

ORIGINAL ARTICLE

Does the computed tomography perfusion imaging improve the diagnostic accuracy in the response evaluation of esophageal carcinoma to the neoadjuvant chemoradiotherapy? Preliminary study

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Summary

Purpose: To estimate whether the computed tomography (CT) perfusion imaging could be useful to predict the pathological complete response (pCR) of esophageal cancer to the neoadjuvant chemoradiotherapy (NACRT).

Methods: Twenty-seven patients with the advanced squamous cell esophageal carcinoma, who were treated with concomitant CRT (CIS/5-FU/LV and 45-50 Gy total radiation dose), were re-evaluated using CT examination, which included the low-dose CT perfusion study. CT perfusion series were analysed using the deconvolution-based CT perfusion software (Perfusion 3.0, GE), and color parametric maps of the blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability surface area product (PS) were displayed. All patients were operated and histopathological analysis of the resected esophagus considered the gold standard for pathologic complete response (pCR).

Results: $BF_{\text{post-NACRT}}$, $BV_{\text{post-NACRT}}$ and $PS_{\text{post-NACRT}}$ were significantly lower, and $MTT_{\text{post-NACRT}}$ significantly higher in

the pCR group. Mean (\pm SD), or median perfusion parameter values in the pCRs (11 patients) vs non-pCRs (16 patients) were: $BF_{\text{post-NACRT}}$ 21.4 \pm 5.0 vs 86.0 \pm 29 ml/min/100 g ($p < 0.001$), $BV_{\text{post-NACRT}}$ 1.3 vs 3.9 ml/100 g ($p < 0.001$), $MTT_{\text{post-NACRT}}$ 5.5 vs 3.7 s ($p = 0.018$), and $PS_{\text{post-NACRT}}$ 5.9 vs 9.8 ml/min/100 g ($p = 0.006$). ROC analysis revealed that $BF_{\text{post-NACRT}}$ (AUC=1.000), $BV_{\text{post-NACRT}}$ (AUC=0.932), $MTT_{\text{post-NACRT}}$ (AUC=0.801), and $PS_{\text{post-NACRT}}$ (AUC=0.844) could predict the pCR ($p < 0.01$), while maximal esophageal wall thickness could not (AUC=0.676, $p = 0.126$). If we set a cut-off value of $BF_{\text{post-NACRT}} < 30.0$ ml/min/100 g, pCR was predicted with sensitivity and specificity of 100%.

Conclusion: CT perfusion imaging enables accurate prediction of pCR of esophageal carcinoma to neoadjuvant chemoradiotherapy.

Key words: chemoradiation, CT perfusion, esophageal cancer, response evaluation

Introduction

NACRT has become a widely applied therapeutic modality for patients with advanced esophageal carcinoma. Results of several trials, which compared the outcome of NACRT followed by surgery vs surgery alone, provided evidence that NA-

CRT improves resectability and survival in those patients who respond to therapy [1]. The main goals of NACRT are reduction of tumor volume and tumor downstaging, to enable radical resectability, to eradicate (micro) metastases if they exist, and to improve patient survival [2]. The most favorable outcome of NACRT is to achieve pCR [3].

Mandard and colleagues proved in their study that the histopathological regression status (tumor regression grade/TRG) of esophageal carcinoma after NACRT was the most significant independent predictive factor of survival after surgery [4]. According to the Mandard's classification, tumor regression status of grade 1 (TRG 1), which means total absence of residual cancer cells and fibrosis of the esophageal wall, defines pCR of esophageal cancer to the NACRT [4].

