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Analyzing the post-contrast attenuation of the esophageal wall on routine contrast-enhanced MDCT examination can improve the diagnostic accuracy in response evaluation of the squamous cell esophageal carcinoma to neoadjuvant chemoradiotherapy in comparison with the esophageal wall thickness

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Abstract

Purpose To evaluate the accuracy of the multidetector computed tomography (MDCT) in the response evaluation of the esophageal squamous cell carcinoma (ESCC) to neoadjuvant chemoradiotherapy (nCRT) by analyzing the thickness and post-contrast attenuation of the esophageal wall after the nCRT.

Methods Contrast-enhanced (CE)-MDCT examinations in portal venous phase of one hundred patients with locally advanced ESCC who received nCRT and underwent esophageal resection and histopathology assessment of tumor regression grade (TRG) were retrospectively analyzed by measuring the maximal thickness and mean density of the esophageal wall in the segment involved by tumor and visually searching for hyperdense foci within it. Diagnostic performance was evaluated using the ROC analysis.

Results Average attenuation of the esophageal wall had stronger diagnostic performance for predicting pathologic complete regression (pCR) (AUC = 0.994; $p < 0.001$) in relation to maximal esophageal wall thickness (AUC = 0.731; $p < 0.001$). Maximal esophageal wall thickness ≤ 9 mm and average attenuation of the esophageal wall ≤ 64 HU predicted pCR with the sensitivity, specificity, and overall accuracy of 62.5%, 77.9%, and 73%, and 96.9%, 98.5%, and 98%, respectively. Combination of both cutoff values enabled correct assessment of pCR with the 100% accuracy. Visual detection of the hyperdense focus within the esophageal wall predicted pCR with the sensitivity, specificity, and overall accuracy values of 100%, 94.1%, and 96%, respectively.

Conclusion Visual analysis and measurement of post-contrast attenuation of the esophageal wall after the nCRT can improve diagnostic accuracy of MDCT in the response evaluation of the ESCC to nCRT in comparison with measuring the esophageal wall thickness.

Keywords Esophageal neoplasms · Multidetector computed tomography · Neoadjuvant therapy · Treatment outcome

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Abbreviations

nCRT	Neoadjuvant chemoradiotherapy
TRG	Tumor regression grade
pCR	Pathologic complete regression
pPR	Pathologic partial regression
CR	Complete response
PR	Partial response
EC	Esophageal carcinoma
ESCC	Esophageal squamous cell carcinoma
MDCT	Multidetector computed tomography
CE-MDCT	Contrast-enhanced MDCT
ROC	Receiving operation characteristics
AUC	Area under the curve
CI	Confidence interval
Pre-nCRT MDCT examination	A MDCT examination before the nCRT
Post-nCRT MDCT examination	A MDCT examination after the nCRT
PPV	Positive predictive value
NPV	Negative predictive value

Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is widely accepted multimodal treatment option for the advanced, loco regionally limited esophageal cancer (EC) [1–3]. The objectives of this therapeutic approach are downsizing and down staging the tumor in order to enable radical surgical resection [1]. After the nCRT of the EC, clinical response rate was 31–86%, and complete histopathological regression was reported in 16–56% of cases [3–7]. Multivariate analysis showed that complete histopathological regression and R0 status after esophageal resection were two most important prognostic factors for disease-free survival and overall survival of patients with the EC after the multimodal therapy [4, 5]. On the other hand, it was demonstrated that esophageal resection had been followed by severe postoperative morbidity and mortality [3, 8]. Therefore, some studies suggest that surgery after the nCRT may be postponed or even avoided, and CRT could be definitive treatment modality in patients who generally responded well to nCRT [4, 9–12]. In any case, accurate assessment of the EC response to nCRT would certainly allow better selection of patients for surgery or follow-up, which could improve the overall success of treatment.

Although computed tomography (CT) has been the most commonly used in the initial staging and reevaluation of the EC after the nCRT in everyday clinical practice, only few papers dealt with the analysis of the CT diagnostic accuracy for response evaluation of the EC to nCRT [13–17]. Spiral CT showed suboptimal diagnostic accuracy for the assessment of the EC response to nCRT, and multidetector computed tomography (MDCT) did not improve diagnostic accuracy for EC restaging after the nCRT [17]. However, in all enumerated studies, only morphologic criteria based on the thickness of the esophageal wall were considered for response evaluation [15–17]. In their review article on CT imaging with pathologic correlation after the neoadjuvant therapy of the EC, Ulla and coauthors documented that quantitating the density of the esophageal wall could be useful for predicting the histopathological response, but this was not further investigated on larger patient series [18]. Accordingly, we hypothesized that analyzing the post-contrast attenuation of the esophageal wall could improve the accuracy of MDCT in the response evaluation of the EC to nCRT. Therefore, the purpose of our study was to evaluate the accuracy of MDCT in the response evaluation of the EC to nCRT by visual and quantitative analyses of the esophageal wall attenuation in addition to measuring its thickness.

Materials and methods

Patients

This retrospective study was approved by the institutional review board, and individual informed consent was waived. Contrast-enhanced (CE)-MDCT examinations of one hundred patients with the locally advanced esophageal squamous cell carcinoma (ESCC), who received the nCRT and then underwent esophageal resection in our hospital from January 2008 to December 2017, were retrospectively analyzed.

Inclusion criteria were (1) biopsy-proven ESCC, (2) receiving the nCRT, (3) performing the CE-MDCT examinations in the portal venous phase before and after the nCRT, and (4) performing surgical esophagectomy with further pathologic analysis. Exclusion criteria were (1) no available CE-MDCT examination before the nCRT, (2) inappropriate post-contrast phase of MDCT (arterial instead of portal venous), (3) intravenous contrast administration prior to portal venous phase due to CT perfusion study, and (4) more than 4 weeks' time interval between the post-nCRT MDCT examination and operation (Fig. 1). The imaging, clinical, and pathologic databases were used for the inclusion and exclusion of patients, and are shown in Fig. 1.

