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Baseline 18F-FDG PET/CT as predictor of the pathological response to neoadjuvant therapy in esophageal cancer

A retrospective study

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Abstract

The type of pathological response to neoadjuvant chemoradiation in patients with locally advanced esophageal cancer predicts overall survival (OS).

We aimed to assess early 18F-FDG positron emission tomography/computed tomography parameters in predicting the pathological response to neoadjuvant treatment.

The cohort included consecutive patients with locally advanced esophageal cancer who underwent baseline 18F-FDG positron emission tomography/computed tomography between September 2006 and February 2015. Positron emission tomography variables of maximum and average standardized uptake values (SUVmax, SUVaverage), metabolic tumor volume (MTV), and total lesion glycolysis were recorded in addition to computed tomography volume. MTV was calculated using cut-off values of 42%, 50% and 60% (MTV 0.42, 0.5, and 0.6) of the tumoral SUVmax. Receiver operating characteristic (ROC) analysis was used to determine sensitivity and specificity.

Sixty-one patients (44 male, 17 female) fulfilled the inclusion criteria. Only MTV values of 13.6 mL (MTV 0.42) and 7.4 mL (MTV 0.5) remained significant on ROC analysis, with an area under the curve of 0.690 (confidence interval 0.557–0.823, p = .02] and 0.664 (confidence interval 0.527–0.802, $P = .048$), respectively in differentiating patients with a complete (n = 44) or incomplete (n = 17) pathological response.

MTV at presentation is associated with the pathological response to neoadjuvant chemoradiation in patients with locally advanced esophageal cancer.

Abbreviations: CRT = chemoradiation, CT = computed tomography, FDG = fluorodeoxyglucose, GEJ = gastro-esophageal junction, LN = lymph node, MTV = metabolic tumor volume, OS = overall survival, pCR = pathological complete response, PET = positron emission tomography, ROC = receiver operating characteristic, SUV = standardized uptake value, TLG = total lesion glycolysis.

Keywords: complete pathological response, locally advanced esophageal cancer, neoadjuvant chemoradiation

1. Introduction

Neoadjuvant chemoradiation (CRT) followed by surgery is the gold-standard treatment for locally advanced squamous cell carcinoma or adenocarcinoma of the esophagus, with studies showing an improvement in overall survival (OS) compared to surgery alone.[1] Patients with a pathological complete response (pCR) to neoadjuvant CRT have a better OS than patients with a nearly complete or partial response.[2] Therefore, clinicians have sought to identify variables at presentation that can predict the pathological response to neoadjuvant CRT in order to better stratify patients and potentially alter their treatment. For instance, observation-only may benefit patients with squamous cell carcinoma and pCR according to several studies,[3] whereas upscaling the CRT regimen might be recommended in high-risk patients in whom only a partial pathological response is expected.

Whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is now standard practice in the evaluation of patients presenting with locally advanced esophageal cancer, providing important information about metabolism and anatomy. There are several reports of correlations of PET metabolic variables, such as maximal standard uptake value (SUVmax), along with variables that

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reflect tumor burden, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), with disease-free survival (DFS) and OS.[4–6] However, most studies have focused on the rate of reduction between pre- and post- treatment measurements or on the post-treatment measurements alone. Only a few evaluated the relationship of metabolic variable measurements at presentation with the pathological response to treatment.[7]

The purpose of the present study was to determine if any of the PET/CT metabolic and morphologic variables at presentation of patients with locally advanced esophageal cancer are predictive of the pathological response to neoadjuvant treatment.

2. Methods

2.1. Subjects

A retrospective cohort design was used. The study group consisted of consecutive patients with biopsy-proven locally advanced esophageal cancer (squamous cell or adenocarcinoma) who underwent baseline 18F-FDG PET/CT at a tertiary medical center between September 2006 and February 2015. Patients who did not undergo treatment with neoadjuvant CRT followed by surgery were excluded, as were patients younger than 18 years. Data on patient age, sex, and body mass index, disease stage, and pathology findings were collected by review of the electronic medical records.

The study was approved by the institutional review board with waiver of informed consent.