Monitoring the response of esophageal carcinoma to NACRT has been performed by using endoscopy, barium esophagography, CT, endoscopic ultrasonography (EUS), and 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) [2]. FDG-PET-CT, as a hybrid functional and morphologic imaging modality, which actually represents the most accurate diagnostic tool in assessing the response of esophageal cancer to NACRT [2]. CT perfusion is a promising imaging tool in oncology, which enables noninvasive estimation of tumor vascularisation *in vivo* and introduces the elements of functional diagnostics in morphologic imaging [5,6]. Respecting this fact, it could be potentially useful in monitoring the response of tumor to the chemoradiation (CRT). However, only few studies dedicated to the monitoring the response of the colorectal, head and neck, esophageal and lung cancer to CRT or chemotherapy have been reported [7-13]. To our knowledge, except as a part of the study of Makari et al. [11], until now there has not been any evidence in the literature that the CT perfusion imaging was used for the assessment of response of esophageal cancer to NACRT. Thus, the aim of our preliminary investigation was to analyse the response of esophageal carcinoma to NACRT using the CT perfusion imaging, which was incorporated in the regular post-NACRT CT examination, owing to re-staging purposes. Histopathological analysis of the resected esophageal specimens served as gold standard for the assessment of tumor response to CRT and TRG 1 considered the pCR according to the Mandard et al. criteria [4].

Methods

Selection of patients

Twenty-seven consecutive patients (23 men, 4 women; mean age 59 years; range 36–75), with the endoscopic biopsy-proved squamous cell carcinoma of the esophagus were enrolled in this prospective study. Inclusion criteria were: 1) receiving NACRT; 2) performing CT perfusion study after NACRT; and 3) performing

surgical esophagectomy. The institutional Ethics Board approved the study, and informed written consent was obtained from each subject.

Diagnostics before NACRT

Initially, i.e. before NACRT, all patients underwent barium esophagography, endoscopy with biopsy of the tumor, and CT examination of the neck, thorax and abdomen. According to the CT criteria of staging, initially, 20 patients had T3 and 7 had T4 neoplasm. Tumors were located in both the cervical and upper thoracic portion of the esophagus in one patient, the upper thoracic portion in 4, the upper and middle thoracic portion in 7, the midthoracic portion in 6, the middle and lower thoracic portion in 7, and the lower thoracic portion in 2 patients. The mean length of tumors, assessed on CT, was 6.79 ± 2.40 cm (range 3-13).

NACRT regimen

Patients were treated with concomitant chemotherapy and radiation [14,15]. Teleradiotherapy was performed through 3-4 fields, with total radiation dose of 45-50 Gy divided into the 24-28 standard fractions, with single daily dose of 1.8 Gy, using high-energy photons (>8 MeV), and lasted 5-6 weeks [14,15]. Concomitantly with radiotherapy, patients received chemotherapy, which consisted of cisplatin, 5-fluorouracil and leucovorin (CIS/5-FU/LV), for 4 cycles administered every 14 days [14,15].

Diagnostics after NACRT

Four to 6 weeks after the end of NACRT, response to therapy was evaluated using endoscopy, barium esophagography, and CT examination, which included the CT perfusion study. CT was performed with the 64-detector row CT (LightSpeed VCT, GE Health-care Technologies, USA). The first series was an unenhanced low-dose thoracic CT scan, which was performed to plan the CT perfusion study (axial-mode, 5 mm-section thickness, 1-s rotation time, detector coverage 40 mm: 8 images per rotation, 80 kV, 40 mAs, 25-cm scan field of view, 16-24 slices, 2-3 s total exposure time). After identification of the most thickened wall segment of the esophagus, 8 contiguous sections at the level of the greatest wall thickness area were chosen for the following perfusion study. To second series was a low-dose CT perfusion study. For the perfusion CT study, 50 ml of non-ionic iodinated contrast (370 mg/ml of iodine), followed by 30 ml of saline, were administered intravenously using a pump injector (Urlich-Missouri, Urlich, Germany), at a flow rate of 7 ml/s, through a 16-gauge cannula that was placed in the ante-cubital vein. Using the cine-mode acquisition, 8 contiguous sections,

