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Role of perfusion CT in the evaluation of metastatic nodal tumor response after radiochemotherapy in head and neck cancer: preliminary findings

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Abstract. – OBJECTIVE: To assess changes of CT perfusion parameters (ΔPCTp) of cervical lymph node metastases from head and neck cancer (HNC) before and after radiochemotherapy (RT-CT) and their association with nodal tumor persistence.

PATIENTS AND METHODS: Eligibility criteria included HNC (Stage III-IV) candidates for RT-CT. Patients underwent perfusion CT (PCT) at baseline 3 weeks and 3 months after RT-CT. Blood volume (BV), blood flow (BF), mean transit time (MTT) and permeability surface (PS) were calculated. PET/CT examination was also performed at baseline and 3 months after treatment for metabolic assessment.

RESULTS: Between July 2012 and May 2016, 27 patients were evaluated.

Overall, only 3 patients (11%) experienced tumor persistence in the largest metastatic lymph node.

A significant reduction of all PCTp values ($p<0.0001$), except MTT (from 6.3 to 5.7 s; $p=0.089$), was observed at 3 weeks post-RT-CT compared to baseline. All PCTp values including MTT were significantly lower at 3-month follow-up compared to baseline ($p<0.05$). Moreover, a statistical significant association was observed between nodal tumor persistence and high BF values ($p=0.045$) at 3 months after treatment that did not occur for the other parameters.

CONCLUSIONS: Our preliminary findings show that all PCTp except MTT are significantly reduced after RT-CT. High BF values at 3 months post-RT-CT are predictive of nodal tumor persistence.

Key Words:
Head and neck cancers, Perfusion Computed Tomography, Radiochemotherapy.

Introduction

Head and neck cancer (HNC) is the fifth most common cancer worldwide accounting for approximately 5% of all tumours[1,2]. Squamous cell carcinoma is the most common histotype (approximately 90%), and generally arises from the mucosa of the upper aerodigestive tract.

HNCs constitute a heterogeneous collection of tumors. This includes five main different subtypes according to the site of the primary tumor: the nasopharynx, oropharynx, oral cavity, hypopharynx and larynx. Nevertheless, they are all characterized by a predominant route of locoregional metastasis through the lymphatic drainage and by a relatively low proportion of distant hematogenous metastases.

The most important treatment modalities for HNC consist of surgery, radiotherapy (RT) and chemotherapy (CT). In recent years, due to improvements in RT treatment delivery such as intensity and modulated RT (IMRT), as well as the increasing use of more intensive altered fractionation schedules, radiochemotherapy (RT-CT) has become a valid alternative to radical surgery showing similar rates of locoregional control[3,4]. However, residual neck disease may be present in as many as 30-60% of patients after completion of RT-CT. For these patients, irrespective of the HNC stage, there seems to be a consensus in the literature favoring immediate neck dissection, because of the very low probability of achieving disease control with salvage surgery when recurrence develops[5-7].

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Therefore, prior assessment of nodal tumor response is crucial due to the importance to refer patients to surgery in case of partial response (PR) and to properly identify those who experienced a complete response (CR) as they would not benefit from a neck dissection[8]. In this regard, an early detection of tumour persistence is desirable in determining a successful salvage surgery[9].

In the current clinical practice, evaluation of nodal tumour response post-RT-CT is based on the combination of computed tomography (CT) and neck ultrasonography (US), reporting a negative predictive value of 95% and 81% and a positive predictive value of 82% and 84%, respectively. The fluoro-deoxy-glucose positron emission tomography (FDG-PET) can provide additional value by adding metabolic information to standard radiological imaging, achieving an excellent negative predictive value (95.1%) despite a low positive predictive value (75%) due to inflammatory changes[10]. As a consequence, interest is rising on new imaging technologies with the potential to more accurately evaluate tumour response in order to identify "non-responder" patients who could benefit from salvage surgery as soon as possible. Diffusion-weighted MR imaging (DW-MRI) allows for differentiation of post RT-CT inflammation and necrosis reporting a negative and positive predictive values of 96% and 70%, respectively[11]. These results are found despite being hampered by several limitations such as relatively poor spatial resolution, susceptibility to artefacts and modest reproducibility of apparent diffusion coefficient (ADC) values[12,13]. Perfusion computed tomography (PCT) can provide quantitative information on the status of tumor microcirculation that might reflect early treatment response or predict outcome. Hence, it has been proposed as a potential additional tool for noninvasive functional assessment of treatment response[14-19]. Although no consensus has yet been reached about the optimal timing of PCT imaging, several experimental studies on both humans and animal models have shown the ability of PCT to detect changes less than 1 month after or even within days of starting therapy (i.e. well before a reduction in tumor size can be demonstrated in conventional morphological CT imaging)[20-22]. Compared with other imaging techniques such as FDG-PET or MRI, PCT retains the advantages of high spatial resolution, fast imaging time and a linear relationship between tissue iodine concentration and CT density. This feature can be exploited to derive absolute quantitative PCT data from deconvolution algorithms[14].