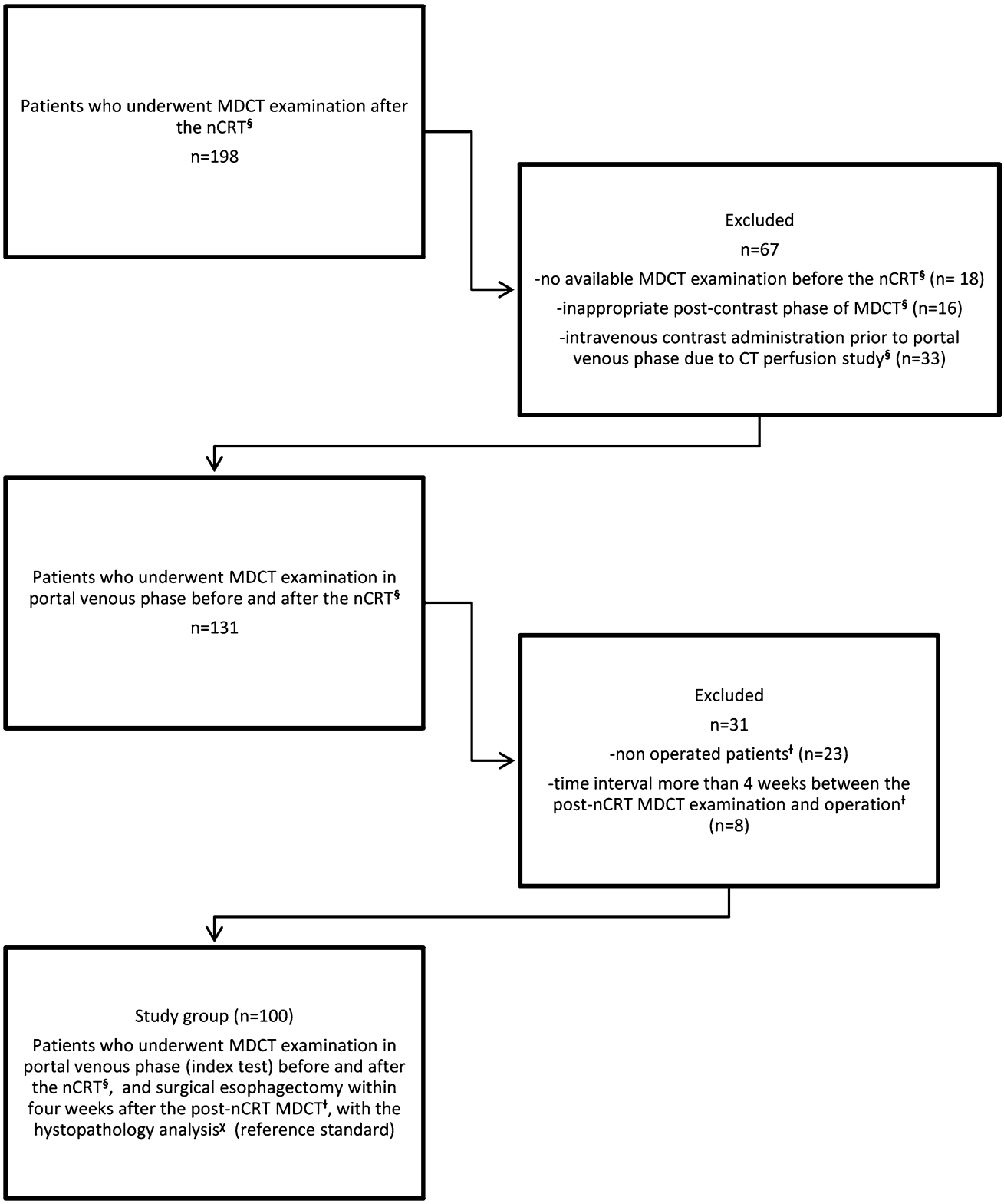

Fig. 1 Inclusion and exclusion criteria and flow of patients (§ from imaging database, † from clinical database, and χ from pathologic database)

nCRT regimen

Neoadjuvant chemoradiation therapy consisted of radiation therapy with a total dose of 45–50.4 Gy, which was administered concomitantly with the chemotherapy, comprising the Cisplatinum, 5-Fluorouracil, and Leucovorine (CIS/5-FU/LV).

MDCT examination

CT examinations before and after the nCRT were performed using the 64-multidetector row scanners (64-MDCT LightSpeed VCT, GE or 64-MDCT Aquilion, Toshiba 64-MDCT). Neck, thoracic, and abdominal scanning was performed after the intravenous administration of 60–100 ml of nonionic iodinated contrast media (iopromid 370 mg/ml or iohexol 350 mg/ml of iodine, 1–1.5 ml of contrast/BMkg), which was injected using the automatic injector, at a flow rate of 3.5 ml/s followed by 30 ml of saline at the same flow rate, with a 55-s scan delay (in a portal venous phase).

Image analysis

CT examinations were analyzed by a single radiologist (corresponding author, with nineteen-year experience in thoracic-abdominal radiology), who was blinded to surgical and histopathology findings.

Maximal thickness and average post-contrast attenuation of the esophageal wall in the segment involved by neoplasm were simultaneously measured in the corresponding sections of the pre- and post-nCRT CE-MDCT examinations in the portal venous phase using the electronic caliper, and the areas of the esophageal neoplasm were manually delineated using free-hand ROIs in each of 5-mm-reconstructed-thickness-section images (Fig. 2a, b). Average density of the esophageal wall segment was calculated as sum of mean densities of all ROIs divided by total number of ROIs. In addition, a reading radiologist visually searched for any hyperdense focus within the esophageal wall (i.e., residual tumor suspected) in the 1-mm-reconstructed-axial sections, and measured its density and density of the surrounding esophageal wall separately using the round ROIs (Fig. 3a, b). Single criterion that we applied in determination of the hyperdense focus was the visually detectable focal hyperdense zone within the esophageal wall no matter of its size and attenuation (Figs. 3a and 4b, c). After the surgery, CT findings were repeatedly compared with the histopathological findings, relating to visual analysis of the presence and severity of hyperdense foci within the esophageal wall in each TRG group. Accordingly, a typical CT pattern of each TRG is presented.