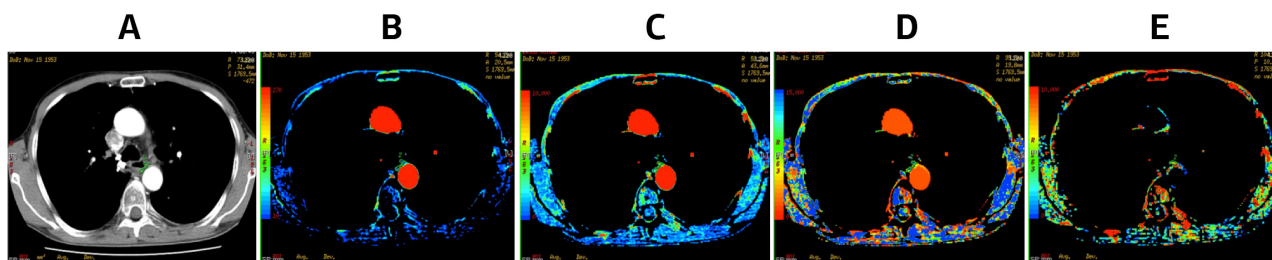


Figure 1A-E. CT perfusion parametric maps after the NACRT in a pCR patient. **A:** One of the 8 5-mm reconstructed axial thickness section of a CT perfusion study (freehand ROI colored green); **B:** BF (15.3 ml/min/100 g); **C:** BV (2.4 ml/100 g); **D:** MTT (12.1 s); **E:** PS (4.9 ml/min/100 g) in a 59-year-old patient with carcinoma of the upper and middle thoracic portion of the esophagus, initially cT3 N1 M0, histologically pT0 N0 M0; TRG 1.

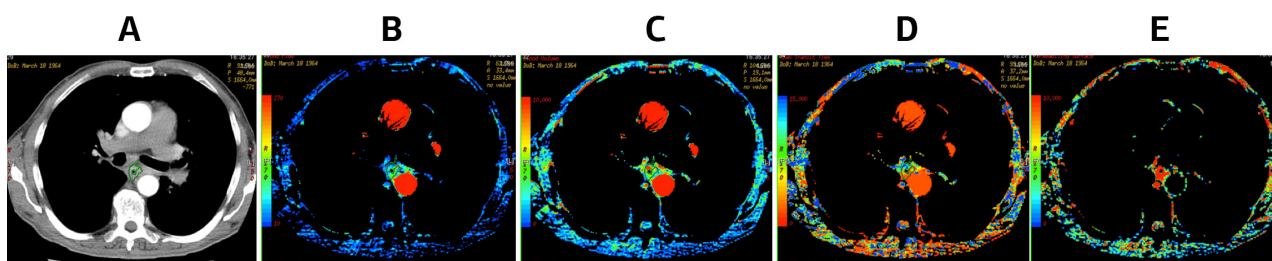


Figure 2A-E. CT perfusion parametric maps after the NACRT in a non-pCR patient. **A:** One of the 8 5-mm reconstructed axial thickness section of a CT perfusion study (freehand ROI colored green); **B:** BF (73.3 ml/min/100 g); **C:** BV (5.2 ml/100 g); **D:** MTT (3.6 s); **E:** PS (16.9 ml/min/100 g), in a 48-year-old patient with carcinoma of the middle thoracic portion of the esophagus, initially cT3 N2 M0, histologically pT3 N1 M0; TRG 3.

with 5-mm reconstructed axial thickness (totally 40 mm z-axis coverage), which were previously chosen in the unenhanced series, were scanned at 1-sec intervals (80 kV, 40 mAs, 25-cm scan field of view, 512 x 512 matrix) (Figures 1-2 A). Scanning started 5 sec after the beginning of the intravenous contrast administration, and total scan duration was 50 sec (400 images per a study). Patients were advised to breathe quietly during the dynamic CT scanning. The third series was a conventional portal venous phase CT of the neck, thorax and abdomen, after the intravenous injection of 60-100 ml iodinated contrast, performed for re-staging purposes. The maximal esophageal wall thickness was measured on this CT series.

