44 CT-staged patients (68%). No significant difference was seen in loco-regional relapses; 23% versus 27%, respectively (p = 0.2).

The incidence of local relapse was 15% (95% Confidence Interval (CI): 10% - 20%) after 12 months and 30% (95% CI: 23% - 37%) after 24 months, for regional relapse 6% (95% CI: 3% - 9%) after 12 months and 8% (95% CI: 4% - 12%) after 24 months, while the incidence for distant metastases was 43% (95% CI: 37% - 49%) after 12 months and 58% (95% CI: 52% - 74%) after 24 months (**Figure 3**).

3.3. Survival

The median overall survival for all patients was 22 months (95% CI: 16 - 28 months) with a one-year overall

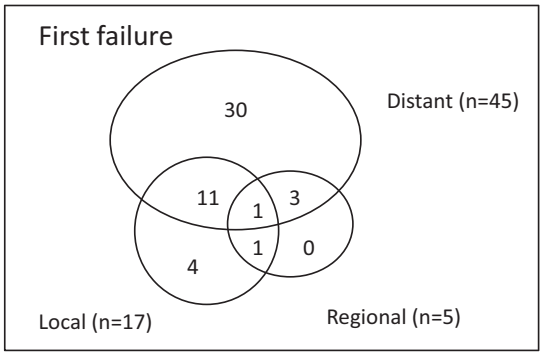

Figure 1. Pattern of first failure showed as local, regional and/or distant relapse.

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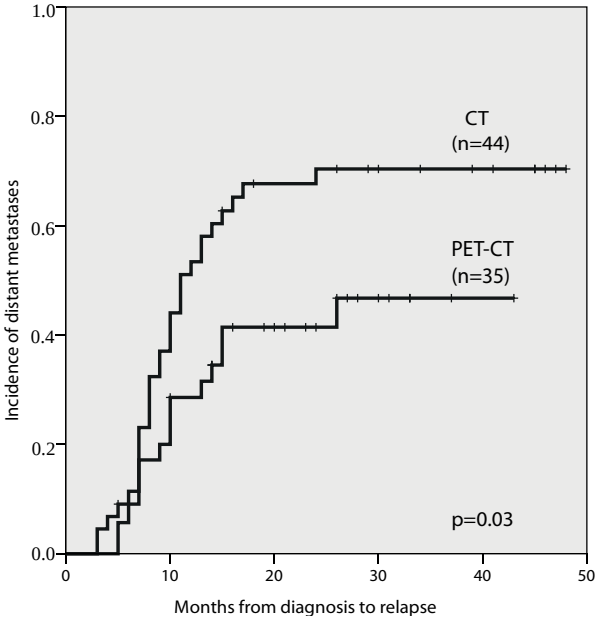

Figure 2. The incidence of distant metastases in all 79 patients related to the pre-treatment staging procedure with PET/CT or CT.

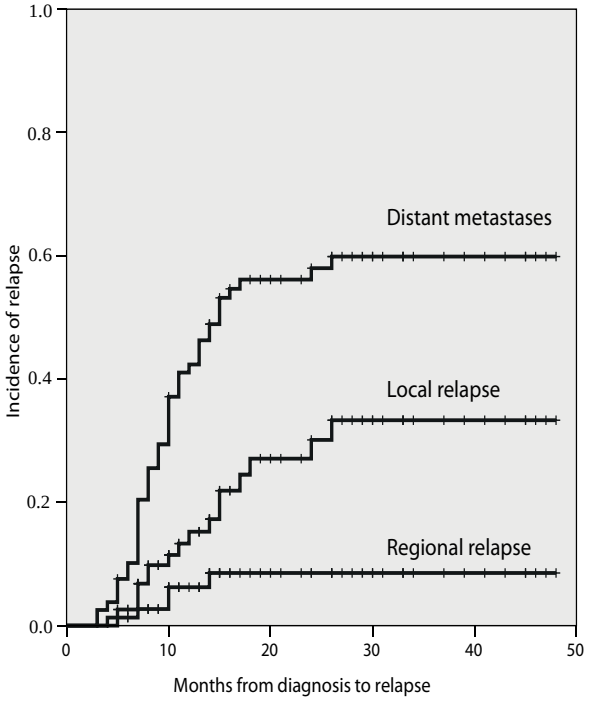

Figure 3. The incidence of local relapses, regional relapses and distant metastases. Each site is analyzed for all 79 patients.

