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3D-conformal radiotherapy for inoperable non-small-cell lung cancer – A single centre experience

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Background. *The purpose of this investigation was to evaluate feasibility, safety and efficacy of 3D-conformal radiotherapy (3D-RT) for inoperable non-small-cell lung cancer (NSCLC). Time to progression (TTP), including local recurrence and/or distant metastasis, local control rate (LCR), time to death (TTD) and side effects were evaluated.*

Patients and methods. *From 1997 to 2002, a total of 84 patients with inoperable NSCLC were treated with 3D-RT according to a prospective protocol at our institution. Depending on performance status, lung function and dose-volume constraints, radiation doses of either 66-70 Gy or 50-60 Gy +/- platin-based chemotherapy were applied.*

Results. *The treatment was well tolerated and the rate of side effects was low. Only one grade 4 pneumonitis was observed, the rate of grade 3 pneumonitis was 6% and 13% for grade 2. Two patients developed a grade 4 oesophagitis and no grade 3 oesophageal toxicity was observed. The analysis of dose-volume histograms (DVH) found a mean V_{20} (lung volume that receives 20 Gy) for the ipsilateral lung (IL) of 42%, a mean V_{20} for the contralateral lung (CL) of 14% and a mean lung dose IL of 25 Gy. The mean V_{20} IL in patients developing a pneumonitis grade 2-4 was 53.3%. The mean follow-up was 24 month. There was no difference in TTP (median 15 months) in the different treatment groups. Patients receiving higher radiation doses (66-70 Gy) had a benefit in an overall survival (OS) when the additional chemotherapy was applied (28 month vs. 16 month). Local control rates of mean 22% after 2 years were low.*

Conclusions. *The application of radiation doses up to 70 Gy is feasible and safe, also in combination with chemotherapy. Still, the local control and OS is poor. Thus, further trials to investigate the possibility of dose escalation in the lung without increasing lung toxicity significantly, also in more advanced tumour stages, are mandatory.*

Key words: carcinoma, non – small – cell lung – radiotherapy; radiotherapy, conformal; radiotherapy planning; computer - assisted

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Introduction

In the European Union (EU) lung cancer is the most common cause of death from cancer. The estimated deaths in 1997 were 180 000, representing one-third of the total

cancer mortality in the EU.[1] In Austria, the mortality in men is declining since the 1980, whereas in women the incidence is rising in the last decades.[2]

For patients with oncological and/or functional inoperable non-small-cell lung cancer (NSCLC), 3D-conformal radiotherapy (3D-RT) has become an established treatment modality. The overall survival and distant failure rate can be improved with chemotherapy (ChT), applied sequential or concurrent to conformal radiotherapy.[3-5] Therefore, combined chemo/radiotherapy is today the standard treatment for patients with advanced inoperable NSCLC in Stage IIIA/IIIB.[6]

Still, the most common pattern of failure is local recurrence. For patients surviving 6-12 months, local tumour control results in the increased overall survival and is directly related to the applied radiation dose.[7-9] With a radiation dose ranging from 64 to 80 Gy, local control rates of 70-92% can be achieved for stage T1-T3 tumours over a period of 12 months which decreases dose-dependently to 73-43% in the following years. Thus, attempts to decrease the rate of intrathoracic recurrence have been concentrated on dose escalation and different fractionation schedules throughout the last years.[3,10-13]

The purpose of this investigation was to evaluate feasibility, safety and efficacy of 3D- conformal radiotherapy with doses up to 70 Gy +/- platinum-based chemotherapy in patients with inoperable NSCLC treated within a prospective protocol in our institution.

Patients and methods

This investigation includes 84 patients with oncological and/or functional inoperable, histologically proven NSCLC consecutively treated from 1997 to 2002 in the potential curative intent at the Radiotherapy Department of the Medical University of Vienna. According to a prospective protocol, 3D-RT with radiation doses up to 66-70 Gy was applied, depending on dose-volume-constraints for lung toxicity, performance status and lung function. All patients had a complete staging before the treatment including CT scan of the chest and upper abdomen, bronchoscopy, CT-guided biopsy or mediastinoscopy, pulmonary function test, bone scan and complete blood cell counts.

