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ORIGINAL ARTICLE

Is there a different dose–effect relation between the primary tumor and involved lymph nodes in locally advanced non-small-cell lung cancer? A hypothesis-generating study

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ABSTRACT

Purpose: It is unknown whether the dose–response relation of the primary tumor in NSCLC is different from that of the involved lymph nodes (LN). As the recurrence rate is much lower in LN, we hypothesized that LN need a lower radiation dose.

Material and methods: A retrospective analysis of prospective data was performed on patients with locally advanced NSCLC treated with (chemo)radiotherapy. The impact of $EQD_{2,T}$ prescription dose on relapse was analyzed using Cox regression modeling correcting for baseline diameter.

Results: From 2006 to 2010, 75 consecutive patients were included, resulting in 142 lymph nodes in the analysis. Any relapse (locoregional/distant) occurred in 58 patients (77%), while involved nodal relapse (INR) was observed in 13% of patients. No dose–response relationship was observed for INR ($p = .22$). Primary tumor progression was seen in 40% of patients together with a significant dose–response relationship ($p = .033$). Baseline nodal diameter was not associated with INR ($p = .76$), while primary tumor diameter was a highly significant predictor for relapse ($p = .0031$).

Conclusions: These results suggest that LN control may be achieved at lower radiation doses than needed for the primary tumor. Prospective dose de-escalation studies on LN are warranted to decrease the incidence of severe esophagitis without compromising local tumor control.

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Introduction

Lung cancer is the leading cause of death amongst all cancer types. Non-small-cell lung cancer (NSCLC) accounts for about 80–85% of all lung cancers. Around 30% of patients have stage III locally advanced NSCLC (LA-NSCLC) at diagnosis. In LA-NSCLC most patients are considered inoperable and the treatment of choice is concurrent chemoradiotherapy where a platinum-doublet and a minimal biological equivalent radiation dose of 60 Gy in 2 Gy fractions is recommended (ESMO guidelines) [1]. With this approach, a 5-year overall survival rate of around 30% is obtained. However, major dose-limiting acute toxicities are associated with this treatment. Severe acute esophagitis (grade 3 or more) is observed in 20% of patients treated with concurrent chemoradiotherapy and is mainly due to the irradiation of involved mediastinal lymph nodes [2]. Acute esophagitis has a significant impact on quality of life and can lead to treatment interruptions jeopardizing outcome [3]. As there is a relation between the dose to the esophagus and the severity of these side effects, decreasing the dose to the esophagus may lead to less esophagitis [4,5]. The most straightforward way to reduce the dose to the esophagus is to diminish the dose to the mediastinal lymph nodes. However, this is only possible if these nodes need less dose to obtain tumor control than the at present recommended dose of 60 Gy or more. It is known that involved nodal relapse (INR) in NSCLC is less frequent than primary tumor progression. INR is seen in about 5–10% of patients whereas 30–40% of patients will have progression of the primary tumor [6,7]. We therefore hypothesized that lymph node control may be achieved at lower radiation doses. If this were true this would allow for a safe dose de-escalation on the involved lymph nodes and hence would reduce acute radiation-induced esophagitis.

Material and methods

Patient selection

We retrospectively identified from a prospective institutional database 298 patients who were treated with

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Supplemental data for this article can be accessed here.

(chemo)radiotherapy with curative intent for a locally advanced NSCLC (stadium IIIA/IIIB) between 2006 and 2010. Inoperable patients with stage II-N1 disease and stage IV patients treated with a radical approach were also included. Disease stages were based on the 6th edition of the TNM classification. All patients had a pathologic confirmation of NSCLC. Patients required adequate follow-up with a chest CT scan 3 months (±2 months) after radiotherapy and at least yearly thereafter. One hundred thirty-six patients were not followed at our center and had to be excluded. Furthermore, four patients were excluded because of administration of systemic treatment before the first follow-up CT scan. Seventy-one patients did not meet the criteria of adequate follow-up and were excluded (27 patients died shortly after treatment, 20 patients only had chest X-rays during follow-up, and 24 patients did not have a chest CT scan at the right interval). Additionally, patients were excluded when no short-axis lymph node diameter was larger than 10 mm at baseline ($n = 9$) or when none of the measured pathologic lymph node stations corresponded with the delineated lymph node stations ($n = 3$). Lymph node stations were defined based on the 7th TNM classification [8]. Eventually the study population consisted of 75 patients.