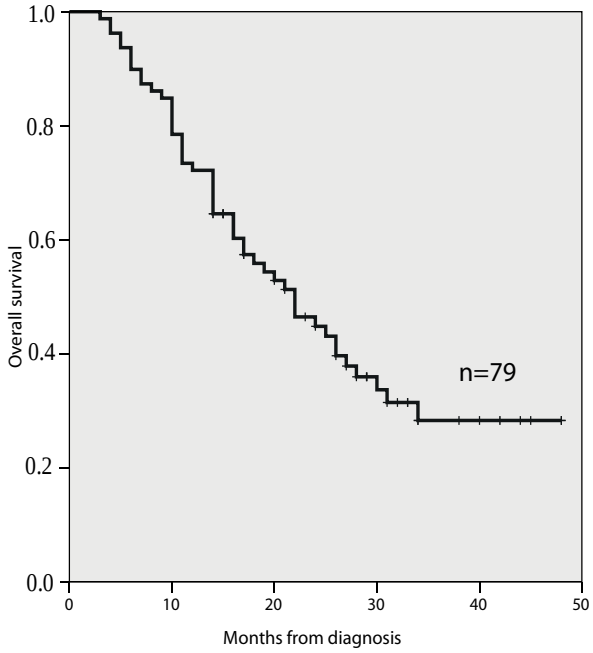

Figure 4. Overall survival of all 79 patients with LD-SCLC treated with chemo-radiotherapy.

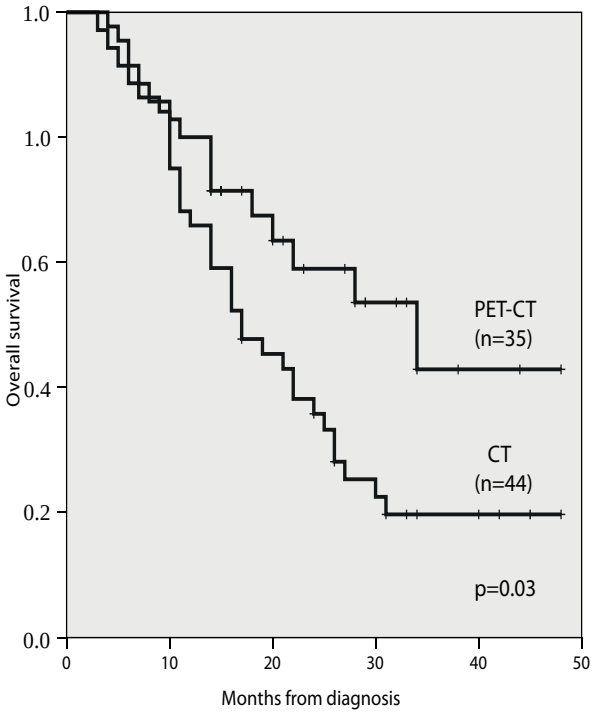

Figure 5. Overall survival of all 79 patients related to the pre-treatment staging procedure with PET/CT or CT.

survival of 72% (Standard deviation (SD): 67% - 77%), a two-year survival of 45% (SD: 39% - 51%) and a three-year survival of 28% (SD: 22% - 34%) (**Figure 4**).

Figure 5 shows a significantly better overall survival in the PET/CT-staged patients with a median overall survival of 34 versus 17 months in the CT-staged patients ($p = 0.03$).