Radiotherapy

All 84 patients received 3D-conformal radiotherapy. The computed tomography (CT) for the planning was performed in inspiration while the patient was lying in a supine position with arms elevated above the head. During the treatment the patients were asked to hold the breath as maximal as possible. The planning CT scan of the entire thorax was done with a slice thickness of 8 mm. For optimal positioning, the breast-board was used. The CT images were transferred to the 3D planning system (HELAX®, MMS 6.1B). Organs at risk (lung, spinal cord, heart), gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) were delineated. The GTV contoured the primary tumour plus involved pathological lymph nodes (≥ 10mm). Patients with supraclavicular lymph node metastases were not included.

The CTV was defined by adding 10mm around the GTV including also regional lymph nodes (mediastinum and ipsilateral hilus). For the PTV an additional margin of 5mm was placed around the CTV. The dose was prescribed to the ICRU point as described in the ICRU 50 recommendations.[14] Dose volume histograms (DVH) have been calculated for both lungs and spinal cord.

For the definition of the dose-volume constraints we followed the recommendations of Graham *et al*.[15] The maximum 20 Gy volume (V_{20}) was tolerated to be 50% for ipsilateral (IL), 30% for contralateral (CL) and 40% for both lungs. The mean lung dose for the ipsilateral lung had not to be more than 25 Gy. The dose to the spinal cord was maximum 50 Gy.

The irradiation was delivered by multiple field arrangements using photons with an energy of 10-25 MV. A dose of 40 Gy was applied by AP/PA fields, followed by a field rearrangement (3-4 fields) to lower the dose to the spinal cord. For boost irradiation to the primary tumour, the shrinking field technique was used. The treatment was performed in conventional fractionation, 5 days a week, with a dose of 2 Gy per fraction.

Chemotherapy

A platinum-based chemotherapy in doublets was applied mainly sequential. Cisplatin was combined with taxotere, navelbine, etiposide, gemcitabine or ifosfamide. The majority of patients (20) received 3 cycles before radiotherapy. A maximum of 6 cycles, 3 before and 3 after irradiation was given in 7 pts. Only 4 patients had concomitant chemo/radiotherapy (Table 1).

Side effects

The diagnosis of pneumonitis was based on clinical symptoms of shortness of breath, cough, fever and in correlation with the radiographic findings on chest X-ray. Radiation pneumonitis and oeosphagitis were evaluated according to the RTOG/EORTC radiation morbidity scoring criteria:[16] grade 2 pneumonitis is defined as cough, requiring medication or mild dyspnea during exercise, grade 3 as clinical or on X-ray visible acute pneumonitis requiring steroids and maybe intermittent oxygen and grade 4 is severe respiratory insufficiency and continuous use of oxygen. Grade 2 oesophagitis is defined as mild dysphagia requiring medication, grade 3 as severe dysphagia with weight loss and dehydration, grade 4 as complete obstruction, ulceration, perforation or fistula.

Patients

Depending on DVH constraints for V_{20} and mean lung dose, forced expiratory volume in 1 second (FEV_1) and performance status, radiation doses of either 66-70 Gy or 50-60 Gy were chosen. The administration of chemotherapy depended on performance status and co-morbidity. Thus, for the retrospective analysis four different treatment groups were defined:

Patients with a Karnofsky-index (KI) of 70-100%, FEV_1 of $\geq$ 1,3 l, treated with 3D-RT in combination with chemotherapy to a total dose of 66-70 Gy were defined as group A and patients with the same KI and FEV_1 but severe co-morbidity, treated with 66-70 Gy without chemotherapy as group C. A poorer performance status and/or a $FEV_1 \leq$ 1,3 l and high values at the DVH analysis resulted in 3D-RT of 50-60 Gy with chemotherapy (group B) and in case of additional severe co-morbidity, 3D-RT (50-60 Gy) was performed without chemotherapy (group D). See details in Table 1.

Follow-up

After the treatment the patients were followed in a 3 months (mo) interval for the first 2 years (y). A thoracic CT-scan and a pulmonary function test were demanded in regularly intervals. If clinically indicated, a blood test and a CT-scan of the brain were performed. The recurrent disease was defined as appearance of new lesions on CT-scan 6 months after radiotherapy.

