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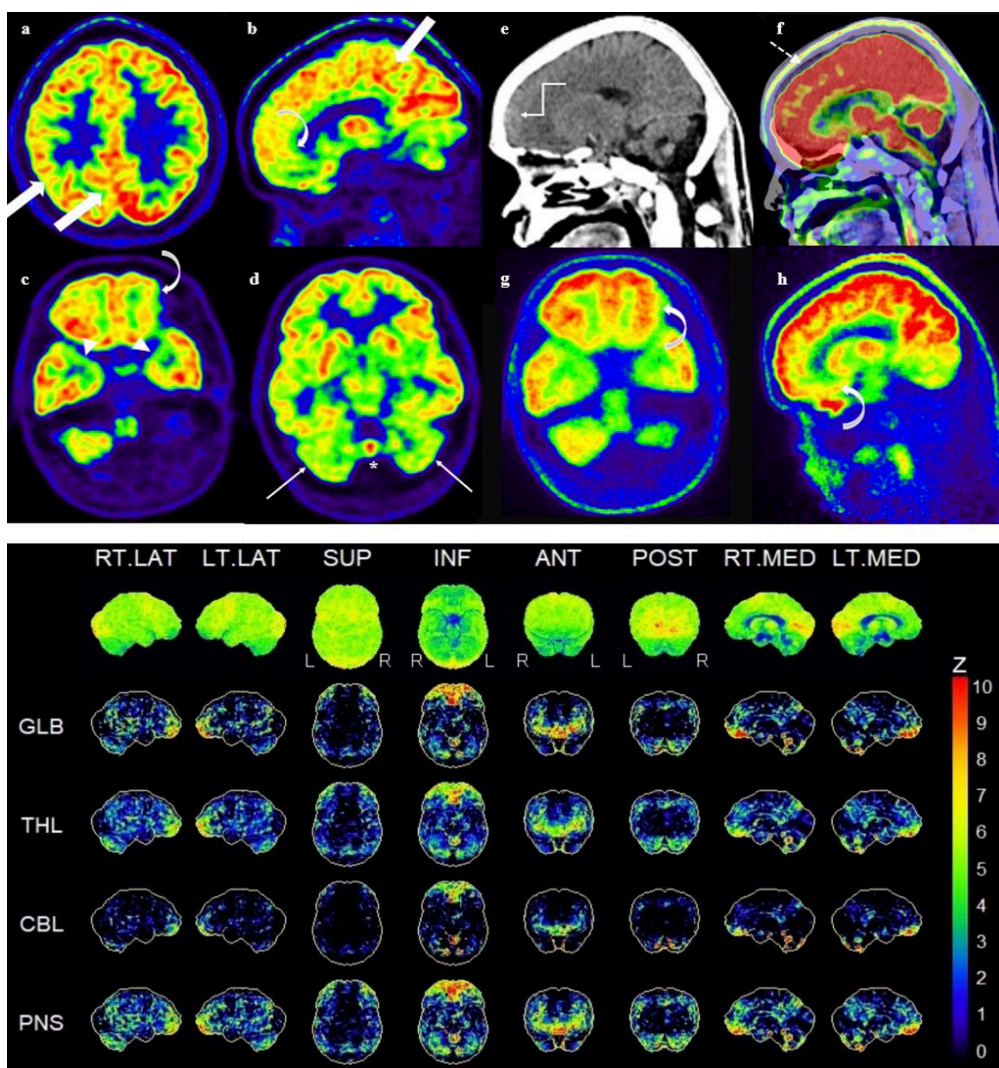
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Evaluation of Cavitory Lung Lesions with ¹⁸F-FDG PET/CT: Differentiating Benign from Malignant Lesions

¹⁸F-FDG PET/BT ile Kaviter Akciğer Lezyonlarının Değerlendirilmesi: Benign ve Malign Lezyonların Ayırt Edilmesi

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Abstract

Objectives: This study aimed to analyze ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) features to differentiate benign from malignant pulmonary cavitory lesions.

Methods: A total of 76 patients with cavitory lung lesions who underwent ¹⁸F-FDG PET/CT imaging were retrospectively analyzed. Patient demographics, histopathological findings, cavitory lesion morphology, CT characteristics, and maximum standard uptake value (SUV_{max}) of lesions were recorded. Cavitory lesions were classified as benign or malignant and further subdivided by maximum wall thickness into two groups: ≤15 mm and >15 mm. Histopathological results, clinical follow-up, or both were used as the reference standard for lesion classification.

Results: Among 76 patients (mean age, 63.4 years), 31 (40.8%) had benign disease and 45 (59.2%) had malignant disease. Malignant lesions were observed at older ages and exhibited significantly greater lesion size, wall thickness, and SUV_{max} than those in benign lesions (p<0.05 for all). There were no significant differences between the malignant and benign groups regarding sex, lesion localization, air-fluid levels, or pleural effusion (p>0.05 for all). Peripheral consolidation, multiple cavitory lesions, and tree-in-bud pattern were significantly more prevalent in benign lesions than in malignant lesions (p<0.05 for all). In lesions with a maximum wall thickness ≤15 mm, SUV_{max} was significantly higher in malignant lesions than in benign lesions (mean values, 9.81 vs. 5.28; p<0.05). Malignant lesions with a maximum wall thickness >15 mm demonstrated higher SUV_{max} values (mean 18.37 vs. 10.45; p<0.05). SUV_{max} was independently associated with malignancy (odds ratio: 1.237, p=0.017) and showed the best diagnostic performance (area under the curve=0.866; cut-off 8.58, sensitivity 80%, specificity 77%).

Conclusion: The morphological characteristics of pulmonary cavitory lesions, associated parenchymal findings, and ¹⁸F-FDG uptake patterns on PET/CT provide valuable information for distinguishing between benign and malignant lesions. In this study, SUV_{max} demonstrated the highest diagnostic performance. The combined evaluation of metabolic and morphological parameters can enhance diagnostic accuracy and support the clinical decision-making process, thereby contributing to the optimal management of patients.

Keywords: ¹⁸F-FDG PET/CT, cavitory lung lesions, wall thickness, lung cancer, differential diagnosis, SUV_{max}

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Öz

Amaç: Bu çalışma, benign ve malign pulmoner kaviter akciğer lezyonlarını ayırt etmede ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸F-FDG PET/BT) özelliklerini analiz etmeyi amaçladı.

Yöntem: ¹⁸F-FDG PET/BT görüntüleme yapılan toplam 76 kaviter akciğer lezyonu olan hasta retrospektif olarak analiz edildi. Hastaların demografik özellikleri, histopatolojik bulguları, kaviter lezyon morfolojisi, BT özellikleri ve lezyonların maksimum standart tutulum değeri (SUV_{max})'ı kaydedildi. Kaviter lezyonlar benign veya malign olarak sınıflandırıldı ve maksimum duvar kalınlığına göre ≤15 mm ve >15 mm olmak üzere iki gruba ayrıldı. Histopatolojik sonuçlar ve/veya klinik takip, lezyon sınıflandırması için referans standardı olarak kullanıldı.

Bulgular: Toplam 76 hastanın (ortalama yaş: 63,4), 31'i (%40,8) benign hastalık, 45'i (%59,2) malign hastalık tanısı aldı. Malign lezyonlar daha ileri yaşlarda gözlemlendi ve benign lezyonlara göre anlamlı olarak daha büyük lezyon boyutu, duvar kalınlığı ve SUV_{max} değerleri bulundu (tümü için p<0,05). Cinsiyet, lezyon lokalizasyonu, hava-sıvı seviyelerinin varlığı veya plevral efüzyon açısından gruplar arasında anlamlı bir fark bulunmadı (tümü için p>0,05). Periferik konsolidasyon, çoklu kaviter lezyonlar ve tomurcuklanmış ağaç paterni benign lezyonlarda anlamlı olarak daha sık gözlemlendi (tümü için p<0,05). Maksimum duvar kalınlığı ≤15 mm olan lezyonlarda, SUV_{max} malign lezyonlarda benign lezyonlara göre anlamlı olarak daha yüksekti (ortalama değerler, 9,81'e karşı 5,28; p<0,05). Maksimum duvar kalınlığı >15 mm olan lezyonlarda, malign lezyonlar benign lezyonlara kıyasla daha yüksek SUV_{max}'a sahipti (ortalama değerler, 18,37'ye karşı 10,45; p<0,05). SUV_{max}, malignite ile bağımsız olarak ilişkili bulundu (olasılık oranı: 1,237, p=0,017) ve en iyi tanılabilir performansı gösterdi (eğri altında kalan alan=0.866; kesim değeri 8,58, duyarlılık %80, özgüllük %77).

Sonuç: Kaviter akciğer lezyonlarının morfolojik özellikleri, eşlik eden parankimal bulgular ve PET/BT'deki ¹⁸F-FDG tutulum paternleri benign ve malign lezyonların ayırt edilmesinde önemli bilgiler sağlamaktadır. Bu çalışmada SUV_{max} en yüksek tanılabilir performansı göstermiştir. Metabolik ve morfolojik parametrelerin birlikte değerlendirilmesi tanılabilir doğruluğu artırarak klinik karar verme sürecine ve hasta yönetiminin optimize edilmesine katkı sağlayabilir.

Anahtar Kelimeler: ¹⁸F-FDG PET/BT, kaviter akciğer lezyonları, duvar kalınlığı, akciğer kanseri, ayırıcı tanı, SUV_{max}

Introduction

A cavitory lung lesion is a gas-filled space within a pulmonary consolidation, mass, or nodule. The evacuation of necrotic tissue through the bronchial tree leads to the development of cavitation (1). Cavities can develop from a variety of causes, including malignancies (such as squamous cell carcinoma, adenocarcinoma, and small cell lung cancer), infections (such as *Streptococcus pneumoniae*, *Streptococcus aureus*, typical and atypical mycobacteria, fungal infections, and parasites), autoimmune diseases (including rheumatoid arthritis or granulomatosis with polyangiitis), sarcoidosis, pulmonary embolism, and congenital abnormalities (such as bronchogenic cyst, pulmonary sequestration, congenital pulmonary airway malformation) (2).

