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Prognostic Factors of Survival After Radiotherapy for Lung Cancer–The Impact of Smoking Pack Years

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Abstract. *Background/Aim: The prognostic role of smoking pack years after thoracic irradiation for lung cancer needs further clarification, since previous studies showed conflicting results. Therefore, this study investigated potential prognostic factors for survival including pack years in 170 lung cancer patients receiving local radiotherapy. Patients and Methods: Twelve factors were retrospectively evaluated for survival including age, sex, tumor site, histology, primary tumor stage, nodal stage, distant metastasis, radiation dose, upfront surgery or systemic treatment, pulmonary function, and number of pack years. Results: On univariate analyses, absence of distant metastasis (p=0.049), radiation dose >56 Gy (p=0.019), and ≤40 pack years (p=0.005) were significantly associated with better survival. In the multivariate analysis, number of pack years (hazard ratio 2.18, 95% confidence interval 1.25-3.82, p=0.006) maintained significance; distant metastasis (p=0.34) and radiation dose (p=0.16) were not significant. Conclusion: Number of pack years was an independent predictor of survival after thoracic irradiation for lung cancer.*

Lung cancer is one of the most threatening malignant diseases with the highest number of disease-associated deaths worldwide (1). Many lung cancer patients with loco-regionally advanced disease receive thoracic irradiation with or without systemic therapies (2). During the last decade, modern precision radiotherapy techniques such as intensity-modulated radiotherapy and volumetric modulated arc therapy have become available in many countries (3, 4). For curative treatment of lung cancer, several dose-fractionation regimens with different overall treatment times are available (4, 5). When selecting the appropriate individual dose-fractionation regimen, the patient's personal situation, age, comorbidity and also the survival prognosis should be considered. In case of non-small cell lung cancer (NSCLC), patients with favorable prognoses are, depending on age, performance status and comorbidity index, often candidates for conventionally fractionated radiotherapy (5×2.0 Gy per week) with total doses of 60-70 Gy (4, 5). Patients with less favorable prognoses or other limitations may receive hypo-fractionated (doses per fraction >2.0 Gy) irradiation, *e.g.* with 2.75 Gy per fraction up to 55 Gy (5). For curative treatment of small-cell lung cancer (SCLC), commonly used dose-fractionation regimens include hyper-fractionated radiotherapy with 45 Gy in 30 fractions (2×1.5 Gy per day) and conventionally fractionated radiotherapy with total doses of 60-66 Gy (4, 6, 7). Like patients with NSCLC, those with SCLC and poor survival prognoses or significant other limitations may also receive hypo-fractionated radiotherapy.

These considerations suggest that it is important to know a patient's survival prognosis as precisely as possible to provide the best individual treatment. Several prognostic factors for survival have already been identified for lung cancer patients receiving thoracic irradiation (8, 9). However, conflicting results were reported regarding the prognostic role of the number of smoking pack years. In two studies of patients with NSCLC and one study of patients with SCLC, the number of pack years prior to treatment had no significant impact on survival (10-12). In another study of patients with limited- SCLC disease, the 2-year survival rate was significantly higher after <40 pack years than after ≥40 pack years, whereas in the multivariate analysis of that study, the number of pack years was not significant (8). Moreover, in several studies of patients receiving radiotherapy or radio-chemotherapy for head-and-neck cancers, a higher number

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Key Words: Lung cancer, thoracic irradiation, survival, prognostic factors, smoking pack years.

Table I. *Distribution of the investigated potential prognostic factors.*

Factor	Subgroup	Frequency, n (%)
Age	≤67 Years	86 (50.6)
	>67 Years	84 (49.4)
Sex	Female	62 (36.5)
	Male	108 (63.5)
Main tumor site	Upper lobe	64 (37.6)
	Lower/middle lobe	41 (24.1)
	Central/main bronchus	60 (35.3)
	Not specified	5 (2.9)
Histology	NSCLC	128 (75.3)
	SCLC	41 (24.1)
	Not specified	1 (0.5)
Primary tumor stage	T1-2	51 (30.0)
	T3-4	115 (67.6)
	Not specified	4 (2.4)
Nodal stage	N0-1	33 (19.4)
	N2-3	120 (70.6)
	Not specified	17 (10.0)
Distant metastasis	No	103 (60.6)
	Yes	67 (39.4)
Total dose of RT	≤56 Gy	94 (55.3)
	>56 Gy	76 (44.7)
Upfront surgery	No	153 (90.0)
	Yes	17 (10.0)
Pre-RT systemic treatment	No	64 (37.6)
	Yes	106 (62.4)
FEV1	≤1.69 l	64 (37.6)
	>1.69 l	62 (36.5)
	Not available	44 (25.9)
Pack years	≤40	103 (60.6)
	>40	40 (23.5)
	Unknown	27 (15.9)

NSCLC: Non-small cell lung cancer; SCLC: small-cell lung cancer; RT: radiotherapy; FEV1: forced expiratory volume in 1 second.

of smoking pack years was negatively associated with survival (13-17). When looking at the available data, it becomes obvious that additional studies are required in order to properly define the prognostic role of the number of smoking pack years in the survival of patients receiving thoracic irradiation for lung cancer. Therefore, this study investigated the number of pack years plus several potential prognostic factors in such a patient cohort.

