

ORIGINAL ARTICLE



Clinical implications of dose to functional lung volumes in the trimodality treatment of esophageal cancer

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ABSTRACT

Background: Trimodality treatment, i.e., neoadjuvant chemoradiotherapy (nCRT) followed by surgery, for locally advanced esophageal cancer (EC) improves overall survival but also increases the risk of postoperative pulmonary complications. Here, we tried to identify a relation between dose to functional lung volumes (FLV) as determined by 4D-CT scans in EC patients and treatment-related lung toxicity.

Materials and methods: All patients with EC undergoing trimodality treatment between 2017 and 2022 in UZ Leuven and scanned with 4D-CT-simulation were selected. FLVs were determined based on Jacobian determinants of deformable image registration between maximum inspiration and expiration phases. Dose/volume parameters of the anatomical lung volume (ALV) and FLV were compared between patients with versus without postoperative pulmonary complications. Results of pre- and post-nCRT pulmonary function tests (PFTs) were collected and compared in relation to radiation dose.

Results: Twelve out of 51 EC patients developed postoperative pulmonary complications. ALV was smaller while FLV10Gy and FLV20Gy were larger in patients with complications (respectively $3141 \pm 858\text{mL}$ vs $3601 \pm 635\text{mL}$, $p = 0.025$; $360 \pm 216\text{mL}$ vs $264 \pm 139\text{mL}$, $p = 0.038$; $166 \pm 106\text{mL}$ vs $118 \pm 63\text{mL}$, $p = 0.030$). No differences in ALV dose-volume parameters were detected. Baseline FEV1 and TLC were significantly lower in patients with complications (respectively $90 \pm 17\%\text{pred}$ vs $102 \pm 20\%\text{pred}$, $p = 0.033$ and $93 \pm 17\%\text{pred}$ vs $110 \pm 13\%\text{pred}$, $p = 0.001$), though no other PFTs were significantly different between both groups. DLCO was the only PFT that had a meaningful decrease after nCRT ($85 \pm 17\%\text{pred}$ vs $68 \pm 15\%\text{pred}$, $p < 0.001$) but was not related to dose to ALV/FLV.

Conclusion: Small ALV and increasing FLV exposed to intermediate (10 to 20 Gy) dose are associated to postoperative pulmonary complications. Changes of DLCO occur during nCRT but do not seem to be related to radiation dose to ALV or FLV. This information could attribute towards toxicity risk prediction and reduction strategies for EC.

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Background

For locally advanced esophageal cancer (EC), defined as clinical T3 or node-positive disease, the standard treatment comprises a combination of neoadjuvant chemotherapy and radiation therapy (nCRT) followed by surgery. This so-called trimodality treatment has shown superior overall survival compared to surgery alone, as supported by the results of the phase III CROSS trial [1,2]. However, trimodality treatment is also associated with an increase in postoperative complications [3,4]. It was previously demonstrated that the dose to the lungs is related to an increase in postoperative pulmonary complications [5,6]. Still, the exact attribution of radiation therapy (RT) towards pulmonary complications in this multimodal therapy is not entirely identified [1,7].

Using dose-volume parameters of the total lung volume is, however, oversimplifying lung physiology that is different among different parts of the lung [8]. It was shown that dose to more or less functional lung tissues can have different biological effects [5,8,9,10,11].

4D-CT-simulation scans encompassing respiratory motion are nowadays recommended for RT in EC. These scans can be used to identify the most functional lung volume (FLV) based on volume expansion between end-expiration and end-inspiration respiratory phases. This technique has demonstrated a fair amount of agreement with FLVs derived out of both ventilation (V) and perfusion (Q) SPECT-CT [12,13]. In lung cancer, 4D-derived FLVs are being investigated as a tool to better predict toxicity and as a strategy towards reducing toxicity by functional avoidance RT planning. The latter is

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actively under investigation after promising results in a recent phase II clinical trial [14].

Although the same strategy could also be used for RT in EC, research on this topic is still limited. Only recently, a few studies by one research group were published, describing a planning methodology for functional lung sparing for EC radiotherapy and evaluating its feasibility based on a dataset of a handful of patients [15,16]. This dataset consisted mostly of squamous cell carcinoma (SCC) which is not representative of the population in Western Europe and the United States, in which adenocarcinoma (AC) is the more common subtype [17]. This results in different radiation fields given SCC is most commonly located in the proximal esophagus while the opposite is true for AC.

The relevance of pulmonary function tests (PFT) in the surgical management of EC is well established as postoperative complications have been related to them [18]. Literature supporting the relationship between PFTs and FLVs, as well as the effect of FLV dose on PFTs is only scarce. A relationship between FLV and FEV1, as well as the effect of dose to FLV on FEV1 and DLCO has been described in lung cancer RT [19,20].

In this exploratory study, we investigated the radiation dose to FLVs during nCRT for EC delivered with state-of-the-art RT and correlated these data with the development of postoperative pulmonary complications. Next, we investigated if we could verify the predictive nature of PFTs for the development of postoperative pulmonary complications. Furthermore, we tried to correlate PFTs with anatomical lung volumes (ALVs) and FLVs. Finally, we investigated if any changes in PFTs after nCRT could be related to the radiation dose to either the ALVs or FLVs.