2.2. 18F-FDG PET/CT study

The 18F-FDG PET/CT evaluation was performed using an integrated PET/CT scanner (DiscoverySTE, GE Medical Systems, Milwaukee, WI). FDG was administered intravenously at a dose range of 370 to 666 MBq (10–18 mCi) depending on patient weight. For bowel opacification, 800 to 1000 mL of diluted iodinated contrast material was administered orally. Patients were asked to hold their breath for the CT scan. Scanning parameters were: tube voltage 120 kVp, spiral mode 0.8 s per rotation, tube current 100 mA, section thickness 3.75 mm, and interval 3.75 mm with image reconstruction every 2.5 mm. Contrast-enhanced CT was performed from skull base to mid-thigh, with tube voltage 120 kVp, spiral mode 0.8 s per rotation, modulated tube current 40–300 mA, section thickness 3.75 mm, and interval 3.75 mm with image reconstruction every 2.5 mm. Iodine contrast medium (Ultravist 300; iopromide 0.623 g/mL, Bayer Schering PharmaAG, Berlin, Germany), 1.5 cm^3/kg, was intravenously administered in all examinations, except for patients with iodine hypersensitivity or renal insufficiency. PET emission images were obtained using a weight-based protocol, with 2 min of acquisition time per bed position. Five to six bed positions from skull base to mid-thigh resulted in an acquisition time of 18–20 min. All PET images were reconstructed using an iterative algorithm, with CT-based attenuation correction. The mean estimated radiation exposure dose is about 14 mSv for whole body diagnostic CT and 7 mSv for the FDG.

2.3. Neoadjuvant regimen

Patients received neoadjuvant CRT based on one of 3 regimens: standard CROSS regimen (weekly carboplatin and paclitaxel with concurrent radiotherapy of 41.4 Gy in 23 fractions); RTOG regimen (3 cycles of cisplatin with 4–5 days of continuous infusion of 5-fluorouracil, every 4 weeks, with concurrent radiotherapy of 50.4 Gy in 28 fractions, starting on the first day of the second cycle of chemotherapy); or. Phase Ib-II investigational regimen (RTOG regimen combined with 10 weekly infusions of the anti-epidermal growth factor receptor monoclonal antibody cetuximab).

2.4. Histopathological evaluation

Tumor regression grade was scored using the College of American Pathologists system, as follows: complete response, no viable cancer cells in the surgical specimen; moderate response, single cells or small groups of cancer cells in the surgical specimen; minimal response and minimal or no tumor kill, residual cancer outgrown by fibrosis; and poor response, extensive residual cancer. Patients were divided into 2 groups of complete responders and non-complete responders on the basis of the histopathological evaluation.

2.5. Imaging analysis

The categorical variables evaluated on PET/CT images included location of the tumor (proximal, middle, distal, and distal and middle), involvement of the gastroesophageal junction and/or stomach, and presence of pathological lymph nodes (LNs) based on CT criteria (long axis > 10 mm) and PET-based criteria (LN SUVmax > mediastinum). The number of LNs was divided into groups based on the node (N) classification of the American Joint Committee for Cancer Staging 7th edition. The continuous PET-based metabolic parameters included SUVmax, SUVaverage, MTV, and TLG, for both the primary esophageal lesion and the largest LN. We used dedicated software (Volume Viewer 2, Voxtool 6.12.3, GE) that automatically defines the contour of the PET-based lesion with cut-off values of 42%, 50%, and 60% of the tumoral SUVmax (Fig. 1). SUV is a semi-quantitative index that is calculated by the ratio of FDG concentration in a selected region of interest to the injected dose which is normalized to body weight. SUVmax reflects the maximal value within a selected region of interest. TLG is the product of SUVaverage and MTV, a measure of the volume of the metabolically active areas of the tumor. We also calculated the SUVmax and SUVaverage of the liver and the lesion-to-liver SUVmax ratio. PET-based liver measurements were performed in segment 7 with a 3 cm diameter spherical volume of interest [8].

The continuous CT-based parameters included the volume of the primary tumor (CTvol) and the product of the short and long axis of the largest LN. CTvol was calculated on the basis of 3-dimensional measurements on the CT scan (volume of ellipsoid = $4/3\pi abc$). Staging was assessed using the tumor-node-metastasis (TNM) classification of the American Joint Committee for Cancer Staging 7th edition for esophageal cancer based on 18F-FDG PET/CT and endoscopic ultrasound findings. A nuclear medicine specialist (with 9 years' experience in 18F-FDG PET/CT reading) and a physician with dual certification in radiology and nuclear medicine (with 4 years' experience in FDG PET/CT reading and 9 years' experience in radiology) read the studies together. Both were blinded to the clinical data.