Radiographic differentiation between malignant and benign cavitory lesions is crucial in clinical practice, as it guides management and treatment decisions. Computed tomography (CT) plays significant role in the detection and differential diagnosis of cavitory lesions. The size, shape, location, and wall characteristics of cavitory lesions can provide important clues to their underlying etiology. The thickness of the cavity wall is the most important criterion for assessing these lesions, as it often helps distinguish malignant from benign etiologies. Several studies indicate that malignant cavitory lesions have thicker walls, whereas thin-walled cavitory lesions are usually benign (3,4,5). However, there is no consensus on the CT threshold for wall thickness. Additionally, there may be considerable overlaps in wall thickness between malignant and

benign lesions. ¹⁸F-fluorodeoxyglucose positron emission tomography with CT (¹⁸F-FDG PET/CT) is an important imaging technique for differentiating benign from malignant lung lesions. Moreover, ¹⁸F-FDG PET/CT can be useful in evaluating disease severity, identifying optimal biopsy sites, and monitoring treatment response in benign lung diseases such as tuberculosis and sarcoidosis (6). Malignant lesions typically exhibit high ¹⁸F-FDG uptake due to increased glycolytic activity. However, ¹⁸F-FDG uptake can also be observed in a variety of inflammatory and infectious disorders, including tuberculosis, pneumonia, abscesses, sarcoidosis, and autoimmune diseases, due to increased metabolic activity. Accordingly, this study evaluated ¹⁸F-FDG PET/CT imaging features to differentiate benign from malignant cavitory lung lesions based on metabolic and morphological characteristics.

Materials and Methods

Clinicopathological Characteristics of the Patients

In this study, patients who had cavitory lung lesions on radiological exams and underwent ¹⁸F-FDG PET/CT for differential diagnosis between 2020 and 2021 at our department were involved. Exclusion criteria included patients with cavitory lesions who had received antibiotic, antiviral, or antifungal therapy prior to ¹⁸F-FDG PET/CT, as well as those with incomplete clinical records or suboptimal PET/CT images. Patients with a primary malignancy or a history of granulomatous, rheumatological, or congenital diseases were excluded from the study.

Cavitory lesions were classified primarily into two groups: benign and malignant. The definitive diagnosis was confirmed by sputum and blood culture results, response to treatment, and histopathological findings. Ethical approval for this retrospective study was obtained from the Local Ethics Committee of the University of Health Sciences Türkiye, Ankara Atatürk Sanatorium Training and Research Hospital, (approval no: 661, date: 06.02.2020).

^{18}F -FDG PET/CT Imaging

Prior to the imaging procedure, all patients fasted for 4-6 hours. After confirming that their blood glucose levels were under 190 mg/dL, an average ^{18}F -FDG dose of 390.8 ± 54.2 MBq (ranging from 310 to 565 MBq) was administered intravenously. Sixty minutes after ^{18}F -FDG administration, whole-body PET/CT imaging from the vertex to the proximal femur was performed for each patient using a Siemens Biograph 6 HI-REZ integrated PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). CT scans were first obtained at 130 kV with automatic real-time amperage modulation, a slice thickness of 0.5 cm, a rotation time of 0.6 seconds, a table speed of 1.5 cm per rotation, and a pitch of 1.5. Following CT acquisition, PET images were acquired for 3 minutes per bed position. PET images were attenuation-corrected using the CT data and reconstructed with the ordered-subsets expectation maximization algorithm, employing 4 iterations and 8 subsets. A gaussian post-filter was applied, resulting in a transaxial spatial resolution of 5 mm at full width at half maximum. Reconstructed transaxial, coronal, and sagittal PET, CT and fused PET/CT images, as well as maximum-intensity projection images, were reviewed on a dedicated workstation for visual and semi-quantitative analysis.

Visual assessment was performed to evaluate ^{18}F -FDG uptake relative to background lung activity. Semi-quantitative analysis was performed by placing a region of interest (ROI) over each cavitory lesion to measure the maximum standard uptake value (SUV_{max}). The ROI was carefully drawn to include only the cavitory lesion, excluding any adjacent parenchymal abnormalities, such as consolidation or tree-in-bud patterns. CT morphological features, including cavity wall thickness, the longest axial diameter, and adjacent parenchymal findings, were also recorded. Based on CT findings, the patients were retrospectively classified into probable benign and probable malignant groups. The presence of a tree-in-bud pattern or multiple cavitory lesions on CT imaging was accepted as a criterion for benignity. Additionally, cavitory lesions were subdivided into two groups based on maximum wall thickness: ≤ 15 mm and > 15 mm. The images were evaluated by two nuclear medicine specialists with over

10 years of experience (OO and ET). Any discrepancies between reviewers were resolved by consensus.

Statistical Analysis

Statistical analyses were conducted with SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The relationships between categorical variables were analyzed using the chi-square test, and correlations were evaluated using appropriate correlation methods. The Mann-Whitney U test was used for pairwise comparisons between groups. Spearman correlation analysis was used to assess the associations among SUV_{max} , lesion diameter, and maximum wall thickness. ROC analysis was performed to evaluate the diagnostic performance of SUV_{max} , maximum wall thickness, and lesion diameter, and to determine their optimal cut-off values for differentiating malignant from benign lesions. Logistic regression analysis was used to determine factors associated with malignancy risk. A p-value less than 0.05 was considered statistically significant throughout the analysis.

Results

Clinicopathological Characteristics of the Patients

A total of 76 patients who underwent ^{18}F -FDG PET/CT scan for the assessment of cavitory lesions were enrolled in the study, comprising 10 females (13.1%) and 66 males (86.8%), with a mean age of 63.4 ± 12.7 years. The clinicopathological characteristics of the patients were presented in Table 1. Of the 76 patients, 31 (40.8%) had benign lesions and 45 (59.2%) had malignant lesions. Sex distribution did not differ significantly between the benign and malignant groups ($p=0.081$). The mean age was significantly lower in the benign group compared with the malignant group (31 ± 12.2 vs. 45 ± 11.8 years, $p<0.001$). Furthermore, the final diagnoses of benign and malignant cavitory lesions were summarized in Table 2.

^{18}F -FDG PET/CT Findings

No significant differences were detected between benign and malignant cavitory lesions with respect to lung side, presence of air-fluid levels, pleural effusion, and perilesional infiltration ($p=0.91$, $p=0.58$, $p=0.66$, $p=0.13$, respectively; Table 3). Malignant cavitory lesions had significantly greater diameters than benign cavitory lesions ($p=0.003$). Consolidation associated with the primary lesion was more common in benign lesions ($p=0.025$). The perilesional tree-in-bud pattern was observed in only 8 (25.8%) of the 31 benign lesions. The tree-in-bud appearance was not associated with malignant cavitory lesions. Additional cavitory lesions in the same or the contralateral lung were observed in 8 (25.8%) of 31 benign lesions (Figure 1),

Table 1. Demographic characteristics and the final clinical classification of patients with benign and malignant cavitory lung lesions

Definitive diagnosis	Benign (n=31, 40.8 %)	Malignant (n=45, 59.2%)	p
Demographic data			
Gender (male/female)	24/7	42/3	0.081
Age (years), mean $\pm$ SD (range)	31 $\pm$ 12.2 (31-91)	45 $\pm$ 11.8 (33-95)	<0.001
Chi-square test for categoric variables, p<0.05 level is significant, Mann-Whitney U test for continuous variable, mean $\pm$ SD, p<0.05 level is significant, SD: Standard deviation			

Table 2. Diagnosis of cavitory lung lesions

Definitive diagnosis	n	%
Benign	31	
Bacterial abscesses	17	54.8
Tuberculosis	12	38.7
Bronchogenic cyst	1	3.2
Aspergillus infection	1	3.2
Malign	45	
Lymphomatoid granulomatosis	2	4.4
Squamous cell carcinoma	35	78
Carcinoid tumor	1	2.2
Adenocarcinoma	3	6.6
Adenosquamous carcinoma	3	6.6
Small cell lung cancer	1	2.2
Total	76	

whereas no additional cavitory lesions were identified in malignant cavities.

When the presence of multiple cavitory lesions or a tree-in-bud pattern on CT scans was considered a benign imaging feature and was interpreted in conjunction with clinical findings, the preliminary clinical assessment classified 16 of the 76 patients as possibly benign and 60 as possibly malignant (Table 3). All patients (n=16) in the possibly benign group were eventually diagnosed with benign disease. In the group classified as possibly malignant, malignant disease was confirmed in 45 patients (75%), whereas benign lesions were identified in 15 patients (25%).

The mean maximum wall thickness in the malignant cavitory lesions (21.2 $\pm$ 9.2 mm, range 6-50 mm) was significantly greater than that of the benign cavitory lesions (12.6 $\pm$ 6.2, range 3-27 mm), (p<0.001; Table 3). Only one cavitory lesion had a maximum wall thickness of less than 4 mm, and it was an infectious cavity. The maximum wall thickness was at least 4 mm in all 45 malignant lesions. Of the 76 patients, 36 (47.4%) had a maximum wall thickness $\leq$ 15 mm, while 40 (52.6%) had a wall thickness >15 mm

(Table 3). Of the 36 cavitory lesions with a maximum wall thickness $\leq$ 15 mm, 23 (63.88%) were benign (Figure 2). The remaining 13 lesions (36.12%) were malignant (Figure 3). Of the 40 cavitory lesions with a maximum wall thickness over 15 mm, 8 (20%) were classified as benign and 32 (80%) were classified as malignant (Figure 4). The proportion of malignant lesions was significantly higher in cavitory lesions with a maximum wall thickness >15 mm compared with those $\leq$ 15 mm (p<0.001; Table 4). Of the 76 patients, 35 (46.1%) had cavitory lesions with a maximum wall thickness of 5-15 mm. Among the 35 cavitory lesions with a maximum wall thickness of 5-15 mm, 22 (62.9%) were benign and 13 (37.1%) were malignant.

Relationship Between SUV_{max}, Maximum Wall Thickness and Lesion Size

Table 4 shows SUV_{max} by maximum wall thickness and lesion status (benign or malignant) based on the final diagnosis. The SUV_{max} of benign lesions was significantly lower than that of malignant lesions, with mean values of 6.62 $\pm$ 4.2 (range: 1.7-21.4) and 15.9 $\pm$ 7.6 (range: 4.3-30.3), respectively (p<0.001). According to maximum wall thickness, the overall mean $\pm$ standard deviation of SUV_{max} was 6.92 $\pm$ 5.15 in lesions with a wall thickness $\leq$ 15 mm and 16.78 $\pm$ 6.95 in those with a wall thickness >15 mm. A moderate positive correlation was found between SUV_{max} and the longest axial diameter of the cavitory lesions (r=0.519, p=0.0001; Figure 5). A positive correlation between the maximum wall thickness and SUV_{max} was also observed (r=0.602, p=0.0001).