Material and methods

Study population

This study was performed after approval of the Ethics Committee Research UZ/KU Leuven (reference number S59667). We identified all patients with a diagnosis of EC that were treated at the Department of Radiation Oncology and underwent subsequent surgery at the Department of Thoracic Surgery in UZ Leuven, between January 2017 and June 2022. Only patients that had 4D-CT-simulation scans and completed trimodality treatment, were selected for this study. Patients' functional lung mapping and identification of FLVs were performed and dose-volume metrics of these FLVs were determined. PFTs and postoperative toxicity scoring were extracted from the medical files, as detailed in the next paragraphs.

CT acquisition, RT-treatment plan, and functional lung mapping

Patients were immobilized in the supine position. All patients received a 4D-CT-simulation scan in free breathing for their treatment using Siemens SOMATOM Definition Edge or Siemens SOMATOM Drive and Varian Respiratory Gating for

Scanners systems. This resulted in either eight or ten respiratory phase image reconstructions at 3 mm slice thickness. The zero and fifty percent respiratory phases represent the maximum inhale and exhale respiratory phases respectively. RT planning was performed on the average CT images, based on the delineation of the target volumes as described by Thomas et al. and using a 7 mm planning target volume margin [21]. Treatment plans were designed in Varian Eclipse software using intensity-modulated and volumetric arc RT techniques with AAA or Acuros XB dose calculation algorithms (Varian, a Siemens Healthineers company, Palo Alto, CA). Dose prescriptions allowed were either 23 or 25 fractions of 1.8 Gy. DICOM data of 4D-CT-simulation, average CT images, and RT-treatment plan and dose were collected.

All patient DICOM data were exported to MIM Software Version 7.2 for further analysis. FLVs were determined using the methodology described by Nyeng et al. [13]. In summary, this encompasses the deformable image registration (DIR) between maximum inhale and maximum exhale respiratory phases using the default DIR algorithm of MIM. Based on this deformation, a map displaying the voxelized Jacobian determinants (grid size 2.56 by 2.56 mm) was created. The maximum Jacobian determinant within the lung contour was determined and 16% of this maximum was used as the threshold for identifying the FLV. Ventilation maps were then constructed by subtracting the Jacobian determinants with one and overlaid on the maximum expiration phase for visual representation (Figure 1 A + B). This methodology was chosen for two reasons: (1) this volume has shown fair agreement with gold-standard functional imaging and determination of the threshold was based on clinical outcome (radiation pneumonitis in lung cancer cases); and (2) its implementation could be easily adopted in a clinical workflow given that the software used to determine the FLV is the same software used for delineation [13].

Dose-volume parameters

As clinical treatment planning was performed on the average CT image, we performed a DIR and transformation of the dose map to the maximum expiration phase (Figure 1 C + D). We then extracted basic parameters such as volume and MLD of the ALV and FLVs. Next, we extracted both relative and absolute (cc) dose-volume parameters for both the FLV and ALV, using the format $ALV/FLV(rel/cc) \times Gy$ depicting the volume that receives a minimum x Gy. For this, we pre-defined 5 different values of x : 40, 30, 20, 10, and 5, as defined in international guidelines [22].

Pulmonary function tests

PFTs were extracted retrospectively from the patient's medical files. All PFTs were registered as a percentage of the predicted volume (%pred): pre- (maximum 6 weeks before the start of nCRT) and post-nCRT forced expiratory volume in the first second (FEV1), gas transfer test (DLCO), and Tiffeneau index (FEV1 divided by forced vital capacity).