2.6. Statistical analysis

Continuous data are expressed as means and standard deviations, and categorical data as frequency. Continuous data were

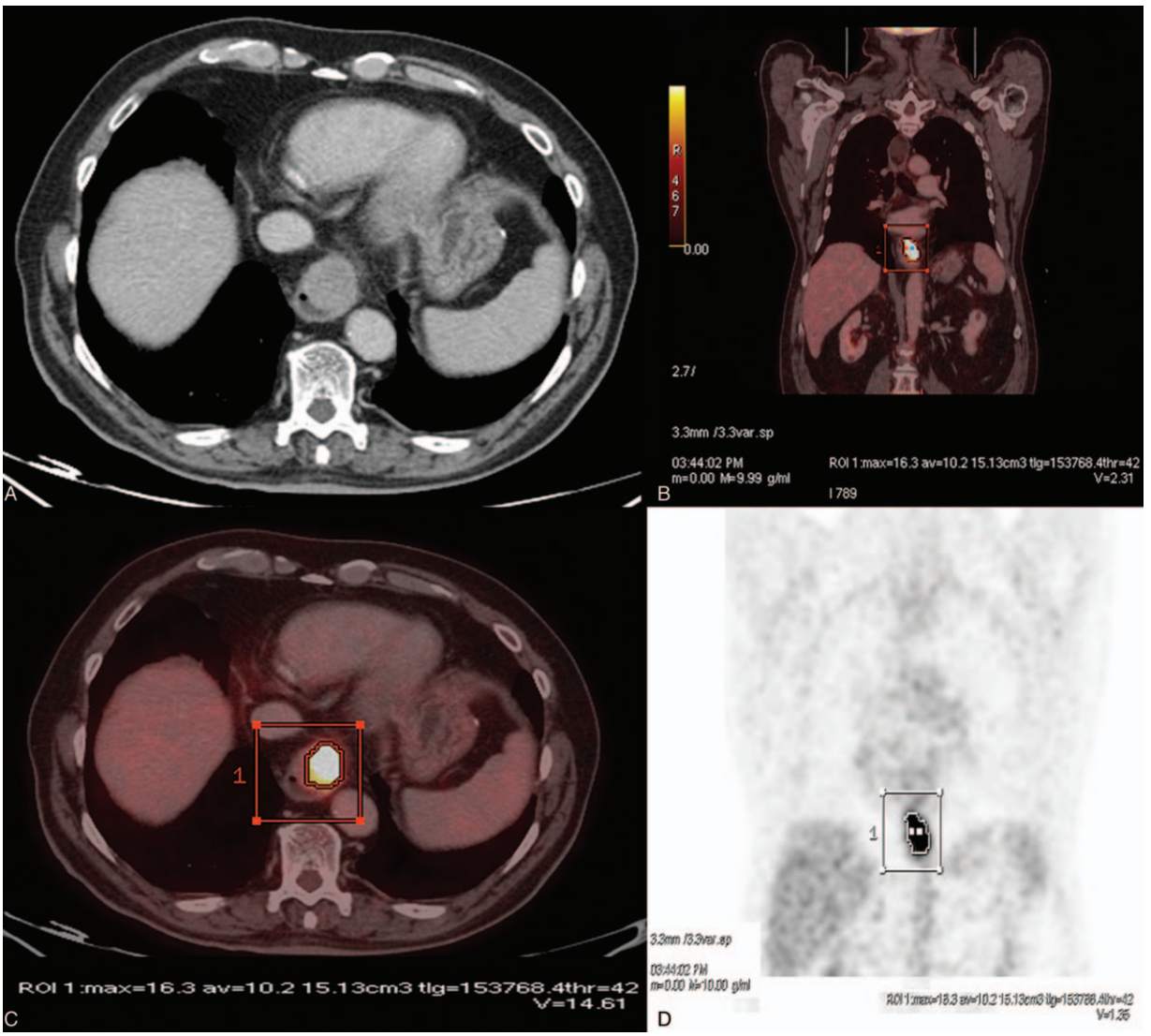

Figure 1. A 75-year-old-man with biopsy-proven esophageal cancer. (A) Axial CT image at the level of the lung bases demonstrates a rounded mass in the distal esophagus. (B,C) Fused coronal and axial 18F-FDG PET/CT reveals intense lesional FDG uptake. (D) Coronal attenuation correction image demonstrates FDG-avid esophageal mass. SUVmax, SUVmean, MTV and TLG were calculated using the PET-based lesion contour with a cut-off value of 42%. CT = computed tomography, FDG = fluorodeoxyglucose, MTV = metabolic tumor volume, PET = positron emission tomography, TLG = total lesion glycolysis.