Univariate and Multivariate Logistic Regression Analyses in Predicting Malign Cavitory Lesion

In univariate logistic regression analysis, increasing age [odds ratio (OR): 1.067, 95% confidence interval (CI): 1.021-1.116, p=0.004], larger lesion diameter (OR: 1.029, 95% CI: 1.007-1.051, p=0.01), greater maximum wall thickness (OR: 1.15, 95% CI: 1.066-1.246, p<0.001), and higher SUV_{max} (OR: 1.316, 95% CI: 1.153-1.502, p<0.001; Table 5) were significantly associated with increased odds of malignancy. In contrast, perilesional consolidation was inversely associated with malignancy

Table 3. The CT findings between benign and malignant cavitory lung lesions based on the final diagnosis			
CT findings	Benign (n=31, 40.8 %)	Malignant (n=45, 59.2%)	p
Localization (left/right lung)	12/19	18/27	0.911
Lesion diameter (mm), mean ± SD (range)	48.5±26 (13-120)	64.6±23.5 (20-120)	0.003
Maximum wall thickness (mm), mean ± SD (range)	12.6±6.2 (3-27)	21.2±9.7 (6-50)	<0.001
Maximum wall thickness <4 mm, n (%)	1 (1.3%)	0	
Maximum wall thickness 5-15 mm, n (%)	22 (28.9%)	13 (17.1%)	
Maximum wall thickness >15 mm, n (%)	8 (10.5%)	32 (42.1%)	
Presence of air-fluid level, n (%)	9 (11.8%)	17 (22.4%)	0.587
Presence of multiple cavitory lesions, n (%)	8 (10.5%)	0	<0.001
Presence of pleural effusion, n (%)	12 (15.8%)	14 (18.4%)	0.661
Presence of perilesional consolidation, n (%)	22 (28.9%)	19 (25%)	0.025
Presence of perilesional infiltration, n (%)	16 (21.1%)	32 (42.1%)	0.136
Presence of tree-in-bud pattern, n (%)	8 (10.5%)	0	<0.001
Preliminary diagnosis based on CT findings			
Possibly benign	16 (21.1%)	0	<0.001
Possibly malign	15 (19.7%)	45 (59.2%)	

Chi-square test for categoric variables, p<0.05 level is significant, Mann-Whitney U test for continuous variables, mean ± SD, p<0.05 level is significant, SD: Standard deviation, CT: Computed tomography

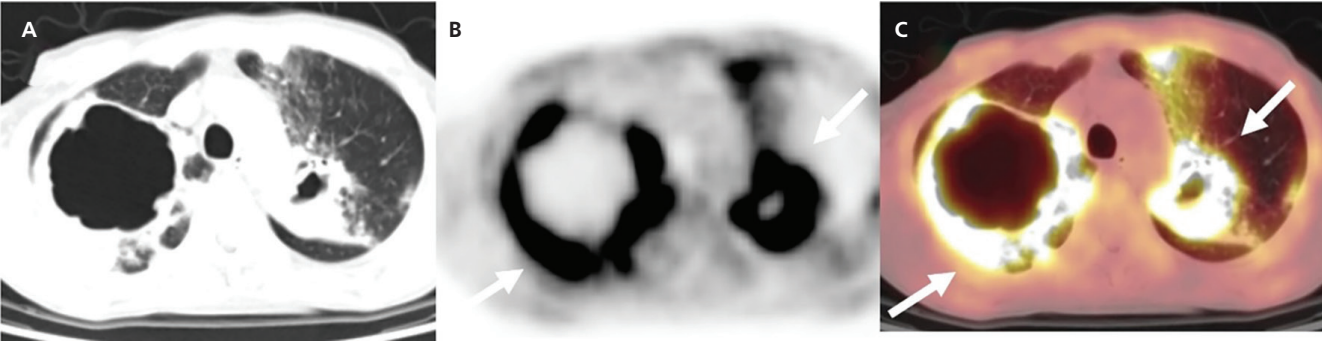


Figure 1. Tuberculosis. Axial CT (A), ¹⁸F-FDG PET (B), and fusion PET/CT (C) images show irregular, thick-walled cavitory lesions surrounded by infiltrated pulmonary parenchyma in both lungs, with the largest lesion located in the right apical region measuring approximately 85 mm (arrows). Increased metabolic activity is observed along the cavity walls (SUV_{max}: 14.34)
¹⁸F-FDG PET/CT: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max}: Maximum standard uptake value



Figure 2. Tuberculosis. Axial CT (A), ¹⁸F-FDG PET (B), and fused PET/CT images demonstrate increased ¹⁸F-FDG uptake in a cavitory mass lesion containing fluid, measuring approximately 63 mm in diameter, with a maximum wall thickness of 15 mm and SUV_{max} of 8.52 (arrows)
¹⁸F-FDG PET/CT: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max}: Maximum standard uptake value

(OR: 0.299, 95% CI: 0.113-0.793, $p=0.015$), indicating lower odds of malignancy. The presence of air-fluid level, pleural effusion, and perilesional infiltration was not associated with malignancy.

In multivariate analysis, increasing age (OR: 1.071, 95% CI: 1.008-1.137, $p=0.025$) and higher SUV_{max} (OR: 1.237, 95% CI: 1.039-1.473, $p=0.017$) remained independently associated with increased odds of malignancy. Conversely, the presence of perilesional consolidation remained independently associated with lower odds of malignancy (OR: 0.142, 95% CI: 0.018-0.649, $p=0.029$). Other parameters were not associated with malignancy in the multivariate model.

ROC Analysis for Diagnostic Performance

ROC analysis showed that SUV_{max} had the highest diagnostic performance [area under the curve (AUC)=0.866, 95% CI: 0.786-0.947, $p<0.001$], followed by maximum wall thickness (AUC=0.780, 95% CI: 0.676-0.884, $p<0.001$) and lesion diameter (AUC=0.701, 95% CI: 0.574-0.828, $p=0.003$; Figure 6). The optimal cut-off values to differentiate malignant from benign lesions were 53.5 mm for lesion size (66% sensitivity, 64.5% specificity), 15.5 mm for maximum wall thickness (71.1% sensitivity, 74.2% specificity), and an SUV_{max} of 8.58 (80% sensitivity, 77% specificity).

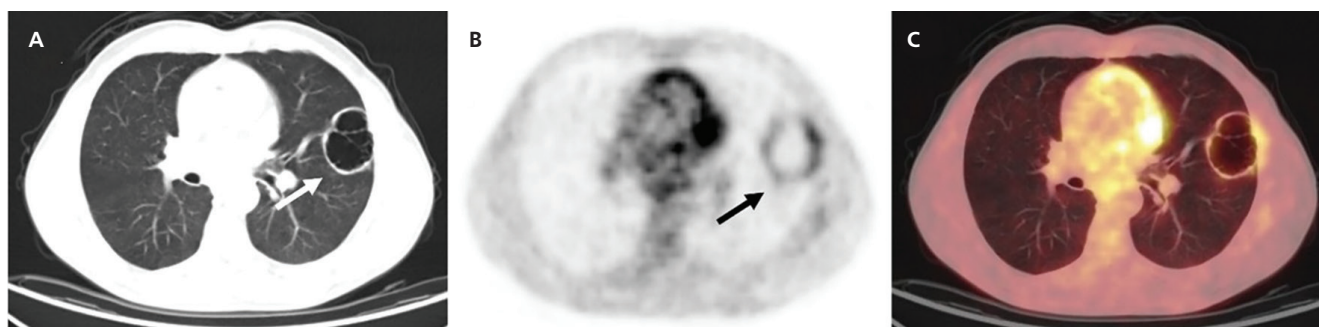


Figure 3. Squamous cell carcinoma. Axial CT (A), ^{18}F -FDG PET (B), and fused PET/CT (C) images show a cavitary mass lesion with mild ^{18}F -FDG uptake, measuring approximately 55 mm in the longest axial diameter, with a maximum wall thickness of 6 mm and an SUV_{max} of 4.22 (arrows)

^{18}F -FDG PET/CT: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max} : Maximum standard uptake value

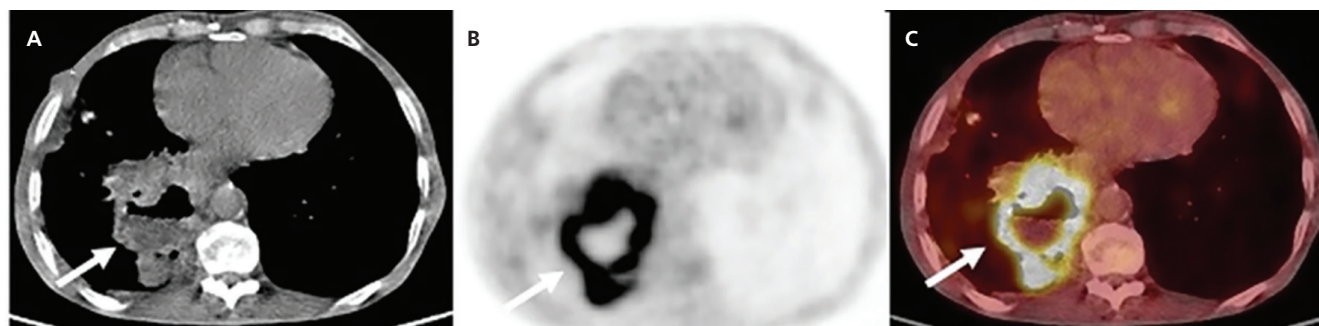


Figure 4. Squamous cell carcinoma. Axial CT (A), ^{18}F -FDG PET (B), and fusion PET/CT (C) images show high ^{18}F -FDG uptake (SUV_{max} : 15.30) on a cavitary mass measuring approximately 93 mm with thick, irregular walls and an internal air-fluid level (arrows)

^{18}F -FDG PET/CT: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max} : Maximum standard uptake value

Table 4. Comparison of SUV_{max} in benign and malignant cavitory lesions based on the maximum wall thickness

	Benign	Malign	p
Maximum wall thickness ≤ 15 mm, n (%)	23 (30.3%)	13 (17.1%)	<0.001
Maximum wall thickness >15 mm, n (%)	8 (10.5%)	32 (42.1%)	<0.001
SUV_{max} , all lesions, mean $\pm$ SD (range)	6.62 $\pm$ 4.2 (1.7-21.4)	15.9 $\pm$ 7.6 (4.3-30.3)	<0.001
SUV_{max} , maximum wall thickness ≤ 15 mm, mean $\pm$ SD (range)	5.28 $\pm$ 2.61 (1.72-11.09)	9.81 $\pm$ 7.13 (4.22-25.28)	0.013
SUV_{max} , maximum wall thickness >15 mm, mean $\pm$ SD (range)	10.45 $\pm$ 5.6 (3.71-21.4)	18.37 $\pm$ 6.38 (7.17-30.31)	0.003

Chi-square test for categoric variables, $p<0.05$ level is significant, Mann-Whitney U test for continuous variables, mean $\pm$ SD, $p<0.05$ level is significant, SD: Standard deviation, SUV_{max} : Maximum standardized uptake value

