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Palliative Thoracic Radiotherapy for Non-small Cell Lung Cancer: Is There any Impact of Target Volume Size on Survival?

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Abstract. *Background/Aim: Recent studies suggested that target volume size impacts survival in patients with non-small cell lung cancer (NSCLC) receiving radical radiotherapy. Little is known about the impact of target volume size in palliative radiotherapy or chemoradiotherapy. Therefore, we analyzed the overall survival stratified for clinical and planning target volume (CTV and PTV) size. Patients and Methods: A retrospective study of 77 patients who received palliative (chemo)radiotherapy (at least 30 Gy) for non-metastatic NSCLC, largely stage III was performed. Typical radiation doses were 10-13 fractions of 3 Gy and 15 fractions of 2.8 Gy. Results: Median survival was 12 months (2-year rate 18%). Three prognostic factors emerged in the multivariate analysis. Hospitalization in the last 4 weeks before radiotherapy increased the hazard of death by a factor of 2.8 (p=0.002). Presence of a T1 or 2 tumor decreased the hazard of death by a factor of 0.5 (p=0.03). Concomitant chemoradiotherapy decreased the hazard of death by a factor of 0.4 (p=0.003). Conclusion: Target volume size was not significantly associated with survival, suggesting that large size should not preclude palliative (chemo)radiotherapy as long as normal tissue dose constraints can be met.*

Patients with inoperable, locally advanced non-small cell lung cancer (NSCLC) are often treated with combined platinum-based chemotherapy and radiotherapy (radical RCT) (1-5). Due to ineligibility resulting from advanced age, comorbidity or reduced performance status, other options may become the preferred approach, *e.g.* radical radiotherapy alone, palliative radiotherapy alone or palliative RCT (6-8).

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Decision-making is tailored to individual patients' ability to tolerate treatment, as well as motivation and goal of treatment. Different survival prediction tools have been developed, which may stratify patients into distinct prognostic groups (9-11). Such information can be used to support pretreatment assessment. However, prognostic scores are commonly derived from a limited number of baseline variables. Newly emerging prognostic factors should be studied to improve already existing tools. In the context of radical RCT, several studies have suggested that gross tumor volume (GTV) or planning target volume (PTV) predicts overall survival (12-15). These metrics of tumor burden have rarely been studied in the setting of contemporary palliative radiotherapy or RCT. Therefore, we performed a retrospective study addressing the prognostic impact of target volume size in patients who started palliative radiotherapy or RCT at our Institution.

Patients and Methods

A retrospective review of 77 consecutive patients treated with palliative 3-dimensional conformal radiotherapy or RCT between 2009 and 2019 was performed. Inclusion was limited to patients with a prescribed total dose of 30-54 Gy and those without distant metastases (stage II or III). Four patients (5%) failed to complete radiotherapy. An additional exploratory analysis of 57 patients with stage IV NSCLC who received identical treatment was also performed. Patients treated with low-dose radiotherapy, primarily 2 fractions of 8.5 Gy, were excluded from both analyses. All 77 study patients had Eastern Cooperative Oncology Group (ECOG) performance status 0-2. In case of RCT, most patients received the Norwegian CONRAD regime (15 fractions of 2.8 Gy, Carboplatin/Vinorelbine before and during radiotherapy) (16, 17). Treatment plans were calculated with Varian Eclipse TPS® and no intensity-modulated or arc-based techniques were employed. Contouring of the GTV was not mandatory. However, the clinical target volume (CTV) and PTV was contoured in all patients. Therefore, analysis was limited to CTV and PTV. Elective lymph node stations were not included in the CTV. The CTV margin expansion varied, depending on availability of 4-D treatment

Table I. *Baseline characteristics before palliative radiotherapy in 77 patients.*

Variable	N (%)
Hospitalization	
During RT	9 (12)
Before, but not during RT	13 (17)
No	55 (71)
Gender	
Male	42 (55)
Female	35 (45)
History of COPD	
Yes	24 (31)
No	53 (69)
Radiation dose	
13 fractions of 3 Gy or higher dose	57 (74)
Lower dose, largely 10 fractions of 3 Gy	20 (26)
Tumor stage	
T1 and 2	24 (31)
T3 and 4	53 (69)
Lymph node stage	
N0 and 1	21 (27)
N2 and 3	56 (73)
Cancer stage	
II	11 (14)
III	66 (86)
Histology	
Adenocarcinoma	33 (43)
Squamous cell carcinoma	35 (45)
Other	9 (12)
Active smoking	
Yes	15 (19)
No	62 (81)
Systemic cancer treatment	
Before RT	41 (53)
Concomitant to RT	35 (45)
Steroid medication	
Yes	20 (26)
No	57 (74)

