Original Article

Diagnostic Accuracy of Dual-Time-Point Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography in Verification Local Recurrence in Pancreatic Cancer Patients

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Abstract

Purpose: The aim of this study was to evaluate the accuracy of dual-time point in differentiating benign from malignant local recurrent lesions in pancreatic cancer. **Patients and Methods:** Thirty-four patients with pancreatic cancer (22 males and 12 females, mean age: 58.3 ± 10.3) who presented with soft-tissue lesions at the operative bed. Early whole-body positron emission tomography/computed tomography (PET/CT) and delayed imaging on the abdomen were performed. The maximum standardized uptake value (SUVmax) of the initial image (SUVmax E) and the delayed image (SUVmax D) were determined. A Retention Index (RI) was also calculated. These indices were correlated with histopathology and follow-up as reference criteria. **Results:** No significant statistical difference in SUVmaxE was found between benign and malignant lesions, while SUVmaxD and RI of the malignant lesions (mean 8.6 ± 2.7 and 35.8 ± 18.3, respectively) were significantly higher than those of benign ones (mean 3.3 ± 1.4 and-6.2 ± 15.2, respectively) ($P < 0.005$). With SUVmaxD 4.9, malignancy could be predicted with the highest sensitivity (95.8%) and accuracy (94.1%) between the whole parameters. The estimated negative and positive predictive values (PPVs) were 90.0% and 95.8%, respectively. A cutoff point 16 for RI showed higher specificity and PPV (100% and 100%, respectively). Forty-seven total (11 benign and 36 malignant) lesions were identified. Increased SUVmax is noted on delayed images in most of malignant lesions, except for two that maintained stationary. **Conclusion:** Dual-time-point 18F fluorodeoxyglucose-PET/CT seems to be a reliable additional method to differentiate between malignant and benign postoperative local soft-tissue lesions in patients with pancreatic cancer.

Keywords: *Dual time point, fluorodeoxyglucose-positron emission tomography/computed tomography, pancreatic lesion, Retention Index, maximum standardized uptake value*

Introduction

Pancreatic cancer is considered one of the most lethal malignancies in the world.[1] It is already advanced at the time of diagnosis in the majority of cases, and only 10%–20% of patients will be considered for curative surgery.[2,3] A median OS of 11–23 months is reported following surgical resection with a 5-year overall survival (OS) of ~20%[4,5] Furthermore, within the first 1 year after curative surgery, 60% of patients experience local and systemic relapse.[4]

Adjuvant chemotherapy is considered the standard of care for resectable pancreatic cancer.[6,7] Early detection of tumor recurrence is very important, as it changes the therapeutic plan. Postoperative follow-up by serum Ca19-9 level and the use of 18F fluorodeoxyglucose (FDG)-positron emission tomography (PET) as a predictor for tumor recurrence has been well established.[8] Differentiation between benign and malignant recurrent soft-tissue lesions is very important to avoid unnecessary surgery and to improve the quality of life of the patient. The aim of this study is to evaluate the added value of dual-time-point FDG-PET/computed tomography (PET/CT) in detection of local recurrence on patients with pancreatic cancer.

Patients and Methods

This retrospective study was conducted on 34 patients with histopathologically proven pancreatic carcinoma, presented with suspected local recurrence. They were referred to Nuclear Medicine Unit in National Cancer Institute Egypt (NCI) from January 2017 to December 2018 for

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18F FDG-PET/CT scan. Clinical information, including sex, age, detailed pathology, laboratory data, and different therapeutics approach was extracted from the medical files. Inclusion criteria include age above 18 years old, histopathologically proved pancreatic cancer (with different pathological types), underwent surgical resection (Whipple surgery, partial pancreatectomy, and total pancreatectomy), and patient received chemotherapy, radiotherapy, or both, according to guidelines. Exclusion criteria include age below 18 years and patients having second primary. All patients were informed about details of the study with a written consent approval.

Imaging

18F-fluorodeoxyglucose-positron emission tomography/computed tomography

Procedure

All patients fasted for 4–6 h prior to the examination. Blood glucose levels did not exceed 170 mg/dL. The procedure details are explained to all patients. The first scan, a whole-body image from skull down to mid-thigh, was performed with a mean time from injection of were 60 min (range, 45–110 min), with a delayed PET/CT images of the upper abdomen was required 110 min (range, 90–150 min).

