Acute Oesophageal Toxicity Related to Paclitaxel-based Concurrent Chemoradiotherapy for Non-small Cell Lung Cancer

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Abstract. *Background: Dosimetric data and acute oesophageal toxicity (AET) during chemoradiotherapy (CRT) were evaluated in patients with non-small cell lung cancer (NSCLC). Patients and Methods: Fifty patients were treated with paclitaxel-based conformal CRT with a mean±SD dose of 60.7±9.8 Gy. The oesophageal toxicity was prospectively registered and evaluated in relation to the maximal dose (D_{max}), mean dose (D_{mean}), length and volume of oesophagus irradiated with 35-60 Gy ($V_{35-60Gy}$), and according to the seriousness of AET. Results: D_{max} and D_{mean} to the oesophagus were 57.0±10.8 Gy and 24.9±9.0 Gy, respectively. AET of grade 1, 2 and 3 developed in 16 (32%), 14 (28%) and three (6%) cases, respectively. The D_{max}, D_{mean}, length and the $V_{35-60Gy}$ were all related to dysphagia ($p<0.001$). V_{45Gy} was the most reliable predictor of AET of grade 2 or more. Conclusion: Our results indicate that keeping oesophageal V_{45Gy} below 32.5% can prevent severe AET during CRT of NSCLC.*

Lung cancer is the most frequent tumour worldwide. Radiotherapy is one of the main treatment modalities for lung cancer and had been the conventional method of treatment until the 1980s (1). Its efficacy alone in locally advanced non-small cell lung cancer is poor (2). Strategies designed to enhance local control include improved tumour targeting (three-dimensional treatment planning and increasingly more sophisticated radiotherapy techniques), escalation of thoracic radiotherapy dose (2-4), and application of different fractionations (5-8). Individualized combinations of various treatment procedures, such as combining radiotherapy with chemotherapy tend to improve local control and survival (9, 10). Radiosensitization has been reported to increase therapy efficacy, but it may also increase therapy-induced toxicity (6, 9, 11-14). The practice of advanced techniques should reduce acute and late treatment-associated toxicities (15, 16). Radiation oesophagitis seems to be one of the most common acute toxicities, especially in the setting of combined concurrent chemoradiation (CRT) (1, 2, 17, 18). This adverse treatment side-effect is often a dose-limiting factor (4), which influences treatment outcomes and patients' quality of life, therefore its dose-volume relationship has been investigated in several trials (1, 2, 5-8, 12-14, 17-21). Results have differed considerably across different institutions regarding which dosimetric factors are more critical than others. Jim Rose and colleagues performed a systematic literature review of published studies addressing radiation oesophagitis after thoracic radiotherapy in 2009 (18). Statistically significant relationships between specific dose-volume parameters [V_{20Gy}, V_{35Gy}, V_{60Gy}, maximal and mean oesophageal dose] with or without chemotherapy and clinically significant acute oesophagitis risk were identified based on the analyzed studies. They found various dosimetric correlations in the literature on oesophageal toxicity regarding the seriousness of the swallowing complaints. Identification of the risk factors for acute oesophagitis in lung cancer is important for optimizing the most effective and favourably-tolerated treatment plan. Our aim was to prospectively investigate the dosimetric correlations of acute oesophageal toxicity (AET) during neoadjuvant and definitive paclitaxel-based three-dimensional conformal CRT in patients with non-small cell lung cancer.

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Patients and Methods

The study was conducted in full accordance with the institutional regulations and all the patients gave their written informed consent to participate in the chemotherapy and radiotherapy.

Table I. *Common Terminology Criteria for Adverse Events, Version 3.0 Dysphagia: (diff*iculty of swallowing).

Grade 1	Symptomatic, able to eat regular diet
Grade 2	Symptomatic and altered eating/swallowing (*e.g.* altered dietary habits, oral supplements); *i.v.* fluids indicated <24 h
Grade 3	Symptomatic and severely altered eating/swallowing (*e.g.*, inadequate oral caloric or fluid intake); *i.v.* fluids, tube feedings, or TPN indicated ≥24 h
Grade 4	Life-threatening consequences (*e.g.* obstruction, perforation)
Grade 5	Death

TPN: Total parenteral nutrition.