Chemoradiotherapy treatment

A 3D-conformal radiotherapy technique was used for all patients but seven who received 2D-conventional radiotherapy. The primary tumor and involved lymph nodes were delineated as the Gross Tumor Volume primary (GTVp) and Gross Tumor Volume nodal (GTVn), respectively. The GTVn included all pathologically proven, FDG-PET positive and CT-graphic suspicious (i.e., larger than 10 mm in their maximal axis, or in case of station 7, larger than 15 mm on CT scan) lymph nodes. No elective nodal irradiation was performed. For the Clinical Target Volume (CTV), a margin of 5 mm was taken, excluding blood vessels and bony structures unless tumor invasion in these structures was observed. An additional isotropic margin of 10 mm for the primary tumor and 7 mm for the lymph nodes was taken to create the Planning Target Volume (PTV). The dose was planned according to the ICRU 50. Dose calculations were made with the AAA algorithm in the Eclipse treatment planning system. In all patients receiving chemotherapy a platinum-doublet was given.

Definitions and primary endpoint

For the prescription dose variable, the 2 Gy equivalent dose corrected for the overall treatment time ($EQD_{2,T}$) was used in order to correct for tumor repopulation when treatment duration exceeded 21 days ($EQD_{2,T} = EQD2 - 0.6 \times$ [overall treatment time – 21]) [9,10]. An α/β ratio of 10 Gy was used. We assumed no repopulation for patients treated with concurrent chemoradiotherapy.

Lymph nodes with a short-axis diameter of 10 mm or more on pre-radiotherapy axial CT planes were defined as pathologic. Lymph node diameters were measured on every follow-up CT scan. All measurements were made by one medical doctor. When in doubt, measurements were reviewed by two radiation oncologists. Follow-up ended when an INR occurred, when systemic therapy for any relapse was administered or was censored at 31 December 2013 for patients remaining disease-free. Therefore all patients had a possible minimal follow-up of 2 years.

The primary endpoint was the occurrence of an involved nodal relapse (INR). A nodal relapse was defined as an increase in short-axis diameter of at least 20% based on RECIST 1.1 [11,12]. The short-axis diameter measured 3 months (±2 months) after the end of radiation therapy was used as the reference diameter because we assumed that this approximates best the smallest short-axis diameter. Involved relapse meant relapse of a lymph node included in the GTVn. Patients with progressive disease on their first follow-up CT scan were also considered to have a nodal relapse when the lymph nodes met the criteria noted above taking as reference the pretreatment short-axis nodal diameter. Primary tumor failure and development of distant metastasis were also registered based on information retrieved from the medical file. Locoregional failure was defined as a relapse of the primary tumor, mediastinal lymph nodes, or both. Distant failure was defined as progression of a known metastasis or occurrence of a new distant lesion. Time to progression was defined starting from the end of radiotherapy.

Statistical analysis

Summary statistics were provided with frequency count and percentage for categorical variables and mean, SD, median, and range for continuous variables. Comparison of patient characteristics between subgroups was done with ANOVA and Kruskal–Wallis for continuous variables and Pearson's Chi-square analysis for categorical variables. A Cox proportional hazard regression was performed to evaluate the relation between $EQD_{2,T}$ dose, initial nodal diameter and incidence of INR, analyzed per lymph node ($n = 142$), and per patient ($n = 75$). Similarly, primary tumor relapse was modeled combining covariates $EQD_{2,T}$ dose, primary tumor baseline diameter, and chemotherapy regimen ($n = 75$).

Kaplan–Meier curves for all endpoints were derived to assess the difference between separate subgroups of patients. The log-rank test assessed the differences between subgroups. p Values $\leq .05$ were considered to be statistically significant.

