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Contralateral esophageal sparing technique in definitive radiotherapy for non-small cell lung cancer: dosimetric parameters and normal tissue complication probability modeling

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ABSTRACT

Background: The purpose of this study was to assess the benefit of the contralateral esophageal sparing technique (CEST) in definitive radiotherapy of non–small cell lung cancer (NSCLC).

Materials and methods: We retrospectively reviewed radiation plans for 13 patients who underwent definitive chemoradiation for locally advanced NSCLC. Alternative plans were prepared with the use of CEST, with an additional margin of 5 mm from planning treatment volume (PTV). Normal tissue complication probability (NTCP) analyses for the esophagus and tumor control probability (TCP) for the PTV were performed for original and CEST plans using the equivalent uniform dose (EUD)-based mathematical model.

Results: In all cases, the CEST plan allowed for the reduction of esophageal dose, with a mean of 3.8 Gy (range, 0.7 to 8.7 Gy). The mean reductions of V40 and V60 to the esophagus were 6.4 Gy (range, 2.1 to 17.2 Gy) and 1.9 Gy (range, 3.4 to 10.0 Gy), respectively. There was no substantial decrease in the maximal dose to the esophagus. Reduction of NTCP was achieved for all patients (range, 5–73%), and TCP was not affected (–1.8 to +6.7%).

Conclusions: The application of CEST in definitive radiotherapy of locally advanced NSCLC allows for reducing selected dosimetric parameters to the esophagus without compromising TCP.

Key words: lung cancer; chemoradiation; esophageal sparing; dosimetric parameters; TCP; NTCP

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Introduction

The objective of radiotherapy is to achieve maximal tumor control probability (TCP) with minimal normal tissue complication probability (NTCP). The relation between TCP and NTCP constitutes a therapeutic window. Higher doses, higher radiation volumes, and the addition of systemic treatments result in increases in both values [1].

Several randomized clinical trials in locally advanced non–small cell lung cancer (NSCLC) have demonstrated that concurrent chemotherapy and radiotherapy result in better outcomes than radiotherapy alone or sequential use of both modal-

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ities [2–6], but at the cost of a higher incidence of acute esophagitis (4% *vs.* 18%) [4]. In the Radiation Therapy Oncology Group (RTOG) 0617 studies, the incidence of grade 3 esophagitis with concurrent chemoradiation in the standard dose arm was substantially lower (7%) than previously described, likely because of recent technical improvements in radiotherapy [7]. However, esophagitis remains an essential issue because resulting radiotherapy breaks may negatively affect long-term survival [8], and subsequent esophageal strictures decrease quality of life [9].

One of the approaches to decreasing esophageal toxicity is the contralateral esophageal sparing technique (CEST) in which the esophageal wall contralateral to gross disease is considered an avoidance structure [10]. The purpose of this modeling study was to explore whether this approach affects dosimetric parameters and esophageal NTCP in NSCLC patients administered definitive chemoradiation.

Materials and methods

We retrospectively reviewed radiation plans for patients with locally advanced NSCLC who underwent definitive chemoradiation. Radiotherapy plans were designed using four-dimensional (4D) computed tomography (CT) or breath-hold CT. For 4D-CT, the internal target volume (ITV) was defined as the gross tumor volume (GTV) plus the internal margin for respiratory tumor motion across the 10 phases of the breathing cycle. For the breath-hold technique, only GTV was contoured. The original clinical target volume was based on the automatic isotropic 5 mm margin around the ITV or GTV. The organs at risk (OARs) were defined according to the RTOG atlas and included the right and left lungs, combined lung volumes, spinal canal, entire esophagus, heart and, in selected cases, brachial plexus. Original plans were designed using the subvolume "esophagus — PTV". In the CEST plans, the contralateral esophagus (CE) was contoured as a separate avoidance structure 5 mm from the PTV edge, allowing for an additional margin to achieve steep dose fall-off across sections of the esophagus. Superior and inferior borders of CE were 2 cm around the PTV (Fig. 1). There was no lower limit of the CE size.