Table 1. Patients characteristics

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
Age (mean)	48y	61y	70y	70y
Sex (n)				
Female	13	6	5	5
Male	16	10	21	8
Histology (n)				
Squamous cell carcinoma	12	7	18	8
Adenocarcinoma	16	6	6	4
Large cell carcinoma	1	3	2	1
Stage (n)				
IA			1	
IB			5	2
IIB	1	1	6	2
IIA	5	2	8	5
IIIB	23	13	6	4
TNM (n)				
T1N0			1	
T1N2	2			
T1N3	1	1		
T2N0			5	2
T2N1			1	
T2N2	3		7	3
T2N3	2			1
T3N0	1	1	4	2
T3N2	1	3	2	2
T3N3	3	3		
T4N0	8	2	4	3
T4N1			1	
T4N2	7	5		
T4N3		1	1	
TXN3	1			
RT dose (n; Gy)				
50		7		7
60		9		6
66	15		12	
70	14		15	
ChT cycles (n)				
6	7	2		
5	1	0		
4	3	2		
3	13	8		
2	1	3		
1	0	1		
?	4	0		

RT= radiotherapy; ChT= chemotherapy; n= number of patients

Table 2. Dose volume histograms (DVH) analysis for all treatment groups (A-D), mean values and range

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
V20IL (%)	39 (23-56)	47 (25-80)	39 (10-75)	47 (37-60)
V20CL (%)	16 (2-40)	15 (0-35)	14 (1-33)	10 (1-30)
Mean lung dose IL (Gy)	23 (16-32)	25 (9-41)	27 (10-36)	24 (15-33)
Mean lung dose CL (Gy)	11 (4-25)	11 (4-24)	10 (3-18)	7 (3-12)

IL= ipsilateral lung, CL= contralateral lung

Statistical analysis

Time to progression (TTP) was defined as an interval from the date of diagnosis to the development of local recurrence and/or distant metastasis or date of the last follow-up visit. Local control rates (LCR) of 1y and 2y were evaluated. Time to death (TTD), TTP and time to pneumonitis (grade 2-4) were estimated using the Kaplan-Meier product-limit method. To test the difference between survival curves, the log-rank test was used.[17]

Results

Data have been analysed until November 2004. The evaluation included TTP, TTD, LCR, distant failure and side effects such as pneumonitis and oesophagitis. Additionally a DVH analysis was done. The mean follow up time was 24 mo (range 1-84), 2 patients were lost to the follow-up.

Although DVH were calculated for all patients at the time of treatment, in 11 patients the calculated DVH could not be retrieved retrospectively from the planning system due to a technical defect on the hard disc.

The DVH analysis showed a mean V_{20} IL of 42% with a range of 10 to 80%. The V_{20} CL was 14% (range 0-40%). The mean lung dose IL was 25 Gy (range 9-36) and CL 10 Gy (range 3-25). Although the mean values correspond to the dose volume constraints we used, in some patients it was due to the tumour volume not possible to refer to those parameters, what explains the large range of the different values. Thus, patients with higher values of V20 IL and mean lung dose IL and low FEV_1 received only 50-60 Gy as already mentioned above (Table 2).

Of all 84 patients, 1 patient (1%) developed a grade 4 pneumonitis, 5 patients (6%) a grade 3 pneumonitis and 11 patients (13%) a grade 2 pneumonitis (Table 3). The median time of the development of pneumonitis in patients who experienced a pneumonitis grade 2-4 was 2 mo, ranging from 1 to 11 mo.

The statistic analysis for all patients showed that in a mean observation time of 24 mo (1-84) the median time of pneumonitis was not reached. The proportion of patients developing a pneumonitis grade 2-4 was after 3 mo 15%, after 6 mo 18% and after 11 mo 22%. Patients with a pneumonitis grade 2-4 had a mean V_{20} IL of 53.3% (33-85) and a mean lung dose IL of 30 Gy (17.2-

Table 3. Incidence of pneumontis and oesophagitis in the different treatment groups

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
Pneumonitis				
Grade 2	4 (13%)	2 (11%)	3 (11%)	3 (23%)
Grade 3	2 (6%)	0	2 (7%)	0
Grade 4	0	0	0	1 (8%)
Oesophagitis				
Grade 2	5 (17%)	3 (17%)	2 (7%)	1 (8%)
Grade 3	0	0	0	0
Grade 4	1 (3%)	1 (6%)	0	0

37.5). The additionally calculated sigmoid dose-response curve (Figure 1) showed a risk of 60% to develop a pulmonary toxicity (> grade 1) when the mean V_{20} IL was more than 50%.

