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Dual-time-point PET/CT study protocol can improve the larynx cancer diagnosis

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ABSTRACT

Aim: To evaluate whether the sequential dual-time-point fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (DTP 18F-FDG PET/CT) study improves the differential diagnosis in the larynx.
Background: In some cases, the clinical and metabolic similarity of laryngitis and larynx cancer make differential diagnostics difficult when performing standard 18F-FDG PET/CT examinations; therefore, an additional study protocol performance seems to be of reasonable value.
Materials and methods: 90 patients (mean age: 61 ± 11 years, range: 41–84 years): 23 women (mean age: 63 ± 10 years, range: 51–84 years) and 67 men (mean age: 61 ± 11 years, range: 41–80 years) underwent delayed 18F-FDG PET/CT examinations at 60 and 90 min post intravenous injection (p.i.) of the radiopharmaceutical 18F-FDG. We compared the metabolic activity of 90 structures divided into following groups: normal larynx (30 patients), laryngitis (30 lesions) and larynx cancer (30 tumors) with maximal and mean standardized uptake value (SUVmax, SUVmean) and the retention index (RI-SUVmax). We used the receiver operating characteristics (ROC) curve to evaluate the SUVmax cut-off values.
Results: The SUVmax cut-off value at 60 and 90 min p.i. of 2.3 (sensitivity/specificity: 96.4%/100%) and 2.4 (94.2%/100%), respectively, distinguished normal and abnormal metabolic activity in the larynx. When laryngitis and tumors were compared, the SUVmax cut-off values obtained after initial and delayed imaging were 3.6 (87.5%/52.0%) and 6.1 (58.3%/84%), respectively. The RI-SUVmax of 1.3% (71.4%/88.1%) suggested abnormality, while RI-SUVmax of 6.6%, malignant etiology (75.0%/80.0%).
Conclusions: In this study, the sequential DTP scanning protocol improved the sensitivity and specificity of the PET/CT method in terms of differential diagnosis within the larynx.

1. Background

The role of imaging in laryngeal cancer patients is to identify the tumor's size, its localization and lymph nodes involvement. The accurate diagnosis helps to limit the number of indications for a significantly mutilating total laryngectomy, affecting patients' postoperative quality of life.[1,2] The vital issue in the laryngeal cancer patients' management seems to be the differentiating between chronic laryngitis and squamous cell cancer (SCC) of the larynx. High metabolic activity of the inflammation may be difficult to distinguish from a malignant tumor, which might provide false-positive results.[3–6] One of the most commonly performed studies in laryngeal cancer patients, aside from physical examination and laryngoscopy, magnetic resonance imaging (MRI) and the contrast-enhanced computed tomography (ceCT),[7,8] is the fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) study.

The standard, single-time-point 18F-FDG PET/CT (STP 18F-FDG PET/CT) studies can improve the oncological management. How-

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ever, in numerous cases, the anatomical and one-step metabolic activity assessment might be insufficient or doubtful. The analysis of 18F-FDG uptake changes over time within the region of interest (ROI), the retention index (RI-SUVmax), might be a reliable metabolic indicator, apart from maximal and mean standardized uptake value (SUVmax SUVmean). The RI-SUVmax describes the differences between SUVmax on initial and delayed scans.[6,9] Most often, the increase of SUV value over time suggests the malignancy,[2,9,10] while the decrease or constant 18F-FDG uptake within the ROI indicates a benign process. The delayed (dual-time-point, DTP) 18F-FDG PET/CT imaging provides valuable information of the glucose metabolism activity changes over time within the observed area and, therefore, may improve differential diagnosis.[6,9]

Most commonly described delayed protocols, investigated mainly in the chest region, have been performed at 60 minutes (min) and 120 min post intravenous injection (p.i.) of the 18F-FDG and at 60 and 180 min p.i.[8,9,11,12] However, using more delayed protocols demand prolonged patients' stay in the nuclear medicine department, which – apart from discomfort – may cause increased radiation exposure for patients and personnel. Therefore, in this study, we have presented the value of sequential DTP 18F-FDG PET/CT scanning protocol, performed at 60 and 90 min p.i. of the 18F-FDG as possibly equally useful but less time-consuming procedure when compared with more delayed protocols.