Results

Study population and patient characteristics

Seventy-five patients were reviewed as part of a retrospective study. The total prescription dose ranged from 39 Gy to 70 Gy with a dose per fraction of 2–3 Gy. The corresponding $EQD_{2,T}$ ranged from 42 Gy to 66 Gy. All patients were in a good general condition at the time of diagnosis. The majority of patients presented with stage IIIA or IIIB NSCLC ($n = 62$, 82%). Twelve patients had stage IV NSCLC. Most patients ($n = 68$, 91%) were active or former smokers. Sequential chemoradiotherapy was the most commonly used treatment

($n = 47$, 63%). For visualization of the results, three dose groups were defined based on the $EQD_{2,T}$: group A <50 Gy, group B 50–55 Gy, and group C > 55 Gy. Twenty-two patients were included in group A, 24 in group B and 29 in group C. Patient characteristics were well balanced between the three groups, except from a higher prevalence of the performance status score 0 in the high-dose group (Table 1). There was no significant difference seen in baseline lymph node diameter between the groups (overall average 15.7 ± 6.5mm, $p = .93$).

Failure patterns and dose–effect relation

Any relapse occurred in 58 patients (77%) of which 19 (33%) had a locoregional failure only. Twenty-two patients (38%) had distant failure only, either by progression of a known metastasis or occurrence of a new distant lesion. Seventeen patients (29%) had a locoregional and distant failure at the same time. The median time to any progression was 6 months (range 1–45) (Table 2).

Involved nodal relapse

Among the 75 patients, 142 lymph nodes (49 in group A, 36 in group B, and 57 in group C) met the criteria of pathological lymph nodes at baseline and were further evaluated for the occurrence of INR. The number of lymph node stations evaluated per patient ranged from 1 to 5. In most patients (77%), 1 or 2 pathological lymph node stations were observed (Supplementary Table S1 in Appendix). An INR was observed in 8%, 6%, and 7% of lymph nodes in group A, B, and C, respectively. Figure 1 shows the cumulative proportion of INR-free lymph nodes per dose group. No significant dose or initial nodal diameter effect was observed in Cox regression ($p = .22$ [HR = 0.95] and $p = .76$ [HR = 0.98], respectively).

Table 1. Patient and treatment characteristics.

	Total ($n = 75$)	$EQD_{2,T}$ < 50 Gy ($n = 22$)	$EQD_{2,T}$ 50–55 Gy ($n = 24$)	$EQD_{2,T}$ > 55 Gy ($n = 29$)	p
Age (years)					
Mean ± SD (range)	64.55 ± 9.91 (45–88)	67.00 ± 10.57 (45–88)	64.00 ± 8.78 (49–80)	63.14 ± 10.27 (45–83)	.37
Gender					.93
Male	61 (81%)	18 (82%)	20 (83%)	23 (79%)	
Female	14 (19%)	4 (18%)	4 (17%)	6 (21%)	
FDG-PET at diagnosiss	67 (89%)	18 (82%)	24 (100%)	25 (86%)	.11
Smoking status					.46
Active	33 (44%)	12 (55%)	9 (38%)	12 (41%)	
Former	35 (47%)	8 (36%)	13 (54%)	14 (48%)	
Never	3 (4%)	None	2 (8%)	1 (3%)	
Unknown	4 (5%)	2 (9%)	None	2 (7%)	
WHO performance status					.25
0	32 (43%)	6 (27%)	11 (46%)	15 (52%)	
1	28 (37%)	10 (45%)	10 (42%)	8 (28%)	
2	5 (7%)	2 (9%)	None	3 (10%)	
Unknown	10 (13%)	4 (18%)	3 (13%)	3 (10%)	
Histology					.40
Squamous cell carcinoma	35 (47%)	13 (59%)	10 (42%)	12 (41%)	
Adenocarcinoma	23 (31%)	5 (23%)	10 (42%)	8 (28%)	
Large cell carcinoma	17 (23%)	4 (18%)	4 (17%)	9 (31%)	
Disease stage					.39
IIB	1 (1%)	None	1 (4%)	None	
IIIA	22 (29%)	4 (18%)	7 (29%)	11 (38%)	
IIIB	40 (53%)	12 (55%)	13 (54%)	15 (52%)	
IV	12 (16%)	6 (27%)	3 (13%)	3 (10%)	
Treatment					**<.001**
Radiotherapy alone	16 (21%)	6 (27%)	4 (17%)	6 (21%)	
Sequential chemoradiotherapy	47 (63%)	16 (73%)	20 (83%)	11 (38%)	
Concurrent chemoradiotherapy	12 (16%)	None	None	12 (41%)	
$EQD_{2,T}$ (Gy)					**<.001**
Mean ± SD (range)	53.51 ± 7.29 (42.20–66.00)	45.07 ± 3.49 (42.20–49.80)	52.78 ± 1.37 (50.4–54.9)	60.51 ± 4.74 (55.50–66.00)	
Primary tumor (mm)					
Mean ± SD (range)	46.96 ± 20.03 (13.70–98.30) $n = 70$	52.40 ± 25.53 (13.70–98.30)	38.40 ± 16.96 (15.40–74.50)	49.71 ± 15.41 (21.80–75.60)	**.05**
Baseline nodal short-axis diameter (mm)					
Mean ± SD (range)	15.66 ± 6.47 (10.00–53.70) $n = 142$	15.58 ± 7.59 (10.00–53.70)	16.23 ± 7.25 (10.00–44.90)	15.38 ± 4.79 (10.00–26.50)	.93
Follow-up					
Number CT scans (mean ± SD; range)	3 ± 2.94 (1–13)	2 ± 1.17 (1–5)	3 ± 3.13 (1–13)	4 ± 3.44 (1–11)	.1
Follow-up months (median; range)	7 (1–86)	5 (1–47)	6 (1–86)	9 (2–54)	.08