In addition, after training in recognizing the hyperdense foci within the esophageal wall, CT examinations were again separately analyzed by two more readers with five-year and 3-year experiences in general and abdominal radiology (A J and D S, respectively) concerning their estimation of complete or partial response and TRG, and compared with the histopathological findings, first reader's estimation and between each other, in order to evaluate the interobserver agreement.

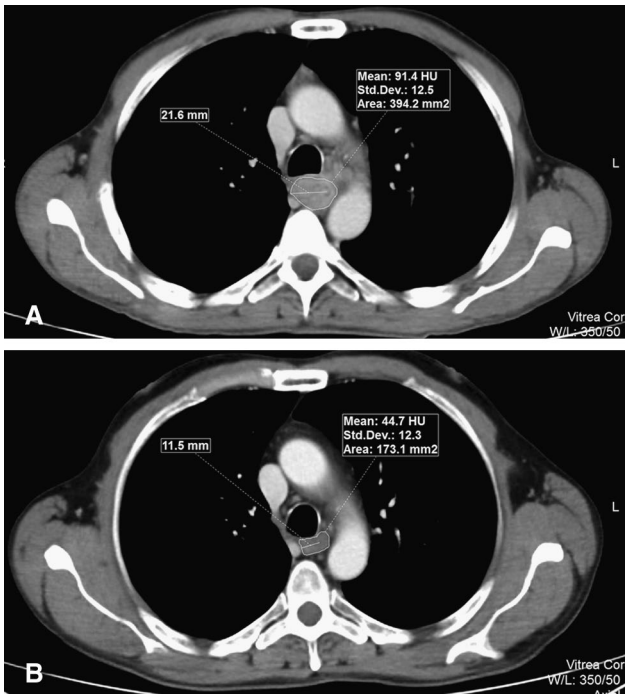

Fig. 2 **a**, **b** Measuring the maximal thickness and post-contrast density of the esophageal wall on corresponding 5-mm-reconstructed-thickness-section images of pre- (**a**), and post-nCRT MDCT examinations (**b**)

Surgical treatment and histopathological evaluation after the nCRT

Patients were operated within 1.5–14 months (median, 2 months) after the end of the nCRT regimen and maximally 4 weeks after the MDCT that was used for the analysis (median, 23 days; range 12–28 days). Subtotal transthoracic esophagectomy (62), total transthoracic esophagectomy (33), and subtotal transhiatal esophagectomy (5 pts) were performed, with transmediastinal "gastric-tube" (67 pts) or "whole-stomach" reconstruction (33 pts).

Histopathological analysis of the resected specimens included staging according to the TNM classification [19], and estimation of the tumor regression grade (TRG) according to the Mandard's criteria [5].

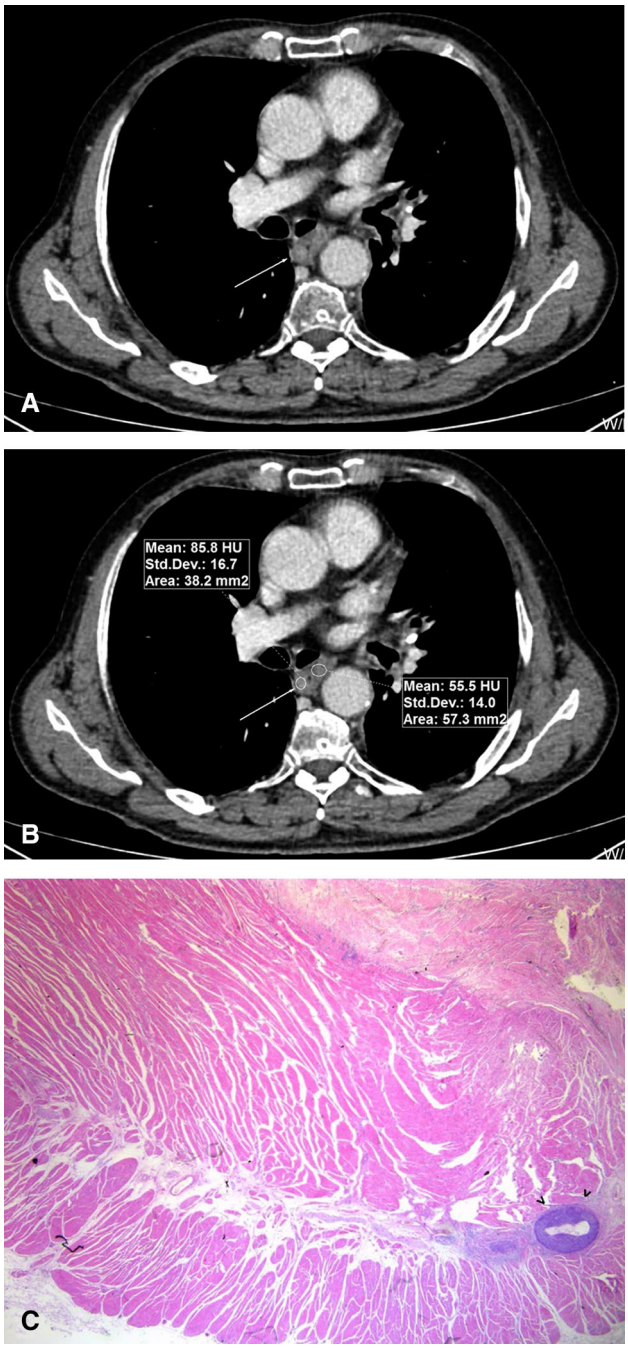

Fig. 3 **a**–**c** A 66-year old male patient with the carcinoma of middle thoracic esophagus, initially cT3 N1, post-nCRT pT2 N0. Hyperdense focus within the esophageal wall (arrow) (**a**). Measuring the post-contrast density of the hyperdense focus (85.8 HU) and surrounding esophageal wall (55.5 HU) (**b**). One focus of residual carcinoma (open arrowheads) was found in completely examined resection specimen- TRG 2 (**c**)

Statistical analysis

Wilcoxon's signed rank test was used to compare the thickness and density of the esophageal wall measured on MDCT at baseline and after the nCRT in each patient and for comparing the densities of the hyperdense foci and surrounding esophageal wall. Kruskal–Wallis's test (X^2) was used to compare the maximal thickness and average density of the esophageal wall among different TRG groups. For assessing the interobserver agreement in estimating the complete vs. partial responses and TRG, Kappa correlation coefficients (r_K) were calculated. Receiving operation characteristics (ROC) analysis was performed to estimate diagnostic performance of the maximal thickness and average density of the esophageal wall after the nCRT in predicting the complete pathologic regression (pCR), and cutoff values were determined following the results of ROC analysis using the Youden's index (maximal sum of sensitivity and specificity).