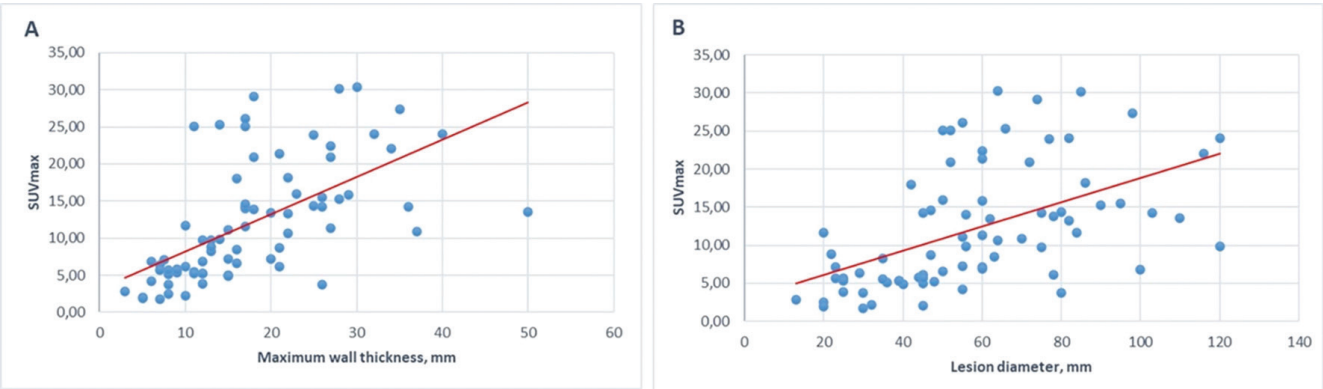


Figure 5. Correlation of SUV_{max} with morphologic parameters. (A) Moderate positive linear correlation between maximum wall thickness (mm) and SUV_{max}. (B) Moderate positive linear correlation between lesion diameter (mm) and SUV_{max}. The red lines indicate linear regression fits
SUV_{max}: Maximum standard uptake value

Table 5. Univariate and multivariate logistic regression analyses in predicting malign cavitory lesion				
Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.067 (1.021-1.116)	0.004	1.071 (1.008-1.137)	0.025
Lesion diameter	1.029 (1.007-1.051)	0.01	1.013 (0.96-1.066)	>0.05
Maximum wall thickness	1.15 (1.066-1.246)	<0.001	1.00 (0.88-1.12)	>0.05
Presence of air–fluid level	1.48 (0.556-3.963)	0.43	1.009 (0.18-5.6)	>0.05
Presence of pleural effusion	0.715 (0.274-1.867)	0.49	1.853 (0.3-11.22)	>0.05
Presence of perilesional consolidation	0.299 (0.113-0.793)	0.015	0.142 (0.018-0.649)	0.029
Presence of perilesional infiltration	2.308 (0.888-5.996)	0.086	2.706 (0.547-13.39)	>0.05
SUV _{max}	1.316 (1.153-1.502)	<0.001	1.237 (1.039-1.473)	0.017

SUV_{max}: Maximum standardized uptake value, OR: Odds ratio, CI: Confidence interval

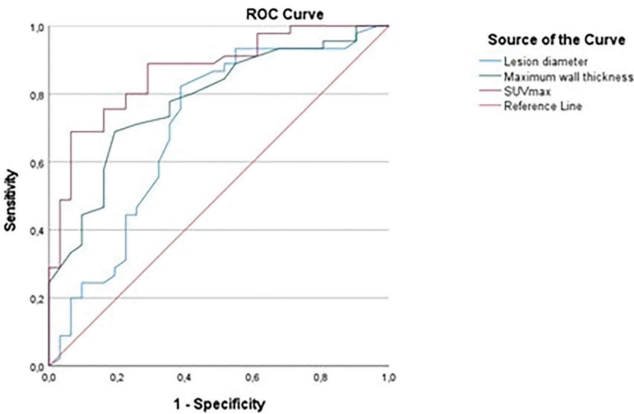


Figure 6. ROC curve analysis showing the diagnostic performance of SUV_{max} (AUC=0.866), maximum wall thickness (AUC=0.78), and lesion diameter (AUC=0.701) for distinguishing benign from malignant cavitory pulmonary lesions
SUV_{max}: Maximum standard uptake value, AUC: Area under the curve

Discussion

Cavitation is observed in approximately 2%-25% of primary lung cancers, with squamous cell carcinoma, adenocarcinoma, and large cell carcinoma being the subtypes most associated with cavitory lesions, respectively (7,8). Differentiating benign from malignant cavitory lesions using radiological imaging methods is a key factor in planning effective treatment strategies. Although CT is the leading imaging technique for detecting cavitory lesions, it can be limited in accurately distinguishing between benign and malignant lesions. CT findings such as multiple cavitory lesions or a tree-in-bud pattern may suggest a benign etiology; however, our results indicate that morphological imaging alone may be insufficient for accurate differentiation. ¹⁸F-FDG PET/CT may change preliminary diagnoses based on CT and clinical evaluation. However, some lesions may be misclassified. This situation emphasizes the need to interpret ¹⁸F-FDG PET in conjunction with other clinical and imaging information to prevent

misdiagnosis. Our findings showed that ^{18}F -FDG PET/CT imaging can offer valuable insights into the metabolic and morphological characteristics of cavitory lung lesions.

Air space surrounded by a wall less than 2 mm thick is called a cyst (9). Sometimes the cyst wall thickness can reach 4 mm. However, cysts and cavities may not always be distinguishable through radiological imaging. To differentiate, air-filled spaces with walls 4 mm or thinner are referred to as cysts, while those with walls thicker than 4 mm are classified as cavities (10). Wall thickness is one of the most important factors in distinguishing benign cavitory lesions from malignant ones. Woodring et al. (5) reported that in a cohort of 61 patients with cavitory lung lesions, 92% of cavities with a maximum wall thickness ≤ 4 mm was benign. In lesions with a wall thickness of 5-15 mm, 51% were benign and 49% were malignant, whereas 95% of cavitory lesions with a wall thickness ≥ 15 mm was malignant. In our study, among the 40 cavitory lesions with a maximum wall thickness > 15 mm, a lower rate of malignancy (80%) was observed. Of the 35 cavitory lesions with a maximum wall thickness of 5-15 mm, 13 (37.1%) were malignant. In our ROC analysis, the cut-off point for maximum wall thickness was 15.5 mm for distinguishing malignant cavitory lesions, with a sensitivity of 71.1% and a specificity of 74.2%. Differences in patient selection, underlying disease prevalence, and diagnostic confirmation methods may explain these discrepancies. Although an increase in wall thickness is strongly associated with malignancy, it is not a definitive indicator. There is considerable overlap in the maximum wall thickness between benign and malignant cavities. Thick, irregular walls are often seen in benign cavitory lesions, such as pulmonary abscess, tuberculosis, aspergillosis, and granulomatosis with polyangiitis (2). Conversely, thin walls can also be present in certain malignant cavitory lesions, including adenocarcinoma, squamous cell carcinoma, and cystic metastases from sarcoma and colon adenocarcinoma (10).

It has been shown that perilesional consolidation is more common in tuberculous cavities than in malignant cavitory lesions (3). Consistent with the literature, perilesional consolidation was significantly more common in benign cavitory lesions in our study. We also observed perilesional tree-in-bud nodularity in 25.8% (8/31) of benign cavitory lesions, whereas no perilesional tree-in-bud nodularity was detected in malignant cavitory lesions. The tree-in-bud pattern is characterized by centrilobular micronodules connected to branching linear opacities that resemble a budding tree (11). This finding usually indicates infectious diseases, including bacterial, fungal, viral, or parasitic infections, as well as inflammatory processes such as aspiration and immunologic

or connective tissue disorders (12). Primary lung malignancies and metastases—especially those from renal cell carcinoma, breast, liver, stomach, prostate, and ovarian cancers—and Ewing's sarcoma may also present with a tree-in-bud pattern (13,14). However, the presence of a perilesional tree-in-bud pattern supports the diagnosis of a benign cavitory lung lesion (4).

In our study, no significant difference in air-fluid levels was observed between benign and malignant cavitory lesions. This finding is consistent with previous reports indicating that air-fluid levels are nonspecific features and may occur in both infectious cavitory processes and cavitating malignancies due to necrosis, hemorrhage, or secondary infection (2,15).

According to our results, multiple cavitory lesions involving the same lung or the contralateral lung were present in 8 of 31 benign cases (25.8%). No additional cavitory lesions were identified within these malignant cavitory lesions. Primary lung cancer usually presents as a solitary nodule or mass. Lung adenocarcinoma rarely presents as a multiple cavitory disease (16). Multiple metastatic cystic or cavitory lung lesions are reported in colorectal cancer, gallbladder cancer, breast cancer, bladder cancer, renal cell carcinoma, and lymphoma (17,18). However, multiple cavitory lesions are more commonly associated with infectious causes (e.g., abscesses, tuberculosis, fungal or parasitic infections, septic emboli), metastatic disease, or autoimmune conditions such as granulomatosis with polyangiitis, rheumatoid nodules, and vasculitis (1,2).

In our study, a positive correlation was found between SUV_{max} and both cavity size and wall thickness. This relationship reflects the biological aggressiveness of malignant lesions in which necrosis and tumor proliferation coexist. According to our data, cavitory lesions with maximum wall thickness > 15 mm showed markedly higher SUV_{max} than those of thinner-walled lesions. Even in cavitory lesions with a maximum wall thickness ≤ 15 mm, ^{18}F -FDG uptake was higher in malignant lesions than in benign ones. Additionally, SUV_{max} demonstrated good diagnostic performance in distinguishing malignant from benign lesions in our study. At a cut-off value of 8.58, it provided moderate sensitivity (80%) and specificity (77%). Logistic regression analysis showed that higher SUV_{max} values were associated with an increased likelihood of malignancy. This result aligns with the known biological behavior of malignant tumors, which exhibit increased glucose metabolism and ^{18}F -FDG uptake. However, it should be noted that benign infectious and inflammatory cavitory lesions such as tuberculosis or abscesses, can also demonstrate intense ^{18}F -FDG accumulation, potentially leading to false-positive results. Furthermore, thin-walled

cystic or cavitory malignant lesions may show low or absent ¹⁸F-FDG uptake. In particular, cystic or cavitory lung adenocarcinomas may show low to moderate ¹⁸F-FDG uptake (19). Therefore, SUV_{max} alone cannot be considered an absolute discriminator between benign and malignant cavitory lesions; it should be interpreted in conjunction with morphological characteristics and clinical findings.

Study Limitations

The main limitations were its retrospective design and the relatively small patient cohort from a single institution. Multicenter investigations with larger sample sizes are required to validate SUV_{max} and wall-thickness criteria for the differentiation of cavitory lung lesions.