The prescribed dose was 60–66 Gy in 30–33 fractions delivered with 6 MV photons and the intensity-modulated radiation therapy (IMRT) technique. The alternative CEST plans were prepared without compromising target coverage and respecting dose constraints to OARs. Efforts were made to minimize the dose to CE. CEST plans were prepared using the same physical parameters — that is, the same radiation technique, the same number of beams, the same energy, and the same AAA 13.026 calculation model. For all patients, original and CEST plans were compared according to prescribed dosimetric parameters. The D_{mean}, V40, V60, and maximal dose (D_{max}) to the esophagus, as well as the V95, V98, V107, and D_{max} for PTV, were extracted from the histograms prepared in the treatment planning system (Eclipse, Aria 13.0, Varian Medical Systems). The NTCP analyses for the esophagus and TCP for the PTV were performed for original and CEST plans using an equivalent uniform dose (EUD)-based mathematical model provided by MATLAB modules [11]. This model can be used for both tumors and normal tissues according to the Niemierko formula [12, 13]:

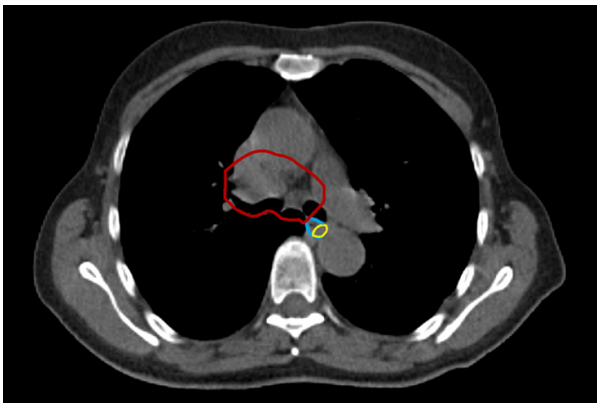

Figure 1. Example of contralateral esophagus delineation. Structures displayed are: planning treatment volume (red), esophagus (blue), and contralateral esophagus (yellow)

$$EUD = \left(\sum_{i=1}(v_i D_i^a)\right)^{\frac{1}{a}}$$

In this formula, {vi, Di} are bins of a histogram and a is a tissue-specific parameter. This parameter is negative for tumors and positive for normal structures. Parameter **i** is unitless and describes the **i**-th partial volume receiving the dose D_i in Gray (Gy). The choice of parameter **a** determines the behavior of the EUD-based model. The EUD-based NTCP was calculated using the logistic function [13]:

Table 1. Radiobiological parameters used in modeling of normal tissue control probability (NTCP) and tumor control probability (TCP)

	NTCP	TCP
Parameter a	19	–12
Parameter γ50	4	2
TD_{50} (Gy)/TCD_{50}(Gy)	68	60
α/β (Gy)	3	10

NTCP — normal tissue complication probability; TCP — tumor control probability

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma 50}}$$

The tolerance dose 50 (TD_{50}) is the 50% complication rate at a specific time interval, and γ_{50} is the normalized dose response *gradient*. The γ50 expressed as %/% is the increment in response in percentage points for a 1% increase in dose, defined at the 50% response level. To calculate TCP, the EUD was substituted in the following equation:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma 50}}$$

The TCD_{50} is the dose to control 50% of the homogeneously irradiated tumor. Parameters for TCP and NTCP (Tab. 1) were selected based on the proposal of Emami et al. Esophageal toxicity in this report included severe complications such as critical stricture and perforation [14].

Results

We analyzed the treatment plans of 13 patients with locally advanced nonmetastatic NSCLC (12 primary tumors and 1 mediastinal relapse) and gross tumor within 1 cm of the esophagus, who underwent definitive sequential or concurrent chemoradiation (Tab. 2). The CEST planning showed no deterioration in parameters for PTV (Tab. 3). The mean esophageal dose with CEST was lower in all patients, with a mean reduction of 3.8 Gy (range, 0.7 to 8.7 Gy). The mean reduction of V40 and V60 to the esophagus was 6.4 Gy (range, 2.1 to 17.2 Gy) and 1.9 Gy (range, –3,4 to +10.0 Gy), respectively (Fig. 2). However, in no case was substantial reduction of the maximal dose to the esophagus achieved (Tab. 4). The delta parameter, defined as the percentage differ-