Differences between prescription dose groups are listed in the last column (p values ≤ .05 were considered significant and are printed in bold).

Table 2. Failure patterns.

	Total ($n = 75$)	$EQD_{2,T}$ < 50 Gy ($n = 22$)	$EQD_{2,T}$ 50–55 Gy ($n = 24$)	$EQD_{2,T}$ > 55 Gy ($n = 29$)
Any relapse	58 (77%)	16 (73%)	19 (79%)	23 (79%)
Locoregional relapse only	19 (33%)	7 (44%)	5 (26%)	7 (30%)
Distant failure only	22 (38%)	2 (13%)	9 (47%)	11 (48%)
Both	17 (29%)	7 (44%)	5 (26%)	5 (22%)
Progression-free survival (months; median [range])	6 (1–45)	5 (1–26)	5 (1–30)	9 (2–45)

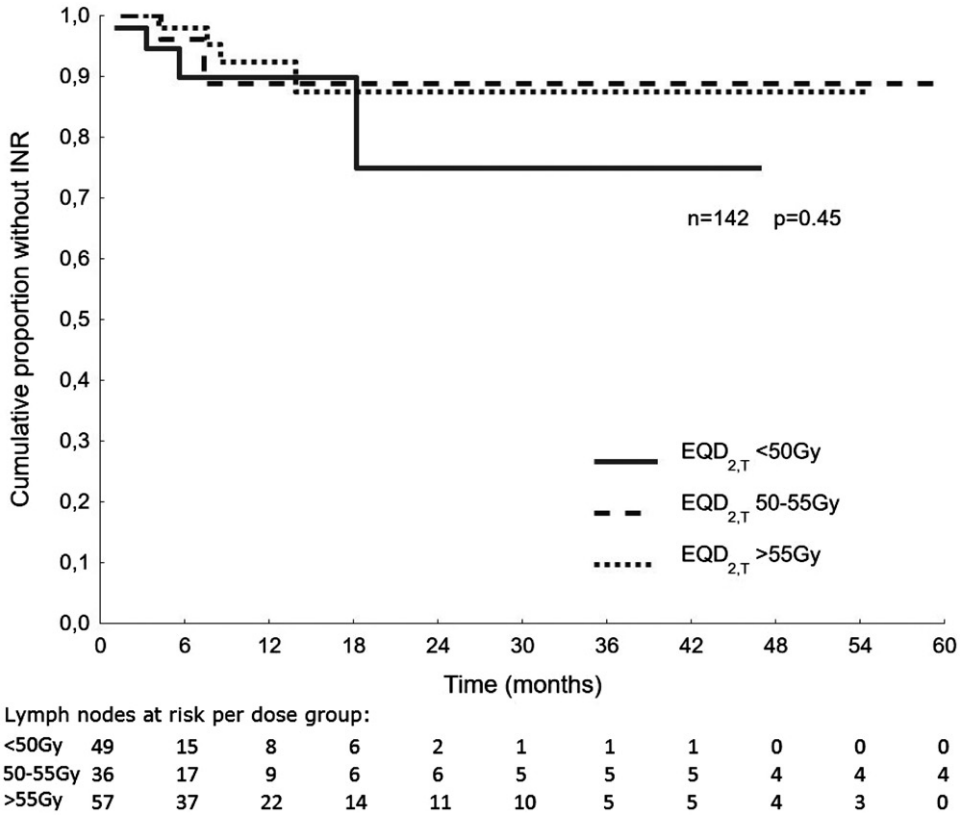

Figure 1. Cumulative proportion of lymph nodes without involved nodal relapse.

A Supplementary Figure S1 in Appendix represents the baseline nodal diameter against EQD2,T of all lymph nodes.

On a patient-based level, an INR was seen in 18%, 8%, and 14% of patients in group A, B, and C, respectively. Figure 2 shows the cumulative proportion of patients surviving without INR per dose group. No significant $EQD_{2,T}$ dose–response relation could be observed in Cox regression ($p = .18$ [HR = 0.94]). The INR-free survival at 12 months was 80%, 85%, and 85% for group A, B, and C, respectively, and 60%, 85%, and 75% at 24 months for group A, B, and C, respectively.

Primary tumor progression

Progression of the primary tumor occurred more frequently than a relapse in the lymph nodes. Figure 3 shows the cumulative proportion of patients without primary tumor progression ($n = 75$). The primary tumor progression-free survival is 36%, 59%, and 71% at 12 months and 24%, 42%, and 71% at 24 months for group A, B, and C, respectively. Cox regression analysis showed that baseline tumor diameter and $EQD_{2,T}$ were significant independent risk factors for primary tumor progression ($p = .0031$ [HR = 1.03] and $p = .033$ [HR = 0.93], respectively), while chemotherapy regimen was not significant. A clear difference in incidence between involved nodal relapse and primary tumor progression at 12 months is shown in Figure 4.