2. Aim

The aim of this study was to evaluate the usefulness of the sequential DTP 18F-FDG PET/CT study protocol in distinguishing laryngitis and larynx cancer.

3. Materials and methods

3.1. Bioethics

The study was designed per the principles of the Declaration of Helsinki. The study was performed upon receipt of the patients' written informed consent and approved by the Local Bioethical Committee as the retrospective analysis based on standardly performed procedures, conducted between January 2014 and May 2018.

3.2. Database

Ninety consecutive patients underwent DTP 18F-FDG PET/CT studies. The inclusion criteria for the diagnostic procedure were as follows: suspicious finding within the larynx of unknown primary with abnormal lesions within the larynx on PET scan. Patients who received any treatment before the PET/CT procedure or in whom DTP protocol criteria were not available were excluded from the analysis. We divided the database into the following groups: normal larynx with no abnormal 18F-FDG uptake observed (lower or comparable to local blood vessels; 30 structures), histologically confirmed inflammation of non-specified origin (granulocytic infiltration; 30 lesions) and SCC larynx (30 primary tumors). We additionally performed an analysis for all structures organized in one group. The above groups were homogenous in terms of age and number of analyzed areas in the region of interest (ROI). Table 1 shows the epidemiological characteristics of studied groups.

Table 1
Epidemiology.

Characteristic	Normal	Laryngitis	Tumor	All structures
	Value			
Women and men	30	30	30	90
Mean age ± SD (years)	62 ± 12	62 ± 9	60 ± 13	61 ± 11
Range (years)	41–80	45–84	48–77	41–84
Women	13	7	3	23
Mean age ± SD (years)	62 ± 7	64 ± 10	60 ± 14	63 ± 10
Range (years)	51–72	52–84	52–77	51–84
Men	17	23	27	67
Mean age ± SD (years)	62 ± 13	61 ± 8	60 ± 13	61 ± 11
Range (years)	41–80	45–52	48–76	41–80

Table 2
The study protocol.

Phase and area of scanning	Characteristic	Value
Initial 60 min p.i.	avg start time p.i. ± SD (min)	63 ± 4
Whole body	Range p.i. (min)	55–67
scanning: skull apex –	avg scanning length (min)	20 ± 2
half-thigh	Range (min)	16–20
Delayed 90 min p.i.	avg start time p.i. ± SD (min)	92 ± 3
Head and neck	Range p.i. (min)	75–94
region: skull apex –	avg scanning lenght (min)	7 ± 2
aortic arch	Range (min)	5–9
Initial and delayed	avg total delay between phases (min)	6 ± 2
	Range (min)	4–7

3.3. Patients' preparation, scanning protocol structure and technical conditions

According to standard preparation protocol, patients fasted for at least 6 hours (h)[9,11] before the scanning procedure, avoided increased physical activity or low-temperature environment in 48 h prior to the study.[14] The 18F-FDG administration preceded the glucose level measurement (the maximal approved level was 150 milligrams per deciliter; mg/dL). Before the examination, patients were asked to remove all metal and plastic elements from their clothing which might disturb PET images reconstruction. An important element of the preparation protocol was the emptying of the urinary bladder due to the high radiopharmaceutical concentration in the urine bladder, which would lower the diagnostic accuracy of the images (not-bounded 18F activity influences the metabolic activity measurements and decreases image resolution). The radiopharmaceutical 18F-FDG was administered in the activity of 3.7 mega Becquerels per kilogram (MBq/kg), mean activity: 301.2 MBq, range: 283.7–305.6 MBq). We performed sequentially delayed examinations with the hybrid PET/CT scanner Gemini TF 16 (Philips, Cleveland, Ohio) with comparable technical conditions in both phases of scanning. The Body Low-Dose CT preceded PET scanning in the first and the delayed phase using beam energy of 120 kilovoltage peak (kVp), beam amperage of 150–200 milliampere-seconds (mAs), Pitch of 0.8 and tube rotation 0.5 second (s). We used a spatial resolution of the image of 5 mm in the first and 3 mm in the delayed phase of scanning. PET scans were performed with the time per section of 1:30 min. We have limited the delayed scanning to the head and neck region only considering patients' radiation safety and avoiding repositioning between phases. All patients underwent the sequential DTP 18F-FDG PET/CT acquisitions as shown in Table 2.