analyzed with the independent *t* test for parametric variables and the Mann-Whitney for nonparametric variables. Categorical data were analyzed with Pearson chi-square test. Continuous variables with a statistically significant difference between groups were further analyzed by receiver operating characteristic (ROC) curve to identify those that were most sensitive and specific. A *P* value of $\leq .05$ was considered statistically significant. All data were generated using IBM SPSS software, version 21.

3. Results

The cohort consisted of 61 patients (44 male, 17 female) of mean age 65.9 ± 11 years. Their clinical data by pathological response to treatment are shown in Table 1. The endoscopic ultrasonography results of 5 patients were not available on the electronic medical records. In addition, because there was only 1 patient with T4N1disease on EUS, the T3N1 and T4N1 groups were combined. PET-based LN measurements were not included as only 8 patients had PET-positive LNs.

There was a statistically significant difference between patients with a complete and a non-complete response in CTvol ($P = .009$), LN dimension ($P = .017$), MTV0.42 ($P = .001$), MTV0.5 ($P = .003$), MTV0.6 ($P = .01$), and disease location ($P = .021$). Of these variables, only MTV0.42 (13.6 mL) and MTV0.50 (7.4 mL) were associated with a pathological response to treatment on ROC curve analysis, with an area under the curve of 0.690 (confidence interval 0.557–0.823; $P = .02$) and 0.664 (confidence interval 0.527–0.802; $P = .048$), respectively (Fig. 2). The remaining variables did not sustain statistical significance on ROC curve analysis: MTV0.6, 0.07 (confidence interval 0.495–0.785); CTvol, 0.177 (confidence interval 0.47–0.755); LN dimension, 0.09 (confidence interval 0.494–0.789).

4. Discussion

The present study demonstrates that MTV with a cut-off value of 42% and 50% is correlated with a pathological response to neoadjuvant CRT.

Table 1

Clinical characteristics and baseline PET/CT findings in 61 patients with locally advanced esophageal cancer, by pathological response to treatment.

Characteristic	Total (N = 61)	pCR = 0† (N = 17)	pCR = 1‡ (N = 44)	*P* value
Age (year)	65.9 ± 11	64.6 ± 9.3	66.4 ± 11.6	.573
Sex				
Male	44	13	31	.448
Female	17	4	13	
CT vol (cm^3)	27.8 ± 29.9	16.3 ± 12.9	32.3 ± 33.4	.009
LN (short*long)(cm)	0.51 ± 0.59	0.31 ± 0.49	1.01 ± 1.71	.017
LN number				
0	29	11	18	.317
1 to 2	19	4	15	
3 to 6	10	1	9	
>7	3	1	2	
LN PET				
No	53	16	37	.281
Yes	8	1	7	
LN CT				
No	30	11	19	.111
Yes	31	6	25	
SUVmax	13.95 ± 7.8	14.8 ± 7.8	13.6 ± 7.9	.57
SUVaverage 0.42	8.4 ± 5.1	8.9 ± 5.1	8.1 ± 5.1	.55
MTV0.42	18.9 ± 14.8	11.9 ± 5.4	21.5 ± 16.4	.001
TLG0.42	174635 ± 277242	108791 ± 88593	200075 ± 319507	.088
SUVaverage 0.5	9.2 ± 5.4	9.9 ± 5.6	8.9 ± 5.4	.504
MTV0.5	12.4 ± 10.7	7.8 ± 4.1	14.1 ± 12.1	.003
TLG0.5	131650 ± 241943	82907 ± 73838	150482 ± 279907	.332
SUVaverage0.6	10.1 ± 5.8	11.1 ± 6.1	9.8 ± 5.7	.465
MTV0.6	7.5 ± 7.6	4.6 ± 2.9	8.5 ± 8.4	.01
TLG0.6	96446 ± 189146	57821 ± 58832	111369 ± 218666	.326
SUVmax liver	3.1 ± 0.8	3.3 ± 0.8	2.9 ± 0.7	.084
SUVaverage liver	2.4 ± 0.7	2.5 ± 0.7	2.3 ± 0.6	.306
SUVmax ratio	0.3 ± 0.1	0.28 ± 0.14	0.29 ± 0.17	.773
SUVaverage 0.42 ratio	0.39 ± 0.25	0.35 ± 0.18	0.41 ± 0.26	.435
SUVaverage 0.5 ratio	0.35 ± 0.21	0.32 ± 0.15	0.37 ± 0.23	.43
SUVaverage 0.6 ratio	0.31 ± 0.19	0.28 ± 0.13	0.32 ± 0.20	.419
E stage				
T2N0	3	2	1	.434
T2N1	2	0	2	
T3N0	18	4	14	
T3N1 and T4N1	33	10	23	
Pathology				
Adenocarcinoma	43	12	31	.625
Squamous cell ca.	18	5	13	
Iodine				
No	24	8	16	.315
Yes	37	9	28	
Location				
Distal	48	15	33	.021
Proximal	2	2	0	
Middle	8	0	8	
Distal and middle	3	0	3	
GEJ involvement				
No	26	9	17	.234
Yes	35	8	27	
Gastric involvement				
No	49	15	34	.281
Yes	12	2	10	