The number of bed positions was adjusted to cover the early whole body with acquisition time, 2–3 min/bed position using a dedicated PET-CT scanner (GE, PET/CT Discovery) which integrates a PET scanner with a dual-section helical CT scanner and allows the acquisition of coregistered CT and PET images in one session. Intravenous contrast agent was administered in most patients in a dose of (1.4 ml/kg body weight), that was automated injected with an overall injection time of 32s, except those with certain contraindication initially. Patients were examined in the supine position with arms elevated, with a CT scanning of: 40 mAs; 120 kV was acquired. PET scanning over the same region was performed after CT images acquisition. Attenuation correction using the reconstructed CT data with 5-mm slices reconstructed images was applied using standard iterative algorithm (ordered-subset expectation maximization).

Interpretation

Images were interpreted at a workstation equipped with fusion software (advantage Window AW version 5, GE) which enables display of the PET images, CT images, and fused PET/CT images. Side-by-side image interpretation was accomplished by two experienced nuclear medicine physicians.

Imaging interpretation

Qualitative (visual) assessment

For 18F FDG-PET/CT, visual (qualitative) interpretation was based on the presence or absence of FDG uptake at the operative bed. Positive lesions interpreted as focal well-defined uptake with increased contrast with time. No uptake or faint uptake reduces over time was defined as negative lesions.

Quantitative assessment

The maximum standardized uptake values were recorded for each lesion after manual application of the regions of interest around the areas demonstrating the greatest accumulation of 18F-FDG on the transaxial attenuation-corrected PET slices, at both early and delayed images (maximum standardized uptake value [SUVmax] E) and (SUVmaxD), respectively. From these semi-quantitative indices, the Retention Index (RI) was calculated using the following equation:

RI = (SUVmaxD − SUVmaxE) ×100/SUVmaxE. These indices were correlated with histopathology and follow-up as reference criteria.

Data analysis was performed depending on the following criteria:

- True positive PET/CT results: metabolically active FDG avid operative bed soft-tissue lesion of SUVmax higher than the reference hepatic activity on early study, or positive tissue pathology in unascertained lesions
- True-negative PET/CT results: CT and PET/CT results within 1 month agreed with clinical follow up (after 3–9 months) were free
- False-positive PET/CT results: Hypermetabolic FDG-avid lesion proved to be benign using pathology (excision or biopsy) or follow-up studies
- False-negative PET/CT results: soft-tissue lesion of low FDG activity of SUV max that show significant progression on the follow-up images, malignant pathology by biopsy, or after excision.

Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Standard diagnostic indices, including sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic efficacy were calculated. ROC curve was constructed with area under curve analysis performed to detect the best cutoff value of different parameters for detection of recurrence. Comparisons between quantitative variables were done using the nonparametric Mann–Whitney test. For comparing categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency is <5. $P < 0.05$ was considered as statistically significant.

Results

Patient characteristics

A consecutive 34 pancreatic cancer patients referred to perform PET/CT examination in the period from January 2017 to December 2018 at NCI, Egypt, were analyzed in the present study. 12 females and 22 males the age of patients ranged from 40 to 78 years with a mean of 58.3 ± 10.3. Their clinicopathological data were analyzed in Table 1.

According to clinical staging, Stage III was more prevalent, including 16 patient followed by Stage II. All patients treated by resection of the primary and nearby lymph nodes if present followed by chemotherapy and/or radiotherapy.

The final diagnosis was confirmed by histologic examination in 14 patients (either by biopsy or surgical resection) and in 20 patients by the clinical, laboratory, and imaging follow-up. Increase in size of detected lesion by CT detected in nine patients associated with increased serum tumor markers, while regression was seen in other four patients, seven patients underwent follow-up FDG-PET/CT which revealed progression in size and metabolic activity in four patients, and CMR in three ones.

Twenty-four patients proved to have local recurrence, while the remaining 10 patients showed posttherapy benign changes.