Conclusion

We concluded that ¹⁸F-FDG PET/CT provides valuable complementary information to CT in distinguishing malignant from benign cavitory lung lesions. According to the findings of our study, advanced age and elevated SUV_{max} were significantly associated with a higher likelihood of malignancy, whereas consolidation surrounding the lesion was more frequently observed in benign lesions. Although lesion diameter and maximum wall thickness tended to be greater in malignant lesions, SUV_{max} showed the best performance among quantitative variables in distinguishing malignant from benign lesions. A comprehensive assessment including cavity morphology, wall thickness, lesion size, SUV_{max}, and associated parenchymal findings on ¹⁸F-FDG PET/CT can improve diagnostic accuracy and assist clinical decision-making in patients with cavitory pulmonary lesions.

Ethics

Ethics Committee Approval: Ethical approval for this retrospective study was obtained from the Local Ethics Committee of the University of Health Sciences Türkiye, Ankara Atatürk Sanatorium Training and Research Hospital, (approval no: 661, date: 06.02.2020).

Informed Consent: This is retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., E.T., Concept: N.A.D., E.T., Design: Ö.Ö., E.T., Data Collection or Processing: Ü.N.D., N.A.D., Ö.Ö., E.T., Analysis or Interpretation: E.T., N.A.D., Ö.Ö., Literature Search: Ö.Ö., E.T., Writing: N.A.D., Ö.Ö., E.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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Association of ¹⁸F-FDG PET/CT Radiomics with Tumor Molecular Features in Breast Cancer

Meme Kanserinde ¹⁸F-FDG PET/BT Radyomiklerinin Tümör Moleküler Özellikleri ile İlişkisi

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Abstract

Objectives: This study aims to investigate the potential relationship between radiomic features extracted from ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/computed tomography (CT) images of patients with breast cancer and molecular markers including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) and Ki-67.

Methods: Radiomic features were obtained via an open-source software (LIFEx) from ¹⁸F-FDG PET/CT images of 162 patients with histopathologically confirmed breast cancer. In order to examine the association between each molecular marker and radiomic features, machine learning models were developed separately using the Python software. After the data were divided into test and training subsets, features were selected and scaled. Using the selected features, five different machine learning models (Random Forest, XGBoost, Support Vector Machine, Logistic Regression and Naive Bayes) were established and their performance was evaluated based on accuracy, sensitivity, specificity, F1 score, balanced accuracy, MCC and area under the curve (AUC) the receiver operating characteristic curve.

Results: For HER-2 status, the model yielded an AUC of 0.76, a balanced accuracy of 0.76, a sensitivity of 62.5% and a specificity of 90.0%. For ER, PR and Ki-67 status, AUC values were 0.59, 0.55, 0.60, balanced accuracies were 0.65, 0.61, 0.62, sensitivities were 96.6%, 81.8%, 68.4% and specificities were 33.3%, 40.0%, 55.2% respectively.

Conclusion: In this study, radiomic features derived from ¹⁸F-FDG PET/CT images demonstrated poor or non-discriminatory performance in the assessment of ER, PR and Ki-67 status. Although a preliminary signal of an association was observed for HER-2 status, this finding should be considered hypothesis-generating only due to the low number of HER-2-positive cases in the test subset and the lack of independent external validation. In larger cohorts prospective, multicenter studies are needed to validate this potential association.

Keywords: Radiomic, machine learning, positron-emission tomography, breast cancer

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Öz

Amaç: Bu çalışmanın amacı, meme kanseri hastalarının ¹⁸F-florodeoksiglukoz (¹⁸F-FDG) pozitron emisyon tomografisi (PET)/bilgisayarlı tomografi (BT) görüntülerinden elde edilen radyomik özellikler ile östrojen reseptörü (ER), progesteron reseptörü (PR), insan epidermal büyüme faktörü reseptörü 2 (HER-2) ve Ki-67 dahil olmak üzere moleküler belirteçler arasındaki olası ilişkiyi araştırmaktır.

Yöntem: Histopatolojik olarak meme kanseri tanısı doğrulanmış 162 hastanın ¹⁸F-FDG PET/BT görüntülerinden, açık kaynaklı bir yazılım olan (LIFEX) aracılığıyla radyomik özellikler elde edildi. Her bir moleküler belirteç ile radyomik özellikler arasındaki ilişkiyi incelemek amacıyla, Python yazılımı kullanılarak ayrı ayrı makine öğrenmesi modelleri geliştirildi. Veriler test ve eğitim alt gruplarına ayrıldıktan sonra özellik seçimi ve ölçeklendirme işlemleri yapıldı. Seçilen özellikler kullanılarak beş farklı makine öğrenmesi modeli (Random Forest, XGBoost, Support Vector Machine, Logistic Regression ve Naive Bayes) oluşturuldu ve bu modellerin performansı doğruluk, duyarlılık, özgüllük, F1 skoru, dengeli doğruluk, Matthews korelasyon katsayısı ve alıcı işletim karakteristiği eğrisi altında kalan alan (AUC) değerleri temel alınarak değerlendirildi.

Bulgular: HER-2 durumu için model 0,76 AUC, 0,76 dengeli doğruluk, %62,5 duyarlılık ve %90,0 özgüllük değerleri elde etti. ER, PR ve Ki-67 durumu için AUC değerleri sırasıyla 0,59, 0,55 ve 0,60; dengeli doğruluk değerleri sırasıyla 0,65, 0,61 ve 0,62; duyarlılık değerleri sırasıyla %96,6, %81,8 ve %68,4; özgüllük değerleri ise sırasıyla %33,3, %40,0 ve %55,2 olarak bulundu.

Sonuç: Bu çalışmada, ¹⁸F-FDG PET/BT görüntülerinden elde edilen radyomik özellikler, ER, PR ve Ki-67 durumunun değerlendirilmesinde zayıf ya da ayırt edici olmayan bir performans göstermiştir. HER-2 durumu için bir ilişkiye dair ön bulgu niteliğinde bir sinyal gözlenmiş olsa da, test alt grubundaki HER-2 pozitif olgu sayısının düşük olması ve bağımsız dış doğrulamanın bulunmaması nedeniyle bu bulgu yalnızca hipotez oluşturu nitelikte değerlendirilmelidir. Bu olası ilişkinin doğrulanması için daha geniş kohortlarda yürütülecek prospektif, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Radyomik, makine öğrenmesi, pozitron emisyon tomografi, meme kanseri

Introduction

Breast cancer is the most prevalent malignancy diagnosed among women across the globe, as reported by the World Health Organization (1). Owing to its high prevalence and heterogeneous biology, accurate molecular characterization and appropriate therapeutic stratification remain crucial.

Conventionally, breast cancer is classified into several histological including invasive ductal carcinoma, invasive lobular carcinoma, tubular carcinoma, and mucinous carcinoma (2). Over time, it has become evident that tumors sharing the same histological characteristics can display distinct biological behaviors (3). Breast cancer constitutes a heterogeneous malignancy characterized by diverse biological and histological properties, clinical presentations, behaviors and therapeutic responses (4,5). Such heterogeneity emphasizes the need to individualize therapeutic approaches according to the histological, molecular, and genetic features of the tumor, thereby highlighting the increasing significance of personalized therapy (6,7).

In the current approach, the European Society for Medical Oncology guidelines for early breast cancer classify the disease into four molecular subtypes: "Luminal A," "Luminal B," "human epidermal growth factor receptor 2 (HER-2)-positive," and "basal-like." This classification is mainly determined by the evaluation of estrogen receptor (ER), progesterone receptor (PR), HER-2, and Ki-67 levels (8).

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) is a functional

imaging modality that reflects tumor glucose metabolism and may reveal biological heterogeneity within tumors beyond conventional visual analysis. Radiomic analysis converts imaging features into quantitative parameters, thereby enabling the investigation of associations between imaging phenotypes and molecular characteristics.

As in breast cancer, most imaging techniques used in medicine primarily rely on shades of gray, which represent transitions between black and white. Although imaging methods are capable of generating a wide spectrum of gray tones, the human eye can only distinguish a limited portion of them. Consequently, when clinicians evaluate medical images, the results often remain constrained by the perceptual limits of human vision. The necessity of computational support in analyzing the vast amount of information embedded within these gray tones is therefore evident. Through radiomic data analysis, the relationships between the smallest image pixels are converted into quantitative data, enabling information beyond the visual perception of the human eye to be processed in greater detail with the aid of machine learning algorithms (9,10,11,12).

In our study, we aim to investigate whether radiomic features extracted from ¹⁸F-FDG PET/CT images of patients with breast cancer are associated with molecular markers (ER, PR, Ki-67, and HER-2) commonly used to determine molecular subtypes. Although tissue sampling is the gold standard for determining these markers, in certain situations, such as when intratumoral heterogeneity limits representation of the whole lesion or in advanced disease when sampling every lesion is not feasible and targeted

tracers are unavailable, imaging-based approaches may provide exploratory information about tumor heterogeneity and potential imaging-molecular associations. This study was designed as an exploratory, hypothesis-generating analysis, and the findings should not be interpreted as supporting clinical implementation without further multicenter validation.

Materials and Methods

Study Population

For this retrospective study, we analyzed data from female patients over the age of 18 with histopathologically confirmed breast cancer based on surgical excision specimens and from available ^{18}F -FDG PET/CT images acquired between January 2015 and January 2022. Molecular marker profiles, including ER, PR, HER-2, and Ki-67, were determined exclusively from surgical pathology specimens, which were considered the histopathological reference standard. The maximum time interval between PET/CT imaging and histopathological evaluation was one month.

The study initially included 477 patients. Patients were excluded if histopathology reports were unavailable. Analyses were performed separately for each molecular marker, and patients without an available result for a specific marker were excluded only from the corresponding endpoint analysis. For cases with HER-2 scores of +2, FISH correlation is recommended; patients without corresponding FISH results were excluded.

Furthermore, patients who had received any local or systemic treatment for breast cancer prior to ^{18}F -FDG PET/CT imaging or who had undergone excisional biopsy before imaging were excluded from the study.

As a result, 162 patients meeting all inclusion criteria were enrolled. Among these, ER and PR data were available for 160 patients each, HER-2 data for 139 patients, and Ki-67 data for 158 patients.

Classification thresholds for ER, PR, HER-2, and Ki-67 were selected according to clinical criteria and standards reported in the literature. ER and PR expression was considered negative when the result was 0% and positive when $\geq 1\%$ (13). HER-2 status was determined by immunohistochemistry, with scores of 0 and +1 classified as negative and +3 classified as positive. Cases with a +2 score were further evaluated using FISH; those with a negative FISH result were categorized as negative, whereas those with a positive FISH result were categorized as positive (14). Ki-67 expression was considered negative for values $< 20\%$ and positive for values $\geq 20\%$ (15).

This study received ethical approval from Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (decision number: 2023/01-17, date: 04.01.2023) and informed consent was not required due to the study's retrospective nature.