In this study, we prospectively evaluated the changes in CT perfusion parameters (ΔPCTp) of the largest cervical adenopathy, measured both at 3 weeks and 3 months after RT-CT and compared with pre-treatment values (Primary Endpoint). Moreover, we sought to find an association between ΔPCTp values and biopsy proven tumor persistence in the largest cervical adenopathy (Secondary Endpoint).

Patients and Methods

This study was conducted according to the Declaration of Helsinki. All patients gave their written consent to all diagnostic and therapeutic procedures.

Study Design

Enrollment criteria, PCT image acquisition protocol and treatment details have been reported in full in a previous paper of ours[23]. In brief, patients affected by Stage III-IVB HNC (undifferentiated nasopharyngeal type or squamous cell carcinoma arising from oropharynx, oral cavity, larynx or hypopharynx) who were candidates to a radical RT-CT, were enrolled.

In addition to the standard diagnostic workup, all patients underwent a contrast-enhanced CT examination of the head and neck for morphological evaluation of the largest adenopathy (as detailed in the dedicated subsection) and a whole body [^{18}F]FDG-PET/CT scan. To the purpose of the PCT analysis, the largest adenopathy was defined as the cervical adenopathy with the largest maximum transverse diameter based on RECIST criteria[24]. Then, PCT was repeated at 3 weeks (early evaluation) and 3 months (late evaluation) after completion of RT-CT, whereas [^{18}F]FDG-PET/CT was repeated 3 months after RT-CT. In case of suspected tumor nodal persistence, an US-guided FNAC or FNAB was performed for cytological or histological confirmation. If confirmed, patients were referred to salvage neck nodal dissection unless in the presence of concurrent distant metastases. Thereafter, routine follow-up was performed based on current international guidelines[25].

Perfusion CT Protocol

The PCT acquisition protocol was described in detail in our previous paper[23]. All PCT studies were performed using a high-definition 64-row CT scanner (Discovery CT750 HD®, General Electric, Milwaukee, WI, USA) opera-

Table I. Patients and tumor characteristics.

Characteristics	No.	%
Site		
Nasopharynx	4	15
Oropharynx	10	37
Oral Cavity	4	15
Hypopharynx	4	15
Larynx	5	18
Histology		
Squamous cell carcinoma	23	85
Undifferentiated carcinoma	4	15
T		
2	13	48
3	3	12
4	11	40
N		
1	11	40
2	12	45
3	4	15
Stage		
III	7	26
IV	20	74
IVA	13	65
IVB	7	35
Concurrent chemotherapy		
Cisplatin 40 mg/mq weekly	26	96
Cisplatin 100 mg/mq every 21 days	1	4

ting in axial mode with a toggling table technique, resulting in a z-axis coverage of 8 cm centered on the lesion site as assessed upon review of preliminary morphological CT or MR images obtained for tumor staging[26,27]. All PCT datasets were transferred in DICOM format to a workstation (Advantage Windows v. 4.5, General Electric Milwaukee, WI, USA) equipped with a dedicated plugin (CT Perfusion 3) for calculation of blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability surface (PS) product based on a deconvolution, two-compartment algorithm[14].

Circular regions of interest (ROI) were positioned inside the nodal tumor, as well as on the ipsilateral common or external carotid artery for sampling of the arterial input function needed to calculate the PCTp. ROIs were placed on the slice containing the largest lymph node section area so as to maximize the amount of sampled data per patient. ROI contours were kept at least 1 mm far away from node borders and care was taken to avoid macroscopic areas of tumor necrosis or calcification. All ROIs were identified independently by two radiologists with 10 and 3 years of experience in HN imaging, respectively, and by a radiation therapist with 9 years of experience. Each PCT parameter is the average of the three measurements by the three readers.