Results

The study group of 100 subjects included 84 male and 16 female patients (mean age, 61 years; range 23–74) who underwent MDCT examination in portal venous phase before and after the nCRT, and surgical esophagectomy within 4 weeks with further histopathological analysis.

Histopathology revealed TRG 1 in 32 patients, TRG 2 in 25, TRG 3 in 38, and TRG 4 in five patients. In three patients who achieved complete regression of the esophageal neoplasm (pT0), the metastatic regional lymph nodes were confirmed by histopathological examination (pN1 in one, and pN2 in two pts). Pathological T and N stages after the nCRT, in comparison with the corresponding clinical stages estimated from the initial MDCT examination, are presented in Table 1.

The characteristics of the esophageal tumor on presentation, which were estimated from the baseline MDCT examination, are summarized in Table 2.

The maximal thickness of the esophageal wall measured by post-nCRT MDCT (median 11 mm; range 5–19 mm) was significantly decreased in comparison with the baseline (median 17 mm; range 10–35 mm) ($Z = -8.445$, $p < 0.001$). Average post-contrast attenuation of the esophageal segment involved by tumor (median 75 HU; range 47–92 HU) was also significantly lowered after the nCRT in the whole study group (median 92 HU; range 67–122 HU) ($Z = -8.128$, $p < 0.001$).

The values of maximal thickness and post-contrast density of the esophageal wall in TRG 1–4 groups are presented in Table 3 and Fig. 5a, b.

ROC analysis revealed that average post-contrast density of the esophageal wall had stronger diagnostic performance in predicting pCR (AUC = 0.994; 95% CI 0.984–1.000; $p < 0.001$) than maximal esophageal wall thickness (AUC = 0.731; 95% CI 0.628–0.835; $p < 0.001$) (Fig. 6). Maximal esophageal wall thickness ≤ 9 mm

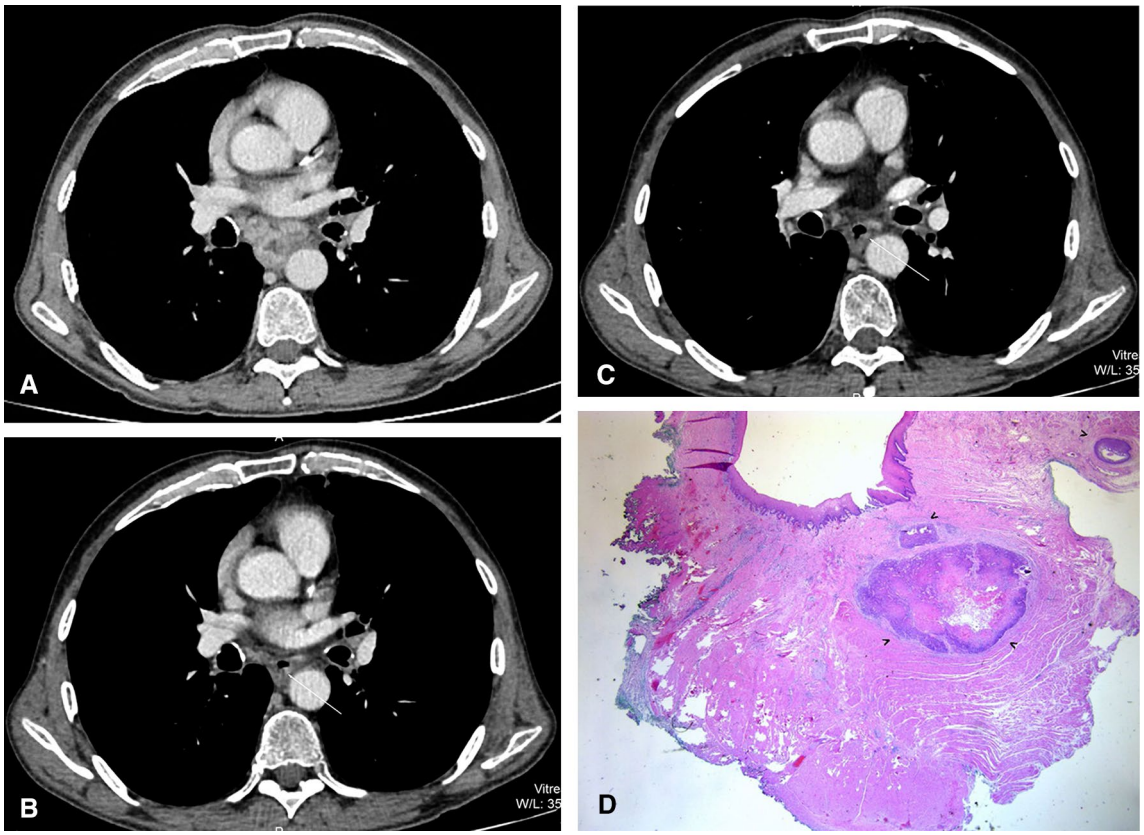

Fig. 4 **a**–**d** A 50-year-old male patient with the carcinoma of the middle thoracic esophagus, initially cT3N2, post-nCRT pT2N0. Pre-nCRT MDCT (**a**) and corresponding axial sections on the post-nCRT MDCT (**b**, **c**). Two small hyperdense foci within the esophageal wall (arrows) (**b**, **c**). Foci of residual carcinoma in the muscularis propria (open arrowheads) were found in the resection specimen but fibrosis was still predominant—TRG 3 (**d**)

Table 1 Pathological T (pT) and N stages (pN) after the nCRT, in comparison with the corresponding clinical stages (cT and cN) estimated from the initial MDCT examination

	Clinical stage initially (pre-nCRT MDCT)	Pathological stage (histopathology)
T		
T0	0	32
T1	0	3
T2	2	15
T3	85	50
T4a	10	0
T4b	3	0
N		
N0	25	60
N1	19	23
N2	42	16
N3	14	1