All CT series were transferred to the workstation (Advantage Windows 4.3, GE Health-care Technologies, USA), and analysed by a single radiologist, using the commercial deconvolution-based perfusion software (Perfusion 3.0, GE Health-care Technologies, USA). A threshold range of 0-120 HU was chosen, and arterial input was defined by the circular region of interest (ROI), the area of which was 4-6 mm² that was placed in the center of the descending aorta, aortic arch, or common carotid artery, depending on the esophageal neoplasm localization. Then, the arterial time-density curve was derived automatically, and parametric maps were computed for each of the 8 contiguous series of the perfusion CT. Freehand ROIs were drawn around the margins of the esophageal wall at the reference im-

age on each of the 8 contiguous slices. Color parametric maps of the following 4 perfusion parameters, which have been automatically computed by the commercial software, were also displayed: blood flow- BF (ml/min/100 g tissue), blood volume- BV (ml/100 g tissue), mean transit time- MTT (s), and permeability surface area product- PS (ml/min/100 g tissue) (Figures 1 B-E, Figures 2 B-E). The average values for completely covered volume were calculated.

The dose of radiation for the CT perfusion study was calculated from the dose-length products (DLP), which was multiplied by a factor of 0.015.

Surgical treatment and histopathological evaluation after the NACRT

All patients were operated within a period of 1-4 months after the end of NACRT. Esophagectomy (trans-thoracic, or transhiatal), with lymphadenectomy (para esophageal, two-field standard, two-field extended, or three-field) was performed. Histopathological analysis of the resected specimens included staging according to the TNM classification (pTNM), residual status, and tumor regression status (TRG) according to the Mandard et al. criteria [4]. TRG 1 was considered as pCR. TRG 2-5 were considered non-pCR.

Statistics

Measurements were presented with mean val-

ues with standard deviation, or median, depending on distribution (normal distribution or not), and range from minimum to maximum value. Shapiro-Wilk's test was performed for testing the normal distribution of measurements. Independent samples t-test, or Mann-Whitney test (Z), were used to compare values of the perfusion and maximal esophageal wall thickness measurements between the pCR group and non-pCR group. Receiver operating characteristic (ROC) analysis was done to estimate the diagnostic performance of every perfusion parameter value in predicting pCR. The SPSS statistical software package 19.0 was used for statistical analysis.

Results

Values of the BF, BV and PS of the esophageal carcinoma after NACRT were significantly lower and MTT significantly higher in 11 patients in whom pCR was verified, compared with 16 patients with non-pCR (Figures 1 B-E, Figures 2 B-E, Figures 3 A-D). Mean $BF_{\text{post-NACRT}}$ (\pm SD) in pCRs was 21.4 ± 5.0 ml/min/100 g in non-pCRs ($p < 0.001$) (Figure 3 A). Median values of the $BV_{\text{post-NACRT}}$, $MTT_{\text{post-NACRT}}$ and $PS_{\text{post-NACRT}}$ in the pCR vs the non-pCR group were 1.3 vs 3.9 ml/100 g ($p < 0.001$), 5.5 vs 3.7 s ($p = 0.018$), and 5.9 vs 9.8 ml/min/100 g ($p = 0.006$), respectively (Figures 3 B-D).

The maximal esophageal wall thickness in the segment which was involved by tumor, measured by CT after NACRT, was lower on average in the group of pCRs (10.7 ± 2.9 mm), than in the group of non-pCRs (14.2 ± 6.1 mm), but the difference did not reach statistical significance ($p = 0.088$) (Figure 3 E).

ROC analysis revealed that post-NACRT CT perfusion values of BF, BV, MTT and PS could predict pCR, while maximal esophageal wall thickness could not (Figure 4, Table 1).

With a cut-off value of BF to < 30.0 ml/min/100g, pCR was predicted with sensitivity and