Study population. Patients receiving CRT for primary unresectable or potentially operable non-small cell lung cancer at the Department of Oncotherapy between December 2006 and June 2011 were eligible for participation in this study. Histological examination was performed before the therapy in all cases. Staging examinations were based on conventional protocols [chest computed tomography (CT), abdominal ultrasound/CT, brain CT, bone scan, bronchoscopy]. For each patient the multimodal treatment strategy was designed by a multidisciplinary team.

Chemo- and radiotherapy, supportive therapy. During the radiotherapy all the patients received concomitant taxane-based chemotherapy (weekly paclitaxel 100 mg/m^2 in 4-6 cycles, depending on toxicity). Out of the 40 patients (stage IIIB) who completed induction chemotherapy (one or two cycles), 38 (95%) received a taxane-based chemotherapy regimen (mainly paclitaxel 175 mg/m^2, carboplatin 400 mg/m^2 or docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, at 3-week intervals), while two patients received a gemcitabine-based regimen (gemcitabine 1250 mg/m^2 on days 1 and 8, cisplatin 70 mg/m^2 on day 1, and then at 3-week intervals) for at least four weeks prior to the concomitant CRT. All patients were irradiated in the supine position, with both arms elevated above the head, on the thorax set of the AIO SolutionTM (ORFIT, Antwerpen Belgium). CT-based three-dimensional treatment planning and conformal radiotherapy were performed in all cases, with use of an individual immobilization system with thermoplastic masks. The gross tumor volume (GTV), macroscopic lung cancer, the involved mediastinal and hilar lymph nodes were defined on [^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography-CT images. The delineation of organs at risk (spinal cord, ipsilateral and contralateral lung, heart and oesophagus) was conducted according to the local protocol. The planning target volume encompassed the GTV, the involved lymph node regions (clinical target volume) and the safety margins. The initial radiation dose was 25×1.8 Gy (and the total dose for neoadjuvant cases); after a repeated CT scan, depending on the tumour response, radiotherapy of the reduced volume was then continued based on a new three-dimensional plan, to an additional average dose of 22-26 Gy, resulting in a total dose of 67-72 Gy. Avoiding smoking and consumption of hot and spicy food, chopped food was recommended in order to prevent from AET. Symptoms were alleviated based on protocols with local anaesthetics, liquid, mushy food, antihistamines, when required with mucosal coating, proton-pump inhibitors, tramadol derivatives, systemic non-steroids, or calcium.

Evaluation of AET. The whole oesophagus was contoured from the anular cartilage to the gastroesophageal junction prior to radiation planning. The following dosimetric data were analysed in relation to dysphagia: the maximal dose (D_{max}), the mean dose (D_{mean}), the length of the irradiated oesophagus with 50 Gy (L_{50Gy}) and the volume of the oesophagus irradiated with 35 Gy to 60 Gy ($V_{35\text{-}60\ Gy}$). AET as dysphagia was evaluated prospectively based on Common Terminology Criteria for Adverse Events, version 3.0 issued by the National Cancer Institute (Table I) (22). The worst grade of toxicity was taken into account. Follow-up visits with the evaluation of swallowing complaints were performed weekly. Patients who smoked during the CRT were defined as smokers.

Table II. *Radiation dose (Gy) to critical organs (except the oesophagus).*

Spinal cord	Mean±SD	12.1±4.5
	Maximal±SD	36±6.7
Ipsilateral lung	Mean±SD	26.6±7.8
	V_{20Gy}±SD (%)	54.1±13.5
Contralateral lung	Mean±SD	10.6±3.6
	V_{20Gy}±SD (%)	14.3±9.1
Heart	Mean±SD	12.5±4.6
	V_{30Gy}±SD (%)	12.1±3.8

Statistical analysis. All statistical analyses were carried out using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The relations between AET, age, gender, smoking habits and the dosimetric data were evaluated. Age, dose and volume were assessed with *t*-test, gender and smoking habits were analysed with chi-square test. The relationship between dose-volume parameters and severity of AET was analysed with logistic regression. Receiver operating characteristic (ROC) analysis was used to find the cut-off point for V_{45Gy}.