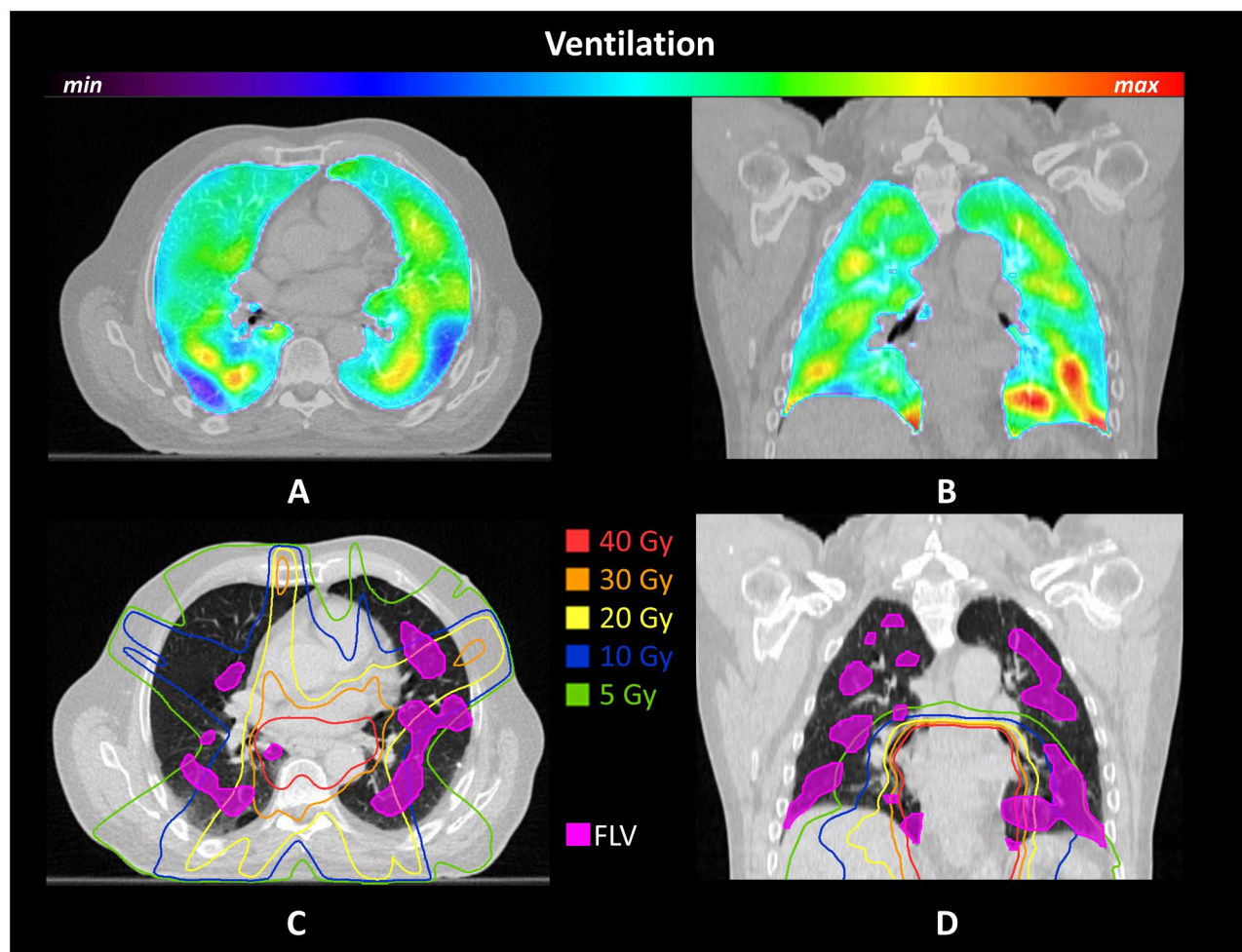


Figure 1. Definition of functional lung volumes.

A + B: Functional lung mapping (A + B) giving shape to the functional lung volume (FLV);
C + D: Projection of the treatment plan isodoses in relation to the FLV.

Postoperative pulmonary complications

Postoperative complications were prospectively recorded in patients' medical files keeping track of complications until 90 days after surgery. Pulmonary complications were defined using the definitions of Thomas et al. [5]. This meant that (1) pulmonary complications consisted of either pneumonia, respiratory failure or ARDS and (2) only toxicities, according to the Esophageal Complications Consensus Group (ECCG) and Comprehensive Complication Index (CCI), with CCI scores more than 300 were included [23,24].

Statistical analysis

We compared dose-volume parameters between the patients who developed postoperative (within 90 days) pulmonary complications versus patients who did not. Similarly, PFTs were compared between both groups. Two-sample *t*-tests and Mann-Whitney *U*-tests (depending on the normal distribution of data) were used for these analyses.

Baseline PFTs were correlated with ALVs and FLVs using the Pearson correlation test and coefficient. Using paired *t*-test we examined if baseline PFTs were different from post-

nCRT PFTs. Parameters that were significantly different between both time points were then correlated to the radiation dose to the ALV and FLV using the Pearson correlation test and coefficient. A complete case analysis was performed on a test-by-test basis.

Statistical significance level (alpha) was set at 0.05 for all analyses rendering $p < 0.05$ as statistically significant. Given the exploratory nature of this research, no multiple testing correction was performed [25]. Statistical analyses were performed in IBM SPSS Statistics for Windows Version 28.0 [26].

Results

Patient characteristics

We identified 51 patients fulfilling all criteria for further assessment (Table 1). Twelve patients (24%) developed postoperative pulmonary complications, of which five were Clavien-Dindo grade $\geq$ IIIb [27]. There were no major differences between both groups in baseline characteristics. Most predominant clinical T-stage and N-stages were cT3 and cN1 in both groups. The majority of tumors were located at the distal third of the esophagus.

Table 1. Comparison of patient baseline characteristics between patients with and without pulmonary complications.