Looking at the detailed results of the different treatment groups, we found in group A a median TTP of 13 mo, with a range of 4-85 mo and a median TTD was 28 mo, ranging from 7-85 mo. The median disease specific survival (DSS) was also 28 mo. The survival after 3 and 5y was 38% and 10% respectively. The LCR was 48% after 1y and 24% after 2y. Eight patients (27%) had progressive disease after radiotherapy, 12 (41%) developed distant metastases and 2 died of other, not cancer related causes. One patient with a stage IIIB tumour, located centrally, close to the oesophagus and the trachea developed a fistula (grade 4 complication) which was treated by a stent implantation. This patient died shortly after radiotherapy due to the local tumour progression.

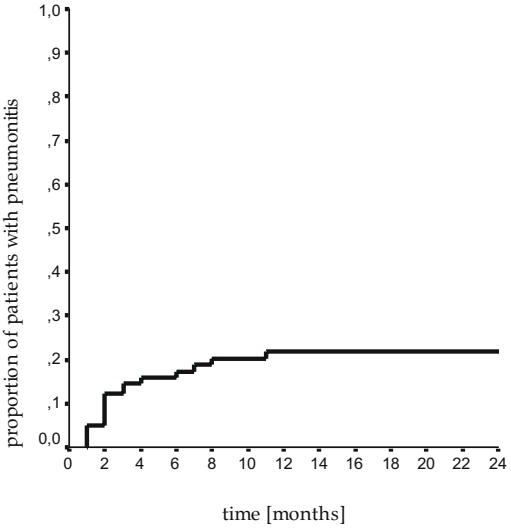

Figure 1. Sigmoid dose-response curve showing the correlation between V20 (%) IL and probability for pulmonary toxicity more than grade 1.

In group B, the median TTP was 15 mo ranging from 3-58 mo, the median TTD was 16 mo (3-27 mo), the LCR 38% after 1y and 25% after 2y. The three and 5y survival was 19% and 6% and the median DSS was 16 mo. The progressive disease after irradiation was seen in 5 patients (31%). A total of 5 patients (31%) developed distant metastases and 1 died of other causes. One 73y old patient with a T4N2 (stage IIIB) tumour developed an ulceration of the oesophageal mucosa (grade 4 complication) after irradiation, requiring hospitalisation, intravenous fluids and hyperalimentation.

In group C the median TTP was 13 mo (range 5-65 mo), the median TTD 16 mo (range 5-78 mo), the median DSS was 15 mo, the LCR was 42% after 1y and 23% after 2y. Nine patients (35%) had a tumour progression after radiotherapy, 6 (23%) had distant failure and 8 (31%) had not cancer

Table 4. Median values for time to progression (TTP), time to death (TTD), disease specific survival (DSS) and local control rate (LCR)

Group	A (66-70 Gy+ChT)	B (50-60 Gy+ChT)	C (66-70 Gy)	D (50-60 Gy)
TTP (month)	13	15	13	13
TTD (month)	28	16	16	22
DSS (month)	28	16	15	16
LCR (%)				
1-year	48	53	42	38
2-year	24	25	23	15

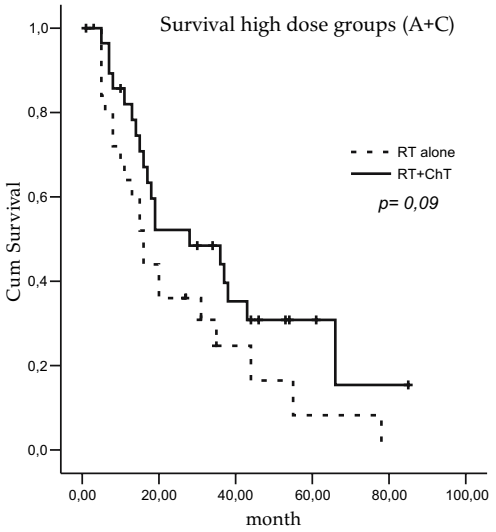

Figure 2. Kaplan-Meier overall survival curve for group A+C (66-70 Gy +/- ChT).