Comparison of positron emission tomography parameters between malignant and benign pancreatic operative bed lesions

Comparisons of different indices of dual-time-point FDG-PET/CT between benign and malignant operative bed recurrent lesions were done and results are shown in Figure 1 and Table 2.

Table 1: Demographic data of included 34 patients with suspected local recurrent pancreatic cancer

Criteria	Data analysis
Age (mean±SD)	58.3±10.3 SD
Pathology	
Adenocarcinoma	25
Mucinous adenocarcinoma	5
Others	3
Stage	
Ia	3
Ib	3
IIa	4
IIb	8
III	16
Surgery	
Whipple surgery	23
Partial pancreatectomy	10
Total pancreatectomy	1
Postoperative therapy	
Chemotherapy	12
Radiotherapy	8
Chemotherapy + radiotherapy	4
None	10

SD: Standard deviation

SUVmaxE was of the malignant lesions was higher than that of benign ones, yet failed to achieve statistically significance difference (malignant, 5.5 ± 2.02 vs. benign, 3.45 ± 1.30; $P = 0.123$) [Figure 1a]. SUVmaxD showed that higher values of the malignant lesions compared to the benign lesions with significant difference between two groups were found (8.63 ± 2.70 vs. 3.30 ± 1.42; $P < 0.001$ for malignant and benign lesions, respectively) [Figure 1b]. RI of malignant lesions proved to be also of statistical significance being higher than that of benign lesions (35.8. ± 18.3% vs-6.2 ± 15.2%; $P = 0.007$) [Figure 1c].

Forty-seven total lesions were detected in 34 patients (mean size 3.28 ± 0.96), 11 lesions in 9 patients were proven benign (5 by histopathology and 4 in follow-up), while 36 malignant lesions were identified. An increase in SUVmax is noted on delayed images in most of malignant lesions compared with the initial ones, except for two lesions that maintained stationary. Regarding the group of the benign lesions, 45.5% (5/11) showed decrease in SUVmax, four elicit no change, while mild increase in SUVmax is observed on two lesions, yet with ratio <1.5. True and false positive and negative results regarding different parameters are illustrated in Table 3.

Aiming to improve FDG-PET accuracy in differentiating postoperative pancreatic bed malignant recurrent from benign lesions, quantitative analysis was used where maximum counts of regions of interest were estimated over CT suspected lesion in both early and delayed PET images. RI was also calculated. Receiver operator characteristic (ROC) curve analysis marked 4.4 and 4.9 as optimal cutoff points for early and delayed scans and 16 as a cutoff value for the RI. The area under the curve of SUVmaxD was 0.969 (95% confidence interval [CI] = 0.918–1.000), and RI was 0.963 (95% CI = 0.9.06–1.000) [Table 4 and Figures 2 and 3].

When a SUVmax of 4.9 on the second image (SUVmaxD) is used as a cutoff threshold, malignancy could be predicted with the highest sensitivity between the whole parameters of 95.8% with specificity of 90%. With a RI cutoff of 16%, malignant recurrent lesions on PET/CT could be expected with a sensitivity of 87.5% yet with the maximum specificity of 100%.

Aiming to enhance the accuracy of interpretation, logistic regression was done to detect recurrence using combined SUVmaxD and RI. A crosstab for relation between actual recurrence and predicted recurrence from regression model of combination of SUVmaxD and RI, showed sensitivity = 95.8% and specificity = 100% [Table 5].