Table 2. Patient characteristics

Patient	Histology	cTNM	Stage	Type of chemoradiation	Chemotherapy regimen	Total radiation dose [Gy] (dose levels)
1	Squamous cell carcinoma	cT4N2	IIIB	Concurrent	2 × CP/EP	66
2	Adenocarcinoma	cT1N2	IIIA	Concurrent	2 × CP/EP	66
3	Adenocarcinoma	cT2N2	IIIA	Concurrent	2 × CP/EP	66/60
4	Adenocarcinoma	cT3N2	IIIA	Sequential	3 × CP/GEM	60
5	Squamous cell carcinoma	cT3N2	IIIA	Sequential	4 × CP/VB	66
6	Adenocarcinoma		Mediastinal relapse	Radiotherapy alone		60
7	Squamous cell carcinoma	cT3N1	IIIA	Concurrent	1 × CP/EP	66
8	Squamous cell carcinoma	cT3N2	IIIA	Concurrent	2 × CP/EP	60
9	Squamous cell carcinoma	cT2N2	IIIA	Concurrent	2 × CP/EP	66/54
10	Adenocarcinoma	cT3N2	IIIA	Sequential	3 × CP/GEM	66
11	Squamous cell carcinoma	cT4N2	IIIB	Sequential	4 × CP/VB	62
12	Adenocarcinoma	cT4N2	IIIB	Concurrent	2 × CP/PEM	60
13	NSCLC-NOS	cT4N2	IIIB	Concurrent	3 × CBDCA/PCL	60

CP — cisplatin; CBDCA —carboplatin, PEM, pemetrexed; VB — vinorelbine; EP — etoposide; GEM — gemcitabine; PCL — paclitaxel; NOS — not otherwise specified

Table 3. Dosimetric planning target volume (PTV) parameters for original and contralateral esophageal sparing technique (CEST) plans

Patient	Plan	PTV			
		V95 (%)	Δ (%)	D_{max} (%)	Δ (%)
1	Original	95.2	−0.1%	108.3	0.3%
	CEST	95.1		108.6	
2	Original	98.3	0.1%	105.7	0.0%
	CEST	98.5		105.7	
3	Original	79.8	0.7%	110.0	−0.9%
	CEST	80.3		109.0	
4	Original	98.7	−0.7%	107.3	2.5%
	CEST	98.0		110.0	
5	Original	98.6	−2.0%	106.9	2.0%
	CEST	96.7		109.0	
6	Original	99.6	0,0%	105.0	0.5%
	CEST	99.6		105.5	
7	Original	99.3	−0.8%	106.7	0.3%
	CEST	98.5		107.0	
8	Original	98.5	−0.2%	107.5	0.3%
	CEST	98.2		107.8	
9	Original	94.5	−0.5%	107.0	0.0%
	CEST	94.0		107.0	
10	Original	97.3	−0.3%	105.9	0.1%
	CEST	97.0		106.0	
11	Original	97.4	1.2%	106.3	−1.5%
	CEST	98.6		104.7	
12	Original	96.6	−1.1%	105.5	2.4%
	CEST	95.6		108.0	
13	Original	100.0	−0.2%	105.0	1.0%
	CEST	99.8		106.0	
	SD		0.8%		1.2 %

Δ — absolute percentage difference between values in CEST and the original plan; V95 — volume receiving the 95% prescribed dose; D_{max} — maximal dose; SD — standard deviation

ence between the maximum dose in the CEST and original plan, varied from −1.5% (reduction) to +2.5% (increase).

The differences in the mean heart dose, mean lung dose, and maximal spinal cord dose were negligible for all patients (Tab. 5). Figure 3 shows an example of the dose-volume histogram of original and CEST plans for a single patient. For the CEST plan, the mean heart dose and the mean lung dose were comparable with the original plans. The reduction of NTCP was reached in all patients (range, 5%–73%), and the TCP was not affected (−1.8% to +6.7%; Fig. 4 and 5).

Discussion

Acute esophagitis accompanying combined chemoradiotherapy for lung cancer remains a significant clinical problem. Pharmacologic prevention of esophagitis has proved unsuccessful [15]. Crucial elements of reducing the risk of esophagitis include the thorough definition of target volumes and dosimetric parameters and improvements in the planning technique and dose delivery.