Table 2 Clinicopathological characteristics of esophageal carcinoma on baseline MDCT examination

	Number of patients	Median (Min–Max)
Location		
Upper	27	
Middle	53	
Lower	20	
Length		6 cm (3–13 cm)
Maximal A-P diameter		27 mm (15–45 mm)
Maximal L–L diameter		35 mm (20–64 mm)
Maximal esophageal wall thickness		17 mm (10–35 mm)
Volume		36 ml (16–110 ml)
Average post-contrast density		92 HU (67–122 HU)

predicted pCR with sensitivity of 62.5%, specificity of 77.9%, positive predictive value (PPV) of 57.1%, negative predictive value (NPV) of 81.5%, and overall accuracy of 73% (Table 4). Average post-contrast density of the esophageal wall ≤ 64 HU predicted complete regression with

Table 3 Maximal thickness and average post-contrast density values of the esophageal wall on post-nCRT MDCT in the TRG 1-4 groups

Post-nCRT MDCT examination	TRG 1 ($n=32$)	TRG 2 ($n=25$)	TRG 3 ($n=38$)	TRG 4 ($n=5$)	Difference	
					p	†X^2
Median (Min–Max)						
Maximal thickness (mm)	9 (5–15)	10 (7–14)	13 (7–19)	15 (12–17)	<0.001	23.724
Average density (HU)	56.5 (47–72)	73 (67–91)	80.5 (60–92)	81 (79–89)	<0.001	74.648

†Kruskal–Wallis's test

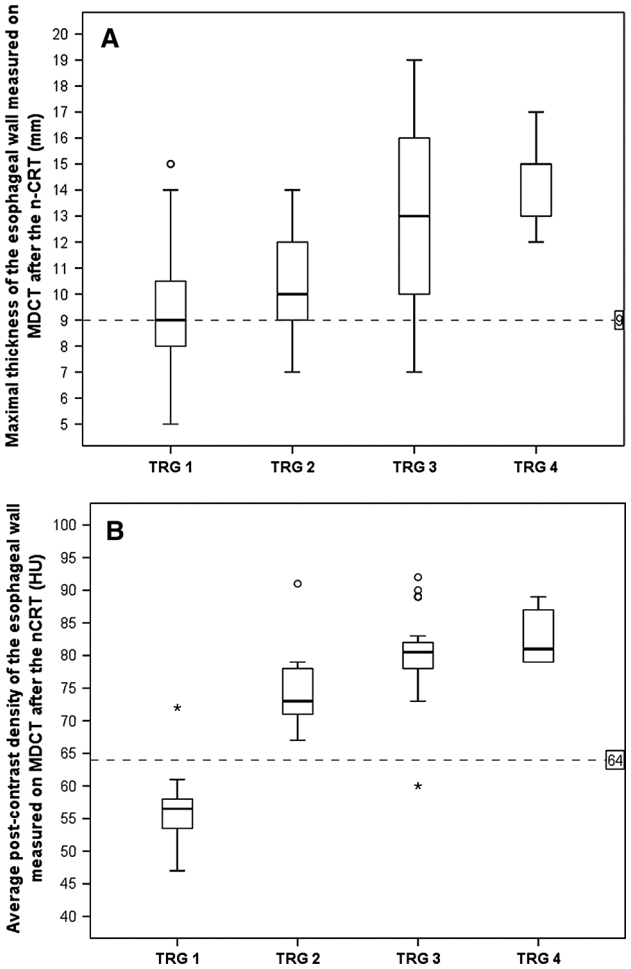

Fig. 5 **a**, **b** Box and whisker plots displaying values of the post-nCRT maximal thickness (**a**) and average post-contrast density (**b**) of the esophageal wall in TRG 1-4 groups. The lines within the boxes represent median values, the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively, and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. Dotted lines in the plots represent the cutoff values that distingiush the TRG 1 group, i.e., pCR from the groups, TRG 2–4, i.e., pPR

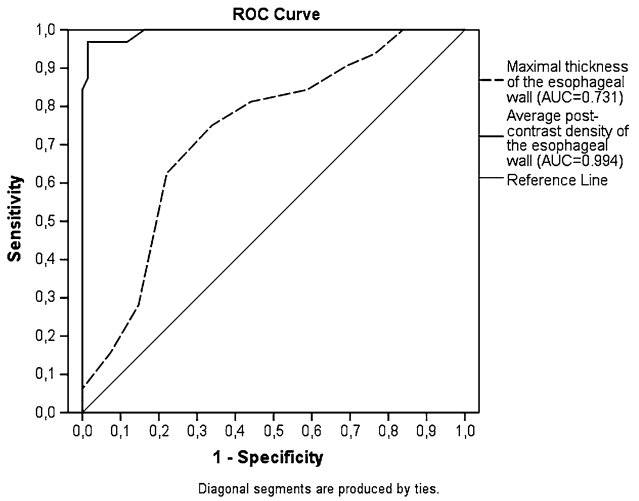

Fig. 6 Comparison of ROC curves presenting the diagnostic performance of the post-nCRT maximal thickness and average post-contrast density of the esophageal wall in the assessment of the TRG 1, i.e. pCR (AUC: area under the curve, mean value)

sensitivity of 96.9%, specificity of 98.5%, PPV of 96.9%, NPV of 98.5%, and overall accuracy of 98% (Table 4). Combined measures of maximal esophageal wall thickness ≤ 9 mm and average post-contrast density ≤ 64 HU correctly predicted pCR with the accuracy of 100% (Table 4).

The results of visual searching for the hyperdense foci within the esophageal wall after the nCRT are presented in Table 4. Hyperdense focus was not detected by first reading radiologist in four patients with the pPR, all TRG 2 on histopathology (false-positive estimations of CR) (Table 4). Mean post-contrast attenuation of the hyperdense foci within the esophageal wall (i.e., residual tumor suspected), which were visually detected (median 88 HU; range 73–120 HU) was significantly higher than the surrounding esophageal wall (median 55 HU; range 42–62 HU) ($Z=-8.128$, $p<0.001$). Post-contrast attenuation of the hyperdense foci within the esophageal wall after the nCRT did not differ significantly from the post-contrast attenuation of the esophageal neoplasm before the CRT in the same patient, which was measured on baseline ($Z=-1.366$, $p=0.172$).