The total time of scanning did not exceed 36 min in any patient. The delay between phases of imaging resulted from the necessity of preparing the head and neck study protocol.

3.4. Method of segmentation and measurements

We evaluated the metabolic activity and its change over time within the larynx using the semi-automatic method of contouring with 50% background cut-off (Philips Fusion Viewer software; Fig. 1).

We analyzed the PET-dedicated indices: SUVmax, SUVmean (automatically-measured) and the SUVmax value surrogate – RI-

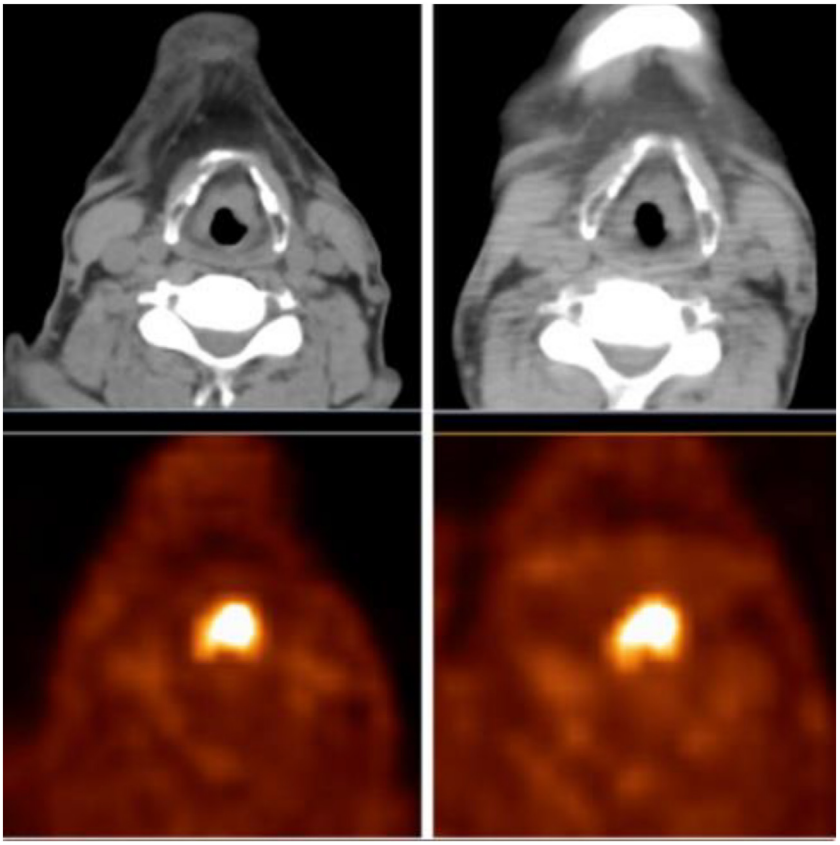


Fig. 1. The method of segmentation – laryngeal cancer (source: original figure).