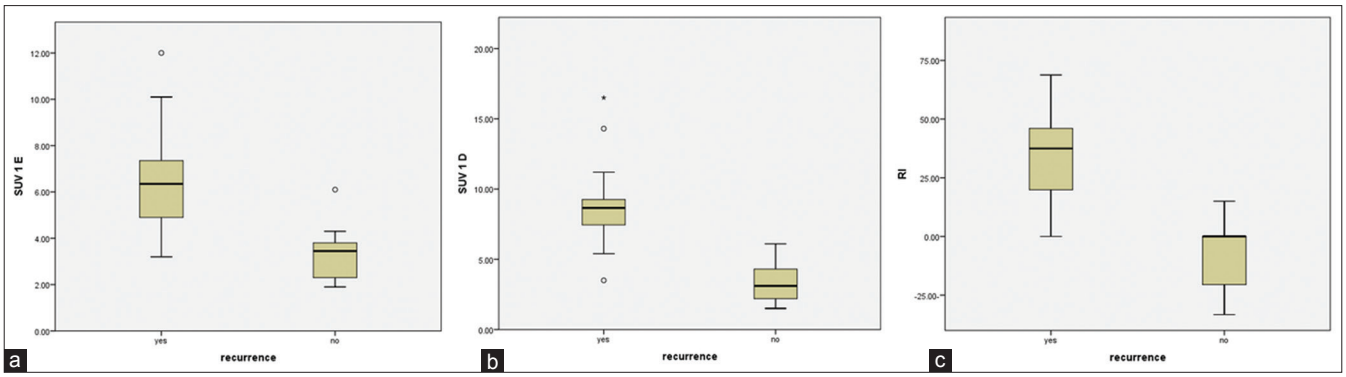

Figure 1: Comparison of semiquantitative indices (early maximum standardized uptake value E (a), delayed maximum standardized uptake value D (b), and Retention Index (c), of dualtimepoint fluorodeoxyglucosepositron emission tomography/computed tomography between local recurrent malignant and benign pancreatic lesions

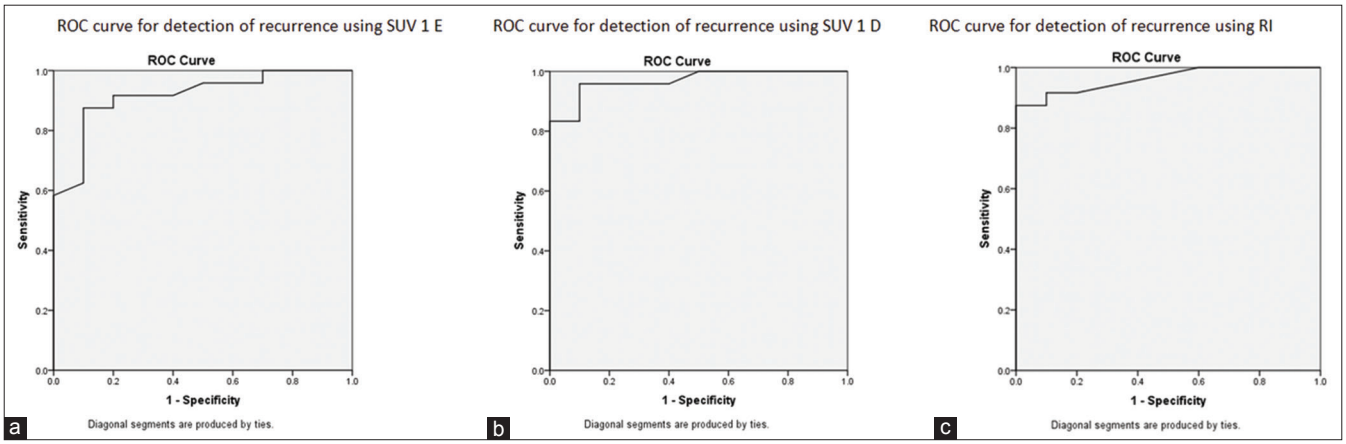

Figure 2: Receiver operator characteristic curves for comparing determined cutoff values with sensitivity and specificity of positron emission tomography parameters. (a) The area under the curve value from the receiver operator characteristic curve of maximum standardized uptake value E was 0.917. (b) maximum standardized uptake value D cutoff of 0.969 for dual-time-point positron emission tomography/computed tomography and (c) the Retention Index with cutoff 16

Table 2: Comparison between different positron emission tomography/computed tomography semi-quantitative parameters in local recurrent malignant and benign pancreatic lesions