In regard to histopathology, post-nCRT MDCT retrospective visual analysis of the esophageal wall revealed that uniformly and moderately thickened esophageal wall without visible hyperdense foci corresponded to TRG 1 (Fig. 7b, c); small hyperdense focus within moderately thickened

Table 4 Results of measuring the maximal esophageal wall thickness (≤9 mm), average post-contrast density (≤64HU), combination of these two cutoff values, and visual detection of hyperdense foci within the esophageal wall and diagnostic performance of MDCT in diagnosing complete regression (pCR) after the nCRT

	n (pCR)	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Maximal esophageal wall thickness ≤ 9 mm	32	20	53	15	12	62.5	77.9	57.1	81.5	73
Average esophageal wall density ≤ 64 HU		31	67	1	1	96.9	98.5	96.9	98.5	98
Maximal thickness ≤ 9 mm and average density ≤ 64 HU		32	68	0	0	100	100	100	100	100
Visual detection of hyper dense focus(es)		32	64	4	0	100	94.1	88.9	100	96

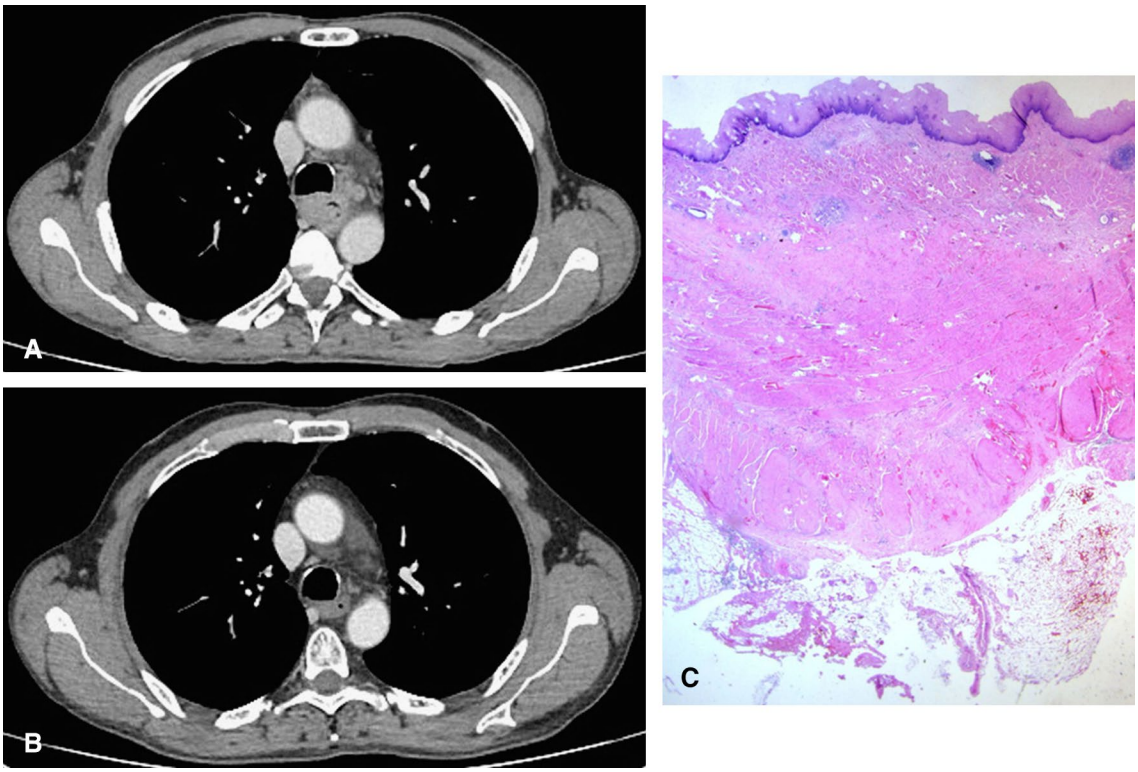

Fig. 7 **a**–**c** A 48-year old male patient with the carcinoma of middle thoracic esophagus, initially cT3N3, post-nCRT pT0N0. Pre-nCRT MDCT (**a**) and corresponding axial sections on the post-nCRT MDCT examination (**b**). Average post-contrast density of the esophageal wall in the segment that was involved by neoplasm on pre-nCRT MDCT was 95 HU, and 47 HU on post-nCRT MDCT. No residual tumor was found in completely sampled resection specimen- TRG 1 (pCR) (**c**)

esophageal wall to TRG 2 (Fig. 3a–c); few separate hyperdense foci within thickened esophageal wall to TRG 3 (Fig. 4b–d); and hyperdense mass within markedly thickened esophageal wall corresponded to TRG 4 (Fig. 8b, c).

Following the proposed classification, first reader correctly assessed TRG in 89%, second reader in 84%, and third reader in 81% of cases. Overall accuracy values in estimating the responses (CR vs. PR) of the first, second, and third reader were 96% (Table 4), 88%, and 87%, respectively. Interobserver agreement between the readers in detecting the hyperdense foci within the esophageal wall (i.e. estimating the response) was good (1st and 2nd reader, r_K=0.780; 1st and 3rd reader, r_K=0.756; and 2nd and 3rd reader, r_K=0.806). Moderate interobserver agreement was obtained in assessing the TRG (1st and 2nd reader, r_K=0.688; 1st and 3rd reader, r_K=0.620; and 2nd and 3rd reader, r_K=0.773).