SUVmax (calculated only for the SUVmax value analysis purposes; obtained manually), recommended for the initial and delayed metabolic activity comparison purposes. The following equations describe the above-mentioned indices[2,6,9,12]:

$$SUVmax = maximum\,tissue\,concentration\,[Mbq/kg] \Big/ (injected\,dose[Mbq]/body\,weight\,[kg])$$

$$SUVmean = average\,tissue\,concentration\,[Mbq/kg] \Big/ (injected\,dose[Mbq]/body\,weight\,[kg])$$

$$RI - SUVmax = 100\% \times [(SUVmax90\,min\,p.i. - SUVmax60\,min\,p.i.) \Big/ SUVmax60\,min\,p.i.)]$$

4. Results

4.1. The phantom simulation

We performed the phantom simulation to show the spatial resolution modification and to prove that the time shift does not affect the SUV value levels. We used five samples of different volume and radiopharmaceutical's activity (Fig. 2). We found that the SUV values measurements did not change significantly when there were no metabolically active lesions within the ROI nor when the technical parameters were changed.

4.2. Statistical analysis

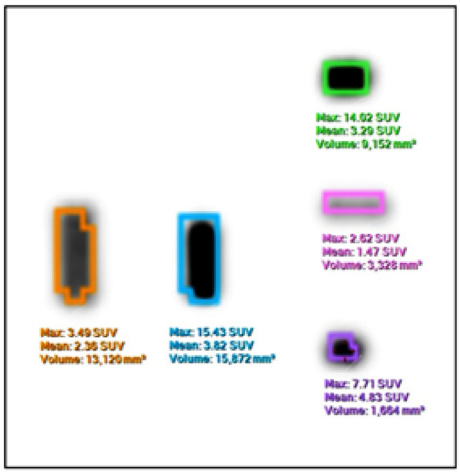
We used the *Statistica*, Statsoft, Poland, software to perform the necessary statistical analyses. We considered 5% as the statistical significance threshold. We evaluated the differences between groups and parameters levels using the following statistical tests: *t*-test for dependent variables, *U* Mann–Whitney's, Wilcoxon's pair and Kruskal–Wallis's test.

4.3. The SUVmax, SUVmean, RI-SUVmax values evaluation

In this study, we observed low and significantly decreasing SUVmax and SUVmean values levels within the normal larynx. The metabolic activity level within the areas of laryngitis was high but constant over time. The 18F-FDG uptake within cancer lesions was the highest and significantly increased over time (Table 3). When we collected all data in one group of structures, we found no significant differences between SUV values changes over time.

4.4. Differential diagnosis

The most clinically challenging analysis was to evaluate the predictive SUVmax and RI-SUVmax cut-off values which might help in the differential diagnosis of normal versus (vs) abnormal metabolic activity within the larynx and in distinguishing laryngitis from the larynx cancer. Since the SUVmean value is an estimated parameter which depends on many factors (i.e. the metabolic activity of close-lying structures and the SUVmax value), the SUVmean value cut-off analysis was omitted. The SUVmax, RI-SUVmax cut-off values obtained with the ROC analysis, which suggests abnormality is shown in Figs. 3 and 4 and Table 4.



	SUVmax		
Volume	Initial phase, 5mm*	Delayed phase, 5mm	Delayed phase, 3mm
2.000mm3	7.69	7.7	7.71
4.000mm3	2.61	2.62	2.67
10.000mm3	14.03	13.99	14.02
15.000mm3	3.51	3.49	3.49
20.000mm3	15.56	14.42	15.46