PET/CT Acquisition Procedure

^{18}F -FDG PET/CT images were acquired using a hybrid PET/CT imaging system (Gemini TF16 PET/CT; Philips Medical Systems). Imaging was performed 60 ± 5 minutes after intravenous administration of 350-550 MBq of ^{18}F -FDG labeled ^{18}F -FDG in patients who had fasted for 4-6 hours and had a blood glucose level < 150 mg/dL. Low-dose, non-contrast CT images (120 kVp, 60-150 mA, 5 mm slice thickness) covering the vertex to the proximal thigh were obtained first; PET acquisition in 3D mode at 3 minutes per bed position was performed immediately afterward. PET images were reconstructed using the line-of-response row-action maximum-likelihood algorithm (LOR-RAMLA; Philips Astonish TF), producing transverse, coronal, and sagittal image planes.

Feature Extraction

For the purpose of segmenting breast cancer lesions and extracting radiomic features from PET/CT images, the Java-based Local Image Feature Extraction (LIFEx, version 7.1.9) software (www.lifexsoft.org) was employed (16). The software allows for standardized texture analysis, and all texture parameters used in this study conform to the guidelines established by the Image Biomarker Standardization Initiative, ensuring reproducibility and consistency in radiomic feature quantification (17).

PET/CT images in DICOM format were exported from the workstation. For texture analysis, a three-dimensional (3D) spherical volume of interest (VOI) encompassing the entire target lesion was delineated on the PET images. Using a semi-automated approach, a fixed threshold corresponding to 40% of the maximum standardized uptake value within the VOI was applied to segment the lesion. The fixed 40% SUV_{max} threshold is a commonly applied method in PET-derived radiomics studies due to its reproducibility (18).

The image-processing stage following segmentation is critically important. To ensure standardization of tissue analysis and facilitate comparison with other studies, it is essential to define appropriate image processing parameters before calculating radiomic features. Experience in this area has increased as the number of studies has grown (19). In the present study, all segmented lesions were spatially resampled to a voxel size of 4 mm along the x, y, and z axes. Absolute resampling, as recommended for intensity rescaling in PET imaging, was applied (20). Since

SUV values in ^{18}F -FDG-based oncological imaging typically range between 0 and 20, these values were set as the minimum and maximum for intensity rescaling. A fixed bin width of 0.3125 was used, resulting in 64 gray levels within the mentioned SUV range. The workflow of the radiomic analysis is illustrated in Figure 1.

In the subsequent step, 45 features — conventional, histogram-based, and texture — were extracted from the segmented lesion. Histogram-based features represent first-order statistics, while texture features correspond to second-order statistics (21). The texture features were primarily derived from the gray-level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), neighborhood gray-level difference matrix (NGLDM), gray-level zone length matrix (GLZLM), and their respective subgroups (22). The full list of features used to develop machine learning models is presented in Table 1.

Machine Learning Model Establishment

Machine learning models were developed separately for the exploratory assessment of associations between radiomic features and ER, PR, HER-2, and Ki-67 molecular profiles.

Due to differences in sample size and class distribution among molecular markers, the train-test split was determined separately for each endpoint. While an 80/20 split was used for ER, PR, and HER-2, a 70/30 split was applied to Ki-67 to ensure adequate class representation in the test set (random seed =42). Class distributions between training and test subsets were comparable for all endpoints. To prevent information leakage, all preprocessing steps are applied exclusively to the training subset.

For each molecular marker, 45 radiomic features were initially considered. The features were scaled using a normalization method to map their minimum and maximum values to a range between 0 and 1. This step was performed only on the training subset, and once the parameters were learned, they were applied to the test subset.

To determine the most relevant features for use in machine learning models, the sequential feature selection (SFS) method was applied only to the training subset. Feature selection was guided by k-scores, which represent the mean cross-validation performance of each candidate feature subset. Through this approach, the test subset was not accessed during feature scaling or feature selection.

Subsequently, the selected features were used to develop five machine learning models. The models implemented in this study included Random Forest, XGBoost, Support Vector Machine, Logistic Regression, and Naive Bayes. These models were trained on the training subset and evaluated on the held-out test subset. As model comparison and selection of the reported model were performed on the same test subset, the overall workflow does not represent a fully nested validation strategy. Accordingly, the reported performance estimates should be interpreted within an exploratory, hypothesis-generating framework and may be optimistically biased.

Statistical Analysis

Data analysis was performed using Python software (version 3.9.13). The performances of the five machine learning models were evaluated and compared using performance metrics including accuracy, precision, recall, F1 score, and

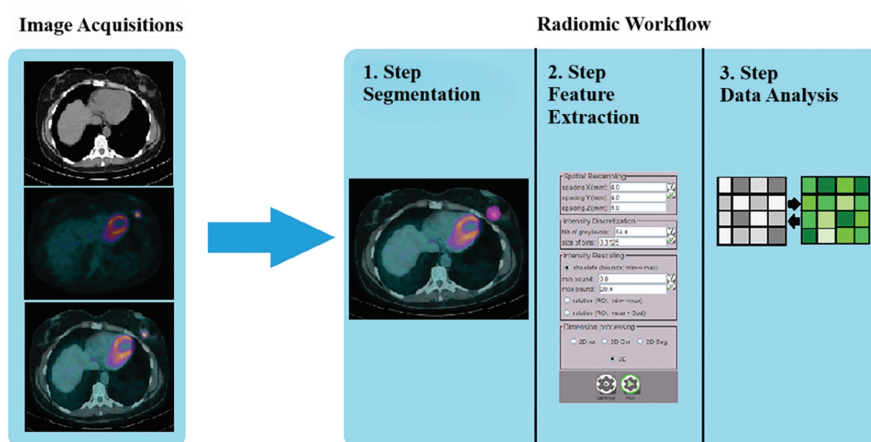


Figure 1. The workflow of the radiomic analysis

Table 1. Conventional, histogram-based, and textures features extracted using the LIFEx software									
Conventional	SUV _{min}	SUV _{mean}	SUV _{max}	SUV _{std}	SUV _{q1}	SUV _{q2}	SUV _{q3}	TLG, SUV _{peaksphere} 0.5mL, SUV _{peaksphere} 1mL	
Histogram-based	Skewness, Kurtosis, ExcessKurtosis								
Shape-based	Volume (mL), Volume (vx), sphericity, surface, compacity								
GLCM	Homogeneity, energy, contrast, correlation, EntropyLog10, EntropyLog2, dissimilarity								
GLRLM	SRE, LRE, LGRE, HGRE, SRLGE, SRHGE, LRLGE, LRHGE, GLNU, RLNU, RP								
NGLDM	Coarseness, contrast, busyness								
GLZLM	SZE, LGZE, SZLGE, GLNU, ZLNU, ZP								
SUV _{min} : Minimum standardized uptake value, SUV _{mean} : Mean standardized uptake value, SUV _{max} : Maximum standardized uptake value, SUV _{std} : Standard deviation of standardized uptake value, SUV _{q1} : First quartile of standardized uptake value, SUV _{q2} : Second quartile/median of standardized uptake value, SUV _{q3} : Third quartile of standardized uptake value, TLG: Total lesion glycolysis, GLCM: Gray-level co-occurrence matrix, GLRLM: Gray-level run-length matrix, NGLDM: Neighborhood gray-level difference matrix, GLZLM: Gray-level zone-length matrix, SRE: Short-run emphasis, LRE: Long-run emphasis, LGRE: Low gray-level run emphasis, HGRE: High gray-level run emphasis, SRLGE: Short-run low gray-level emphasis, SRHGE: Short-run high gray-level emphasis, LRLGE: Long-run low gray-level emphasis, LRHGE: Long-run high gray-level emphasis, GLNU: Gray-level non-uniformity, RLNU: Run-length non-uniformity, RP: Run percentage, SZE: Short-zone emphasis, LGZE: Long-zone emphasis, SZLGE: Short-zone low gray-level emphasis, ZLNU: Zone-length non-uniformity, ZP: Zone percentage									

support. Additionally, balanced accuracy and the matthews correlation coefficient (MCC) were calculated to account for class imbalance. Confidence intervals for sensitivity and specificity were calculated using binomial proportion methods. Based on the exploratory comparisons on the held-out test subset, one model for each molecular marker was selected. The confusion matrix of the selected model was further examined and its sensitivity and specificity were calculated. Additionally, ROC curves were plotted for all models, and the corresponding area under the curve (AUC) values were determined.

Results

The distribution of patients, the machine learning model selected for detailed reporting for each molecular marker, and the corresponding model performance metrics are presented in Tables 2 and 3.

ER Prediction

For the assessment of ER status, the most relevant 7 features out of 45 radiomic features were SUV_{min}, SUV_{q1}, SUV_{q2}, skewness, GLCM Contrast, GLRLM_LRE and GLRLM_SRLGE. Although the accuracy of Random Forest, XGBoost, Support Vector Machine, and Logistic Regression models was 0.91, this performance metric is misleading because of

a marked class imbalance, with ER-positive cases comprising 89% of the cohort. When the Random Forest model was used to predict ER expression from radiomic data, the sensitivity, specificity, and AUC were 96.6%, 33.3%, and 0.59, respectively. The combination of high sensitivity and low specificity indicates inadequate discrimination of ER-negative tumors. The balanced accuracy was 0.65, and the MCC was 0.37, further confirming the weak discriminatory performance despite high sensitivity.

PR Prediction

For the assessment of PR status, the five most relevant radiomic features were identified as SUV_{std}, SUV_{q2}, SUV_{peakSphere} 0.5ml, GLZLM_SZE and GLZLM_ZP. The Random Forest model achieved an accuracy of 0.69, with

Table 2. Summary of class distribution				
Molecular feature	Cohort n (+)	Cohort n (-)	Test n (+)	Test n (-)
ER	143	17	29	3
PR	110	50	22	10
HER-2	39	100	8	20
Ki-67	95	63	19	29
ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2				

Table 3. Selected machine learning model performance metrics for molecular marker assessment							
Molecular feature	Selected model	Sensitivity (95% CI)	Specificity (95% CI)	Balanced accuracy	MCC	F1	AUC
ER	Random forest	0.97 (0.82-0.99)	0.33 (0.06-0.79)	0.65	0.36	0.93	0.59
PR	Random forest	0.82 (0.60-0.94)	0.40 (0.17-0.69)	0.61	0.23	0.75	0.55
HER2	Random forest	0.63 (0.26-0.90)	0.90 (0.68-0.99)	0.76	0.55	0.67	0.76
Ki-67	XGBoost	0.68 (0.44-0.86)	0.55 (0.36-0.73)	0.62	0.23	0.58	0.60
ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2, CI: Confidence interval, MCC: Matthews correlation coefficient, AUC: Area under the curve							

sensitivity, specificity, and AUC of 81.8%, 40.0%, and 0.55, respectively. The balanced accuracy was 0.61 and the MCC was 0.23. These findings suggest that the model performs similarly to a majority-class classifier. No discriminatory performance was observed for PR status.

