

Survival after palliative radiotherapy in nondisseminated nonsmall cell lung cancer treated with 30 Gy in 10 fractions or 39 Gy in 13 fractions using conformal technique

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Introduction

The main object of palliative radiotherapy (pRT) in nonsmall cell lung cancer (NSCLC) has been to alleviate symptoms rather than to prolong life. In general, the use of higher radiation doses using standard techniques has not increased survival or led to more durable palliation than fractionation schedules using lower doses [1]. However, the majority of studies have used radiation technique based on simple radiation portals. The use of volumetric arc therapy (VMAT) and modern dose planning systems makes it feasible to produce more advanced conformal treatment plans in the palliative setting in order to reduce the radiation side effects [2,3], and this technique on the other hand makes it possible to increase radiation dose without increasing side effect. For selected patients, this could lead to better tumor control and increased survival.

Since 2014 we have treated selected patients with local advanced NSCLC with conformal VMAT pRT to a dose of 39 Gy in 13 fractions (39 Gy/13F). These were patients not suitable for curative treatment but still expected to have a fair prognosis. Other patients with NSCLC were treated with a standard dose schedules of 30 Gy in 10 fractions (30 Gy/10F). *A priori*, the patients offered the high-dose pRT should have better survival due to selection. The object of this retrospective study was to evaluate if that actually was the case-adjusting data for factors that potentially might affect survival, and to test if it was possible to select a subgroup of patients benefiting from the increased radiation dose.

Data material

The study consisted of patients with histologically or cytologically confirmed NSCLC with tumors located in lung or mediastinum consecutive treated from 1 January 2014 to 31 December 2020 with 30 Gy/10F or 39 Gy/13F. Included were patients with unilateral or mediastinal tumors, no distant metastases at the time of radiation, no previous pRT, and

performance status (PS) 0–3. Patients with recurrent disease, multiple ipsilateral lung lesions, and concurrent other malignancy were accepted in the study. Cutoff date for analyses was 1 October 2021 resulting in a median and shortest potential follow-up of 58 and 10.5 months. Vital status was known for all patients.

From the patient files, we obtained date of treatment, radiation dose and fractionation, site, and the gross tumor volume (GTV), age, gender, date of diagnosis, histology, tumor stage, white blood count (WBC), performance status, Charlson comorbidity index (CCI), body mass index (BMI), time span since diagnoses, and the date of death.

Radiation technique

Which treatment schedule to use was decided by the physician: 39 Gy/13F were preferentially offered to patients with a tumor which could be encompassed in a reasonable treatment volume and who had an expected survival of ≥ 6 months.

For all patients, the GTV was delineated, but no i.v.-contrast was used. For tumors treated with 39 Gy, a PTV surrounded GTV by 2 cm, and the dose to the GTV and PTV was 95% and 90% of the prescribed dose. The radiotherapy was planned as VMAT. For patients treated by 30 Gy, simple opposing portals were mostly used with field edges 1 cm from the GTV. For both groups, daily conebeam verification of the setup was used with a dual match of the tumor and bone.

Statistics

Multivariable overall survival Cox proportional hazard analyses (forward selection) included factors with $p < 0.20$ in univariate analyses.

Some factors were dichotomized in the analyses: PS ≤ 2 , Age ≤ 70 year, WBC ≤ 12 mmol/L, BMI ≤ 18.5 kg/m², CCI ≤ 2 , and time since primary diagnosis

$</\geq 12$ months. The volume of GTV was included logarithmically. The radiation dose appeared to be time depended, and dose and WBC were significantly correlated with each other for patients living shorter than 6 months, but not for patients with a longer survival. The analyses were therefore stratified for WBC $</\geq 12$ mmol/L.

Results

Patient characteristics is seen in Table 1. The 39Gy/13F group consisted of 83 patients and the 30Gy/10F of 101 patients. The median, one-year, two-year, and three-year

survival for 39Gy/13F and 30Gy/10F was 11.0 months, 48%, 174%, 14%, and 7.8 months, 37%, 14%, 5% respectively ($p = 0.08$), Figure 1.

Insignificant factors in univariate analyses left out of the Cox models included age, BMI, gender, N-stage, and time span since diagnosis of the primary tumor. In the stratified cox analyses of the remaining factors, the radiation dose for patients with an overall survival shorter than six months was significant with $HR = 0.57$ ($p = 0.03$), while the radiation dose was insignificant for patients with a survival ≥ 6 months ($HR = 0.91$, $p = 0.67$). Increased values of GTV ($p = 0.001$) and CCI ≥ 2 ($p = 0.005$) were significantly associated with poor

Table 1. Patient characteristics.