Discussion

Irradiation of involved mediastinal lymph nodes in NSCLC is a major cause of radiation esophagitis. This may lead to an important deterioration in quality of life and treatment interruptions, jeopardizing the patient's outcome [3]. Aupérin et al. reported acute grade 3 and 4 esophageal toxicity rates of 4% and 18% for patients treated with sequential and concurrent chemoradiotherapy, respectively [2]. Lowering the radiation dose on pathological mediastinal lymph nodes could be an important beneficial factor in reducing the adverse effects [4]. Since locoregional disease control is of paramount importance for outcome, lowering the dose to the involved lymph nodes can only be considered when there is no increased risk of relapse. Involved lymph node relapse occurs less frequently compared to primary tumor progression. Some studies make a distinction between local (i.e., tumor) progression and regional (i.e., mediastinal) progression. Mediastinal progression can be further divided into in-field and out-of-field nodal relapse but definitions vary across studies. Albain et al. reported first relapse rates of 14% at the primary tumor site, 7% in hilar, mediastinal, or supraclavicular nodes only, and 5% at both sites in patients treated with induction chemoradiotherapy (45 Gy) followed by chemoradiotherapy up to 61 Gy [6]. Similar results were seen in a retrospective study by van Diessen et al. in patients with locally advanced NSCLC where local tumor failure was observed in 16% of patients and regional (i.e., involved lymph node) failure in 6% of patients [7]. In a systematic review, recurrence in mediastinal lymph nodes ranged from 4% to 56% [13]. All these studies show that the incidence of lymph node relapse is lower compared to primary tumor progression. However, the datasets in these studies contained highly uniform prescription doses and were thus unable to answer the dose–response question. Thus, we hypothesized