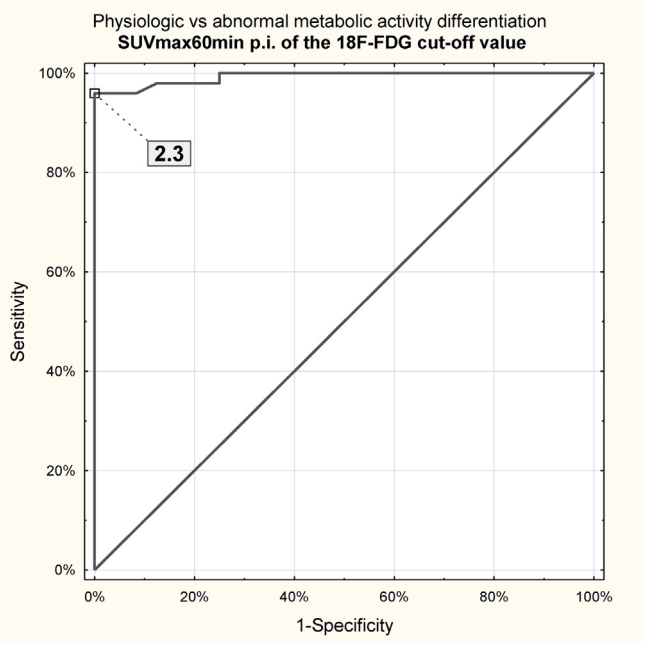
*spatial resolution

Fig. 2. The phantom simulation (source: original figure).

Table 3
The metabolic indices measurements: SUVmax, SUVmean, RI-SUVmax.

Group	Normal	Laryngitis	Tumor	All structures
Characteristic	Value			
avg SUVmax60min ± SD	1.8 ± 0.4	4.1 ± 1.6	5.3 ± 1.7	3.7 ± 2.0
Range	1.1–2.3	2.1–7.1	2.8–8.3	1.1–8.3
avg SUVmax90min ± SD	1.6 ± 0.4	4.1 ± 1.6	6.0 ± 2.0	3.9 ± 2.3
Range	1.0–2.1	2.1–7.8	3.3–9.4	1.1–9.4
avg SUVmean60min ± SD	1.2 ± 0.3	2.9 ± 1.1	4.1 ± 2.4	2.7 ± 1.9
Range	0.8–1.8	1.4–5.8	2.4–10.7	0.7–10.7
avg SUVmean90min ± SD	1.2 ± 0.2	2.9 ± 1.1	4.5 ± 2.8	2.8 ± 2.2
Range	0.6–1.7	1.6–5.0	2.4–11.8	0.6–11.8
avg RI-SUVmax (%)	−9.1 ± 1.0	+0.3 ± 9.6	+11.9 ± 13.5	1.1 ± 13.7
Range	−35 to +11	−19.3 to +15.9	−13.4 to +46.1	−35 to +46.1
Change over time	Decreasing	No change	Increasing	No change*
p-Value: change	<0.001	0.98	<0.001	0.12

* Insignificant increase of the SUV value over time.



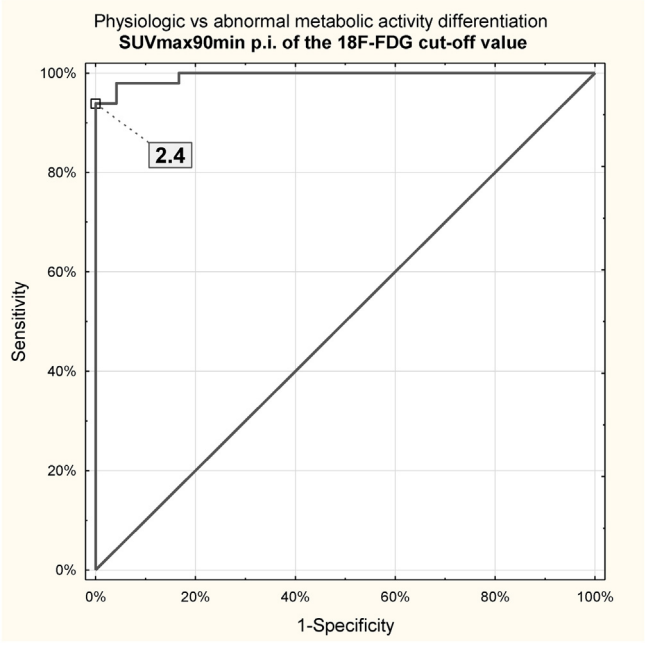


Fig. 3. Physiologic vs. abnormal metabolic activity: the SUVmax cut-off value at 60 min p.i. of the 18F-FDG (source: original figure).