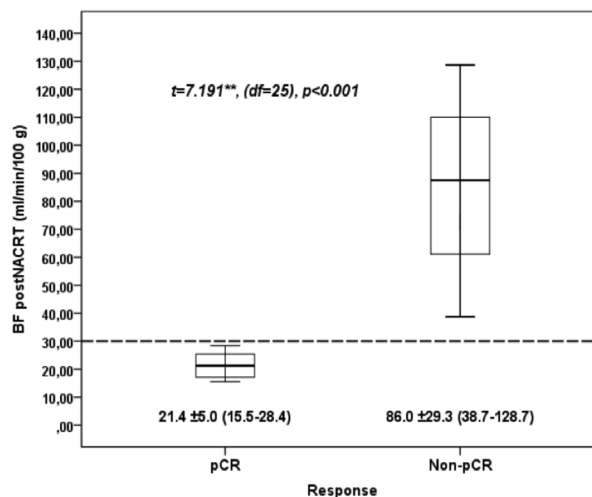


Figure 3A. Values of the $BF_{\text{postNACRT}}$ (Mean \pm SD, and Min - Max), in the pCR group (N=11), and non-pCR group (N=16), and their difference (t) (**: $p < 0.01$). Dotted line represents the cut-off value of $BF_{\text{postNACRT}}$ of 30.0 ml/min/100 g.

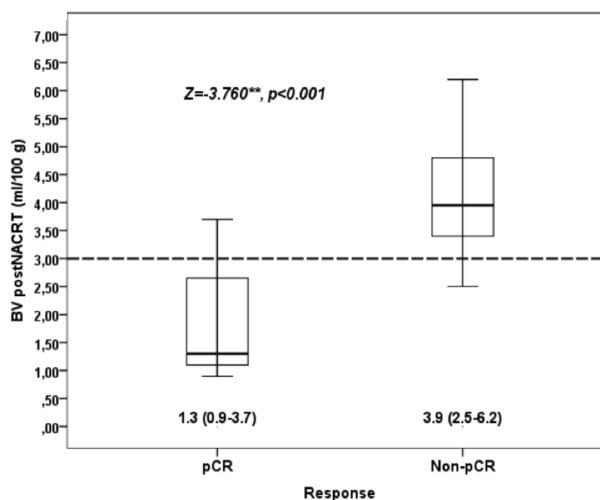


Figure 3B. Values of the $BV_{\text{postNACRT}}$ (Median, and Min - Max), in the pCR group (N=11), and non-pCR group (N=16), and their difference (Z) (**: $p < 0.01$). Dotted line represents the cut-off value of $BV_{\text{postNACRT}}$ of 3.0 ml/100 g.

Table 1. Results of the ROC analysis of the $BF_{\text{postNACRT}}$, $BV_{\text{postNACRT}}$, $MTT_{\text{postNACRT}}$, $PS_{\text{postNACRT}}$ and maximal esophageal wall thickness $_{\text{postNACRT}}$ in discrimination of the pCRs from the non-pCRs (AUC: area under the curve; **: $p < 0.01$). Sensitivity and specificity for the proposed cut-off values of the $BF_{\text{postNACRT}}$, $BV_{\text{postNACRT}}$ and $PS_{\text{postNACRT}}$ in prediction of the pCR

	ROC			Cut-off value	Sensitivity %	Specificity %
	AUC	95% confidence interval of AUC	p			
$BF_{\text{post-NACRT}}$ (ml/min/100 g)	1.000**	1.000-1.000	0.000	< 30.0	100	100
$BV_{\text{post-NACRT}}$ (ml/100 g)	0.932**	0.841-1.000	0.000	≤ 3.0	81.8	87.5
$MTT_{\text{post-NACRT}}$ (s)	0.801**	0.634-0.968	0.009			
$PS_{\text{post-NACRT}}$ (ml/min/100 g)	0.844**	0.693-0.995	0.003	≤ 6.5	90.9	75.0
Maximal wall thickness $_{\text{post-NACRT}}$	0.676	0.474-0.878	0.126			

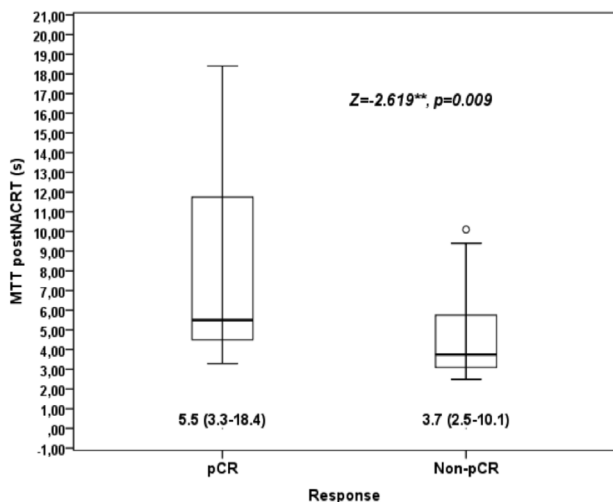


Figure 3C. Values of the $MTT_{postNACRT}$ (Median, and Min - Max), in the pCR group (N=11), and non-pCR group (N=16), and their difference (Z) (**: $p < 0.01$).