COPD: Chronic obstructive pulmonary disease; RT: radiotherapy.

planning scans allowing for an internal target volume (ITV) concept. In case of ITV contouring, 5 mm were added to create the PTV. Otherwise, the CTV was expanded by 8-10 mm to create the PTV. Positron emission tomography (PET) was available in a minority of patients. The typical approach was computed tomography (CT)-based contouring without 4-D registration of respiratory motion. IBM SPSS v.25 was employed for statistical analyses. The latter included chi-square test and univariate Cox regression for associations between overall survival from the start of radiotherapy and clinical and dosimetric variables. Significant variables, *i.e.* $p \leq 0.05$ in two-sided tests, were then included in multivariate forward conditional Cox regression analysis. Actuarial overall survival was calculated according to the Kaplan-Meier method and the log-rank test was employed for comparison of survival curves. At the time of the analysis, 22 patients were alive (censored observations after a median follow-up of 12.6 months). Date of death was known for all remaining patients.

Table II. *Prognostic factors for overall survival in 77 patients.*

Variable	*p*-Value univariate	*p*-Value multivariate
Hospitalization		
During RT	0.003	0.14
Before, but not during RT	0.002	0.002
No		
Gender		
Male	0.58	
Female		
History of COPD		
Yes	0.48	
No		
Radiation dose		
13 fractions of 3 Gy or higher dose	0.035	0.26
Lower dose, largely 10 fractions of 3 Gy		
Tumor stage		
T1 and 2	0.041	0.03
T3 and 4		
Lymph node stage		
N0 and 1	0.60	
N2 and 3		
Cancer stage		
II	0.32	
III		
Histology		
Adenocarcinoma	0.51	
Squamous cell carcinoma		
Other		
Active smoking		
Yes	0.44	
No		
Systemic cancer treatment		
Before RT	0.005	0.64
Concomitant to RT	0.002	0.003
Steroid medication		
Yes	0.004	0.11
No		
CTV		
Continuous variable	0.05	0.096
PTV		
Continuous variable	0.24	
Mean lung dose		
Continuous variable	0.47	
Lung volume exposed to 20 Gy		
Continuous variable	0.16	

COPD: Chronic obstructive pulmonary disease; CTV: clinical target volume; Gy: Gray; PTV: planning target volume; RT: radiotherapy.

Results

The baseline characteristics of the study population are shown in Table I. The median age was 72 years, range=47-89 years. The median CTV size was 135 ml, range=10-860 ml (25th percentile 60.5 ml, 50th percentile 135 ml, 75th percentile 261.5 ml). The median PTV size was 402 ml, range=45-1272 ml. Table II shows the results of the survival analyses. Three

prognostic factors emerged in the multivariate regression analysis. Having been hospitalized in the last 4 weeks before radiotherapy increased the hazard of death by a factor of 2.8 (p=0.002). Having a T1 or 2 tumor decreased the hazard of death by a factor of 0.5 (p=0.03). Receiving concomitant RCT decreased the hazard of death by a factor of 0.4 (p=0.003). Median survival in this study was 12 months (all 77 patients; 2-year rate 18%). Among four patients who failed to complete radiotherapy, three had been hospitalized in the last 4 weeks before start. In the additional exploratory analysis, target volume size did not predict overall survival in patients with stage IV disease, identical to the result of the main study.

Discussion

Patients with NSCLC not amenable to radical treatment commonly receive palliative thoracic radiotherapy (6, 7, 18, 19). Heterogeneity between studies has been observed regarding prognostic factors for survival (9, 20). A relevant impact of GTV or PTV size has emerged from the literature on radical radiotherapy (12-15) and therefore, we performed this retrospective study in patients treated palliatively. Typical patients were in their 70s, had stage III disease and received 13 fractions of 3 Gy without chemotherapy or 15 fractions of 2.8 Gy with up to 4 cycles of Carboplatin/Vinorelbine. The concomitant RCT regime emerged as a major factor associated with improved survival. The same was true for the presence of T1-2 disease, but not N stage, CTV and PTV. Finally, a history of previous hospitalization (4 weeks before radiotherapy, any cause) impacted survival. The hospitalization variable might be related to other potential predictors of survival, which were not available in our database, *e.g.*, weight loss, comorbidity and frailty. This would also explain why three of four patients who failed to complete radiotherapy had a history of previous hospitalization. Concomitant RCT for patients without contraindications is also endorsed in a recent American guideline (7).