Fig. 4. Physiologic vs. abnormal metabolic activity: the SUVmax cut-off value at 90 min p.i. of the 18F-FDG (source: original figure).

Table 4
The ROC analysis report: physiologic and abnormal structures differentiation.

Parameter	SUVmax60min	SUVmax90min	RI-SUVmax (%)
Characteristic	Value		
Cut-off value	2.3	2.4	1.3
Sensitivity/Specificity (%)	96.4/100	94.2/100	71.4/88.1
AUC (%)	99.3	99.5	82.8
Youden Index (%)	93.9	95.9	58.8
p-Value*	<0.001	<0.001	<0.001

* Differences between groups significant when $p < 0.05$.

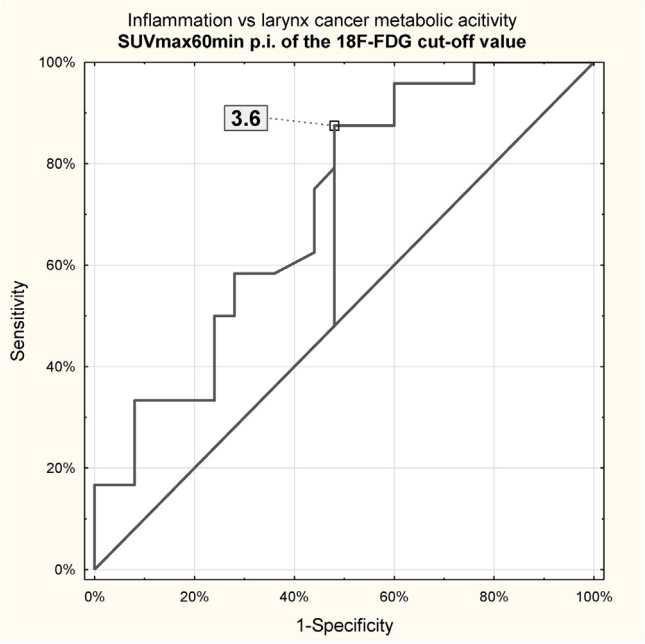


Fig. 5. Laryngitis vs. larynx cancer: the SUVmax cut-off value at 60 min p.i. of the 18F-FDG (source: original figure).

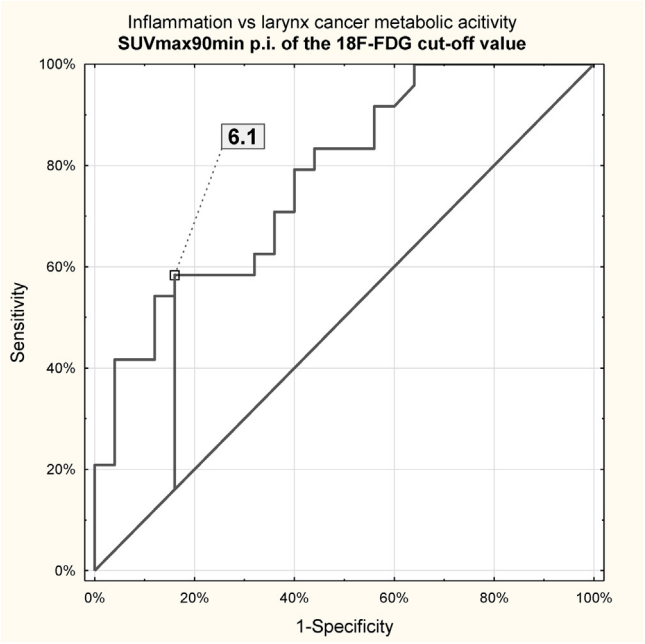


Fig. 6. Laryngitis vs. larynx cancer: the SUVmax cut-off value at 90 min p.i. of the 18F-FDG (source: original figure).

Table 5
The ROC analysis report – laryngitis and larynx cancer differentiation.