In 1991, Emami et al. published normal tissue constraints for use in radiotherapy practice [14]. With a particular emphasis on partial volume ef-

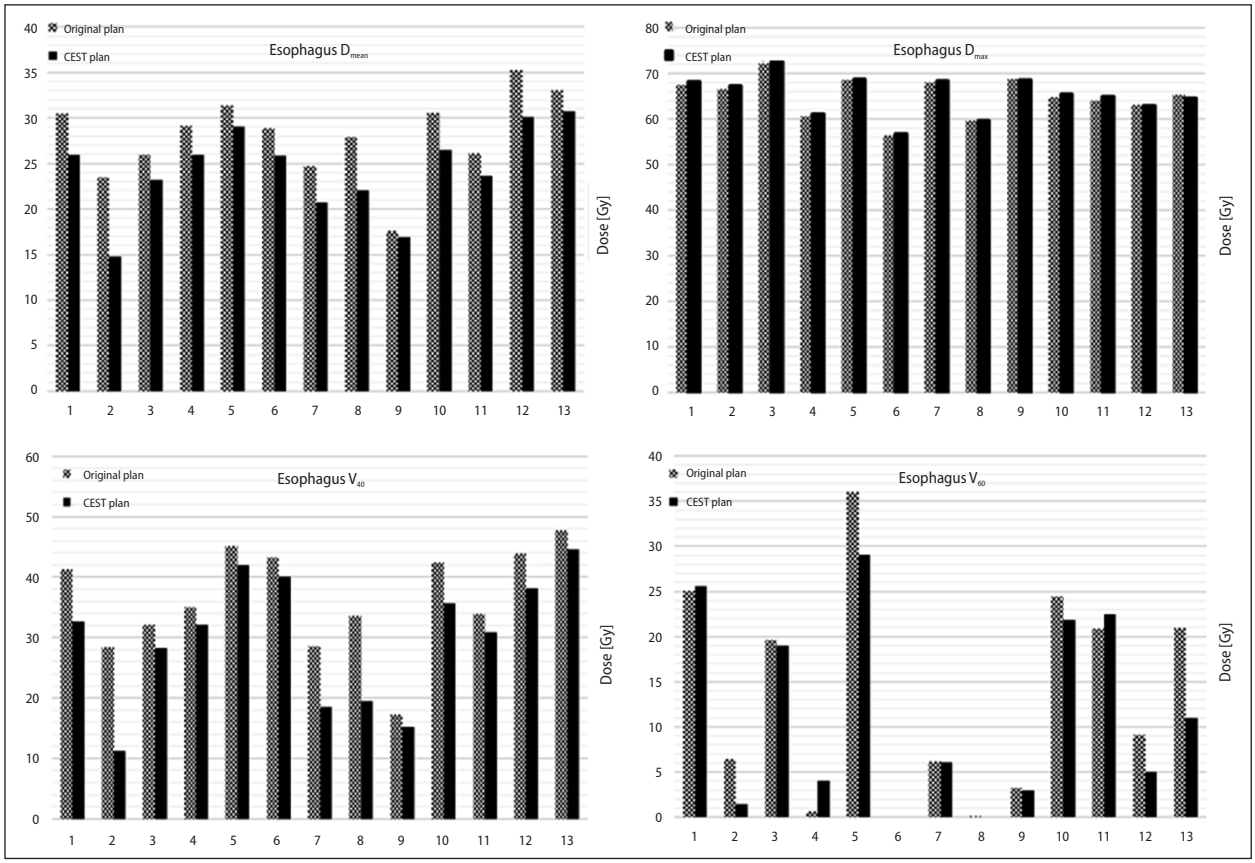

Figure 2. Comparison of esophageal parameters for original (ORG) and contralateral esophageal sparing technique (CEST) plans

Table 4. Dosimetric parameters for esophagus for original and contralateral esophageal sparing technique (CEST) plans

Patient	Plan	Esophagus			
		D_{mean}	Δ [Gy]	D_{max}	Δ [Gy]
1	Original	30.5	−4.55	67.5	0.64
	CEST	25.9		68.1	
2	Original	23.5	−8.65	66.5	0.68
	CEST	14.8		67.2	
3	Original	26.0	−2.82	72.2	0.23
	CEST	23.2		72.5	
4	Original	29.1	−3.21	60.4	0.54
	CEST	25.9		61	
5	Original	31.4	−2.34	68.6	0.14
	CEST	29.0		68.7	
6	Original	28.9	−3.02	56.3	0.28
	CEST	25.9		56.6	
7	Original	24.7	−4.06	68	0.43
	CEST	20.7		68.4	
8	Original	27.9	−5.88	59.6	0.05
	CEST	22.1		59.7	