Patient Characteristics		Postoperative pulmonary complications				p
		No (n = 39)		Yes (n = 12)		
		N	%	N	%	
Sex	Male	34	87%	10	83%	.735
	Female	5	13%	2	17%	
ECOG	0	21	54%	5	42%	.401
	1	16	41%	5	42%	
	2	2	5%	2	17%	
Charlson Comorbidity Index	≤ 1	28	72%	8	67%	.733
	> 1	11	28%	4	33%	
Smoking	Never	2	5%	2	17%	.592
	Active	12	31%	4	33%	
	Stopped < 1 year	5	13%	1	8%	
	Stopped > 1 year	20	51%	5	42%	
Age diagnosis		Mean (SD)		Mean (SD)		.203
BMI (kg/m2)		64 (10)		68 (8)		.205
		26 (3)		28 (5)		
Tumor Characteristics		N	%	N	%	p
Tumor Location	Mid 1/3	5	13%	3	25%	.388
	Distal 1/3	25	64%	8	67%	
	GEJ	9	23%	1	8%	
Histology	SCC	12	31%	4	33%	.849
	AC	26	67%	8	67%	
	Other	1	3%	0	0%	
cT	1	1	3%	0	0%	.732
	2	2	5%	1	8%	
	3	35	90%	10	83%	
	4	1	3%	1	8%	
cN	0	7	18%	1	8%	.602
	1	21	54%	9	75%	
	2	10	26%	2	17%	
	3	1	3%	0	0%	
Tumor Characteristics		N	%	N	%	
Surgery Type	Open	18	46%	7	58%	.460
	MIE	21	54%	5	42%	
PTV (cc)		Mean (SD)		Mean (SD)		.684
		683 (258)		648 (239)		

cT and cN as staged according to TNM8; PTV: planning target volume for irradiation expressed in cc.

SCC: squamous cell carcinoma; AC: adenocarcinoma.

p-value for significance <0.05.

Lung dose-volume parameters and postoperative complications

Comparing lung dose-volume parameters of patients that did not have complications versus patients that did, we found a statistically significantly smaller ALV in the latter (3601 cc (SD: 635 cc) versus 3141 cc (SD: 858 cc) respectively, $p = 0.025$). There was no statistically significant difference in FLV (661 cc (SD: 340) versus 862 cc (SD: 428 cc) respectively, $p = 0.125$). No statistically significant differences in MLD of the ALV (respectively 10.0Gy (SD: 2.9Gy) versus 10.4Gy (SD: 3.2Gy), $p = 0.325$), nor the FLV (respectively 11.2Gy (SD: 3.1Gy) versus 10.9Gy (SD: 3.0Gy), $p = 0.404$) were identified. The FLVs that received 10 Gy and 20 Gy were statistically significantly larger in patients that developed complications: FLV10Gy(cc): 360 cc (SD: 216 cc) versus 264 cc (SD: 139 cc) ($p = 0.038$) and FLV20Gy(cc): 166 cc (SD: 106 cc) versus 118 cc (SD: 63 cc) ($p = 0.030$) (Table 2). However, this difference was not statistically significantly different in relative dose-volume parameters (Supplementary Table S1-A). No statistically

Table 2. Comparison of dose-volume parameters of anatomical and functional lung volumes Expressed in cc between patients with and without pulmonary complications.

	Postoperative pulmonary complications				
	No (n = 39)		Yes (n = 12)		p-value
	Mean	SD	Mean	SD	
ALV Mean Dose (Gy)	10.0	2.9	10.4	3.2	.335
FLV Mean Dose (Gy)	11.2	3.1	10.9	3.0	.404
ALV (cc)	3601	635	3141	858	.025
FLV (cc)	661	340	862	428	.125
ALV40Gy (cc)	45	26	57	48	.594
FLV40Gy (cc)	11	7	16	16	.484
ALV30Gy (cc)	159	102	153	154	.464
FLV30Gy (cc)	11	7	16	16	.484
ALV20Gy (cc)	580	256	593	316	.444
FLV20Gy (cc)	118	63	166	106	.030
ALV10Gy (cc)	1352	534	1274	627	.336
FLV10Gy (cc)	264	139	360	216	.038
ALV5Gy (cc)	2057	809	1851	915	.229
FLV5Gy (cc)	404	229	514	274	.149

ALV: anatomical lung volume; FLV: functional lung volume; SD: standard deviation; cc quantifies the absolute volume that is exposed to x Gy.

p-value for significance <0.05.

significant correlations between PTV and FLV exposed to 10 and 20 Gy were found (Supplementary Table S1-B). No significant differences in dose to the ALV were identified between both groups at the investigated dose levels.

Pulmonary function tests and postoperative pulmonary complications

PFTs were compared between patients that did not develop postoperative pulmonary complications versus those that did (Table 3). TLC was statistically significantly lower in the group that developed complications (93%pred (SD: 17%) versus 110%pred (SD: 13%) ($p=0.001$)). The baseline FEV1 was also lower in the group developing postoperative complications (90%pred (SD: 17%) versus 102%pred (SD: 20%) ($p=0.033$)). After nCRT, this difference was no longer statistically significant ($p=0.101$). We found no statistically significant differences in DLCO between both groups at baseline nor after neoadjuvant treatment. However, no patients with baseline DLCO >100%pred ($n=8$ (16%)) developed postoperative pulmonary complications, as shown in Supplementary Figure 1. This figure also shows a trend that patients with good performing PFTs, can tolerate larger volumes of FLV exposed to 20 Gy before they develop postoperative complications and vice versa.