HER-2 Prediction

The ten most relevant radiomic features for HER-2 status assessment were SUV_{mean} , SUV_{max} , $\text{SUV}_{\text{peak-sphere-1}}$, mL, sphericity, compactity, GLCM dissimilarity, GLRLM_LRLGE, GLRLM_RLNU, NGLDM Contrast and GLZLM_GLNU. Among the models evaluated, Random Forest achieved the highest balanced accuracy of 0.76. When this model was used to predict HER-2 expression from radiomic data, sensitivity and specificity were 62.5% and 90.0%, respectively, and the highest AUC was 0.76 (Figure 2). These results indicate a preliminary discriminatory signal for HER-2 status. However, given the limited number of HER-2 positive cases in the test subset and the exploratory model selection framework, these findings should be considered hypothesis-generating rather than evidence of robust predictive capability.

Ki-67 Prediction

For the assessment of Ki-67 status, the six most relevant radiomic features were identified as SUV_{max} , SUV_{q3} , compactity, GLRLM_LRE, GLZLM_LGZE and GLZLM_GLNU. The highest accuracy for Ki-67 prediction was 0.60, achieved using both XGBoost and Logistic Regression models. The F1 scores were 0.58 for XGBoost and 0.42

for Logistic Regression. Using the XGBoost model, Ki-67 prediction yielded sensitivity, specificity, and AUC of 68.4%, 55.2%, and 0.60, respectively. No discriminative performance was observed for Ki-67 expression relative to the radiomic features in this study.

Discussion

The present study aimed to explore whether radiomic features extracted from ^{18}F -FDG PET/CT images were associated with ER, PR, HER-2, and Ki-67 status in breast cancer. Radiomic analysis may provide information regarding tumor tissue heterogeneity which is presumed to be reflected in but remains imperceptible to the human eye (10).

In this context, radiomic analysis may be capturing tumor metabolic heterogeneity rather than the molecular marker directly.

In the present exploratory analysis, model performance for ER, PR, and Ki-67 status was weak or nondiscriminatory. For HER-2 status, a preliminary signal of discrimination was observed, with the Random Forest model achieving a balanced accuracy of 0.76 and an AUC of 0.76. Nevertheless, this finding should be interpreted cautiously because of the limited number of HER-2-positive cases in the test subset and the exploratory nature of the model selection framework.

Because model comparison was performed on the held-out test set, the reported performance estimates may be optimistically biased. Therefore, the results should be interpreted as exploratory and not be considered sufficient to support robust prediction or clinical decision-making. Also, the results require external validation.

For studies in the literature to be comparable and reproducible, it is essential to examine not only the imaging protocols but also the parameters used for texture feature extraction and the statistical methods applied. Various software tools are available for extracting texture features. However, the nomenclature of radiomic features often differs across platforms. Moreover, the choice of parameters during the feature extraction process significantly influences the results. Therefore, studies should provide detailed descriptions of how these parameters are defined to enable meaningful comparisons across studies. A review of the literature reveals that many studies fail to report the texture analysis parameters in sufficient detail, which hampers the reliability of cross-study comparisons. In the present study, the parameters used for feature extraction are described comprehensively. Establishing standardized parameters for texture analysis is crucial to ensure consistency and reproducibility in future research.

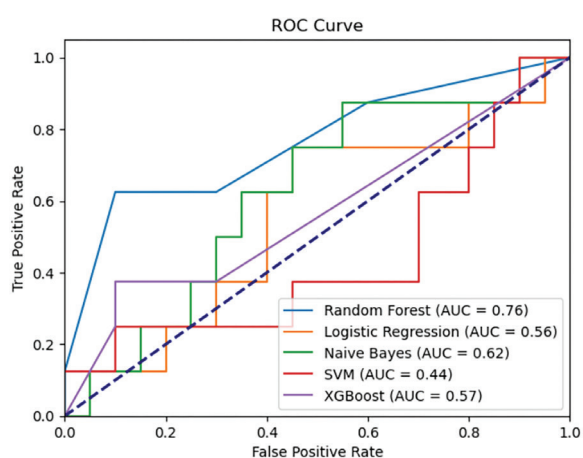


Figure 2. Comparison of ROC curves and AUCs among machine learning models for assessment of HER-2 status
AUC: Area under the curve, HER-2: Human epidermal growth factor receptor 2, SVM: Support Vector Machine

Recent years have witnessed a substantial increase in texture analysis studies.

In the literature, studies investigating the relationship between ER status and radiomic features, such as those by Ha et al. (23), Antunovic et al. (24), Moscoso et al. (25) and Araz et al. (26) have reported no discriminatory performance. However, Acar et al. (27) reported discriminatory performance for ER using GLRLM_GLNU, GLRLM_RLNU, GLZLM_GLNU and GLZLM_ZLNU features while Soussan et al. (28) reported an association using the HGRE feature. In the present study, despite the high observed sensitivity for ER status, the low specificity, the balanced accuracy of 0.65, and the AUC of 0.59 indicate weak discriminatory performance, particularly for identifying ER-negative tumors.

Likewise, the studies in the literature investigating PR status, such as those by Ha et al. (23), Antunovic et al. (24), Acar et al. (27) and Lemarignier et al. (29) have not demonstrated discriminatory performance. However, studies by Soussan et al. (28) for HGRE feature and Moscoso et al. (25) reported potentially relevant findings for PR status. The present study yielded an AUC of 0.55, a balanced accuracy of 0.61, and an MCC of 0.23. These findings indicate no discriminatory performance with respect to PR status.

For HER-2 status, studies by Ha et al. (23), Soussan et al. (28) and Lemarignie et al. (29) with limited sample sizes did not demonstrate discrimination between HER-2 status and radiomic features, whereas other studies including those by Moscoso et al. (25) and Chen et al. (30), reported varying degrees of discriminatory performance. In the present study, the Random Forest model achieved an AUC of 0.76, a balanced accuracy of 0.76, a sensitivity of 62.5%, and a specificity of 90.0%. These findings suggest a preliminary imaging-molecular association with HER-2 status. Due to the limited number of HER-2-positive cases in the test subset and the absence of independent external validation, these results should be interpreted as hypothesis-generating rather than evidence of clinically reliable predictive utility. Therefore, these findings require confirmation in larger, prospective, multicenter cohorts and independent external validation.

From a biological perspective, while ^{18}F -FDG uptake reflects higher glycolytic activity, which is influenced by cellular proliferation, hypoxia, and oncogenic signaling pathways, HER-2 overexpression is associated with increased tumor aggressiveness and activation of downstream pathways such as PI3K/Akt/mTOR. This pathway is known to regulate cell growth, proliferation and metabolism and may promote glycolysis (31,32,33). Consequently, HER-2 positive tumors may demonstrate increased metabolic

activity and heterogeneous spatial metabolic patterns on ^{18}F -FDG PET imaging (25, 34).

Notably, some conventional features, such as SUV_{mean} , SUV_{max} , and SUV_{peak} , which are among the most relevant, are also selected for HER-2 status. This may suggest that both global metabolic activity and intratumoral heterogeneity contribute to HER-2 imaging patterns. As conventional PET features reflect overall tumor metabolism, radiomic features may contribute by quantifying intratumoral spatial heterogeneity. However, this interpretation remains hypothesis-generating and should be specifically investigated in future studies.

Regarding Ki-67 status, previous studies by Antunovic et al. (24) and Acar et al. (27) have not demonstrated that radiomic features meaningfully discriminate Ki-67 expression. However, Ha et al. (23) reported a significant association ($p=0.006$). In the present study, the AUC of 0.60, sensitivity of 68.4%, and specificity of 55.2% indicate a lack of discriminatory performance for Ki-67 status.

In this study, several factors, including tumor grade, size, distribution of intrinsic molecular subtypes, and uptake time, may confound ^{18}F -FDG uptake and radiomic features. Although all efforts were made to standardize imaging protocols, the possibility of some residual variability cannot be entirely excluded.

Study Limitations

This study has several limitations. The retrospective, single-center design and the relatively limited sample size restrict the generalizability of these findings. In particular, the small number of HER-2 positive cases in the test subset may have limited the reliability of performance estimates for predicting HER-2 status.

Although feature scaling and SFS were performed exclusively within the training subset, the same held-out test subset was used both to compare candidate models and to select the final model. Therefore, the present workflow does not constitute independent validation; consequently, the performance estimates may be optimistically biased.

Furthermore, lesion segmentation was performed by a single observer, and interobserver variability was not assessed. This may limit the reproducibility of the extracted radiomic features. In addition, a fixed 40% SUV_{max} threshold was applied to extract radiomic features. Although this is a commonly used method in PET-derived radiomic studies, segmentation based on a fixed threshold may affect the robustness of radiomic features, especially in small or heterogeneous tumors.

This was a single-center study, and no external validation was performed. Therefore, the present findings should

be interpreted strictly within an exploratory, hypothesis-generating framework. Prospective, multicenter studies with independent external validation are needed to further confirm and generalize these findings.

Conclusion

In this exploratory study, PET-derived radiomic features demonstrated weak or no discriminatory performance in assessing ER, PR, and Ki-67 status. A preliminary imaging-molecular association for HER-2 status was observed. However, these findings should be interpreted as hypothesis-generating because of the limited number of HER-2-positive cases in the test subset, the model selection framework, and the absence of independent external validation. Therefore, these results do not support robust predictive capability or clinical implementation of ¹⁸F-FDG PET radiomics for molecular marker assessment. Larger, prospective, multicenter studies with independent external validation are required to confirm the potential association between ¹⁸F-FDG PET radiomic features and HER-2 status.

Ethics

Ethics Committee Approval: This study received ethical approval from Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (decision number: 2023/01-17, date: 04.01.2023).

Informed Consent: This is retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.A.P., S.U., Concept: B.A.P., S.U., Design: B.A.P., S.U., Y.S.S., Data Collection or Processing: B.A.P., S.U., Y.S.S., R.U.E., Analysis or Interpretation: B.A.P., S.U., Y.S.S.,

Literature Search: B.A.P., S.U., Y.S.S., R.U.E., Writing: B.A.P., S.U.