Table 4. Dosimetric parameters for esophagus for original and contralateral esophageal sparing technique (CEST) plans

Patient	Plan	Esophagus			
		D_{mean}	Δ [Gy]	D_{max}	Δ [Gy]
9	Original	17.6	–0.66	68.6	–0.06
	CEST	17.0		68.6	
10	Original	30.6	–4.07	64.8	0.58
	CEST	26.5		65.3	
11	Original	26.1	–2.43	63.9	0.98
	CEST	23.7		64.9	
12	Original	35.2	–5.10	63	–0.15
	CEST	30.1		62.8	
13	Original	33.0	–2.26	65.3	–0.8
	CEST	30.7		64.5	
	SD		2.01		0.46

Δ — absolute percentage difference between values in CEST and the original plan; D_{mean} — mean dose; D_{max} — maximal dose; SD — standard deviation

Table 5. Dosimetric parameters for selected organs at risk for original and contralateral esophageal sparing technique (CEST) plans

Patient	Plan	Heart		Lungs		Spinal cord	
		D_{mean} [Gy]	Δ [Gy]	D_{mean}	Δ [Gy]	D_{max}	Δ [Gy]
1	Original	12.7	–0.59	20.1	0.27	45.4	1.33
	CEST	12.2		20.4		46.7	
2	Original	7.0	–0.41	18.3	–0.21	50.1	0.12
	CEST	6.5		18.1		50.2	
3	Original	3.8	0.04	17.4	–	48.4	0.70
	CEST	3.9		17.4		49.1	
4	Original	17.9	0.7	18.8	–0.14	44.7	0.42
	CEST	18.6		18.7		45.2	
5	Original	3.5	1.18	17.6	–0.13	47.7	0.07
	CEST	4.6		17.4		47.7	
6	Original	17.1	–0.09	16.7	–0.15	45.3	0.57
	CEST	17.0		16.6		45.8	
7	Original	3.2	0.33	15.6	0.05	47.1	1.55
	CEST	3.5		15.7		48.6	
8	Original	11.6	–0.09	19.1	–0.1	45	2.39
	CEST	11.5		19.0		47.4	
9	Original	6.3	–	14.7	–0.05	37.3	–0.20
	CEST	6.3		14.6		37.1	
10	Original	13.0	0.15	19.1	–0.07	48.1	0.23
	CEST	13.1		19.0		48.3	
11	Original	38.0	0.98	12.9	–0.14	45.6	–0.45
	CEST	39.0		12.8		45.2	
12	Original	13.8	1.20	18.9	–	40.5	2.40
	CEST	15.0		18.9		42.9	

→

Table 5. Dosimetric parameters for selected organs at risk for original and contralateral esophageal sparing technique (CEST) plans

Patient	Plan	Heart		Lungs		Spinal cord	
		D_{mean} [Gy]	Δ [Gy]	D_{mean}	Δ [Gy]	D_{max}	Δ [Gy]
13	Original	22.5	–0.63	19.3	0.20	14.2	0.60
	CEST	21.9		19.5		14.8	
	SD		0.63		0.14		0.91

Δ — the percentage difference between values in CEST and original plan; D_{mean} — mean dose; D_{max} — maximal dose; SD — standard deviation