Results

Patients' characteristics. Altogether, data from 50 patients were analyzed. Thirty-two (64%) patients were men, 18 (36%) were women. The mean±SD age was 59.8±8 (range=39-78) years. Histological examination showed squamous cell carcinoma and adenocarcinoma in 22 (44%) and 28 (56%) patients, respectively. Four (8%) patients had stage II/B and six (12%) patients had stage III/A carcinoma. Forty (80%) participants had stage III/B carcinoma. These stages were determined according to the sixth edition of the TNM system. Twenty-nine (58%) patients were smokers and 21 (42%) were non-smokers. Twelve (24%) patients underwent operation, in one case, despite remission only exploration was performed due to inoperable conditions.

Table III. *Incidence of acute oesophageal toxicity (AET).*

Severity of AET n=50	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4-5
Patients on (%)	17 (34%)	16 (32%)	14 (28%)	3 (6%)	0

Dose parameters. The mean dose to the planning target volume was 60.7±9.8 Gy for the whole investigated population, while it was 64.7±5.5 Gy in the definitively treated patients with irresectable disease. The preoperative dose given was 45.0 Gy in all 10 cases. Irradiation doses to spinal cord, heart, ipsilateral and contralateral lung are shown in table II. The D_{max} to the oesophagus was 57±10.8 Gy, and the D_{mean} was 24.9±9 Gy. The mean L_{50Gy} was 6.99±6.7 cm.

Toxicity. Among the 50 participants, oesophageal toxicity did not develop in 17 (34%) cases, while side-effects were registered in 66%. AET of grade 1 and grade 2 developed in 16 (32%) and 14 (28%) cases, respectively (Table III). Grade 3 toxicity occurred in three (6%) cases. Life-threatening, grade 4 or 5 AETs were not seen. Temporary interruption due to vomiting, fever, neutropenia and acute oesophagitis was necessary in 18 (36%) patients. The mean duration of the interruption was 9.0 days. Out of 18 patients, the reason for interruption was oesophageal toxicity in 12 (24%) cases. Complaints were treated with local anaesthetics in all cases with dysphagia. Use of drinkable nutrients was also indicated for all patients, while tramadol treatment was needed in eight (16%) cases. No association was found between oesophageal toxicity and gender (p=0.584), age (p=0.271) or smoking habit (p=0.196) of the patients.

Correlations of the dose- and volume data with AET. The maximum and mean dose to the oesophagus correlated well with moderate and severe swallowing toxicity. The D_{max} to the esophagus in cases of grade 0-1 and grade 2-3 toxicity was 56±11.45 and 64.07±5.55 Gy, respectively (p<0.001). The average D_{mean} for the cases with AET of grade 0-1 and grade 2-3 was 21.87±8.24 and 30.98±7.57 Gy, respectively (p<0.001). The average mean dose to the oesophagus among the three patients with grade 3 AET was 34.46±5.58 Gy. The L_{50Gy} was also related to the symptoms (p<0.001). In cases of grade 0-1 and grade 2-3 AET, the L_{50Gy} was 5.10±5.66 and 10.54±3.83 cm, respectively (p<0.001). $D_{30\%}$ ±SD was 39.82±14.17 and 53.74±7.21 Gy in grade 0-1 and grade 2-3 esophagitis, respectively (p<0.001). The $V_{35\text{-}60Gy}$ in relation to toxicity is shown in Table IV. Examining the relationship between oesophageal toxicity and dose-volume parameters with logistic regression, we found that $V4_{5Gy}$ predicts most reliably the development of grade 2 or higher AET (odds ratio=1.089, 95%-confidence interval: 1.033-1.148, p=0.001). A one percent increase of V_{45Gy} elevates the risk of grade 2 or higher AET by 8.9%. The risk of the development of AET of grade 2-3 was the highest above a cut-off value for V_{45Gy} ≥32.5% according to ROC analysis.

Table IV. *Dosimetric parameters of acute esophageal toxicity. Data are means ±SD.*

	Grade 0-1	Grade 2-3	p-Value (t-test)
n	33 (66%)	17 (34%)	
D_{max} (Gy)	54.56±11.45	64.07±5.55	<0.001
D_{mean} (Gy)	21.87±8.24	30.98±7.57	<0.001
V_{35Gy} (%)	34.87±17.71	49.23±11.55	0.004
V_{40Gy} (%)	30.93±17.67	46.41±12.04	0.002
V_{45Gy} (%)	20.15±18.71	43.23±12.20	<0.001
V_{50Gy} (%)	15.90±18.06	37.88±11.45	<0.001
V_{55Gy} (%)	13±15.85	29.29±16.36	0.001
V_{60Gy} (%)	8.03±12.31	19.23±16.22	0.009
Length $_{50Gy}$ (cm)	5.10±5.66	10.54±3.83	<0.001