Differences in pulmonary function tests before versus after nCRT

Comparing baseline versus post-nCRT PFTs, there was a statistically significant decrease in DLCO and Tiffeneau index. While this difference was large in DLCO (85% (SD:17%) versus 68% (SD: 15%), ($p<0.001$)), the difference in Tiffeneau index was small (93% (SD: 9%) versus 91% (SD: 9%) ($p=0.019$)) (Table 4). The baseline versus post-nCRT differences in DLCO and Tiffeneau index in patients that developed pulmonary complications were not statistically significantly

different to those that did not develop complications (Table 3).

Using Pearson correlation coefficients, TLC and ALV were strongly positively correlated (Supplementary Table S2). No other statistically significant correlations between ALV and the lung function test results were found. Furthermore, we could not identify any significant correlation between the CT-based FLV and the PFTs.

No correlations between ALV or FLV dose and effects on PFTs were found to be statistically significant (Supplementary Table S3).

Discussion

The use of FLVs determined by 4D-CT-scans to predict and reduce toxicity has already been proposed in lung cancer. Meanwhile, only limited research on this topic is performed in EC. This study is, to our knowledge, the first of its kind both in terms of population size as well as its firm clinical endpoint examined, i.e., postoperative pulmonary complications, as opposed to changes in biomarkers like PFTs.

We found that the FLV exposed to 10 and 20 Gy (in cc), was significantly larger in patients that developed postoperative pulmonary complications. This intermediate-dose level is an established value for dose constraints to ALV in RT planning for EC and correlates with postoperative complications [28,29]. This difference was not observed in the relative dose-volume parameters of the FLV (FLV volume exposed to x Gy divided by the total FLV). These findings do not have to be contradicting as a minimal absolute (functional) lung volume might be required to maintain normal pulmonary function capable of proper recovery after surgery.

We could not find any difference in ALV dose between groups of patients with and without postoperative pulmonary complications. This is unlike some previous reports including the toxicity prediction model of Thomas et al. [5]. Possibly, our sample size was too small to detect such a rather small difference (odds ratio of 1.15 for predicting pulmonary postoperative complications in that model). It could be that functional lung dose exposure has a larger effect size thus explaining the early significance of results in this volume. We did, however, find that the ALV was significantly lower in patients that developed the complications. In lung cancer RT, this relation between ALV and treatment toxicity has already been established [30,31]. In FLV, there was a nonsignificant trend towards larger FLV in patients with pulmonary complications. Possibly, patients with smaller ALV have a compensatory larger volume of the high-functional

Table 3. Comparison of pulmonary function tests between patients with and without pulmonary complications.

	Postoperative pulmonary complications							<i>p</i> -value
	No (<i>n</i> = 39)			Yes (<i>n</i> = 12)				
	Mean	SD	Missing	Mean	SD	Missing		
TLC (% pred)	109.6	12.8	11	93.1	17.3	2	0.001	
FEV1 (% pred) baseline	101.8	20.0	0	89.8	17.5	0	0.033	
FEV1 (% pred) post	99.9	20.8	0	90.6	21.0	1	0.101	
ΔFEV1 (% pred)	−1.9	8.3	0	.5	8.9	1	0.206	
DLCO (% pred) baseline	87.4	18.0	6	82.3	9.3	0	0.180	
DLCO (% pred) post	69.4	13.2	15	65.1	18.5	4	0.238	
ΔDLCO (% pred)	−17.7	12.9	19	−15.3	13.0	4	0.327	
Tiff (% pred) baseline	93.4	9.1	3	92.9	9.4	1	0.725	
Tiff (% pred) post	91.6	7.5	3	91.6	12.1	1	0.489	
ΔTiff (% pred)	−1.7	5.4	4	−1.3	4.1	1	0.403	

FEV1: forced expiratory volume in 1 s; TLC: total lung capacity; DLCO: diffusing capacity for carbon monoxide; Tiff: tiffeneau index as calculated by FEV1 divided by vital capacity. Δ quantifies the differences before versus after neoadjuvant chemoradiotherapy.

% pred quantifies the pulmonary function test in comparison with predicted normal values, based on a patient's sex, height, age and race.

SD: standard deviation; *p*-value for significance <0.05.

Table 4. Comparison of pulmonary function test results before versus after neoadjuvant Chemoradiotherapy.

	Mean baseline	SD	Mean post-nCRT	SD	<i>p</i> -value
FEV1 (% pred)	99.2	20.0	97.8	21.0	0.122
DLCO (% pred)	85.0	17.2	68.0	15.0	<0.001
Tiff (% pred)	93.1	9.0	91.5	8.7	0.019

FEV1: forced expiratory volume in 1 s; DLCO: diffusing capacity for carbon monoxide; Tiff: tiffeneau index as calculated by FEV1 divided by vital capacity.

% pred quantifies the pulmonary function test in comparison with predicted normal values, based on a patient's sex, height, age and race.

SD: standard deviation; *p*-value for significance <0.05.

lung (thus FLV) to maintain adequate gas exchange. Therefore, this nonsignificant trend may just be the result of a reduced ALV.