Values given as mean ± SD or number.

†Patients with a complete pathological response.

‡Patients with a non-complete pathological response.

CT = computed tomography, GEJ = gastro-esophageal junction, LN = lymph node, MTV = metabolic tumor volume, PET = positron emission tomography, pCR = pathological complete response, SUV = standardized uptake value, TLG = total lesion glycolysis.

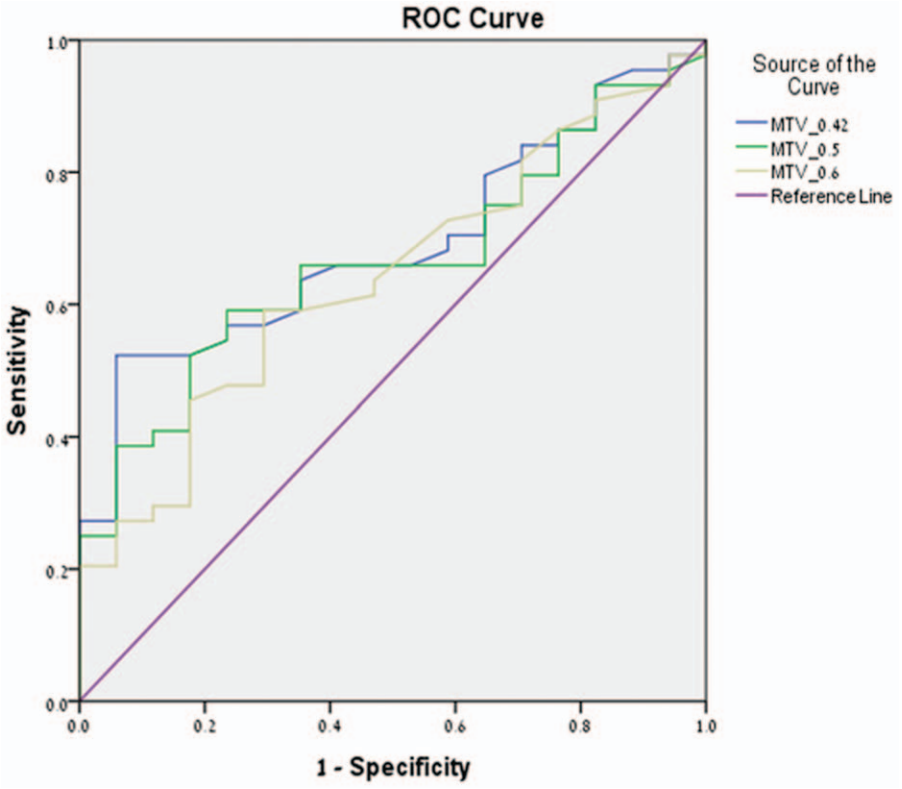

Figure 2. ROC curves for MTV0.42, MTV0.5, MTV0.6 with AUC 0.69, 0.664 and 0.640, respectively. MTV = metabolic tumor volume, ROC = receiver operating characteristic.