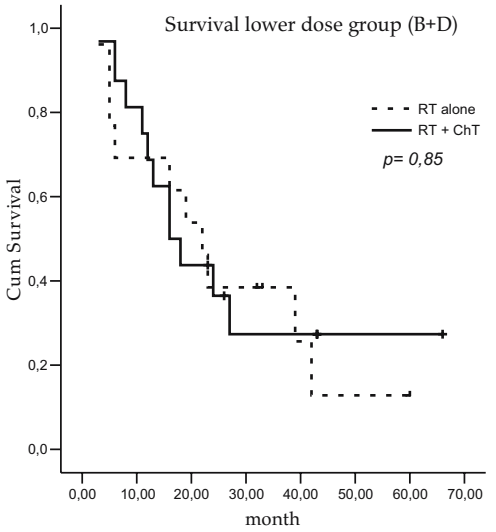

Figure 3. Kaplan-Meier overall survival curve for group B+D (50-60 Gy +/- ChT).

related death. The three and 5y survival was 11% and 8%. No grade 3 or 4 oesophageal toxicity was found.

Group D had a median TTP of 19 mo (range 3-22 mo), a median TTD of 22 mo (range 3-42 mo) and a median DSS was 16 mo. The LCR was 53% after 1y and 15% after 2y. Four patients (31%) had progressive disease after radiotherapy, no distant metastases were observed. Three patients died of other causes. The survival after 3 and 5y was 23% and 8%. No grade 3 or 4 oesophagitis was seen. One patient with a T2N2 (stage IIIA) tumour developed a grade 4 pneumonitis, requiring continuous oxygen. The ipsilateral V_{20} for this patient was 60% and the ipsilateral mean lung dose was 32 Gy. Recurrent disease was found after 10 months and death occurred 42 mo after diagnosis, without distant metastases.

Long-time survivors

For all treatment groups together a total of 14 patients survived more than 2 y with a median survival of 40 mo, ranging from 26

to 61 mo. Concerning long-time survival there was no significant difference between the different treatment groups (Figures 2, 3); however, patients receiving higher radiation doses (66-70 Gy) had a benefit in an overall survival (OS) when the additional chemotherapy was applied (28 month *vs.* 16 month).

Discussion

In the last decades, different treatment strategies were developed for locally advanced non-small cell lung cancer. For inoperable stage III NSCLC, 3D-conformal radiotherapy in combination with chemotherapy has lead to a better local control and longer survival.[7] Nevertheless, the local control remains poor, although the first results in dose escalation trials are promising.[3,13,18]

All patients included in this retrospective analysis received a 3D-conformal radiotherapy within a prospective protocol with the aim to apply a maximum dose of 70 Gy. Depending on performance status, lung function and dose volume constraints such as calculated mean lung dose and 20 Gy lung volume (V_{20}) different radiation doses ± chemotherapy have been applied on an individual basis resulting in four treatment groups. Our analysis showed that the application of radiation doses up to 70 Gy also in combination with sequential chemotherapy is feasible and safe. The treatment could be finished in all patients and no treatment related death occurred. Four grade 3 pneumonitis (9%) were found in the "higher dose" (66-70 Gy) groups (A+C) and no grade 4 pneumonitis.

The DVH analysis emphasised that the V_{20} IL in patients with grade 2-4 pneumonitis was mean 53.3%, with a mean lung dose IL of 30 Gy. Furthermore, the sigmoid dose-response curve shows that a V_{20} IL of more than 50% leads to a risk of 60% for pulmonary toxicity. This underlines the correlation of V_{20} IL with the incidence of radiation pneumonitis as reported by Graham *et al.*[15] The authors showed that a mean V_{20} of the total lung (including both lungs minus PTV) of more than 32% was significantly correlating with high grade pneumonitis (≥ grade 3). The final toxicity results of a dose-escalation study of Kong *et al.* showed that the grade 2 and 3 lung toxicity was not directly associated with the prescribed tumour dose but correlated with dosimetric parameters. The risk of pneumonitis was significantly associated with a mean lung dose ≥ 14 Gy (p = 0.002) and a V_{20} ≥ 27% (p = 0,0008).[19]

For all 84 patients, no grade 3 oesophagitis was observed. Two grade 4 oesophageal toxicities were seen in patients with central, bulky tumours close to oesophagus and trachea.