PFTs are typically used to assess operability in patients. The TLC was significantly lower in patients that developed postoperative pulmonary complications. This parameter was highly correlated with the CT-determined ALV. Our results do not confirm earlier findings of the importance of DLCO in major postoperative complications [18]. We hypothesize this is due to the fact that patients with poor PFTs were excluded from surgery and thus not accounted for in our study. Furthermore, in our population pulmonary complications were dichotomized based on CCI-score >300 yes/no, which corresponds to >grade I toxicity using the Clavien-Dindo scoring scale [23]. Meanwhile, in existing literature PFTs were mainly related to the occurrence of high-grade toxicity (e.g. Clavien-Dindo $\geq$ IIIb) [5,18,27]. The baseline FEV1 was significantly lower but both groups had normal FEV1, resulting in questionable clinical relevance of these findings. Furthermore, no statistically significant difference in FEV1 was detected post-nCRT.

We found a statistically significant decrease after nCRT in both Tiffeneau and DLCO. This expresses the need for post-nCRT re-evaluation of the operability of patients. The extent of these decreases was, however, not significantly different between patients with and without postoperative pulmonary complications. We could not find a decrease or increase in FEV1 after nCRT, similar to earlier research in EC RT and opposed to lung cancer RT [32]. While the difference in the Tiffeneau index between pre- and post-nCRT was statistically significant, it was very small (72% versus 70% respectively). This is similar to the decrease reported in the eleven EC-patients cohort of Zhou et al. [16]. This small difference is clinically negligible and within the range of acceptable measurement error [33]. For DLCO the difference between pre- (85%pred) and post-nCRT (68%pred) was both statistically significant and clinically relevant. The decline reported in our study (from 85% to 68%) is compatible with findings reported in other studies [32,34]. We did not, however, find a significant correlation between this drop in DLCO and dose to the ALVs nor FLVs. To our knowledge, only a few and non-univocal correlations have been described between dose to ALVs or FLVs and changes in PFTs [19,35]. The lack of supporting literature could be explained by a more complex physiology that is responsible for the changes in PFTs, for example, the effect of RT on both pulmonary and cardiac function [36]. Another reason is that clinical implications of dose to FLV and PFTs can influence one another as is exemplified by our observation that less postoperative pulmonary complications are seen in patients with well-performing PFTs for a set FLV dose exposure.

Our analysis has some limitations. First of all, there is the bias associated to its retrospective design: our database is constructed on patients who all underwent surgery, meaning all patients were deemed eligible for surgery (which includes selection based on adequate PFTs). Patients who initially were eligible for surgery but became ineligible after nCRT were also not included. Arguably this group could have even

more pronounced drops in PFTs. Additionally, a retrospective analysis cannot properly identify the causal nature of RT to postoperative pulmonary complications. This is especially true in a treatment scheme that also includes chemotherapy and surgery. Secondly, our population size, while to our knowledge being the largest reported on in the context of FLVs in EC, is still limited. Our results should therefore be regarded as exploratory and interpreted with caution. Especially for some PFTs, due to missing data, our analyses were performed on subsets, down to 28 patients for comparing pre- versus post-nCRT DLCO. Therefore, we also did not propose any effect sizes or multivariate analyses based on our data from this exploratory analysis. Confirmatory studies with a prespecified hypothesis and control for multiple significance tests should validate our findings [25]. Third and finally, there is a lot of heterogeneity in the methodology of defining FLV [37]. This can include different threshold values of Jacobian determinants to determine the FLV but also methods based on differences in Hounsfield units [15]. We opted for the former and used a threshold that was clinically relevant in lung cancer. In EC, this threshold could be different but given our limited patient numbers, trying to identify a different threshold could result in overfitting. Future research should be directed towards optimizing this threshold in larger datasets. Additionally, variation based on extent of respiration has been reported though seems rather reassuring with variations in a similar order of magnitude to variations in PFTs [38]. Caution should be given, however, when using these techniques in patients that undergo treatment in non-standardized positioning. Furthermore, regional V/Q mismatches might influence the validity of this 4D-CT (thus ventilation) based method since endothelial cells play an important role in the pathophysiology of radiation-induced lung injury [39]. However, the methodology we used has shown a substantial agreement between the 4D-CT derived FLVs and both V and Q-SPECT in lung cancer cases which can have a varying degree of V/Q mismatch [40].

Although aware of these limitations, our exploratory research indicates the importance of FLVs for toxicity prediction in nCRT for EC. This can lead to the implementation of functional lung avoidance RT dose planning strategies. Further research should be performed to validate these results and integrate this knowledge into toxicity models.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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Data availability statement

Raw data were generated at UZ Leuven. Derived data supporting the findings of this study are available from the corresponding author on request.