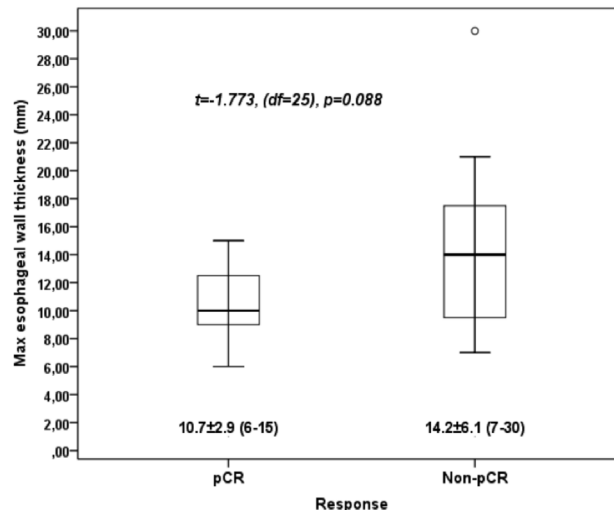


Figure 3E. Maximal esophageal wall thickness $_{postNACRT}$ (Mean \pm SD, and Min - Max), in the pCR group (N=11), and non-pCR group (N=16), and their difference (t).

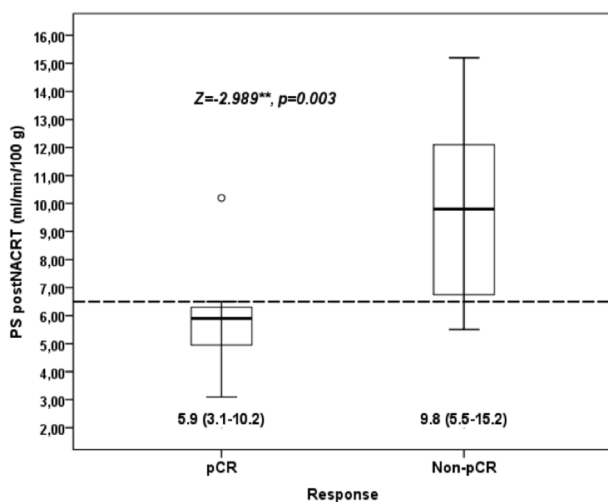


Figure 3D. Values of the $PS_{postNACRT}$ (Median, and Min - Max), in the pCR group (N=11), and non-pCR group (N=16), and their difference (Z) (**: $p < 0.01$). Dotted line represents the cut-off value of $PS_{postNACRT}$ of 6.5 ml/min/100 g.

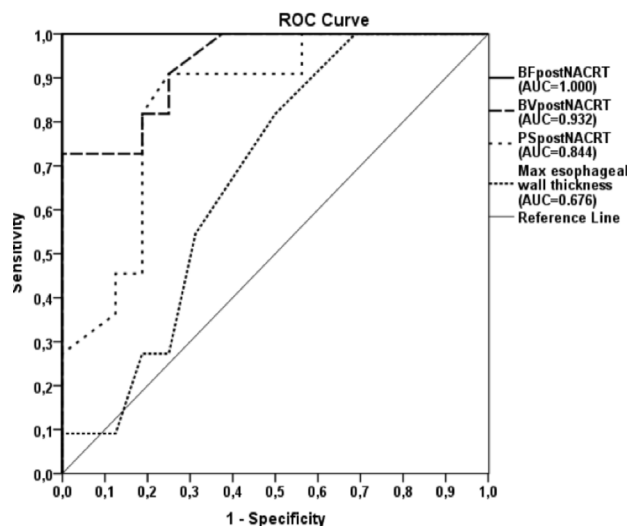


Figure 4. ROC analysis of the $BF_{postNACRT}$, $BV_{postNACRT}$, $PS_{postNACRT}$ and maximal esophageal wall thickness $_{postNACRT}$ in discrimination of the pCRs from the non-pCRs. (AUC: area under the curve).

specificity of 100% (Table 1). Lower sensitivity and specificity was achieved for the proposed cut-off values of $BV (\leq 3.0 \text{ ml}/100 \text{ g})$, and $PS (\leq 6.5 \text{ ml}/\text{min}/100 \text{ g})$ (Table 1).