Our results also showed that in the group with higher radiation doses (66-70 Gy) the application of chemotherapy prolonged the survival compared to exclusive radiotherapy of 66-70 Gy (28 *vs.* 16 mo). Considering the DSS we found the same results (28 *vs.* 15 mo). Comparable results have been reported by Rengan *et al.*[12] In this study a group of 35 patients with stage IIIB NSCLC received 64-84 Gy plus chemotherapy with a median overall survival (OS) of 20 mo for and local failure rate of 64%. Sim *et al.*[5] reported for 152 patients with stage III NSCLC a median OS of 18 mo for the combined treatment compared to 11.7 mo for the radiotherapy alone group ($p \leq 0{,}001$).

In the lower dose (50+60 Gy) groups (B+D) there has been no benefit in OS for patients receiving ChT as it was seen in the higher dose groups (A+C). The median survival time for the lower dose groups +/- ChT (16 *vs.* 22 mo) is also comparable with results in the literature. Different studies report a median OS of 13.8-16 mo

for chemoradiotherapy and 9.7-16 mo for exclusive radiotherapy in stage III NSCLC with radiation doses between 50-63 Gy.[12,20-22] The slightly better results for the group with exclusive radiotherapy (22 mo) for OS could not be confirmed for the DSS where no difference was found (median 16 mo for both groups).

Concerning the development of distant metastases we could not obtain the same results as stated in several studies.[6,20,23] In our analysis the rate of distant failure was not lower in patients with radio-/chemotherapy as in patients receiving RT alone. The reason might be that especially in the higher dose groups, the majority of patients receiving chemotherapy had stage IIIB whereas in the exclusive radiotherapy groups, also stages I and II were included. The LCR at 1y was in all 4 treatment groups nearly the same with mean 45% and no advantage for higher radiation doses could be observed. Probably the number of patients was too small. The LCR at 2y was low in all four groups with the poorest result (15%) for the group receiving 50-60 Gy without chemotherapy.

To improve the local control, different efforts have been made in the last years. Developments in 3D-planning and new techniques like self-gated radiotherapy at deep-inspiration breath hold (DIBH) enable a better tumour targeting and sparing of normal tissue which allows an escalation of the radiation dose up to 100 Gy. Local control rates of 50-80% have been reported with radiation doses varying from 70.2 to 90 Gy.[3,8,13,17,24,25] The limiting factor for dose escalation is the surrounding normal lung tissue. Radiation doses of ≥ 90 Gy lead to severe pulmonary toxicity.[3,13] Several studies showed that intensity modulated radiotherapy (IMRT), especially if guided by PET/CT imaging, has the ability to spare more normal lung tissue and allows 25-30% higher doses than with 3D-conformal radiotherapy.[26,27] Advances in tumour staging could result in smaller treatment volumes, which would enable the application of higher radiation doses. Especially PET/CT improves the detection of lymphnode metastases and the differentiation between tumour tissue and atelectasis. De Ruysscher *et al.* showed in a planning study that the use of a combined PET/CT simulator reduced the radiation dose to normal lung tissue and oesophagus and thus allowed a significant radiation dose escalation.[28]

Still, the risk of normal tissue toxicity should not be underestimated[3,27] and new trials to evaluate a safe dose-escalation technique are obligatory.

Conclusions

The low incidence of severe side effects confirms that the application radiation doses up to 70 Gy with 3D-conformal radiotherapy is feasible and safe, taking into account 3D dose volume constraints. Our work suggests that the combination of chemotherapy and 3D-conformal radiotherapy of 66-70 Gy prolongs moderately the overall survival for patients with inoperable non-small-cell lung cancer with a low risk of severe pneumonitis.

Nevertheless, local control rates remain low, especially after 2y. Thus the possibility of further dose escalation also in more advanced tumour stages with a special regard to the long-term pulmonary and oesophageal toxicity should be investigated.

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