	Recurrence								*P*
	Yes				No				
	Mean±SD	Median	Minimum	Maximum	Mean±SD	Median	Minimum	Maximum	
Age	57.75±9.54	57.50	41.00	78.00	59.60±12.39	60.00	40.00	78.00	0.838
size	3.28±0.96	3.10	1.50	5.00	2.42±1.56	1.95	1.00	6.00	0.020
SUV 1 E	5.50±2.02	5.25	3.20	11.00	3.45±1.30	3.34	2.30	5.10	<0.123
SUV 1 D	8.63±2.70	8.65	3.50	16.50	3.32±1.42	3.10	1.50	6.10	<0.001
RI	35.86±18.38	37.50	0.00	68.80	-6.20±15.26	0.00	-33.30-	15.00	<0.001
Tumor marker	475.29±613.03	271.00	62.00	2980.00	66.90±30.80	61.00	26.00	115.00	<0.001

SD: Standard deviation, SUV: Standard uptake value, RI: Retention Index

Discussion

The role of FDG-PET/CT for pancreatic cancer is well established for initial staging, diagnosis of recurrence, monitoring therapy, and predicting prognosis.[9] Although FDG uptake is generally higher in neoplastic lesions than in benign ones, it is sometimes difficult to differentiate between them which can give rise to false-positive or equivocal FDG-PET findings.

Dual-time-point FDG-PET/CT is introduced to explain the differences in the FDG kinetics between benign and malignant pathologic entities.[10-18] The uptake of FDG in malignant lesions reach a maximum within 2–4 h of injection, whereas most inflammatory lesions typically achieve maximum uptake within 1 h. FDG-PET images at two different time points are believed to be helpful in differentiating benign from malignant lesions, as malignant

tissue tends to increase in uptake between the two images, whereas benign lesions remain stationary or slightly decrease with time.[10-18]

The purpose of the current study is to investigate the added value of dual-point FDG-PET/CT for the differentiation of malignant from benign operative bed soft-tissue lesions in pancreatic cancer patients through demonstrating the relationship between the semi-quantitative indices of dual-time-point PET/CT. The results illustrated that delayed SUVmax and RI showed higher values of the malignant lesions compared to the benign lesions with significant difference between the two groups was found. The early SUVmax of the malignant lesions also was higher than that of benign ones, yet failed to achieve statistical significance. With demonstrated RI of 16, it showed the highest specificity (100%) on detected malignant lesions with an accuracy of ~92%.

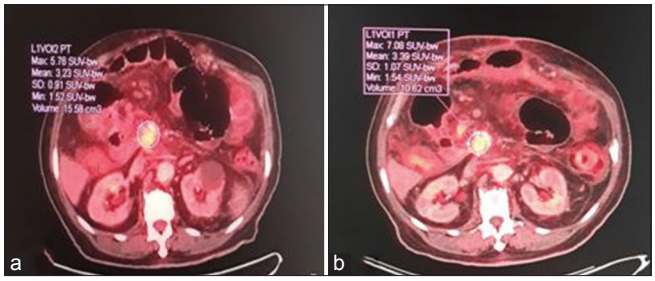

Figure 3: A 54-year-old patient with a history of Whipple operation for pancreatic head cancer adenocarcinoma. (a) Focal fluorodeoxyglucose uptake is detected at the operative bed early (1 h) axial positron emission tomography/computed tomography fusion image showing (maximum standardized uptake value E: 5.7). (b) The 2-h axial positron emission tomography/computed tomography fusion image showed increased 18F-fluorodeoxyglucose uptake (maximum standardized uptake value D: 7.1). This soft-tissue lesion was confirmed local malignant recurrence by pathology

Table 3: Comparison of different detection parameter of positron emission tomography/computed tomography and diagnostic computed tomography

	TP	TN	FP	FN
CT	21	5	5	2
SUVmaxE	23	6	4	1
SUVmaxD	23	7	3	1
RI	21	9	1	3

TP: True positive, TN: True negative, FP: False positive, FN: False negative, RI: Retention Index, CT: Computed tomography, SUVmaxE: Maximum standard uptake value early, SUVmaxD: Maximum standard uptake value delayed

This study is considered one of other few studies described the value of dual-time-point FDG on pancreatic cancer. Nakamoto *et al*. evaluate the optimal time for FDG-PET/CT in preoperative pancreatic lesions with different conclusions,[19,20] the first one conclude that delayed 2 h scan may contribute to differentiation between malignant and benign lesions in the pancreas. In contrary to the other study showed no significant statistical differences in diagnostic accuracy when either 1 or 2 h images were interpreted.