Statistical Analysis

A descriptive analysis of data was carried out before performing inferential tests. Categorical data were described by frequency and continuous data by mean and range. The normality of the distribution of BV, BF, MTT and PS was evaluated using Kolmogorov-Smirnov test. Temporal variations of PCTp at baseline and at 3-week and 3-month follow-up, were assessed using the Friedman test and the two-tailed Wilcoxon test for multiple comparisons. Furthermore, temporal differences of PCTp between patients with and without tumor nodal persistence and/or recurrence, were evaluated using the two-tailed Mann-Whitney. A p-value less than 0.05 was set as threshold for statistical significance. Statistical analysis was performed using software SPSS 24 (IBM, SPSS Inc., Armonk, NY, USA).

Results

Patient and Tumor Characteristics

Between July 2012 and May 2016, 37 patients were enrolled in our study. Among them, 27 patients were able to be evaluated for adenopathy response after RT-CT. Baseline patient and tumor characteristics are summarized in Table I. All datasets were of diagnostic quality.

According to standard radiological RECIST criteria, at 3 months after treatment, 21/27 patients (78%) exhibited CR in the largest adenopathy and the remaining 6/27 patients (22%) exhibited PR. Indeed, the FDG-PET adenopathy response evaluation showed a CR in 23/27 patients (85%) and a PR in 4/27 patients (15%). Therefore, 2 patients had conflicting results of a radiological PR yet a metabolic CR.

In total, 3 patients (11%) showed biopsy-proven tumor persistence in the largest adenopathy after treatment. Only one patient was classified with both a radiological and metabolic PR, while 2 patients had conflicting results of a radiological PR yet a metabolic CR.

Finally, 2 patients underwent salvage neck dissection that confirmed the tumor persistence in the

Table II. Primary adenopathy perfusion parameters variations scores from baseline to post-treatment.

	BV (ml/100 g/min)	BF (ml/100 g)	MTT (s)	PS (ml/100 g/min)
Baseline				
Mean	29.9	280.9	6.3	48.1
Range	2.7-117.9	50.3-902.4	2.3-7.19	6.9-184.1
3 weeks				
Mean	8.3	79.3	5.7	10.6
Range	0-62.1	0-556.6	0-21.1	0-60.1
3 months				
Mean	1.8	34.3	2.3	5.8
Range	0-19.5	0-287.1	0-16.1	0-44.8

Abbreviations: BV: Blood Volume; BF: Blood Flow; MTT: Mean Transit Time; PS: Permeability Surface.

largest adenopathy, whereas one patient received systemic chemotherapy due to the concurrent presence of lung metastases. After a median follow-up of 20 months (range 9-56 months), no patients had a cancer-related death, whereas 1 patient died due to concurrent cardiovascular disease.

Variations of Tumor Perfusion Parameters of the Largest Adenopathy

The primary analysis was aimed at assessing the ΔPCTp of the largest adenopathy in the post-treatment PCT (both at 3 weeks and at 3 months) compared to the pretreatment values.

The mean and range values of the PCTp at baseline, 3 weeks and 3 months after treatment are reported in Table II. Besides, the variations observed at each time-point (baseline, 3 weeks and 3 months after treatment) with the significant *p*-values are shown in Table III.

Overall, all PCTp values were significantly reduced at 3-weeks post RT-CT compared to baseline, except MTT (p=0.089). All PCTp values were significantly lower compared to baseline 3 months after treatment. Moreover, a statistically significant reduction of all PCTp values was found between the 3-week and the 3-month follow-up PCT examinations (Table III).

Association Between Variations of Tumor Perfusion Parameters (ΔPCTp) and Tumor Persistence in the Largest Adenopathy

A secondary analysis was aimed at assessing the relationship between adenopathy response and ΔPCTp both at 3 weeks and at 3 months after treatment. The results are reported in Table IV.

As shown, patients who had tumor persistence in the largest adenopathy showed a higher mean value of BF compared to those who had a CR at 3 months after treatment (118.74 ml/100 g *vs*. 33.76 ml/100 g; p=0.045). In comparison, the BF mean value did not show a significant association at 3 weeks after treatment in patients who had tumor persistence in the largest adenopathy compared to those who experienced a CR (52.01 ml/100 g *vs*. 74.54 ml/100g; p>0.05). Indeed, no statistical significant association was observed between tumor persistence and changes of the other perfusion parameters both at 3 weeks and 3 months (p>0.05).

Table III. Statistical significance of primary adenopathy perfusion parameters variations.