Parameter	SUVmax60min	SUVmax90min	RI-SUVmax (%)
Characteristic	Value		
Cut-off value	3.6	6.1	6.6
Sensitivity/Specificity (%)	87.5/52.0	58.3/84.0	75.0/80.0
AUC (%)	71.1	77.6	79.1
Youden Index (%)	39.5	42.3	55.0
p-Value*	<0.001	<0.001	<0.001

* Differences between groups significant when $p < 0.05$.

The SUVmax cut-off value at 60, 90 min p.i. of the 18F-FDG distinguishing laryngitis and larynx cancer are shown in Figs. 5 and 6. The ROC analysis report indicated delayed scanning as less sensitive but more specific than standard single-time-point imaging (Table 5). We observed a significant difference in SUVmax values on initial and delayed scans ($p < 0.001$).

5. Discussion

In this study, we evaluated the usefulness of the sequential DTP 18F-FDG PET/CT study protocol at 60 and 90 min p.i. in terms of benign and malignant lesions differential diagnosis within the larynx. In accordance with the previously published data,[8,9,11–13] the delayed imaging may improve the specificity of the PET/CT method in the differential diagnosis of benign and neoplastic lesions in breast cancer patients as well as soft tissue sarcomas, lymphomas and, in some cases, of lung cancer patients. Furthermore, the DTP studies have been successfully used in the hepatic lesions examinations and recurrent rectal cancer assessment. Despite the widespread clinical use, the biphasic protocol has not been widely investigated in terms of differential diagnosis within the head and neck region.

According to some authors,[9,10,15–17] the 18F-FDG uptake increases over time within malignant tumors, while within normal and non-malignant lesions, the metabolic activity changes tendency over time would be most likely reversed. However, the analysis of the 18F-FDG PET/CT scans showed that high and increasing over time SUV value level could be observed within inflammatory and cancer lesions as well.[8,9] In that case, the calculation of the SUV value changes over time may suggest the etiology of the evaluated lesion (benign vs. malignant). In this study, we observed the high glucose uptake within laryngitis and cancer lesions and low glucose metabolism activity level within normal larynx mucosa. While the sensitivity and specificity of the initial scanning assessment in distinguishing normal and abnormal 18F-FDG uptake was high (96.4%, 100%, respectively), the review of initial scans in terms of differentiating between laryngitis and larynx cancer infiltration showed low specificity of the method when compared to delayed images (52.0%, 84.0%, respectively). According to our results, the sequential DTP protocol can differentiate between normal and abnormal metabolic activity regardless of the etiology of the lesion with the specificity of up to 100%.

The crucial step of the analysis in our protocol was to obtain the predictive SUVmax and the RI-SUVmax cut-off values, which might differentiate between normal and abnormal glucose metabolism activity and distinguish between laryngitis and larynx cancer. Based on the ROC analysis results, the SUVmax, RI-SUVmax cut-off values which suggest abnormality at 60 and 90 min p.i. scans were 2.3%, 2.4% and 1.3%, respectively. When comparing laryngitis and larynx tumor, the cut-off values were 3.6 and 6.1, respectively, and the SUV value increase over time by 6.6% suggested a malignant etiology. When compared to the available literature,[11–13,18] we found our results comparable with those obtained by the authors investigating different anatomical regions with delayed protocols

performed at 60 and 120 min and 60 and 180 min p.i. of the 18F-FDG.

We found that the sequential DTP 18F-FDG PET/CT studies helped to collect the valuable pieces of information about the lesions' metabolism and made the scanning less time-consuming, more convenient considering patient's comfort, radiation safety and more accessible for the investigator than other delayed protocols. Moreover, sequentially performed imaging helped to avoid patients' repositioning between phases of scanning, which resulted in more stable structures segmentation and SUV value measurements.

6. Conclusions

In this study, the sequential DTP scanning protocol improved the sensitivity and specificity of the PET/CT method in terms of differential diagnosis within the larynx.

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Conflict of interest

None declared.

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