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Prevalence and Characteristics of Symptomatic Pneumonitis After Radiotherapy of Patients With Locally Advanced Lung Cancer

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Abstract. *Background/Aim: Radiotherapy of locally advanced lung cancer often requires high doses potentially leading to pneumonitis. This study evaluated the rate of symptomatic pneumonitis and characteristics in these patients. Patients and Methods: This study included 278 patients irradiated for locally advanced lung cancer between 2016 and 2019. In patients experiencing symptomatic pneumonitis, patient and treatment characteristics were analyzed. Results: Pneumonitis was diagnosed in 21 patients (7.6%) after a median of 9 (1-23) weeks. Ipsilateral lungs received mean doses >13 Gy in 21 (100%) and >20 Gy in 15 patients (71.4%). Seventeen patients (81.0%) received chemotherapy and/or immunotherapy, 12 (57.1%) had significant cardiovascular disease (all 21 patients had risk factors), 11 (52.4%) were heavy smokers (≥40 pack years), 7 (33.3%) were aged ≥74 years, 5 (23.8%) had chronic inflammatory disease and 4 (19.0%) had previous tumors. Conclusion: Overall pneumonitis rate was 7.6%. Frequent characteristics included high mean lung doses, systemic treatment, cardiovascular disease (and risk factors), heavy smoking, older age, chronic inflammatory disease and history of a previous tumor.*

Lung cancer is the second most common solid cancer in Europe and Northern America (1). The majority of patients with small-cell lung cancer (SCLC) receive radiotherapy in combination with chemotherapy. Also, many patients with locally advanced non-small-cell lung cancer (NSCLC) receive radiotherapy, if they are not candidates for surgery. Major goals of radiotherapy include local disease control and improvement of the patients' overall prognoses (2). In the majority of cases, the treatment approach is curative. Therefore, high radiation doses are often required that may lead to pneumonitis. Pneumonitis can occur up to 21 weeks following radiotherapy (3). Radiation pneumonitis must be considered a serious complication that was reported to be fatal in approximately 2% of the patients (2). Therefore, it would be desirable to identify patients, who are at high risk of developing radiation pneumonitis, prior to the start of treatment. These patients would require a closer monitoring during the course of radiotherapy and several months following treatment. Moreover, in the literature, the prevalence of symptomatic pneumonitis after irradiation of lung cancer varies considerably (4-7). Thus, more studies are required to properly identify the rate of symptomatic pneumonitis, particularly studies using modern precision radiotherapy techniques. Therefore, this study was performed aiming to identify the prevalence of pneumonitis and potential risk factors for this complication in patients with locally advanced lung cancer irradiated with volume-modulated arc therapy (VMAT).

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Key Words: Lung cancer, advanced disease, radiotherapy, symptomatic pneumonitis, prevalence, characteristics.

Patients and Methods

In this retrospective study, which was approved by the ethics committee of the University of Lübeck, 278 patients irradiated for locally advanced lung cancer between 2016 and 2019 were evaluated with respect to the development of symptomatic (grade ≥2) pneumonitis. Patients with locally advanced disease who had distant metastases were also included. Radiotherapy was performed as modern precision therapy, *i.e.* VMAT. Patients received conventionally fractionated radiotherapy of 5×2 Gy per week (on 5 consecutive days).

In these patients developing pneumonitis following radiotherapy, clinical and treatment characteristics were analyzed to detect potential risk factors for this treatment-related complication. Clinical characteristics included age, gender, histology, tumor stage, tumor site, co-morbidity, history of smoking and history of another tumor. Treatment characteristics included mean dose to the ipsilateral lung and type of systemic treatment. In addition, time to progression

(local and/or distant failure) was evaluated in the patients developing pneumonitis, which was calculated from the end of radiotherapy.

Results

In the entire cohort of 278 patients, pneumonitis was diagnosed in 21 patients (7.6%) after a median of 9 weeks (range=1-23 weeks) following irradiation. Leading symptoms were dyspnea in 18 patients (85.7%) and cough in 12 patients (57.1%). All patients received prednisolone for up to 13 weeks. Pneumonitis resolved in 18 patients (85.7%). In one patient, symptoms had already improved but became worse after prednisolone was stopped. A second course of prednisolone was administered, and finally pneumonitis resolved. In one patient, dyspnea and cough were persistent for 1 year, before they markedly improved. Also, one patient was lost to follow up soon after initiation of the prednisolone treatment.

Of the 21 patients, 4 (19.0%) had SCLC, 9 (42.9%) adenocarcinoma (AC) and 8 patients (38.1%) squamous cell carcinoma (SCC). The median total radiation dose was 60 Gy in the entire cohort, as well as in all three histologic subgroups. Mean doses to the ipsilateral lung were >13 Gy in 21 patients (100%), >20 Gy in 15 patients (71.4%) and >27 Gy in five patients (23.8%). According to Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), these doses are associated with a risk of 10%, 20% and 40%, respectively, to develop symptomatic pneumonitis (8).