Perfusion parameters	*p*-value
PCTp baseline-3 weeks	
BV	<0.0001
BF	<0.0001
MTT	0.089
PS	<0.0001
PCTp baseline-3 months	
BV	<0.0001
BF	<0.0001
MTT	<0.0001
PS	<0.0001
PCTp 3 weeks-3 months	
BV	<0.0001
BF	0.001
MTT	0.04
PS	0.018

Abbreviations: BV: Blood Volume; BF: Blood Flow; MTT: Mean Transit Time; PS: Permeability Surface; PCTp: Perfusion CT parameters.

Table IV. Association between variations of perfusion parameters (ΔPCTp) and tumor nodal persistence.

Δ parameters		Baseline – 3 months		Baseline – 3 weeks	
		Mean	*p*-value	Mean	*p*-value
BV (ml/100 g/min)	NP	8.1	0.247	5.7	0.315
	NR	13.9		6.7	
BF (ml/100 g)	NP	67.3	**0.045**	106.1	0.416
	NR	166.4		131.9	
MTT (s)	NP	2.3	0.210	1.5	0.465
	NR	4.8		2.1	
PS (ml/100 g/min)	NP	14.8	0.495	11.7	0.896
	NR	25.7		41.5	

Abbreviations: NP=nodal persistence NR=nodal remission.

Discussion

The primary endpoint of this work was to investigate changes in the PCTp of the largest adenopathy from baseline to post RT-CT treatment in order to evaluate their potential role as predictive factors of nodal tumor persistence in patients affected by HNC. To this purpose, both an early (3 weeks) and late (3 months) assessment of ΔPCTp was performed after treatment. Firstly, our results showed a significant reduction of all PCTp values, except for MTT (from 6.3 to 5.7 s; p=0.089), early after treatment whereas all parameters showed a significant late reduction (thus demonstrating a strong effect of RT-CT on such parameters). Our findings are in line with those reported in our previous paper regarding the primary tumor response[23] as well as by similar studies published in the literature[28-30]. In particular, we had already observed a lower sensitivity of MTT compared to all other PCTp to predict response early after treatment, whereas a significant reduction of BV, BF and PS was reported both early and late after treatment. In this regard, the trend toward reduction of those latter PCTp has already been explained as caused by the radiation and chemotherapy damage of low resistance neoangiogenetic vessels[31,32]. The study by Surlan-Popovic et al[33] was the only research specifically investigating the changes of the primary tumor perfusion parameters during the course of RT reporting a significant reduction of BV and BF along with a nonsignificant variation of MTT and PS.

To the best of our knowledge, this study is the first one specifically aimed at assessing the variations of PCTp values of cervical adenopathies from before to after RT-CT, showing a potential role of all PCTp to predict treatment response. At a more detailed analysis, our preliminary findings suggest a specific perfusion pattern of early treatment response characterized by a significant reduction of BV, BF and PS together with a nonsignificant variation of MTT. In this context, our findings appear to be similar to those by Trojanowska et al[34], who reported that metastatic lymphnodes from hypopharyngeal and laryngeal squamous cell carcinoma have significant higher BF, BV and PS than nonmetastatic ones. Moreover, a high baseline BF in primary HNC before RT-CT (followed by a significant decrease of BF and BV after treatment, such as in our study) was found to be 83.3% predictive of complete treatment response. It suggests that BF may reflect similar functional changes in metastatic lymphnodes[35,36].

While most investigations[36-40] seem to agree in a significant treatment-related reduction of BV and BF, they also report contradictory findings regarding the changes in PS and MTT values, sometimes describing no significant variations in the post-treatment *vs.* the pretreatment values.

These results add weight to the finding of our previous paper[23], showing a superimposable trend of these parameters from before to after treatment. Based on the above observations, we believe that the role of MTT should be further investigated, as it might be pivotal in the interpretation of tumor response both in primary site and in adenopathies.