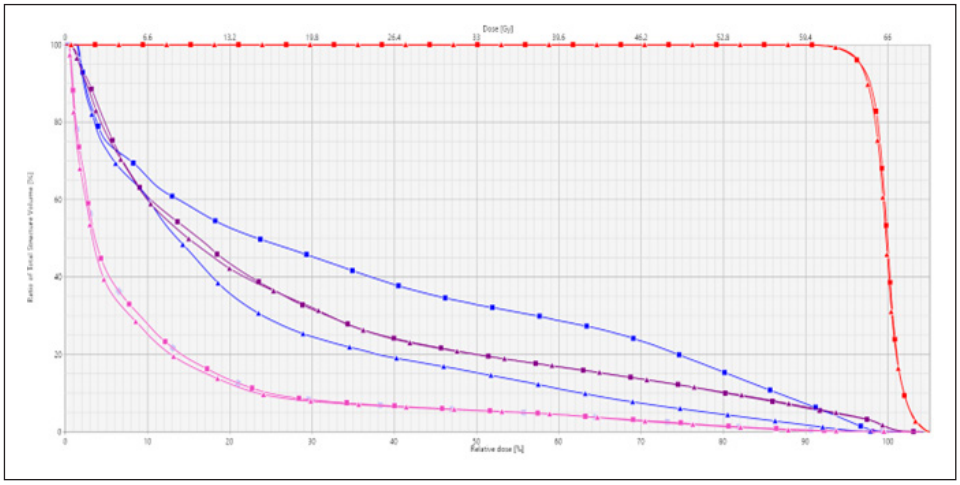

Figure 3. Example of dose-volume histogram for original (squares) and contralateral esophageal sparing technique (CEST) plan (triangle lines) for a single patient. Structures displayed are planning target volume (PTV) (red), esophagus (blue), lungs (violet), and heart (pink)

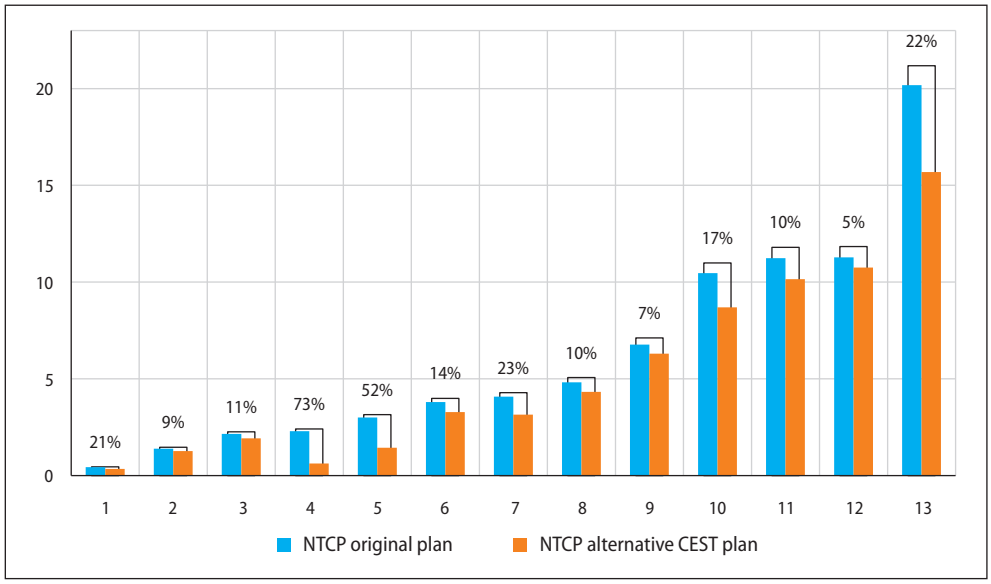

Figure 4. Normal tissue complication probability (NTCP) comparison for the original and contralateral esophageal sparing technique (CEST) plans

fects, tolerance doses were proposed for irradiation of one-third, two-thirds, or whole organs. Further studies involving large patient populations and using three-dimensional dosimetry was the basis of