When stratifying the median survival for Eastern Co-

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operative Oncology Group status (0 versus 1), stage, gender, RT schedule (twice-daily RT versus once-daily), concomitant CT-RT versus sequential, cisplatin versus carboplatin and the number of cycles of CT; none showed any significant difference in overall survival.

3.4. Treatment Time

The median overall treatment time (from start of any treatment to the end of radiotherapy) was 57 days (range; 25 - 246 days). We stratified the patients in three groups of equal size according to their overall treatment time and compared the survival between the groups, but found no significant difference in the overall survival ($p = 0.9$).

3.5. Deaths

At the time of analysis, 49 patients (62%) had died. Seven patients died without a diagnosed relapse; one patient died of febrile neutropenia during chemotherapy and the death was related to the treatment. One patient died 2.5 months after end of treatment with symptoms of radiation pneumonitis. The V_{20} for this patient was 34% and the MLD 18 Gy. The last five patients died of causes not related to the treatment or to lung cancer.

4. Discussion

These data describe the outcome of a consecutive patient population over a period of four years. The survival data are comparable with other retrospective consecutive studies of non-selected patients [7,8].

We stratified for differences in patient characteristics and treatment and found no significant difference in overall survival, which was expected due to the low number of patients. However, did we observe a significantly improved overall survival for the 44% of the patients staged with [18]FDG-PET/CT scans. Additionally, these patients had a lower incidence of distant failure; 43% versus 68%. This difference most likely indicates a more exact staging in the PET/CT group with some patients with extended disease (ED) erroneously staged with limited disease in the CT-staged group. However, as patients staged with a PET/CT scan were primarily diagnosed in 2009 and 2010, the median follow-up time for these patients was shorter than for the CT-staged group (25 months versus 33.5 months, respectively for surviving patients) and this could influence the result.

A PET scan was found to be superior to a CT scan in the detection of lymph nodes and distant metastases in NSCLC and is now established in the staging of NSCLC patients [9]. However, the documentation for the use of PET in SCLC is not as robust as in NSCLC [6], and its usefulness is still debated. Studies have been made to evaluate the stage migration phenomenon in SCLC patients staged using a PET/CT scan, and these seem to upstage 0% - 33% of the patients from LD seen on conventional imaging to ED after PET scan [6,10,11]. These results, however, have to be interpreted with caution since the studies were small and half of them retrospective. However, the use of [18]FDG-PET in the staging of SCLC has increased in recent years. Azad A. *et al.* [11] have evaluated the difference in overall survival in a retrospective group of 46 consecutive patients undergoing staging by PET scans and found a significantly longer overall survival in patients with LD on PET staging compared with patients upstaged to ED on the PET scan (median 18.6 months versus 5.9 months). However, this result could easily be confounded by different subsequent treatments.

One important question remains: Is the right staging in patients with a low burden of metastatic disease clinically important? These patients might benefit from a combined treatment with CT and RT. In a randomized study by Jeremic *et al.* [12], the effects of RT in patients with SCLC-ED were evaluated. A total of 206 patients with a complete response at distant sites and a complete or partial response in the thorax after three cycles of CT were randomized to either CT alone or accelerated hyperfractionated RT (54 Gy; 1.5 Gy/F). The median overall survival was found to be significantly higher in the RT-group (17 months versus 11 months). Two other trials are now ongoing to confirm this result (REST (NTR 1527) and RTOG-0937) [13,14]. Until this matter is properly clarified, it is of a great importance that patients are protected from potentially toxic thoracic RT as a standard procedure.