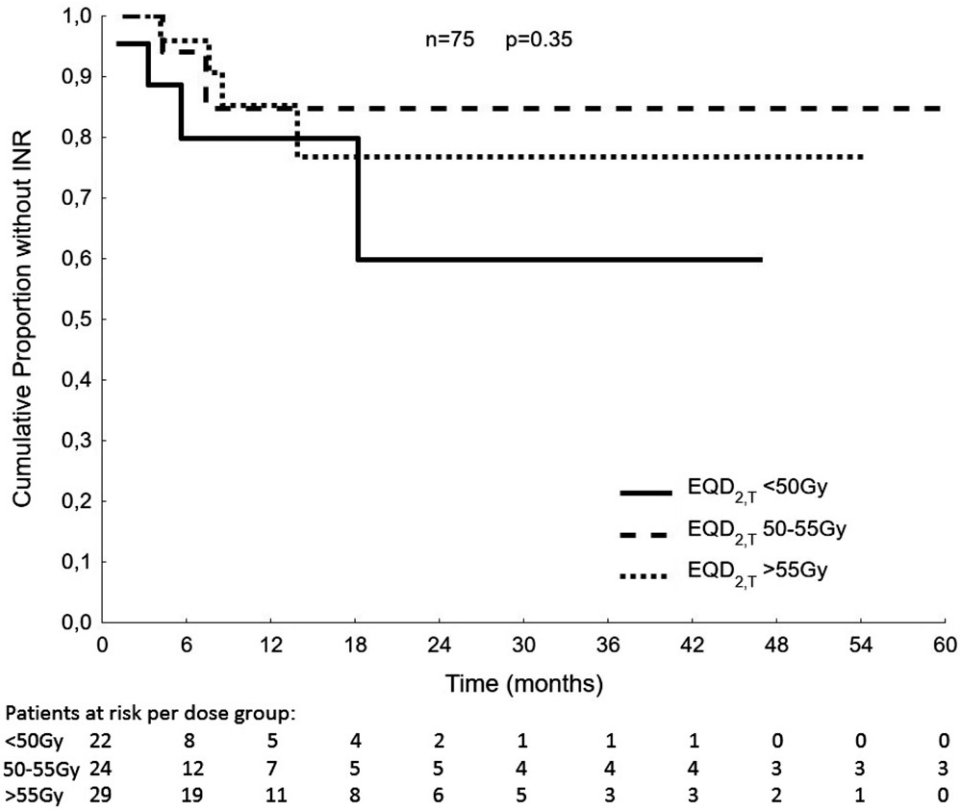

Figure 2. Cumulative proportion of patients without involved nodal relapse.