Radiotherapy was combined with systemic treatment in 17 patients (81.0%). The type of systemic treatment depended on the histology of the primary tumor. Of the patients with SCLC, three patients received 4 courses of cisplatin/etoposide (2 courses concurrently with radiotherapy) and one patient 2 courses of carboplatin/etoposide concurrently with radiotherapy. Of the patients with AC, three patients received 2-4 courses of cisplatin/pemetrexed (2 courses concurrently with radiotherapy in 2 patients), one patient 6 weekly applications of paclitaxel during radiotherapy, one patient afatinib over 6 months prior to radiotherapy and one patient durvalumab over 2 months as consolidation therapy after radiotherapy. Three patients with AC did not receive systemic treatment. In the group of patients with SCC, two patients received 4 courses of cisplatin/vinorelbine (2 courses concurrently with radiotherapy). One patient additionally received durvalumab consolidation therapy, two patients 6 weekly applications of paclitaxel during radiation, one patient 6 weekly applications of vinorelbine, one patient 2 courses of carboplatin/nab-paclitaxel and one patient pembrolizumab over 2 months after radiation treatment. One patient with SCC did not receive systemic treatment.

With respect to the patients characteristics (Table I), it should be noted that 12 patients (57.1%) had significant cardiovascular disease (all 21 patients had corresponding risk factors including diabetes mellitus, hypertension and/or history of smoking), 11 patients (52.4%) were heavy smokers (defined as ≥40 pack years), seven patients (33.3%) were aged ≥74 years and 12 patients (57.1%) >65 years, five patients (23.8%) had chronic inflammatory disease (four patients with bronchial asthma and one with rheumatoid arthritis) and four patients (19.0%) had a history of a previous tumor (two patients with larynx cancer, one with breast cancer and one with bilateral adrenal incidentaloma).

In the 18 patients with a follow up of at least 6 months, progression of lung cancer occurred in 15 patients (83.3%) after a median of 9 months (range=3-17 months) following radiotherapy. Five patients (27.8%) experienced progression within 6 months and 12 patients (66.7%) within 12 months. Sites of first failure were local progression alone in one patient (5.6%), distant progression alone in 12 patients (66.7%) and both in two patients (11.1%). In the group of patients with SCLC, progression occurred in all four patients (100%) after a median of 8 months (range=3-11 months). Of the nine patients with AC, six patients (66.7%) had progression of their disease after a median of 10.5 months (range=3-17 months) months, and all five evaluable (appropriate length of follow up) patients with SCC (100%) had progression after a median of 7 months (range=6-17 months).

Discussion

Radiotherapy alone or in combination with systemic therapies is commonly used for treating locally advanced lung cancers (2). As the prognosis of these patients is often limited, considerable research is carried out to improve their outcomes (9-13). If radiotherapy is administered, high doses are often required, particularly if the treatment approach is considered curative. These radiation doses may be associated with pneumonitis that can be severe and, in a very small proportion of patients, even fatal (2).

Therefore, it would be important to identify patients, who are at high risk of experiencing radiation pneumonitis, before starting the treatment to adjust the dose-fractionation regimen and provide close monitoring of the patients during and after radiotherapy. The present study aimed to contribute to the identification of potential risk factors for this complication in patients irradiated for locally advanced lung cancer. In the present cohort, the prevalence of pneumonitis following radiotherapy was lower than in previous studies (4-7). This finding may be explained by the facts that in the present study radiotherapy was performed with a high-precision technique (VMAT), that the patients were monitored closely during radiation treatment, which led to premature termination of the radiation treatment in case of severe symptoms, complications or significant deterioration

Table I. *Patient characteristics of the 21 patients with pneumonitis.*

Patient number	Age (years)	Gender	Tumor site	Histology	TNM stage	UICC stage	Cardiovascular disease and risk factors
1	59	Male	LL	SCLC	T1 N3 M0	LD	CHD, DM, HT, AS
2	54	Female	UL	AC	T2 N3 M0	IIIB	30py
3	68	Female	LL	AC	T2 N2 M0	IIIA	CS, TIA, 40py
4	74	Female	LL	SCC	T3 N3 M0	IIIC	CHD, HT, PAD, >50py
5	56	Female	UL	SCLC	T4 N3 M0	LD	CS, HT, 35py
6	74	Male	Central	AC	T4 N3 M1a	IVA	CHD, HT, 30py
7	53	Female	UL	AC	T2 N3 M0	IIIB	50py
8	87	Male	UL	AC	T2 N3 M1a	IVA	CHD, MI, HT
9	61	Male	Central	SCLC	T4 N3 M1	ED	HT, 40py
10	46	Male	Central	AC	T4 N3 M1c	IVB	20py
11	82	Female	ML	SCC	T4 N2 M0	IIIB	CHD, HT
12	78	Male	LL	SCC	T4 N2 M1c	IVB	CHD, CMP, HT, 50py
13	69	Female	UL	SCC	T4 N2 M0	IIIB	DM, HT
14	88	Male	UL	AC	T2 N3 M0	IIIB	CS, apoplexy, HT, >50py
15	68	Male	UL	SCLC	T1 N2 M0	LD	40py
16	68	Female	UL	AC	T1 N3 M0	IIIB	Apoplexy, HT, 35py
17	62	Female	UL	SCC	T4 N2 M1b	IVB	HT
18	59	Male	UL	SCC	T3 N3 M0	IIIC	DM, 40py
19	75	Male	Central	SCC	T4 N2 M0	IIIB	HT, AS, 50py
20	68	Male	LL	AC	T3 N3 M1c	IVB	Apoplexy, HT, 45py
21	58	Male	UL	SCC	T3 N2 M0	IIIB	HT, 60py