The main limitations of our study are its retrospective design, group size (or statistical power), lack of GTV data, and heterogeneity regarding PET utilization. PET-assisted treatment planning might have resulted in different CTV contouring and should be considered mandatory in the radical treatment setting (21, 22). However, in elderly patients with comorbidity and limited treatment options, routine PET staging is economically difficult to justify, especially if transportation to an outside PET center is needed like in our healthcare region (23). Given that early palliative interventions may influence the outcomes of care for patients with NSCLC (24), it would be interesting to study this paradigm in a patient population like ours, and not just in patients who receive primary systemic therapy. Fortunately, the radiation treatment strategies continue to evolve and it will be interesting to see whether immune checkpoint inhibitors show added benefit in the palliative, non-metastatic setting (25). Overall, our study suggests that large CTVs should not preclude palliative RCT (or monotherapy) as long as normal tissue dose constraints can be met. Recently, recommendations for esophageal dose were published (17), but the risk of pneumonitis must also be considered.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. KSI collected patient data. CN, KSI, BM and RY conceived the study and drafted the article. All Authors read and approved the final article.

References

1 Brown S, Banfill K, Aznar MC, Whitehurst P and Faivre Finn C: The evolving role of radiotherapy in non-small cell lung cancer. Br J Radiol *92(1104)*: 20190524, 2019. PMID: 31535580. DOI: 10.1259/bjr.20190524

2 Baldini E, Tibaldi C and Delli Paoli C: Chemo-radiotherapy integration in unresectable locally advanced non-small-cell lung cancer: a review. Clin Transl Oncol *22(10)*: 1681-1686, 2020. PMID: 32128671. DOI: 10.1007/s12094-020-02326-6

3 Nieder C, Pawinski A and Andratschke NH: Combined radio- and chemotherapy for non-small cell lung cancer: systematic review of landmark studies based on acquired citations. Front Oncol *3*: 176, 2013. PMID: 23847765. DOI: 10.3389/fonc.2013.00176

4 Ueda Y, Suzuki O, Ohira S, Yagi M, Sumida I, Wada K, Inui S, Isono M, Miyazaki M, Ogawa K and Teshima T: The promising treatment schedule of concurrent chemoradiotherapy for stage III non-small cell lung cancer: Alternative for conventional fractionation using mathematical analysis. Anticancer Res *40(7)*: 4095-4104, 2020. PMID: 32620658. DOI: 10.21873/anticanres.14408

5 Wada K, Kishi N, Kanayama N, Hirata T, Morimoto M, Konishi K, Imamura F, Teshima T and Ogawa K: Radiation dose escalation in accelerated hyperfractionated radiotherapy for stage III non-small-cell lung cancer. Anticancer Res *38(10)*: 5951-5958, 2018. PMID: 30275224. DOI: 10.21873/anticanres.12941

6 Jumeau R, Vilotte F, Durham AD and Ozsahin EM: Current landscape of palliative radiotherapy for non-small-cell lung cancer. Transl Lung Cancer Res *8(Suppl 2)*: S192-S201, 2019. PMID: 31673524. DOI: 10.21037/tlcr.2019.08.10

7 Moeller B, Balagamwala EH, Chen A, Creach KM, Giaccone G, Koshy M, Zaky S and Rodrigues G: Palliative thoracic radiation therapy for non-small cell lung cancer: 2018 Update of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol *8*: 245-250, 2018. PMID: 29625898. DOI: 10.1016/j.prro.2018.02.009

8 Nieder C, Tollåli T, Yobuta R, Reigstad A, Flatøy LR and Pawinski A: Palliative thoracic radiotherapy for lung cancer: What is the impact of total radiation dose on survival? J Clin Med Res *9(6)*: 482-487, 2017. PMID: 28496548. DOI: 10.14740/jocmr2980w

9 Nieder C, Tollåli T, Haukland E, Reigstad A, Flatøy LR and Dalhaug A: External validation of a prognostic score for patients receiving palliative thoracic radiotherapy for lung cancer. Clin Lung Cancer *18(4)*: e297-e301, 2017. PMID: 28189593. DOI: 10.1016/j.cllc.2017.01.006

10 Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N and Aasebø U: Poor prognosis patients with inoperable locally advanced NSCLC and large tumors benefit from palliative chemoradiotherapy: a subset analysis from a randomized clinical phase III trial. J Thorac Oncol *9(6)*: 825-833, 2014. PMID: 24807158. DOI: 10.1097/JTO.0000000000000184

11 van Oorschot B, Assenbrunner B, Schuler M, Beckmann G and Flentje M: Survival and prognostic factors after moderately hypofractionated palliative thoracic radiotherapy for non-small cell lung cancer. Strahlenther Onkol *190(3)*: 270-275, 2014. PMID: 24413894. DOI: 10.1007/s00066-013-0507-y