Patients and Methods

Twelve potential prognostic factors (Table I) were retrospectively investigated for survival in a cohort of 170 patients who received thoracic irradiation for lung cancer at our institution between 2016 and 2019. These factors included age at the start of irradiation (≤67 *vs.* >67 years, median=67 years), sex (female *vs.* male), main tumor site (upper lobe *vs.* lower or middle lobe *vs.* central location or main bronchus), histology of lung cancer (NSCLC *vs.* SCLC), primary tumor stage (T1-2 *vs.* T3-4), nodal stage (N0-1 *vs.* N2-3), presence of distant metastasis (no *vs.* yes), total radiation dose (≤56 *vs.* 56 Gy, median=56 Gy) upfront surgery (no *vs.* yes), systemic treatment prior to thoracic irradiation (no *vs.* yes), pulmonary function represented by the forced expiratory volume in 1 second (FEV1 ≤1.69 *vs.* >1.69 l, median=1.69 l), and number of pack years (≤40 *vs.* >40). The number of pack years was calculated according to the generally available definition of the National Cancer Institute, namely by multiplying the average number of packs of cigarettes smoked per day by the number of years the patient has smoked.

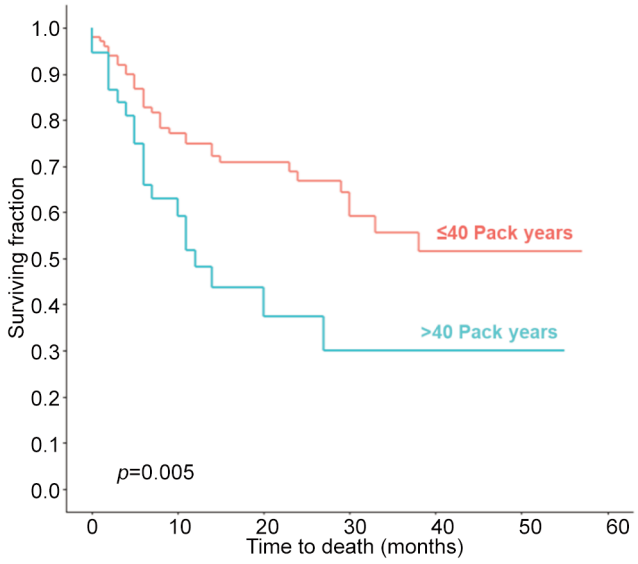

Figure 1. *Kaplan-Meier curves for survival of patients with ≤40 smoking pack years and those patients with >40 pack years. The p-value was calculated using the log-rank test.*

Statistical analyses were performed with the Kaplan-Meier method and the log-rank test. *p*-Values <0.05 were considered indicating significance and *p*-values <0.10 indicating a trend. Those factors that were found to be significant on univariate analysis were subsequently analyzed for independence in a multivariate analysis performed with the Cox proportional hazard model. Again, *p*-values <0.05 and <0.10 were considered indicating significance and a trend, respectively. The study has obtained approval from the responsible ethics committee (University of Lubeck, 22-049).

Results

On univariate analyses (Table II), better survival was significantly associated with absence of distant metastasis (p=0.049), radiation dose >56 Gy (p=0.019), and ≤40 pack years (p=0.005, Figure 1). A trend was observed for nodal stage N0-1 (p=0.09). In the multivariate analysis, number of pack years [hazard ratio (HR)=2.18, 95% confidence interval (CI)=1.25-3.82, p=0.006] was significant and, therefore, identified as independent predictor of survival. Distant metastasis (HR=1.31, 95%CI=0.75-2.30, p=0.34) and radiation dose (HR=1.49, 95%CI=0.85-2.63, p=0.16) did not achieve significance.

Table II. *Survival rates of the analyzed potential prognostic factors at 1, 2, and 3 years following radiotherapy.*