During follow-up, only few isolated loco-regional relapses (no = 5; 6%) and no isolated regional relapses were observed. The RT was planned so only the primary tumour and the pathological lymph nodes were encompassed with omission of ENI resulting in a smaller radiation field. This strategy is, however, debated due to the potential risk of increasing the isolated nodal failure outside the radiation field. In 2006 two phase II [15,16] studies was preformed to evaluate concurrent CT and involved-field RT (45 Gy, 1.5 Gy/F) in 27 and 37 patients, respectively. Baas *et al.* [15] observed an isolated regional relapse rate of 6% and De Ruysscher *et al.* [16] a higher rate of 11%. In both studies the RT was based solely on the pre-treatment CT imaging, and it was stated that a more precise staging with an [18]FDG-PET scan might improve the rate of isolated regional nodal failures. A prospective study [17], by the same Dutch research group including De Ruysscher, in 2009 used [18]FDG-PET scans to make omission of ENI in 60 LD-SCLC patients receiving concurrent CT (carboplatin and etoposide) together with twice-daily RT (45 Gy, 1.5 Gy/F) and

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observed a low rate of isolated nodal failures (3%). However, it should be noticed that a difference in definition of isolated nodal failure was used in this study compared to the phase II trial by De Ruysscher *et al.* [16] making comparison difficult. In 2010 ^{18}FDG-PET guided omission of ENI was evaluated in a retrospective study by Shirvani *et al.* [18], where data on 60 patients treated with concurrent CT and RT resulting in a low rate of isolated elective nodal failure (1.7%). In contrast to the previously mentioned study, intensity-modulated radiation therapy (IMRT) was used and the authors concluded that omission of ENI was safe using a combination of ^{18}FDG-PET and IMRT. Recently, two studies [19,20] again evaluated the omission of ENI guided by only a CT scan and found low rates of loco-regional relapses in 108 and 38 patients respectively, treated with RT concomitant with CT. In our study, omission of ENI was guided by ^{18}FDG-PET in 44% of the patients and by CT scan in the remaining, and we observed no difference in locoregional relapse rate between the two groups. Further studies are needed to clarify the safety of omission of ENI. Results from two ongoing studies [13] evaluating RT regimes are expected. In the UK-led phase III CONVERT trial comparing the twice-daily RT regime (45 Gy in 30F) with a once-daily RT regime (66 Gy in 33 F), the use of ENI is not allowed. This differs from the US-led CALGB 30610/RTOG 0538 trial, evaluating three different RT regimes where mediastinal lymph nodes are irradiated electively.

Another question is timing of the RT. Several authors support an early start of RT concomitant with CT [3,4, 21]. In a meta-analysis comparing phase III trials in LD-SCLC, De Ruysscher [22] showed that the most important predictor of five-year survival is the time from the start of any treatment until the end of RT (SER). The significantly higher five-year survival rate (>20%) was found in patients with a short SER of less than 30 days. In our study we had a median SER of 57 days with only one patient having a SER shorter than 30 days.

We acknowledge that the limitation of this study is the small number of patients included and the retrospective design. There were variations in the diagnostic work-up and the treatment, resulting in the possibility of selection bias for both the use of PET scans, imaging of the brain and for the choice of treatment. PET/CT was incorporated in the diagnostic process during this time period and there might be a selection bias due to the availability of PET scanners. Patients were staged at three different institutes and only one of the institutes had a specific PET center. This could have influenced the patient selection.

Carboplatin was the primary choice of platinum derivative. This is in contrast to most other studies where cisplatin is the treatment of choice and considered superior to carboplatin. Whether this could have affected the frequency of relapse and the overall survival is unknown.

Despite the retrospective design of this study, the population is consecutive and no patients were lost to follow-up. Our data on relapse is therefore validated. Time and course of death are validated as well due to a complete registration of all patients in Denmark.

5. Conclusions

The pattern of failure in patients with LD-SCLC undergoing CT-RT showed that the challenge is still a very high risk of distant metastases. The incidence of isolated loco-regional failure was low, and this supports the safety of a treatment strategy of selective irradiation of pathological lymph nodes.

Patients staged with an ^{18}FDG-PET/CT scan had a significantly lower incidence of distant failure and a significantly better overall survival compared to patients staged with a CT scan only. This probably indicates the value of including an ^{18}PET-CT scan in the staging of patients with SCLC before deciding on a treatment regimen.

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