	30Gy/10F N = 101	39Gy/13F N = 83	Total N = 184
Age (median years)	72.8 (43.6; 91.5)	75.9 (49.3; 92.6)	73.9 (43.6; 92.6)
Gender			
Female	45 (45%)	35 (42%)	80 (43%)
Male	56 (55%)	48 (58%)	104 (57%)
Performance status			
0-1	36 (36%)	28 (34%)	64 (35%)
2	58 (57%)	57 (57%)	105 (57%)
3	7 (7%)	8 (10%)	15 (8%)
Charlson CI			
0-1	67 (66%)	50 (60%)	117 (64%)
2-3	22 (22%)	24 (29%)	46 (25%)
≥ 4	12 (12%)	9 (11%)	21 (11%)
Body Mass Index			
< 18.5 kg/cm ²	13 (13%)	8 (10%)	21 (11%)
≥ 18.5 kg/cm ²	88 (87%)	75 (90%)	163 (89%)
White Blood Count (mmol/L)	9.0 (2.6; 34.5)	9.2 (3.4; 61.9)	9.1 (2.6; 61.9)
White Blood Count ≥ 12 mmol/L	26 (26%)	21 (25%)	47 (26%)
Histology			
Squamous	41 (41%)	43 (52%)	84 (46%)
Adenocarcinoma	52 (51%)	37 (45%)	89 (48%)
Other histology	8 (8%)	3 (4%)	11 (6%)
Tumor volume (cm ³)	91.5 (7.5; 1990)	62.7 (4.3; 728)	76.4 (4.3; 1990)
Tumor volume			
< 50 cm ³	26 (26%)	37 (45%)	63 (34%)
≥ 50 cm ³	75 (74%)	46 (55%)	121 (66%)
T-stage at time of radiotherapy			
T0	5 (5%)	6 (7%)	11 (6%)
T1	11 (11%)	7 (8%)	18 (10%)
T2	15 (15%)	13 (16%)	28 (15%)
T3	17 (17%)	19 (23%)	36 (20%)
T4	53 (53%)	38 (46%)	91 (50%)
N-stage at time of radiotherapy			
N0	21 (21%)	24 (29%)	45 (25%)
N1	7 (7%)	9 (11%)	16 (9%)
N2	30 (30%)	32 (39%)	62 (34%)
N3	43 (43%)	18 (22%)	61 (33%)
Time since primary diagnosis (months)	2.2 (0.2; 84.0)	0.7 (0.2; 121.2)	0.9 (0.2; 121.2)
Potential follow-up (months)	70.9 (13.4; 92.8)	41.3 (10.5; 88.7)	58.2 (10.5; 92.8)
Radiation technique			
Opposing paired portals			
VMAT			
Chemotherapy			
None	45 (45%)	59 (71%)	104 (57%)
Prior to radiotherapy only	19 (19%)	7 (8%)	26 (14%)
After radiotherapy	36 (36%)	16 (19%)	52 (28%)
After radiotherapy unknown	1 (1%)	1 (1%)	2 (1%)
Tyrosinkinase inhibitor			
None	99 (98%)	83 (%)	182 (99%)
Prior to radiotherapy only	0 (0%)	0 (0%)	0 (0%)
After radiotherapy	2 (2%)	0 (0%)	2 (1%)
After radiotherapy unknown	0 (0%)	0 (0%)	0 (0%)
Immunotherapy			
None	87 (86%)	75 (90%)	162 (88%)
Prior to radiotherapy only	8 (8%)	1 (1%)	9 (5%)
After radiotherapy	6 (6%)	7 (8%)	13 (7%)
After radiotherapy unknown	0 (0%)	0 (0%)	0 (0%)