LL: Lower lobe; UL: upper lobe; ML: middle lobe; SCLC: small-cell lung cancer; AC: adenocarcinoma, SCC: squamous cell carcinoma; UICC: Union for International Cancer Control; LD: limited disease; ED: extensive disease; CHD: coronary heart disease; DM: diabetes mellitus; HT: hypertension; AS: arteriosclerosis; py: pack years; CS: carotid stenosis; TIA: transient ischemic attack; PAD: peripheral arterial disease; MI: myocardial infarction; CMP: cardiomyopathy.

of the patient's performance score, and that there has been a very close collaboration with the department of pulmonology. Another important reason may be the design of the study. Since the data were obtained retrospectively from patient files, radiation pneumonitis may have been missed in some patients following radiotherapy.

The main goal of the present study was the identification of potential risk factors for symptomatic pneumonitis. We found that in patients experiencing radiation pneumonitis, some characteristics were comparatively common. These characteristics included high mean radiation doses to the ipsilateral lung, administration of chemotherapy and/or immunotherapy during or close to radiotherapy, cardiovascular disease or corresponding risk factors, history of heavy smoking (≥40 pack years), older age (≥74 years), history of chronic inflammatory disease and history of a previous tumor. Some of these characteristics have been previously described to be associated with pneumonitis after irradiation of lung cancer. A pooled analysis of 88 studies identified the mean lung dose as a significant (p=0.027) risk factor for radiation pneumonitis after stereotactic radiation therapy of thoracic tumors (14). Moreover, according to QUANTEC, mean lung doses can be correlated with the risk of symptomatic pneumonitis (8). The fact that chemotherapy and immunotherapy can increase the risk of radiation pneumonitis has been suggested in several studies (15-18). This association can be explained by the fact that these agents have a radio-sensitizing effect that also affects normal tissues.

The risk factors of cardiovascular disease, diabetes mellitus and hypertension, have been described by several authors to be potential risk factors for radiation pneumonitis (18-21). The prognostic role of pre-treatment cardiac co-morbidity has been investigated only in one retrospective study (22). In that study, 259 lung cancer patients were included, who received definitive radiotherapy or radio-chemotherapy. Of 75 patients with pre-treatment cardiac co-morbidity, 33 patients (44.0%) developed radiation-induced lung toxicity (odds ratio=2.58, p<0.001). This association may be explained by the reduced blood flow due to arteriosclerosis, which may impair defense mechanisms necessary to prevent pneumonitis. Smoking has also been previously identified as a risk factor for pneumonitis (18, 23). In the study of Li *et al*., ≥40 pack years, the cut-off used for the present study, were significantly (p=0.012) associated with grade ≥3 radiation pneumonitis (23). Older age is another previously described risk factor (14-16). In our study, more than half of the patients were >65 years of age

and one third ≥74 years, which supports the findings of the previous studies.

In addition to these characteristics, history of chronic inflammatory disease and history of another tumor were present in our cohort more frequent than expected. Potential associations of these two characteristics with radiation pneumonitis were found also in our previous study investigating pneumonitis following irradiation of breast cancer (24). Bronchial asthma is a chronic inflammatory lung disease, and rheumatoid arthritis can also be associated with pulmonary involvement (25, 26). The history of another tumor may be explained by a reduced DNA repair capacity, which has been described for several tumor types including lung cancer and can result in increased radio-sensitivity and radiation-related toxicity (27-29). The idea that patients developing radiation pneumonitis may have a reduced DNA repair capacity is further supported by the fact that the patients in our cohort had a poor prognosis in terms of progression-free survival.

In conclusion, the overall pneumonitis rate was comparatively low. Characteristics potentially associated with radiation pneumonitis included high mean lung doses, systemic treatment, cardiovascular disease (and corresponding risk factors), heavy smoking, older age, history of chronic inflammatory disease and history of another tumor.

Conflicts of Interest

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

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Authors' Contributions

D.R., E.G., E.M.W. and S.B. participated in the design of the study. D.R., E.G., E.M.W. and S.B. provided data and performed analyses and interpretation of the data. D.R. drafted the manuscript, which was reviewed and approved in its final form by all Authors.

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