References

- [1] van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074–2084. doi: [10.1056/NEJMoa1112088](#).
- [2] Eyck BM, van Lanschot JJB, Hulshof MCCM, et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: the randomized controlled CROSS trial. *J Clin Oncol*. 2021;39(18):1995–2004. doi: [10.1200/JCO.20.03614](#).
- [3] Bosch DJ, Muijs CT, Mul VEM, et al. Impact of neoadjuvant chemoradiotherapy on postoperative course after curative-intent transthoracic esophagectomy in esophageal cancer patients. *Ann Surg Oncol*. 2014;21(2):605–611. doi: [10.1245/s10434-013-3316-8](#).
- [4] Reynolds J V, Ravi N, Hollywood D, et al. Neoadjuvant chemoradiation may increase the risk of respiratory complications and sepsis after transthoracic esophagectomy. *J Thorac Cardiovasc Surg*. 2006;132(3):549–555. doi: [10.1016/j.jtcvs.2006.05.015](#).
- [5] Thomas M, Defraene G, Lambrecht M, et al. NTCP model for postoperative complications and one-year mortality after trimodality treatment in oesophageal cancer. *Radiother Oncol*. 2019;141:33–40. doi: [10.1016/j.radonc.2019.09.015](#).
- [6] Visser S, Ribeiro CO, Dieters M, et al. Robustness assessment of clinical adaptive proton and photon radiotherapy for oesophageal cancer in the model-based approach. *Radiother Oncol*. 2022;177:197–204.
- [7] Reynolds JV, Preston SR, O'Neill B, et al. Neo-AEGIS (neoadjuvant trial in adenocarcinoma of the esophagus and esophago-gastric junction international study): preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (modified MAGIC or FLOT protocol). (NCT01726452). *J Clin Oncol*. 2021;39(suppl 15; abstr 4004). doi: [10.1200/JCO.2021.39.15_suppl.4004](#).
- [8] Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. *Br J Anaesth*. 2007;98(4):420–428. doi: [10.1093/bja/aem036](#).
- [9] Farr KP, Kallehauge JF, Møller DS, et al. Inclusion of functional information from perfusion SPECT improves predictive value of dose-volume parameters in lung toxicity outcome after radiotherapy for non-small cell lung cancer: a prospective study. *Radiother Oncol*. 2015;117(1):9–16. doi: [10.1016/j.radonc.2015.08.005](#).
- [10] Hoffmann L, Mortensen H, Shamshad M, et al. Treatment planning comparison in the PROTECT-trial randomising proton versus photon beam therapy in oesophageal cancer: results from eight European centres. *Radiother Oncol*. 2022;172:32–41. doi: [10.1016/j.radonc.2022.04.029](#).
- [11] Chang DS, Lasley FD, Das IJ, et al. Normal tissue radiation responses. In: Chang DS, Lasley FD, Das IJ, et al., editors. *Basic radiotherapy physics and biology*. Cham: Springer International Publishing; 2014. p. 265–275.
- [12] Ding K, Cao K, Fuld MK, et al. Comparison of image registration based measures of regional lung ventilation from dynamic spiral CT with Xe-CT. *Med Phys*. 2012;39(8):5084–5098. doi: [10.1118/1.4736808](#).
- [13] Nyeng TB, Møller DS, Farr K, et al. A comparison of two methods for segmentation of functional volumes in radiotherapy planning of lung cancer patients. *Acta Oncol*. 2021;60(3):353–360. doi: [10.1080/0284186X.2021.1877811](#).
- [14] Vinogradskiy Y, Castillo R, Castillo E, et al. Results of a multi-institutional phase 2 clinical trial for 4DCT-ventilation functional avoidance thoracic radiation therapy. *Int J Radiat Oncol Biol Phys*. 2022;112(4):986–995. doi: [10.1016/j.ijrobp.2021.10.147](#).
- [15] Zhou PX, Wang RH, Yu H, et al. Different functional lung-sparing strategies and radiotherapy techniques for patients with esophageal cancer. *Front Oncol*. 2022;12:898141. doi: [10.3389/fonc.2022.898141](#).
- [16] Zhou P, Wang R, Yu H, et al. 4DCT ventilation function image-based functional lung protection for esophageal cancer radiotherapy. *Strahlenther Onkol*. 2023;199(5):445–455. doi: [10.1007/s00066-022-02012-2](#).
- [17] Morgan E, Soerjomataram I, Rumgay H, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates From GLOBOCAN 2020. *Gastroenterology*. 2022;163(3):649–658.e2. doi: [10.1053/j.gastro.2022.05.054](#).
- [18] Goense L, Meziani J, Bülbül M, et al. Pulmonary diffusion capacity predicts major complications after esophagectomy for patients with esophageal cancer. *Dis Esophagus*. 2019;32:1–7.
- [19] Miller R, Castillo R, Castillo E, et al. Characterizing pulmonary function test changes for patients with lung cancer treated on a 2-Institution, 4-dimensional computed tomography-ventilation functional avoidance prospective clinical trial. *Adv Radiat Oncol*. 2023;8(2):101133. doi: [10.1016/j.adro.2022.101133](#).
- [20] Brennan D, Schubert L, Diot Q, et al. Clinical validation of 4DCT-ventilation with pulmonary function test data. *Int J Radiat Oncol Biol Phys*. 2015;92(2):423–429. doi: [10.1016/j.ijrobp.2015.01.019](#).
- [21] Thomas M, Mortensen HR, Hoffmann L, et al. Proposal for the delineation of neoadjuvant target volumes in oesophageal cancer. *Radiother Oncol*. 2021;156:102–112. doi: [10.1016/j.radonc.2020.11.032](#).
- [22] McMillian N, Lenora Pluchino MA, Ajani JA, et al. NCCN guidelines version 2.2023 esophageal and esophagogastric junction cancers continue NCCN. *J Natl Compr Canc Netw*. 2023;21(4):393–422. doi: [10.6004/jnccn.2023.0019](#).
- [23] Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258(1):1–7. doi: [10.1097/SLA.0b013e318296c732](#).
- [24] Low DE, Alderson D, Ceconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: esophagectomy complications consensus group (ECCG). *Ann Surg*. 2015;262(2):286–294. doi: [10.1097/SLA.0000000000001098](#).
- [25] Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol*. 2001;54(4):343–349. doi: [10.1016/s0895-4356\(00\)00314-0](#).
- [26] IBM Corp. IBM SPSS Statistics for Windows, Version 28.0. 2021.
- [27] Clavien PA, Barkun J, De Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250(2):187–196. doi: [10.1097/SLA.0b013e3181b13ca2](#).
- [28] Wilke TJ, Bhirud AR, Lin C. A review of the impact of preoperative chemoradiotherapy on outcome and postoperative complications in esophageal cancer patients. *Am J Clin Oncol*. 2015;38(4):415–421. doi: [10.1097/COC.0000000000000021](#).
- [29] Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. *Int J Radiat Oncol Biol Phys*. 2003;57(5):1317–1322. doi: [10.1016/s0360-3016\(03\)01373-7](#).
- [30] Briere TM, Krafft S, Liao Z, et al. Lung size and the risk of radiation pneumonitis. *Int J Radiat Oncol Biol Phys*. 2016;94(2):377–384. doi: [10.1016/j.ijrobp.2015.10.002](#).
- [31] Tatsuno S, Doi H, Okada W, et al. Risk factors for radiation pneumonitis after rotating gantry intensity-modulated radiation therapy for lung cancer. *Sci Rep*. 2022;12(1):590. doi: [10.1038/s41598-021-04601-0](#).
- [32] Niezink AGH, de Jong RA, Muijs CT, et al. Pulmonary function changes after radiotherapy for lung or esophageal cancer: a systematic review focusing on dose-volume parameters. *Oncologist*. 2017;22(10):1257–1264. doi: [10.1634/theoncologist.2016-0324](#).
- [33] Belzer RB, Lewis RJ. The practical significance of measurement error in pulmonary function testing conducted in research settings. *Risk Anal*. 2019;39(10):2316–2328. doi: [10.1111/risa.13315](#).
- [34] Chen X, Du M, Tang H, et al. Comparison of pulmonary function changes between patients receiving neoadjuvant chemotherapy and chemoradiotherapy prior to minimally invasive esophagectomy: a randomized and controlled trial. *Langenbecks Arch Surg*. 2022;407(7):2673–2680. doi: [10.1007/s00423-022-02646-x](#).
- [35] Niezink AGH, Jong R D, Muijs CT, et al. Pulmonary function changes after radiotherapy for lung or esophageal cancer: a systematic