The effective radiation dose of the CT perfusion study (DLP: 181.68 mGy \times cm), together with the unenhanced series (DLP: 10.90-14.00 mGy \times cm), was 2.84-2.89 mSv.

Discussion

Diagnostic imaging methods that are commonly used for the initial staging and assessment

of response of esophageal cancer to NACRT are CT, EUS and FDG-PET-CT [2]. In the systematic review of Westertep and colleagues, the overall accuracy rates that were summarized for the single-section CT, EUS and FDG-PET were 54, 86 and 85%, respectively [2]. For the spiral CT, both the sensitivity (33-55%), and specificity rates (50 - 71%), which were summarized from the literature data, were low [2]. At the same time, CT remains the most widely used diagnostic imaging tool in the monitoring treatment response of solid tumors in the actual daily clinical practice. However, in all available studies for esophageal cancer,

only morphological criteria (reduction of tumor volume or esophageal wall thickness) were estimated in assessing response to NACRT using CT [2,16,17]. Although proved as a most accurate imaging modality for primary local staging of esophageal carcinoma, EUS is significantly less accurate in assessing response to CRT [2,18]. Thickness of the esophageal wall and maximal cross sectional area of tumor are the main EUS-based assessment criteria of response, while distinguishing the residual neoplastic tissue from the edematous and/or fibrotic esophageal wall is not possible using EUS [2,18]. FDG-PET-CT actually seems to represent the most accurate imaging tool in the evaluation of pathologic response of esophageal cancer to the CRT, probably because this functional and morphologic imaging method enables visualization of the metabolically hyperactive residual neoplastic tissue in the esophageal wall [2].

By using the CT perfusion imaging for the diagnosis of neoplastic lesions and the prediction and monitoring of response to radiation and chemotherapy, the component of the functional diagnostics has been introduced into the morphological imaging of tumors [5,6]. Multi-detector computed tomography (MDCT), which actually is widely used, enables the presentation of the perfusion of the whole or near whole tumor volume, depending on the available CT equipment [5,6].

In both available (preliminary) studies on rectal cancer, authors reported that perfusion parameter values significantly changed after the NACRT, which is in concordance with our results [7,8]. Sahani et al. found that BF significantly decreased (from 62.57 ± 26.50 before, to 23.36 ± 13.18 ml/min/100 g after NACRT), and MTT increased (from 8.40 ± 3.55 before, to 17.09 ± 6.89 s after NACRT), in the group of 9 patients with rectal carcinoma, where 7 patients responded to the preoperative CRT [7,8]. Bellomi et al. reported similar results using the same CT perfusion software that we used: significantly lower median values of the BF (65.4 before vs 39.2 ml/min/100 g after NACRT), BV (5.6 before vs 2.4 ml/100 g after NACRT), and PS (12.8 before vs 7.8 ml/min/100 g after NACRT), in the group of 19 patients, of whom 15 were responders [7,8]. In both studies, local downstaging of rectal carcinoma, estimated by CT or EUS, considered the criteria for the response, while the mean perfusion parameter values were calculated for the whole group of patients who received NACRT, but not separately for the responders and non-responders groups, like we did [7,8]. In two studies of advanced oropharyngeal squamous cell

carcinoma, the authors also proved significant decrease of tumor BF and BV in patients who responded to concomitant definitive CRT and induction chemotherapy [9,10]. Surlan-Popovic et al. reported that the mean values of BF and BV post-CRT in the group of 14 responders were 53.0 ± 15.1 ml/min/100 g and 5.00 ± 1.4 ml/100g, respectively, vs 87.8 ± 30.1 ml/min/100 g and 8.3 ± 2.4 ml/100 g in 6 non-responders, while Gandhi et al. reported that the median values of the BF and BV after induction chemotherapy were 45.1 ml/min/100 g and 3.1 ml/100g in 7 responders, vs 75.9 ml/min/100 g and 4.71 ml/100g in 2 non-responders [9,10]. A criterion for the assessment of response was the reduction of tumor volume measured by CT in the first mentioned study, or estimated by endoscopy in second [9,10].