Our results are agreed with other numerous other studies which have reported promising results of dual-time-point FDG-PET/CT in differentiating malignant from benign lesions, in different conditions.[10,13,15-24]

Two studies evaluated dual-time-point FDG-PET in malignant lung nodules , the first concluded that it has a potential impact on increasing its diagnostic accuracy. (10) while the other studies showed no prognostic value of the dual-time-point FDG for OS and diseasefree survival in surgically resected early-stage NSCLC.[21]

Uesaka *et al*.[22] also examined the dual-time-FDG in pulmonary nodules and stated that RI SUV raised the accuracy for metastatic lung nodules and was superior to both early and delayed scans in differentiating malignant from nonmetastatic uptake. Kumar *et al* showed that dual-time-point shows higher sensitivity and specificity in differentiating inflammatory breast conditions from malignant lesions.[14]

Regarding bone tumors, it may provide more help in the differentiation of malignant tumors from benign ones, as concluded by Tian *et al*.[18]

For pediatric tumors, dual-time-point FDG-PET/CT proved to be useful in distinguishing malignant from benign lesions in pediatric patients.[23]

Furthermore, Sinae suggests that dual-time-point FDG-PET/CT imaging seems to have a complementary role to discriminate malignant from benign incidental thyroid lesions.[24]

Table 4: Performance of different cutoff values in the detection of local tumor recurrence in cases with pancreatic cancer (*n*=34 patients)

	Area under the curve	*P*	95% CI		Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
			Lower bound	Upper bound						
SUVmaxE	0.917	<0.001	0.819	1.000	4.4	87.5	90	95.45	75.00	88.24
SUVmaxD	0.969	<0.001	0.918	1.000	4.9	95.8	90	95.83	90	94.12
RI	0.963	<0.001	0.906	1.000	16	87.5	100	100	76.92	91.18

SUVmaxE: Maximum standard uptake value early, SUVmaxD: Maximum standard uptake value delayed, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, RI: Retention Index

Table 5: Performance of combined maximum standard uptake value delayed and Retention Index in the detection of pancreatic local tumor recurrence (*n*=34 patients)

Predicted group	Recurrence			
	Yes		No	
	Count	Column, *n* (%)	Count	Column, *n* (%)
Yes	23	95.8	0	0.0
No	1	4.2	10	100.0

*Sensitivity=95.8% and specificity=100%

In the current study, an increase in SUVmax was noted on delayed images in most of malignant lesions compared with the initial ones, except for two lesions that maintained stationary. Regarding the group of the benign lesions, 45.5% (5/11) showed decrease in SUVmax, four elicit no change, while mild increase in SUVmax is observed on two lesions, yet with ratio of <1.5. This can be explained by the nature of some inflammatory lesions which may show increased uptake over time.

Therefore, we may suggest that focal FDG uptake at pancreatic operative bed which shows decreased SUVmax on delayed scan could be predicted as a benign lesion and better to avoid further invasive diagnostic procedures such as biopsy, and the patients should be kept under follow-up. However the other lesions with significantly increased activity should be considered malignant. Differentiation between benign and malignant lesions prevents unnecessary surgical procedure and improves the quality of patient's life. However, we still have the few patients with indeterminate low-grade activity and patient with unchanged lesion FDG uptake between the early and the delayed images, correlation with the clinical data, serum tumor marker, and maybe other functional radiologic imaging may help.

The limitations of the present study include: First, this is a highly selected and retrospective study. Second, a small number of participants with relatively short period of follow-up. Third, PET parameters using dual-time-point imaging depending on SUVmax being not fully accurate and unfortunately affected by many factors, so it lacks proper standardization. Finally, SUVmax reflects only the most active part of the tumor and does not represent its overall characteristics, so assessment by other PET parameters as TLG and MTV can be more accurate.

Conclusion

SUVmaxD and RI show higher diagnostic accuracy of the local recurrent pancreatic malignant lesions. Therefore, dual-time-point FDG-PET/CT could be considered a simple and noninvasive diagnostic tool in evaluating local recurrent lesions in patients with pancreatic cancer.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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