As a secondary endpoint of our paper, the ΔPCTp were associated to the tumor persistence cytologically or histologically confirmed in

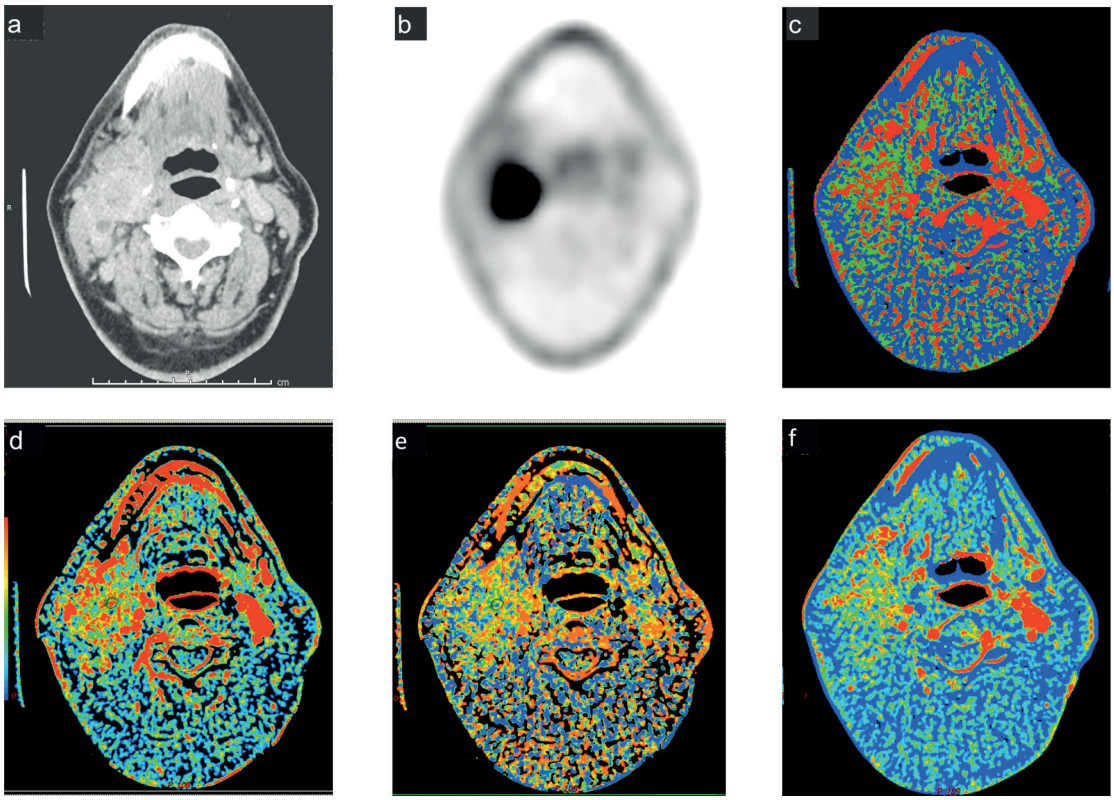

Figure 1. A 64-year-old patient with squamous cell carcinoma of hypopharynx treated with exclusive RT-CT: ***(a)*** pre-treatment morphologic CT image obtained from first-pass perfusion CT (PCT) data set. ***(b)*** pre-treatment metabolic FDG-PET shows abnormal tracer uptake in the IIA level adenopathy of the right side of the neck (SUV_{max}18.25). Quantitative measurement of pre-treatment PCT parameters revealed ***(a)*** BV=112.15 ml min^{-1}, ***(b)*** BF=654.14 ml min^{-1} per 100 g, ***(c)*** MTT=11.22 s and ***(d)*** PS=56.05 ml min^{-1} per 100 g.

the largest adenopathy. We found that the persistence of relatively high BF values at 3 months (a small reduction of BF between 3 months and baseline) was statistically associated to a high risk of tumor persistence. This is probably due to a high degree of tumor neovascularization in lymphnodes, which did not undergo a complete remission after treatment. In any case, we believe that the main limitation of this secondary analysis was the low number of events, as only 3 patients (11%) had biopsy-proven tumor persistence in the largest adenopathy whereas most patients showed complete CT remission.

Therefore, it is desirable that a greater sample size and higher number of events will lead to understanding the predictive role of other investigated parameters. Noteworthy, 2 of the 3 nodal recurred patients (67%) in our study were FDG-PET negative, thus confirming the need to integrate morphological and functional data in advanced imaging technologies for a complete and accurate assessment of tumor response.

Figures 1 and 2 report the imaging findings in a patient that summarizes our preliminary results. This patient was affected by a locally advanced hypopharynx cancer (Stage cT3N2b) that exhibited both an early and late radiologic PR of the largest adenopathy associated with a progressive reduction of all PCTp (except MTT at 3 weeks) as well as a metabolic PR.