Factor	Subgroup	Survival rate (%)			*p*-Value
		At 1 year	At 2 years	At 3 years	
Age	≤67 Years	71.8	58.6	50.0	0.25
	>67 Years	61.4	53.8	44.3	
Sex	Female	63.1	50.1	42.1	0.38
	Male	68.9	60.6	51.5	
Main tumor site	Upper lobe	71.9	58.0	47.3	0.83
	Lower/middle lobe	65.1	55.2	42.6	
	Central/main bronchus	61.9	53.1	53.1	
Histology	NSCLC	70.0	60.5	49.6	0.22
	SCLC	54.9	36.1	36.1	
Primary tumor stage	T1-2	74.9	63.8	54.6	0.16
	T3-4	62.7	51.9	43.3	
Nodal stage	N0-1	79.5	74.2	65.9	0.09
	N2-3	62.7	49.5	40.2	
Distant metastasis	No	73.3	62.1	50.1	**0.049**
	Yes	56.1	45.7	45.7	
Total dose of RT	≤56 Gy	60.7	44.5	41.1	**0.019**
	>56 Gy	73.8	69.4	55.7	
Upfront surgery	No	65.8	54.9	44.5	0.34
	Yes	75.5	67.1	67.1	
Pre-RT systemic treatment	No	69.4	58.2	46.5	0.71
	Yes	64.9	53.8	47.3	
FEV1	≤1.69 l	67.2	58.0	40.6	0.65
	>1.69 l	70.0	51.3	42.0	
Pack years	≤40	74.8	66.8	55.6	**0.005**
	>40	48.1	37.5	30.0	

NSCLC: Non-small cell lung cancer; SCLC: small-cell lung cancer; RT: radiotherapy; FEV1: forced expiratory volume in 1 second; significant *p*-values are shown in bold.

Discussion

The outcomes after thoracic irradiation for lung cancer can be improved with precision radiotherapy and novel systemic agents (4, 18-23). Another modern approach to improve the outcomes after loco-regional radiotherapy for lung cancer is the use of personalized treatment programs. These programs consider particularly a patient's individual situation including the survival prognosis. Therefore, it is very important to have an idea, as precisely as possible, of a patient's remaining lifespan. This can be considerably facilitated with the knowledge of prognostic factors independently associated with survival. Several predictors have already been identified for lung cancer patients receiving thoracic irradiation alone or in combination with chemotherapy or immunotherapy (8, 9). In 2016, female sex (p=0.003), a Karnofsky performance score of 80-100 (p<0.001) and pre-radiotherapy hemoglobin levels of ≥12 g/dl (p=0.04) were identified as independent predictors of survival in a retrospective cohort of 71 patients receiving definitive radio-chemotherapy for limited-disease SCLC (8). Moreover, in a systematic review and meta-analysis, primary tumor size, nodal size, and pleural effusion had a prognostic impact on survival of patients treated with radio-chemotherapy for stage III NSCLC (9).

However, conflicting results exist regarding the prognostic role of the number of pre-radiotherapy smoking pack years. In two retrospective studies from 2008 and 2012, respectively, the number of pack years (≤50 *vs.* >50) was not significantly associated with survival in patients with NSCLC (10, 11). In one study (10), the 2-year survival rates were 35% and 27%, respectively (p=0.46), and in the other study (11), the rates were 50% and 50%, respectively (p=0.78). Moreover, in a retrospective study of 284 patients with limited-stage SCLC, the number of smoking pack years (0 *vs.* ≤40 *vs.* 41-60 *vs.* ≥61) had no significant impact on survival, either (12). In another retrospective study of patients with limited-disease SCLC, the 2-year survival rate was significantly higher after <40 pack years when compared to that after ≥40 pack years (48% *vs.* 36%, p=0.04) on univariate analysis (8). However, in the multivariate analysis of that study, the number of pack years was not significant (risk ratio=1.33, 95%CI=0.71-2.52, p=0.37).

Since the prognostic role of the number of smoking pack years for survival in lung cancer patients receiving thoracic

irradiation with or without systemic treatment is still controversial, additional studies are warranted. The present study was performed to contribute to further clarification of this issue. According to its results, a lower number of pack years (≤40 *vs.* >40) was significantly associated survival in both the univariate and the multivariate analysis. Thus, the number of smoking pack years can be considered an independent predictor of survival in lung cancer patients receiving loco-regional radiotherapy. This prognostic factor should be considered when designing personalized treatment programs including the optimal radiotherapy approach. Patients with NSCLC and favorable survival prognoses should preferably receive conventionally fractionated radiotherapy with total doses of 60-70 Gy (4, 5, 24). Those patients with less favorable prognoses may be considered for hypo-fractionated irradiation (5). For patients with SCLC and favorable survival prognoses, hyper-fractionated radiotherapy (45 Gy, 2×1.5 Gy per day) and conventionally fractionated radiotherapy with 60-66 Gy are generally used, whereas for patients with SCLC and poor survival prognoses also hypo-fractionated radiotherapy programs may be an alternative option (4, 6, 7). When considering these recommendations, the retrospective nature of the present study including the risk of hidden selection biases should be noted.

In summary, the number of pre-radiotherapy smoking pack years was shown to be an independent predictor of survival after thoracic irradiation for lung cancer. This prognostic factor should be considered when designing personalized (radiation) treatment programs for these patients.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest related to this study.

Authors' Contributions

E.M.W., E.G., S.B. and D.R. participated in the study design. E.G. provided the data that were analyzed by D.R. and S.E.S., and interpreted by all Authors. The manuscript drafted by E.M.W., S.E.S. and D.R. was reviewed and approved by all Authors.

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