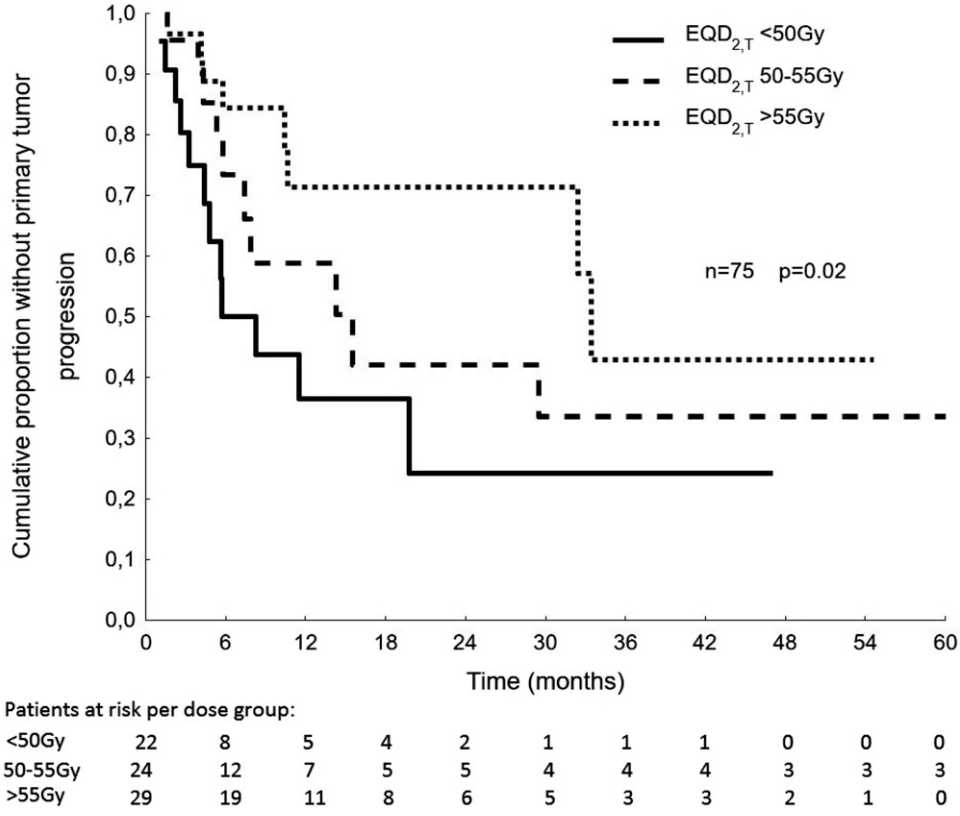

Figure 3. Cumulative proportion of patients without primary tumor progression.

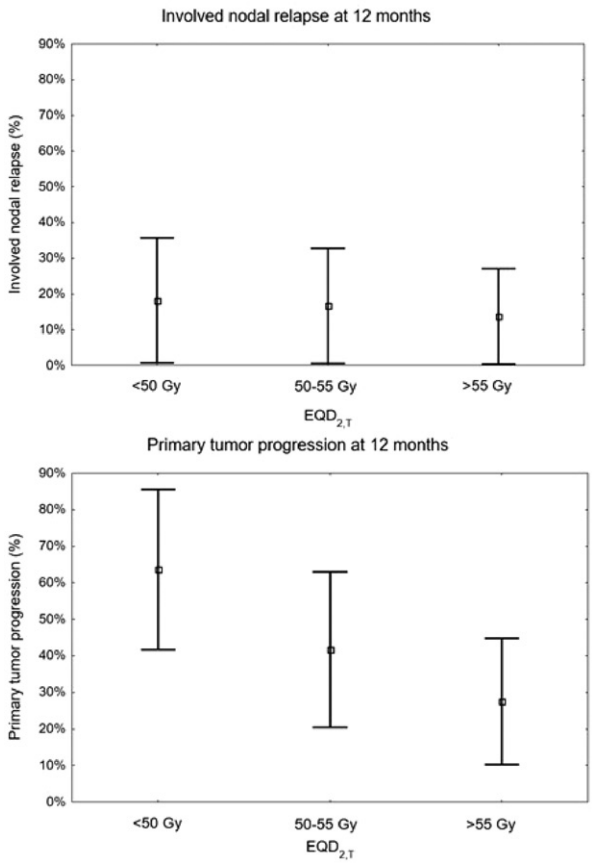

Figure 4. Incidence of INR and primary tumor progression at 12 months.

that lymph node control may be achieved at lower radiation doses. The aim of our study was to investigate whether a dose–response relation could be seen in involved mediastinal lymph nodes.