Discussion

The analysis of the esophageal wall on MDCT examination in portal venous phase, which was routinely performed in patients with the ESCC after the nCRT due to response evaluation, showed that the maximal thickness and mean post-contrast attenuation of the esophageal wall in the segment involved by tumor were gradually increasing as the TRG

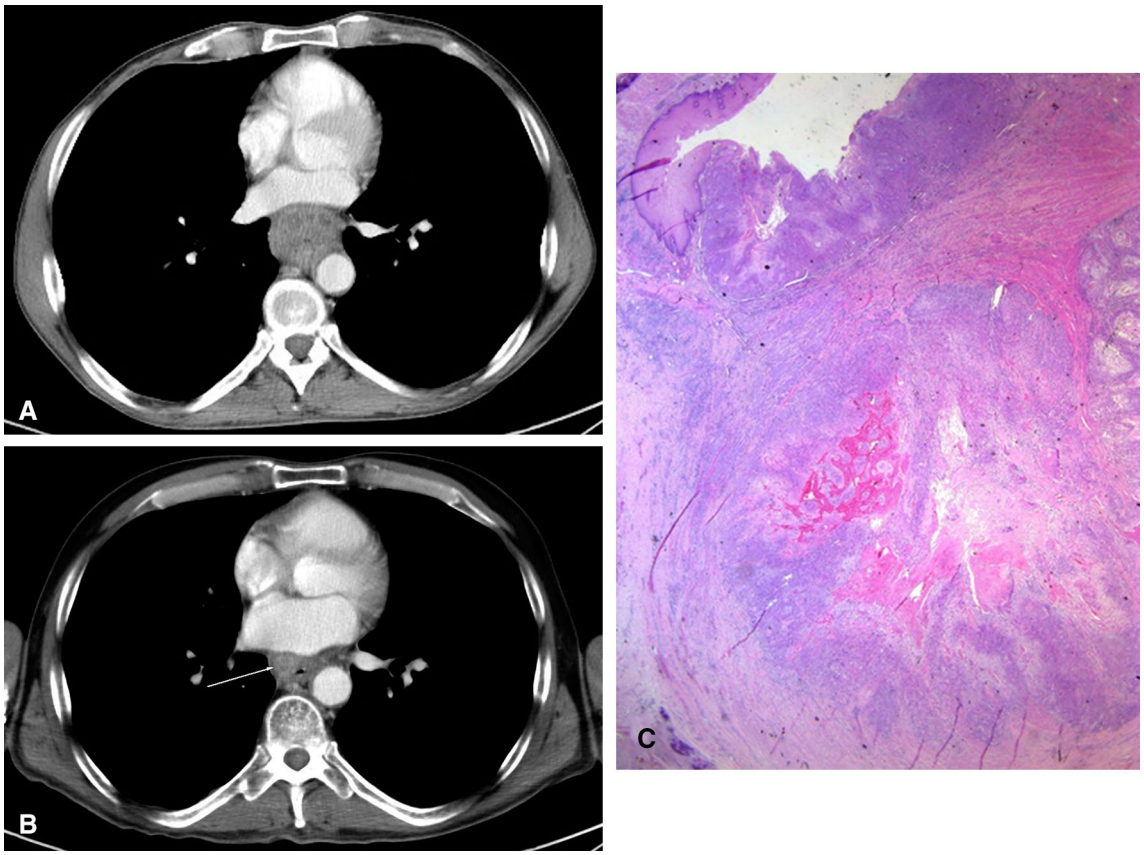

Fig. 8 **a**–**c** A 62-year-old male patient with the carcinoma of the mediodistal esophagus, initially cT4aN2, post-nCRT pT3N1. Pre-nCRT MDCT (**a**) and corresponding axial section on the post-nCRT MDCT: significant downsizing of neoplasm occurred but hyperdense mass remained within markedly thickened right esophageal wall (arrow) (**b**). Residual carcinoma in the esophageal wall was predominant in the resection specimen—TRG 4 (**c**)

grew, but the post-contrast attenuation predicted response more accurately than the thickness of the esophageal wall. Esophageal wall commonly remained thickened after the nCRT, but the hyperdense foci within the esophageal wall indicated the partial regression. Contrarily, moderately thickened esophageal wall of the uniformly low post-contrast attenuation indicated complete regression.

The complete regression of the ESCC in the esophageal wall (TRG 1, pT0) was confirmed by histopathological examination in 32% of patients in our study group, which is comparable to reported rates [4–7, 14–17]. All other patients manifested reduction of tumor volume, and tumor down staging was recorded in 60% of patients, which is in line with the results of the available studies [16, 17].

The maximal thickness of the esophageal wall measured by MDCT examination after the nCRT in the segment, initially involved by tumor, ranged from 5 to 19 mm in the whole study group, and from 5 to 15 mm in pCR group, on average 9 mm, which is comparable to the results of reported series [7, 13, 17, 20, 21]. Study of Li and colleagues revealed that post-CRT average maximal esophageal wall thickness in patients with the ESCC was significantly less in the pCR group (14.5 ± 2.1 mm) than in partial response group (16.2 ± 3.1 mm) [20]. Similarly, in the study of Swisher and coauthors, significant correlation of the esophageal wall thicknesses after the CRT and pCR was confirmed in patients with the ESCC and adenocarcinoma (median 13.3 mm in the pCR group vs. 15.3 mm in pPR group) [7]. In two studies on CT accuracy in restaging the EC after the nCRT, in which the maximal esophageal wall thickness less than 5 mm was considered T0, from 5 to 10 mm T1/T2, and higher than 10 mm T3 or T4, the majority of T0 cases was overstaged [16, 17]. In particular, the esophageal wall thickness less than 5 mm was measured in only two of 11 patients with T0 stage after the nCRT in the series of Koznecny et al., and in three out of 21 in the series of Jones et al. [16, 17], what is comparable with our results. Since normal thickness of the esophageal wall measured by cross-sectional imaging is generally considered less than 5 mm, these results clearly show that the esophageal wall thickening is a common sequel of the CRT, regardless of the tumor regression grade. However, gradual increase of the

esophageal wall thickness was observed from TRG 1 to TRG 4 group of patients. Significant difference was evidenced between TRG 1 and TRG 2 groups on one side and TRG 4 group on the other, while the esophageal wall thickness after the nCRT mostly varied in TRG 3 group.