Discussion

In our prospective study, the occurrence of AET during paclitaxel-based CRT for patients with non-small cell lung cancer was analyzed in relation to patient and dosimetric parameters. Combination of radiotherapy with chemotherapy is directed to improve local control and survival of patients with lung cancer patients (9, 10). Several studies have shown that compared to radiotherapy-alone, concurrent CRT appears to lower oesophageal radiation tolerance (21). AET is often a dose-limiting factor that influences the treatment efficacy (4). In our study, dose reduction or permanent interruption of therapy were not necessary due to oesophageal toxicity. No association was found between oesophageal toxicity and gender, age or smoking habit of the patients. Similarly to the literature, mild, acute swallowing toxicity or its absence was detected in most of our cases (grade 0-1 in 66%) (1, 5, 13, 19, 21). These mild side-effects were easily managed but grade 2 or higher dysphagia causes clinically relevant symptoms (22) and remarkably influences the patient's quality of life. The incidence of grade 2 or more severe oesophagitis was slightly higher in our cohort than in Ozgen *et al*.'s trial (19), but lower than that in the study of

Rodriguez *et al*. (1), in which patients with lung cancer were treated with 3D-CRT technique. Definitive differences were detected in the applied concomitant chemotherapeutic agents between the present and the mentioned studies. None of their results perceived life-threatening grade 4 or 5 AETs. The incidence of AET and its dose volume relationship has been investigated in several trials (1, 2, 5-8, 12-14, 17-21). Although dose-volume parameters are commonly used to analyze the risk of acute oesophagitis, there are large differences in the results, and in which of these parameters have the most dominant effect on the risk of AET due to the different approaches for evaluation. We compared dosimetric parameters of the group of patients with mild swallowing toxicity, or absence of it (grade 0-1) to the group with moderate or severe dysphagia (grade 2 or more). In corcordance with numerous other studies, grade 2 or higher AET strongly correlated with the mean and the maximal dose, and the length and volume of the irradiated oesophagus (1, 8, 13, 19, 20). Many researchers have found association between AET and mean or maximal dose to the oesophagus. In the study of Qiao *et al*., during concurrent platinum-based chemotherapy, mean and maximal dose (above 60 Gy) to the oesophagus were related to grade 3 or more oesophageal toxicity (17). Singh *et al*. had similar results, and found the mean and maximal dose (higher than 58 Gy) to be associated with grade 3 or more severe AET (12). In the study of Ozgen *et al*., the mean dose to the oesophagus of 28 Gy or more correlated with grade 2 or worse toxicity (19). Other authors evaluated the correlation between AET and V_{dose}, which describes the percentage of the oesophagus receiving specific dose (V_{20Gy}, V_{30Gy}, V_{40Gy}, *etc*.). In Takeda *et al*.'s study, the incidence of grade 1 AET increased if more than 30% (V_{35Gy} >30%) of the oesophageal volume received 35 Gy (21). By Rodriguez *et al*., V_{50Gy} >30% was the most statistically significant factor associated with AET of grade 1 or more (1). Belderbos and Bradley found a correlation between grade 2 or worse dysphagia and $V100\%_{20\text{-}60Gy}$, or $V_{5\text{-}70Gy}$, respectively (13, 20). From our results, the parameter which mostly correlated with grade 2 or more swallowing toxicity was a mean dose of 45 Gy to the oesophagus with 32.5% as a cut-off value. A one-percent increase elevated the risk of swallowing toxicity by 8.9%. L_{50Gy} was also related to symptoms. Association between length of irradiated oesophagus with 40-50 Gy or more and AET were also detected in relation to grade 2 or 3 or more swallowing toxicity in the literature (5, 13). Elevated radiation dose and combining radiotherapy with chemotherapy in the hope of better survival may increase the incidence of oesophagitis. Development of AET is the most important limiting factor in the radiotherapy of chest tumours, therefore during treatment planning, a significant aim is to reduce the oesophageal irradiated volume and dose to protect patients from serious events. Our results indicate that keeping oesophageal V_{45Gy} lower than 32.5% during paclitaxel-based CRT for non-small cell lung carcinoma helps to avoid moderate and severe swallowing toxicity in patients.

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