Our data suggest that there is no significant dose–response relation for involved nodal relapse (INR) within the used dose range. It is important to emphasize that all patients received a minimal $EQD_{2,T}$ of 42 Gy. The INR-free survival was 80%, 85%, and 85% at 12 months and 60%, 85%, and 75% at 24 months in the groups having been treated with an $EQD_{2,T}$ of <55 Gy, 50–55 Gy, and >55 Gy, respectively. Since all patients treated with concurrent chemoradiotherapy were included in the high-dose group (>55 Gy), this might have caused a selection bias favoring this group. The fact that INR was not seen less frequently in this group only reinforces the fact that higher radiation dose does not lead to better lymph node control. Cox regression modeling including the covariate EQD2 dose (without treatment time correction) instead of $EQD_{2,T}$ yielded non-significant results (EQD2 $p = .19$ and $p = .06$ for INR on nodal and patient level, respectively). For primary tumor relapse, the dose effect remained significant ($p = .027$) using EQD2. However, the general suggestion that for concurrent chemotherapy and radiotherapy lower doses may be achieved remains valid. A possible masking of nodal relapse cases at low dose due to the high primary tumor relapse in these patients cannot be completely ruled out. However, the median time of relapse being similar for the observed primary tumor and lymph node relapses in the low-dose group A (4.6 and 4.5 months, respectively) does not support that hypothesis. The initial nodal short-axis diameter was taken into consideration as a possible influencing factor on INR because patients with larger baseline nodal volumes might have been considered to have more extensive disease and thus might have received a lower radiation dose. A possible higher incidence of INR in the low-dose group might be caused by higher baseline nodal diameters rather than the lower radiation dose prescribed. However, baseline nodal short-axis diameter was not significantly related to INR (HR = 0.98 $p = .76$). For the primary tumor, there was a clear dose–response relation ($p = .033$ in the Cox model). This only validates the evidence that a higher radiation dose on the tumor gives higher local control rates [1,14,15]. After successful validation of our findings in larger datasets, this study could be the basis for future prospective dose de-escalation studies on the mediastinal LN with the aim to reduce acute esophagitis. A dose reduction from 66 Gy to 50 Gy on the LN would reduce the risk of dysphagia grade 2 from 50% to 30% for a 70-year-old male in a good general condition (WHO PS 0-1), treated with concurrent chemoradiotherapy. For grade 3 dysphagia, a risk reduction from 10% to 5% would be seen [16].

This study is limited by methodological shortcomings inevitably associated with a retrospective analysis; 27 patients were not included as they died in the first months after treatment, that is, before the first follow-up scan. We cannot rule out completely that some of them might have progressed at the time of death. The inclusion of stage IV patients with some metastases remaining untreated could potentially have biased the outcome results. However, only 1 patient out of the 12 included stage IV patients developed a progression of a metastasis as the only event recorded at the follow-up timepoint. Finally, in the patients included in the highest dose group, a better baseline performance status was observed in comparison to the two other dose groups.

A power calculation using our dataset size showed that the significant difference in primary tumor relapse detected between the low- and high-dose group (33% versus 55% relapse rate) was the result of a test with 76% power (for a Type I error risk of 10%). For the comparison of the proportions of patients with INR (13% prevalence overall) between these dose groups, our dataset was powered to detect a similar absolute increase (3% versus 25%) with a power of 95%. However, the detection of a similar relative increase (10% versus 17%) had only a power of 35%. Therefore, prescription dose was incorporated as a continuous variable in Cox regression instead of using the three dose categories. The limited size of the dataset did also not allow to incorporate more covariates into the Cox regression models. Also, some involved lymph nodes could have been missed as we defined pathological lymph nodes solely on CT criteria; neither increased FDG-uptake nor pathological confirmation with EBUS was taken into account. This could potentially also have resulted in the inclusion of some non-involved nodes into the study. However, our CT-based LN diameter measurements showed that more than 83% of LN decreased in size after RT, which is an indication that they might be

considered pathological. Furthermore, relapse was only defined on CT criteria and was not pathologically proven. However, these CT-based analyses are very unlikely to have influenced the resulting findings of absence of INR dose response. The planning CT scan was used for baseline nodal diameter measurements possibly causing a selection bias as patients receiving sequential chemoradiotherapy might have had smaller lymph nodes on their planning CT scan, which did not meet the RECIST 1.1 criteria. Last, the analyses were performed with and without the overall treatment time correction applied to the equivalent doses. As this was shown to have some impact on the resulting figures, it seems important for future studies to explicitly take this dose modeling issue into account.

To the best of our knowledge, this is the first hypothesis-generating study analyzing the dose–response relation for control of involved mediastinal LN. No indication of a dose–response was observed between 42 Gy and 66 Gy for INR, and in that way, our initial hypothesis was not rejected in this dataset. A highly powered follow-up study validating our findings using a larger dataset with longer follow-up times is crucial to exclude any minimal INR dose response. This could then be the basis for a step-wise prospective dose de-escalation study on mediastinal LN to reduce the incidence of acute esophagitis while maintaining a standard dose for the primary tumor.

Disclosure statement

None of the authors have a conflict of interest to declare.

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