Accurate estimation of the complete regression after the nCRT is important because "watch and wait" strategy may be applied in this group of patients, contrary to those with partial regression requiring the operation without doubt. Accordingly, to evaluate accurately whether thickened esophageal wall consists only of fibrotic tissue or contains residual tumor has remained the main challenge. Available diagnostic tools, endoscopy with biopsy, endoscopic ultrasonography (EUS), CT, magnetic resonance imaging (MRI) and 18-FDG-PET, separately showed suboptimal accuracy in the assessment of the response of the EC to nCRT [11, 13–17]. Although 18-FDG-PET showed the highest overall accuracy, more recent systematic meta-analysis studies emphasize its usefulness in predicting the response of EC early during the neoadjuvant treatment rather than in assessing the response after the nCRT [7, 13, 14, 22, 23]. Combined multimodality analysis improved the diagnostic performance, according to the results of a few recent studies [24, 25]. However, in those multimodality protocols, CT was used only for the assessment of the metastatic spreading, while endoscopy, EUS, MRI, or PET was used for the assessment of the primary tumor response to neoadjuvant therapy by detecting the residual neoplasm within the esophageal wall [24, 25].

ROC analysis showed superior diagnostic performance of post-contrast density of the esophageal wall for predicting the pCR in comparison with the esophageal wall thickness, although AUCs of both measurements reached the statistical significance. In our study, maximal esophageal wall thickness ≤ 9 mm predicted complete regression with the accuracy of 73%, while average post-contrast attenuation of the esophageal wall ≤ 64 HU predicted CR with the accuracy of 98%. Moreover, combination of these two cutoff values enabled correct assessment of CR with the accuracy of 100%.

Esophageal wall attenuation, measured in the segment that was initially involved by tumor in the portal phase, ranged from 47 to 72 HU, on average 56.5 HU, in the group of patients who achieved pCR, and it was significantly higher in patients who achieved partial tumor regression (on average from 73 to 81 HU in TRG 2–4 group). In the study of Li and colleagues, it was reported that mean post-contrast density of the esophageal wall in the previously existing tumor region after the CRT was 64.35 ± 12.89 HU, with values ranging from 34.07 to 94.82 HU [21]. This is in line with our results, although the reported values of post-contrast esophageal wall density in the study of Li et al. pertained to the whole group of patients undergoing CRT, without classification of subjects into groups with complete and partial tumor responses as was done in our study. Another significant result reported by Li and coauthors in the same paper was that the post-contrast densities of healthy esophageal wall were 53.77 ± 7.04 HU, in nonirradiated patients, and 55.09 ± 7.30 HU in patients after the CRT [21], which are almost in agreement with our results of the post-irradiated esophageal wall, post-contrast density. Karmazanovsky and colleagues reported slightly lower post-contrast densities of the normal esophageal wall in the late arterial (42.45 ± 8.18 HU) and portal venous phase (median, 48 HU) [26].

Visual detection of the hyperdense foci within the esophageal wall after the nCRT enabled correct estimation of complete response with high sensitivity but lower specificity. In all cases of false-positive findings of CR, TRG 2, i.e., strong tumor regression, was revealed on histopathology specimens. In those cases, residual tumor nests probably were too small to be optically visible as hyperdense foci within the esophageal wall on post-contrast MDCT scan. Average post-contrast density of the visible hyperdense foci within the esophageal wall after the CRT in portal phase was approximately 30 HU higher than the density of the surrounding esophageal wall, with no significant difference compared with the attenuation of the esophageal tumor before the CRT, which is comparable to the results of other studies [18, 21]. Post-contrast hyperattenuation is probably a consequence of hypervascularization of the residual neoplastic tissue that remained after the CRT, as shown in head and neck SCC [27]. Therefore, hyperdense foci within the hypodense fibrotic esophageal wall probably represent the nests of residual neoplasm, which remained after the CRT, and this finding could be a key hallmark for the detection of the residual esophageal tumor by CT. Further investigations are needed to prove this assumption by performing section-by-section radiology–histopathology comparisons. Similar CT criteria of detecting and measuring post-contrast hyperattenuation of the residual tumor have been already applied by Choi and some other authors in the evaluation of response of various malignant tumor types to neoadjuvant therapy (GIST, renal cell carcinoma, hepatocellular carcinoma, lung cancer, liver colorectal cancer metastases, soft tissue sarcomas, pancreatic adenocarcinoma, etc.) [28–36]. Visual and quantitative analyses of post-contrast density after the nCRT could be also useful in the response evaluation of the lymph node metastasis. In addition, the cutoff values of the post-contrast esophageal wall attenuation, which were found to be distinct for complete and partial responses in our study, and the attenuation values of hyperdense foci and surrounding fibrotic esophageal wall after the nCRT, which were measured in our investigation, after further external reproducibility validation, might be potentially used as a threshold for utilizing the computer-aided diagnosis (CAD) in the response evaluation of the ESCC to nCRT.

There are a few limitations in our study worth mentioning. First is the fact that single radiologist measured the esophageal wall thickness, which is challenging because it is commonly uneven and dependent upon luminal distension. This might reduce the reproducibility of the threshold value of the esophageal wall thickness, which was obtained in our investigation. Second, a single reading radiologist performed both quantitative and visual analyses of the esophageal wall density, which could be the source of bias, because the results of measurements of density might influence the results of visual analysis. As single reading radiologist measured the thickness and density of the esophageal wall, reproducibility of those measurements was not validated. However, good interobserver consistency in visual detection of the hyperdense foci was clearly demonstrated. Certainly, further external validation on other patient groups is necessary. Third, only portal venous phase of CT examination was analyzed. Although dual- or triple-phase CT examination of the esophagus was proposed in some studies [21, 26, 37], we performed only single-phase CT examination in the portal venous phase since it had been carried out in previously published studies on the response evaluation of the EC to CRT [16–18] and is being routinely used in the oncology imaging and, above all, we intended to achieve wide applicability of our results in routine clinical work. In addition, two contrast mediums with slightly different iodine concentrations were used (350 and 370 mg I/ml) depending on availability, which could have an impact on the attenuations of the esophageal wall and residual tumor. Another limitation was the lack of response evaluation of the lymph node metastasis to nCRT, which will be the goal of our future investigation.

In summary, we may conclude that the combined visual analysis and measurement of the post-contrast density of the esophageal wall after the nCRT on the routine CE-MDCT examination can provide improved diagnostic accuracy in the response evaluation of the ESCC to nCRT in comparison to that achieved by measuring only the esophageal wall thickness.

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