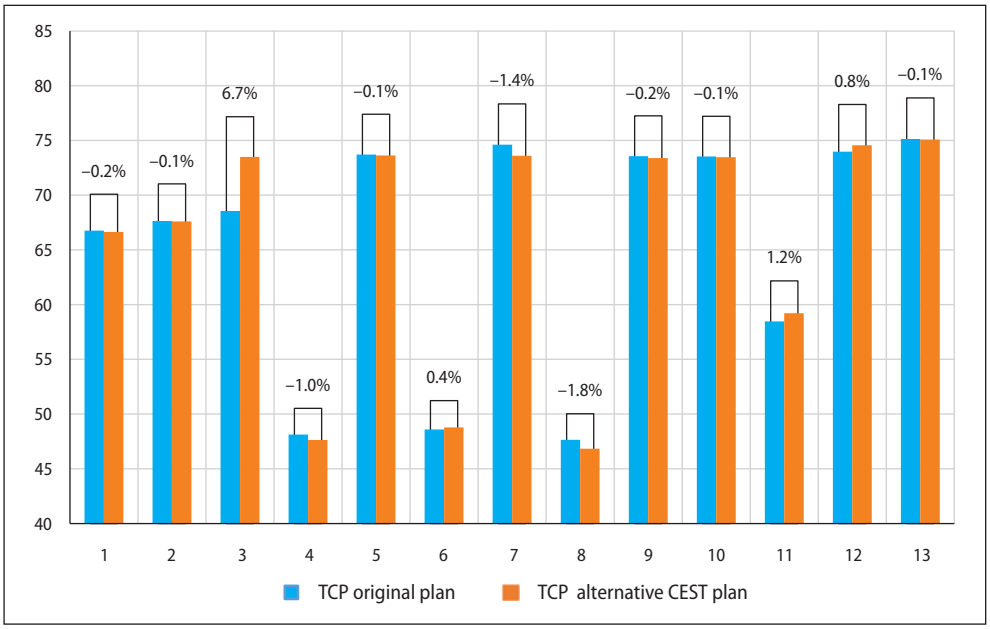

Figure 5. Tumor control probability (TCP) comparison for the original and contralateral esophageal sparing technique (CEST) plans

subsequent Quantitative Analysis of Normal Tissue Effects which defines volumetric parameters predictive for radiation esophagitis [16]. Recommended dosimetric constraints included V35, V50, and V70 for grade ≥ 2 esophagitis and the median dose (MD) for grade ≥ 3 toxicity. The MD has been widely adopted as a parameter; however, its predictive value for esophagitis in particular studies has been inconsistent [17–20].

The advent of IMRT allowed for the reduction of the esophagus dose while maintaining adequate target coverage. In addition, interfraction motion does not compromise the quality of treatment plans [21]. IMRT appears to be particularly beneficial in node-positive patients and in cases with target volumes located close to the esophagus. While meeting all normal-tissue constraints in node-positive patients, IMRT can deliver RT doses that are 25%–30% greater compared with three-dimensional radiotherapy [22].

The primary objective of the present study was to use NTCP and TCP modeling to evaluate whether CEST potentially allows for decreasing esophageal toxicity compared with conventional treatment.

A prospective CEST trial showed promising results, with no incidence of grade ≥ 3 esophagitis [10]. The authors suggested the following CE dose constraints: maximum dose 60 Gy (to 0.03 cc), V55 < 0.5 cc, and V45 < 2.5 cc, with acceptable deviations being 63 Gy, 3 cc, and 7.5 cc, respectively. In another phase 1 nonrandomized clinical trial including 27 participants, the CE-sparing technique was associated with reduced risk of esophagitis among patients treated uniformly with chemoradiation (to 70 Gy) [23]. There was no grade 3 or higher esophagitis despite the tumor being located within 1 cm of the esophagus. The 2-year progression-free survival and overall survival rates were 57% [95% confidence interval (CI): 33–75%] and 67% (95% CI: 45–82%), respectively.

In the 1980s, probabilistic radiobiology models introduced concepts of *serial* and *parallel* tissue organization and *functional subunits [24]*. According to this concept, the esophagus is an organ with functional subunits arranged in the longitudinal axis and high-dose irradiation of the entire cross-section of the esophagus can result in whole organ dysfunction. The CEST concept suggests that avoiding high radiation doses to the entire cross-section of the esophagus may lead to more efficient regeneration of the esophageal mucosa. It has been also speculated that preserving the contralateral esophageal wall converts this organ from a serial to parallel one [23].

In our study, there was no substantial reduction of the maximal esophageal dose. Evaluation of this aspect revealed that D max reduction would affect parameters of the PTV coverage with prescribed

dose, thus being unacceptable. On the other hand, the increase in the maximal dose was elevating the NTCP, regardless of the obtained improvement in volumetric parameters such as mean dose, V40, V60. It can be explained by the nature of the assumptions used in the modeling formulas strictly related to paradigm of esophagus as a serial organ [10, 25].

The limitations of our study are a relatively small number of radiation treatment plans, the shortcomings of the NTCP modeling and its assumptions, and lack of testing of internal and external model validity. Nevertheless, our results show that CEST, with its additional margin (5 mm from PTV), allows for the reduction of selected dosimetric parameters to the esophagus in radiotherapy of NSCLC. The usefulness of CEST in reducing esophageal toxicity should be assessed in prospective clinical trials.

Conflict of interests

None declared

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Data sharing statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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