Conclusions

We report the preliminary results of a pilot study aimed at investigating the potential role of a morphologic-functional integrated imaging technique in the interpretation of nodal tumor response after RT-CT. Although the real benefits of an early *vs.* delayed salvage neck surgery after RT-CT has not been proved yet, it will likely be

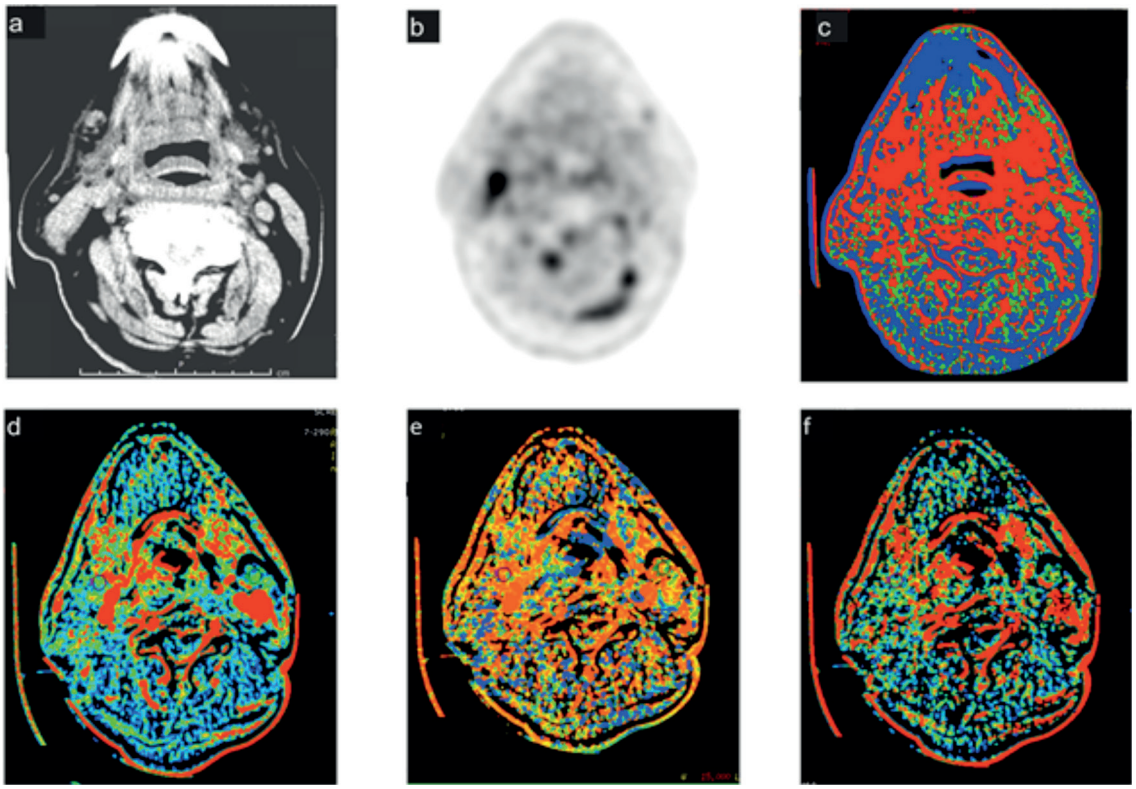

Figure 2. Post-treatment evaluation of the same patient as in Figure 1: ***(a)*** post-treatment morphologic CT image obtained from first-pass perfusion CT (PCT) data set. ***(b)*** Post-treatment metabolic FDG-PET shows the persistence of abnormal tracer uptake in the IIA level adenopathy of the right side of the neck (SUV_{max} 6.0). Quantitative measurement of post-treatment PCT parameters revealed (a) BV=6.08 ml min^{-1}, ***(b)*** BF=118.74 ml min^{-1} per 100 g, ***(c)*** MTT=2.84 s, ***(d)*** PS=4.49 ml min^{-1} per 100 g.

so in the future. As a consequence, early identification of partial or non-responder patients based on PCT findings might be extremely useful in clinical practice to refer patients towards surgery as soon as possible in order to improve oncologic outcomes. Thus, longer follow-up and greater sample size will be useful to correlate the ΔPCTp to the more important clinical outcomes, such as regional recurrence-free survival.

Conflict of interest

"Travel, Congress and Courses Grants (Merck Serono; Nestlè; Kyowakirin)" have to be declared for author, Stefano Ursino; "Travel, congress and courses grants (Merck Serono; Nestlè; Kyowakirin; Varian)" have to be declared for author Fabiola Paiar. No conflicts of interest for the other authors.

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