12 Bradley JD, Ieumwananonthachai N, Purdy JA, Wasserman TH, Lockett MA, Graham MV and Perez CA: Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys *52*: 49-57, 2002. PMID: 11777621. DOI: 10.1016/s0360-3016(01)01772-2

13 Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces YI, Narayan S, Iyengar P, Robinson C, Wynn RB, Koprowski C, Meng J, Beitler J, Gaur R, Curran W Jr and Choy H: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol *16*: 187-199, 2015. PMID: 25601342. DOI: 10.1016/S1470-2045(14)71207-0

14 Kim YH, Ahn SJ, Kim YC, Kim KS, Oh IJ, Ban HJ, Chung WK, Nam TK, Yoon MS, Jeong JU and Song JY: Predictive factors for survival and correlation to toxicity in advanced stage III non-small cell lung cancer patients with concurrent chemoradiation. Jpn J Clin Oncol *46(2)*: 144-151, 2016. PMID: 26590014. DOI: 10.1093/jjco/hyv174

15 Ladbury CJ, Rusthoven CG, Camidge DR, Kavanagh BD and Nath SK: Impact of radiation dose to the host immune system on tumor control and survival for stage III non-small cell lung cancer treated with definitive radiation therapy. Int J Radiat Oncol Biol Phys *105(2)*: 346-355, 2019. PMID: 31175902. DOI: 10.1016/j.ijrobp.2019.05.064

16 Strøm HH, Bremnes RM, Sundstrøm SH, Helbekkmo N, Fløtten O and Aasebø U: Concurrent palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomised trial by the Norwegian Lung Cancer Study Group. Br J Cancer *109*: 1467-1475, 2013. PMID: 23963145. DOI: 10.1038/bjc.2013.466

17 Nieder C, Imingen KS, Mannsåker B, Yobuta R and Haukland E: Risk factors for esophagitis after hypofractionated palliative (chemo) radiotherapy for non-small cell lung cancer. Radiat Oncol *15(1)*: 91, 2020. PMID: 32357936. DOI: 10.1186/s13014-020-01550-2

18 Tataru D, Spencer K, Bates A, Wieczorek A, Jack RH, Peake MD, Lind MJ and Lüchtenborg M: Variation in geographical treatment intensity affects survival of non-small cell lung cancer patients in England. Cancer Epidemiol *57*: 13-23, 2018. PMID: 30268078. DOI: 10.1016/j.canep.2018.09.001

19 Støchkel FM, Schou Nørøxe D, Nygård L and Fredberg PG: Fractionated palliative thoracic radiotherapy in non-small cell lung cancer - futile or worth-while? BMC Palliat Care *17(1)*: 15, 2018. PMID: 29304789. DOI: 10.1186/s12904-017-0270-4

20. Angelo K, Norum J, Dalhaug A, Pawinski A, Aandahl G, Haukland E, Engljähringer K and Nieder C: Development and validation of a model predicting short survival (death within 30 days) after palliative radiotherapy. Anticancer Res *34(2)*: 877-885, 2014. PMID: 24511026.

21 Brodin NP, Tomé WA, Abraham T and Ohri N: ^{18}F-Fluorodeoxyglucose PET in locally advanced non-small cell lung cancer: From predicting outcomes to guiding therapy. PET Clin *15(1)*: 55-63, 2020. PMID: 31735302. DOI: 10.1016/j.cpet.2019.08.009

22 Grootjans W, de Geus-Oei LF and Bussink J: Image-guided adaptive radiotherapy in patients with locally advanced non-small cell lung cancer: the art of PET. Q J Nucl Med Mol Imaging *62(4)*: 369-384, 2018. PMID: 29869486. DOI: 10.23736/S1824-4785.18.03084-4

23 Norum J, Søndergaard U, Traasdahl E, Nieder C, Tollåli G, Andersen G and Sundset R: PET-CT in the sub-arctic region of Norway 2010-2013. At the edge of what is possible? BMC Med Imaging *15*: 36, 2015. PMID: 26316132. DOI: 10.1186/s12880-015-0073-0

24 Nieder C, Tollåli T, Haukland E, Reigstad A, Flatøy LR and Engljähringer K: Impact of early palliative interventions on the outcomes of care for patients with non-small cell lung cancer. Support Care Cancer *24(10)*: 4385-4391, 2016. PMID: 27209479. DOI: 10.1007/s00520-016-3278-z

25 Fitzgerald K and Simone CB 2nd: Combining immunotherapy with radiation therapy in non-small cell lung cancer. Thorac Surg Clin *30(2)*: 221-239, 2020. PMID: 32327181. DOI: 10.1016/j.thorsurg.2020.01.002

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