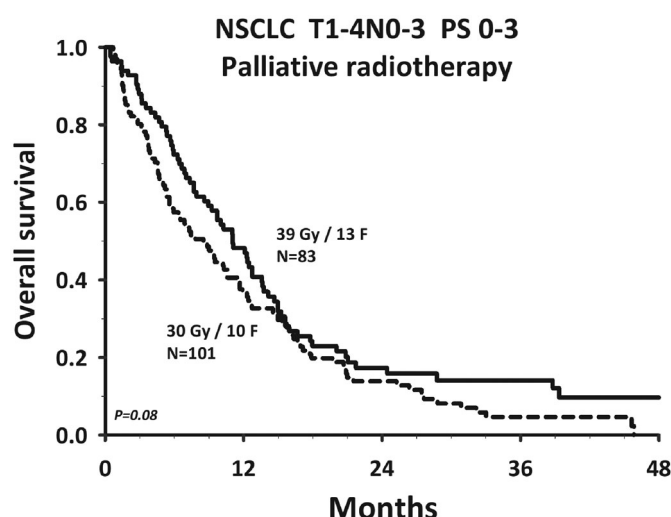


Figure 1. Overall survival after palliative radiotherapy 30 Gy/10 fractions and 39 Gy/13 fraction in patients with NSCLC.

prognosis while smoking habit ($p = 0.065$), PS ($p = 0.085$) and histology (0.40) were not. In 20 patients with PS 0–1 and GTV ≤ 50 cc, the median survival was 15.6 and 11.7 months for 39 Gy/13F and 30 Gy/10F, and the one-year survival was 67% and 36%, but the difference was insignificant ($p = 0.22$) in univariate analyses. In patients with tumors ≥ 50 cc and PS 0–1, or patients in tumors < 50 cc and PS 2–3, there was no indication for benefit of high-dose pRT ($p > 0.72$ and $p > 0.78$).

Discussion

Radiotherapy added to chemotherapy may improve survival NSCLC as shown in a randomized Norwegian study [4], but the optimal radiation dose is not known. The dose used in the Norwegian study was 42 Gy in 15 fractions which is an equivalent dose of 44.8 Gy in 2 Gy fractions with $\alpha/\beta = 10$ (EQD₂). The two levels of EQD₂ dose in the present study was 42.25 Gy in the 39 Gy/13F group and 32.5 Gy in the 30 Gy/10F group but this did not translate to a survival benefit for patients. Although the data were inconclusive for patients in good performance status and small tumors which constitutes about 10% of the patients, the study failed to demonstrate any subgroup of patients benefitting from high-dose pRT used in the study. Furthermore, the high dose was of no benefit in survival for patients with tumors ≥ 50 cc, and patients in PS 2–3.

One explanation for the missing effect on survival might be that increased biological effect of about 10 Gy is not enough to produce a difference in tumor control, and another cause might be that modern medical treatment including immunotherapy may offset any benefits of potential higher doses of pRT. We have no data in the present study to test that.

Several other studies have failed to demonstrate that higher doses of palliative radiotherapy increase survival as summarized in an Cochrane review from 2015, and another systematic review from 2014 [1,5]. Our result is also in line

with the result in a small study published by Nieder *et al* [6] who analyzed 77 patients with NSCLC treated with palliative radiotherapy in different doses. No effect of increased radiation dose was seen in multivariable analyses. However, in contrast to our findings, they did not find an association between the tumor volume and overall survival. In our study, the tumor volume is highly associated with survival. We also found a significant association between CCI and survival similar to what we have reported being the case for patients with NSCLC treated with stereotactic radiotherapy [7]. We found no association between age and survival which is similar to the findings in [8].

Although all patients have been prospectively identified, major parts of the data have been retrospectively recorded. This and the low number of patients of patients in good PS having a small tumor burden is an important obstacle for a clear conclusion for these patients.

There was no indication of more early toxic death during in the high-dose pRT group, and if high-dose pRT should result in better local control and therefore improved survival, this should be more evident for the long-term survival than for the short-term survival. The observation that high-dose pRT was associated with superior survival for patients living less than six months, and not for patients living more than six months indicates that it is the selection of patients to treatment, not the treatment itself that leads to improved outcome.

We have previously performed a prospective study comparing Quality of Life (QoL) in patients with NSCLC receiving palliative radiotherapy 25–30 Gy in 5–10 F and in patients receiving 39 Gy in 13 F (Data under publishing). Clinically significant differences in changes from baseline to 5 weeks follow-up was observed for global QoL, dyspnea, and appetite loss between the 25/30 Gy-group and the 39 Gy-group favoring the lower radiation dose group. This finding and the lack of survival benefit for the majority of the patients indicates that pRT doses higher than 30 Gy in 10 fractions in general cannot be recommend in patients with local advanced NSCLC not candidate for curative treatment.

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