- review focusing on dose-volume parameters. *Oncologist*. 2017; 22(10):1257–1264. doi: [10.1634/theoncologist.2016-0324](https://doi.org/10.1634/theoncologist.2016-0324).
- [36] Agostoni P, Bussotti M, Cattadori G, et al. Gas diffusion and alveolar-capillary unit in chronic heart failure. *Eur Heart J*. 2006; 27(21):2538–2543. doi: [10.1093/eurheartj/ehl302](https://doi.org/10.1093/eurheartj/ehl302).
- [37] Bucknell NW, Hardcastle N, Bressel M, et al. Functional lung imaging in radiation therapy for lung cancer: a systematic review and meta-analysis. *Radiother Oncol*. 2018;129(2):196–208. doi: [10.1016/j.radonc.2018.07.014](https://doi.org/10.1016/j.radonc.2018.07.014).
- [38] Du K, Bayouth JE, Cao K, et al. Reproducibility of registration-based measures of lung tissue expansion. *Med Phys*. 2012;39(3): 1595–1608. doi: [10.1118/1.3685589](https://doi.org/10.1118/1.3685589).
- [39] Giuranno L, Ient J, De Ruyscher D, et al. Radiation-induced lung injury (RILI). *Front Oncol*. 2019;9:877. doi: [10.3389/fonc.2019.00877](https://doi.org/10.3389/fonc.2019.00877).
- [40] Nakajima Y, Kadoya N, Kimura T, et al. Variations between dose-ventilation and dose-perfusion metrics in radiation therapy planning for lung cancer. *Adv Radiat Oncol*. 2020;5(3):459–465. doi: [10.1016/j.adro.2020.03.002](https://doi.org/10.1016/j.adro.2020.03.002).