To our knowledge, this is the first investigation of response of advanced esophageal carcinoma to NACRT using the analysis of the CT perfusion parameter values. Our results were comparable with those, which were reported for the rectal and oropharyngeal cancers [7-10]. However, we found generally lower BF, BV, and PS values after NACRT in our group with pCR than the mentioned authors found in their series of clinical responders [7-10]. The criterion of pCR probably could explain a clear distinction between the responders and non-responders, which we found in our series, based on significantly different perfusion parameter values in the two groups after the NACRT (Figures 1-3 A-D). BFpost NACRT was the most accurate predictor of pCR (Figures 3 A and 4, Table 1). The average value of BFpost NACRT in the pCR group was 21.4, and the maximum value was 28.4 ml/min/100 g, while the minimum value in the non-pCR group was 38.7, and the mean value was 86.0 ml/min/100g (Figure 3 A). Performing ROC analysis resulted in the maximal overall diagnostic performance (AUC=1.0) in the discrimination between pCR and non-pCR before surgery (Figure 4, Table 1). BV, PS and MTT also showed statistically significant predictive value in identifying potential pCRs, but certain overlapping among the maximum values in the pCRs group and minimum values in the non-pCR group, especially for the MTTpost NACRT, depreciated their accuracy (Figure 3 B-D, Table 1). The cut-off value of BFpost NACRT < 30 ml/min/100g, most accurately predicted pCR in our series (Figure 3 A, Table 1).

BF, BV and PS values that we found in the group of patients who achieved pCR generally were moderately higher, but comparable with the same perfusion parameter values that were

reported for healthy skeletal muscles, using the same CT perfusion software (CT perfusion 3.0, GE) [20,21]. We suppose that such results could suggest that reduction of the perfusion parameter values that could be measured using CT perfusion imaging reflected the lack of residual neovascularisation in the fibrotic esophageal wall in those patients who achieved pCR. Further histological investigations of changes in the vascular architecture after CRT are necessary to prove this assumption.

In our series, maximal esophageal wall thickness, which was measured by CT after NACRT in the segment which was involved by the tumor, was not proved to be an accurate factor for prediction of the pCR (Figure 3 E, Figure 4, Table 1). On the contrary, in two studies with larger patient cohorts, the authors established its statistical significance in discriminating responders from non-responders [17,22].

However, what is the potential benefit of predicting pCR after NACRT and before surgery? Trimodality therapy (i.e. CRT followed by surgery) actually is considered the treatment of choice for advanced esophageal carcinoma. Multivariate analyses have revealed that pCR and resection

status (R0) are two independent prognostic factors for disease-free and overall survival after trimodality treatment [3,4,14,15]. At the same time, it has been proved that esophagectomy had one of the highest mortality rates among all surgical procedures [23]. Thus, in some studies, definitive CRT has been suggested as a preferred treatment modality [24-26]. Anyway, accurate prediction of pCR after NACRT certainly could improve the selection of patients for surgery.

Limitations of our study were the relatively small number of patients and the available CT equipment that we used, with detector coverage restricted to 4 cm-long-z-axis, which might not be enough long to achieve whole tumor volume coverage.

In summary, according to our preliminary results, we may conclude that CT perfusion imaging enables accurate prediction of pCR of esophageal carcinoma to NACRT, which could be useful to improve patient selection for further treatment (surgery or radical CRT). If studies with larger patient numbers will support our findings, the CT perfusion study could be incorporated into the regular CT examination protocol of these patients due to re-staging purposes.

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