The prognostic value of 18-FDG PET/CT for the initial treatment strategy in esophageal cancer is controversial. Most studies correlating SUV with OS and DFS have found it to be significant on univariate analysis, but only a few studies demonstrated its significance on multivariate analysis.[4] The use of PET variables that reflect the tumor metabolic burden, such as MTV and TLG, have yielded more promising results. Hyun et al[5] demonstrated that the pretreatment MTV was an independent predictive factor for OS on multivariate analysis, and Chen et al[9] reported that in patients with unresectable locally advanced esophageal cancer, a pretreatment MTV value of >40 mL with a fixed threshold of 20% was correlated with lower 1-year survival and DFS. Pretreatment MTV and TLG were also found to be good prognostic variables for OS in patients with non-operable esophageal squamous cell cancer, with thresholds of 15.6 mL for MTG and 183.5 for TLG.[6]

Studies have shown that a pCR to neoadjuvant therapy further improves OS compared to a near-complete or partial response.[2] Therefore, evaluation of the pathological response may have added value when stratifying patients into treatment groups. Roedl et al[10] reported that a reduction of 63% in MTV and 78% in TLG from between the pre-treatment and post-treatment PET scans predicted the pathological response with a sensitivity of 91% and specificity of 93%. In the study of Molena et al,[11] $>$ 65% of the patients with a pCR were characterized by at a $>70\%$ reduction in SUVmax, combined with normal-appearing endoscopic findings and a lack of residual disease on biopsy. Higuchi et al[7] identified a post-treatment SUVmax of <2.5 as the only prognostic variable for pathological response. Makino et al have shown that reduction in MTV is an independent predictor for histological response to pre-operative chemoradiation[12] and Sharma et al demonstrated similar results showing that the amount of SUVmax reduction in patients treated either with neoadjuvant chemotherapy or neoadjuvant chemoradiation was correlated with tumor regression grade.[13]

To the best of our knowledge, only the study of Jayachandran et al[14] in patients with stage I-IV esophageal cancer showed no correlation of pretreatment variables with the pathological response, although the post-treatment MTV and TLG, at a fixed threshold of 2.5, were predictive. The discrepancy from the present study, showing that pre-treatment PET variables can predict the pathological response, may be explained by differences in imaging analysis and study population. We calculated the MTV with different cut-off values referred to the lesional SUVmax, and our study population included only patients with locally advanced disease.

The present study has several limitations: first, given its retrospective design, it has intrinsic biases, and differences in the neoadjuvant regimen of some of the patients. Second, we did not evaluate the correlation of the PET/CT parameters to DFS and OS to determine the clinical significance of the findings. Third, correlation of PET/CT parameters with novel imaging techniques and modalities such as diffusion weighted imaging.[15] and PET/MR should be made in any planned studies.

In summary, in patients with locally advanced esophageal cancer, MTV at a cut-off value of 42% and 50% is correlated with the pathological response to neoadjuvant CRT. A larger study is necessary to consolidate our findings and to correlate these variables with survival.

Author contributions

L. Domachevsky – study design, data collections, data analysis, writing, final corrections
H. Kashtan – study design, data collections, final corrections
B. Brenner – study design, data analysis, final corrections
M. Nidam – study design, data analysis
S. Morgenstern – study design, final corrections.
Y. Kundel – study design, final corrections.
D. Groshar – study design, data analysis, writing, final corrections
H. Bernstine – study design, data collections, data analysis, final corrections
All authors approved the final version of the paper for submission.
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Funding acquisition: Jing Xuand Jianmin Zhang.
Investigation: Xianyi Chen and Zeyu Sun.
Methodology: Xianyi Chen, Zeyu Sun, and Liang Xu.
Project administration: Jing Xu and Jianmin Zhang.
Resources: Jun Yu, Bing Fang, Jingwei Zheng, and Jianmin Zhang.
Software: Ligen Shi.
Supervision: Jing Xu.
Writing – original draft: Xianyi Chen and Zeyu Sun.
Writing – review & editing: Ligen Shi, Jing Xu, and Jianmin Zhang.

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