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The Role of ⁶⁸Ga-FAPi PET/CT in Staging and Restaging of Breast Cancer Subtypes with Limited ¹⁸F-FDG Uptake

Düşük ¹⁸F-FDG Tutulumu Gösteren Meme Kanseri Alt Tiplerinde ⁶⁸Ga-FAPi PET/BT'nin Evreleme ve Yeniden Evrelemedeki Rolü

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Abstract

Objectives: Breast cancer is highly heterogeneous, and certain histopathologic subtypes—particularly invasive lobular carcinoma—exhibit low glucose metabolism that limits ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) performance. Fibroblast activation protein inhibitor (FAPi) imaging with Gallium-68 (⁶⁸Ga)-FAPi PET/CT has emerged as a promising alternative for such tumors. The aim of this study was to evaluate the efficacy of ⁶⁸Ga-FAPi PET/CT in staging, restaging, and recurrence detection of breast cancer, with emphasis on subtypes for which ¹⁸F-FDG PET/CT has low sensitivity.

Methods: Twenty-nine women with pathologically confirmed breast cancer (mean age 57.7±11.6 years) were prospectively enrolled. Histopathology (available in 24 patients) showed lobular carcinoma in 16, ductal carcinoma in 6, signet ring cell carcinoma in 1, and mucinous carcinoma in 1. All underwent both ⁶⁸Ga-FAPi and ¹⁸F-FDG PET/CT within one week for staging or restaging. Maximum standardized uptake values (SUV_{max}) of primary tumors and metastases were recorded for both tracers and compared using paired t-tests.

Results: In 7/29 patients (24.1%), neither ¹⁸F-FDG PET/CT nor ⁶⁸Ga-FAPi PET/CT detected pathological findings. Disease stage increased in 13/29 (44.8%) after ⁶⁸Ga-FAPi PET/CT, including 10 patients with no pathologic findings on ¹⁸F-FDG PET/CT; nine were upstaged to stage 4 and one to stage 3. Additionally, one patient progressed from stage 1 to 2, one from 2 to 3, and another from 3 to 4. Among patients with lobular carcinoma, 8/16 (50%) were upstaged with ⁶⁸Ga-FAPi PET/CT. Detection of nodal and distant metastases in lobular carcinoma was higher with ⁶⁸Ga-FAPi than ¹⁸F-FDG. ⁶⁸Ga-FAPi PET/CT also demonstrated higher SUV_{max} in primary lesions and metastases (p<0.05).

Conclusion: ⁶⁸Ga-FAPi PET/CT provides a significant advantage for staging and restaging breast cancer—especially lobular carcinoma and other low ¹⁸F-FDG-avid subtypes—supporting its potential role in clinical decision-making and treatment planning.

Keywords: ⁶⁸Ga-FAPi PET/CT, invasive lobular carcinoma, breast cancer, staging, restaging

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Öz

Amaç: Meme kanseri oldukça heterojendir ve bazı histopatolojik alt tipler—özellikle invaziv lobüler karsinom—düşük glukoz metabolizması göstererek ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸F-FDG PET/BT) performansını sınırlandırmaktadır. Galyum-68 (⁶⁸Ga)-FAPi PET/BT ile fibroblast aktivasyon protein inhibitörü (FAPi) görüntüleme, bu tür tümörler için umut vadeden bir alternatif olarak ortaya çıkmıştır. Bu çalışmanın amacı, meme kanserinin evrenmesi, yeniden evrenmesi ve nüksünün saptanmasında ⁶⁸Ga-FAPi PET/BT'nin etkinliğini değerlendirmek ve özellikle ¹⁸F-FDG PET/BT'nin duyarlılığının düşük olduğu alt tiplere odaklanmaktır.

Yöntemler: Patolojik olarak meme kanseri tanısı doğrulanmış 29 kadın hasta prospektif olarak çalışmaya dahil edildi. Hastaların ortalama yaşı 57,7±11,6 yıl idi. Histopatolojik değerlendirme 24 hastada mevcut olup, 16 hastada lobüler karsinom, 6 hastada duktal karsinom, 1 hastada taşlı yüzük hücreli karsinom ve 1 hastada müsinöz karsinom saptandı. Tüm hastalara evreleme veya yeniden evreleme amacıyla bir hafta içinde ⁶⁸Ga-FAPi ve ¹⁸F-FDG PET/BT uygulandı. Primer tümörlerin ve metastazların maksimum standardize tutulum değerleri (SUV_{maks}) her iki izleyici için kaydedildi ve eşleştirilmiş t-testleri kullanılarak karşılaştırıldı.

Bulgular: Yirmi dokuz hastanın 7'sinde (%24,1) nüks ve metastaz saptanmadı. ⁶⁸Ga-FAPi PET/BT sonrasında 29 hastanın 13'ünde (%44,8) hastalık evresi yükseldi; bunların 10'unda ¹⁸F-FDG PET/BT'de patolojik bulgu yoktu. Bu hastaların dokuzu evre 4'e, biri ise evre 3'e yükseltildi. Ayrıca bir hastada evre 1'den 2'ye, bir hastada evre 2'den 3'e ve bir hastada evre 3'ten 4'e evre artışı saptandı. Lobüler karsinomlu hastalar arasında 16 hastanın 8'inde (%50) ⁶⁸Ga-FAPi PET/BT ile evre yükseldi. Lobüler karsinomda nodal ve uzak metastazların saptanması ⁶⁸Ga-FAPi ile ¹⁸F-FDG'ye kıyasla daha yüksekti. Ayrıca ⁶⁸Ga-FAPi PET/BT, primer lezyonlarda ve metastazlarda daha yüksek SUV_{maks} değerleri gösterdi (p<0,05).

Sonuç: ⁶⁸Ga-FAPi PET/BT, meme kanserinin evrenmesi ve yeniden evrenmesinde—özellikle lobüler karsinom ve düşük ¹⁸F-FDG tutulumu gösteren diğer alt tiplerde—önemli bir avantaj sağlamaktadır. Bu bulgular, ⁶⁸Ga-FAPi PET/BT'nin klinik karar verme ve tedavi planlamasında potansiyel bir role sahip olduğunu desteklemektedir.

Anahtar Kelimeler: ⁶⁸Ga-FAPi PET/BT, invaziv lobüler karsinom, meme kanseri, evreleme, yeniden evreleme

Introduction

Breast cancer is the most common malignancy among women and represents a significant public health issue due to its high incidence and mortality rates (1). This heterogeneous disease exhibits considerable variability in biological behavior, histopathological characteristics, and treatment response (2). Accurate staging and restaging are critical components in the diagnosis and management of breast cancer. ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) is a key modality in breast cancer management, contributing to diagnosis, staging, restaging, treatment assessment, and prognostic evaluation. While ¹⁸F-FDG PET/CT demonstrates high diagnostic accuracy, particularly for metastases, its sensitivity is limited for detecting small tumors (<1 cm), peritoneal micrometastases, and lymph node metastases (3). Moreover, its diagnostic efficacy is limited in certain histopathological subtypes, such as lobular carcinoma, which typically demonstrates low metabolic activity (4). These limitations underscores the need for more sensitive and effective imaging modalities in these patients. Studies have demonstrated that PET/CT performed with Gallium-68 (⁶⁸Ga)-labeled fibroblast activation protein inhibitor (FAPi) a new theranostic candidate, provides superior sensitivity and specificity in detecting primary and metastatic breast cancer lesions compared to ¹⁸F-FDG PET/CT, offering improved diagnostic accuracy and staging precision (5,6).

FAPi targets fibroblast activation protein, which is highly expressed in the tumor stroma, providing effective imaging even in cases with low ¹⁸F-FDG uptake. ⁶⁸Ga-FAPi PET/CT

has been shown to outperform conventional methods in detecting primary tumors and metastatic lesions with low ¹⁸F-FDG affinity. In particular, it is thought to offer enhanced sensitivity for histological subtypes such as lobular carcinoma, for identifying lymph node metastases and distant metastases.

The aim of this study was to evaluate the efficacy of ⁶⁸Ga-FAPi PET/CT in staging, restaging, and recurrence detection of breast cancer patients, particularly in tumors such as lobular carcinoma, in which the diagnostic value of ¹⁸F-FDG is limited.

Materials and Methods

Patients

This single-center prospective clinical study enrolled 29 female patients (mean age 57.7±11.6 years) with pathologically confirmed breast cancer. All patients underwent both ¹⁸F-FDG and ⁶⁸Ga-FAPi PET/CT imaging within one week for staging or restaging. The inclusion criteria were as follows: I) histologically confirmed invasive breast carcinoma (primary staging or restaging), II) a prior ¹⁸F-FDG PET/CT performed within the clinical work-up, III) ¹⁸F-FDG PET/CT that showed: a) no abnormal ¹⁸F-FDG uptake (¹⁸F-FDG-negative), b) low-grade, equivocal, or clinically non-explanatory ¹⁸F-FDG uptake, insufficient to account for clinical suspicion, rising tumor markers, or abnormalities on other imaging modalities, IV) a clinical expectation that ⁶⁸Ga-FAPi PET/CT might clarify disease extent or reveal additional metastatic sites not visualized on ¹⁸F-FDG PET/CT, V) age ≥18 years and ECOG performance status <3.

Exclusion criteria were: I) ^{18}F -FDG PET/CT demonstrating clear and disseminated ^{18}F -FDG positive metastatic (stage IV) disease, for which ^{68}Ga -FAPi PET/CT was not expected to provide further diagnostic benefit and would only add unnecessary radiation exposure, II) ^{18}F -FDG-avid primary breast cancers in which staging was already conclusive based on ^{18}F -FDG PET/CT findings, III) history of a second primary malignancy.

Informed consent was obtained from all patients. This prospective study was approved by the Ethics Committee of Yeditepe University (decision no: 1576, date: 02.03.2022).

Preparation and Quality Control of ^{68}Ga -FAPi

^{68}Ga -DOTA-FAPi-46 (used in 19 patients) and ^{68}Ga -DOTA-FAP-2286 (used in 10 patients) were prepared using a modular-based fully automated synthesizer (GRP V4, Scintomics GmbH, Germany). The use of two FAP-targeting ligands was related to radiopharmaceutical availability and logistical changes in the local radiochemistry workflow. The imaging acquisition protocol, scanner, reconstruction parameters, and interpretation criteria were kept consistent throughout the study. The study was not designed as a head-to-head comparison of these two ligands. Briefly, the ^{68}Ga obtained from the $^{68}\text{Ge}/^{68}\text{Ga}$ generator (iThemba LABS) was sent to the reaction vial containing DOTA-FAPi-46 or DOTA-FAP-2286. After completion of the labelling process, the reaction solution was purified using an extraction cartridge and then subjected to sterile filtration to prepare the final patient dose. The total synthesis time was 25 minutes. The radiochemical purity and radiolabeling efficiency of ^{68}Ga -DOTA-FAPi-46 and ^{68}Ga -DOTA-FAP-2286 were determined by combining a radioactive detector with reversed-phase high-pressure liquid chromatography. ^{68}Ga -FAPi with a radiochemical purity of $\geq 95\%$ was administered to patients.

^{18}F -FDG and ^{68}Ga -FAPi PET/CT Imaging

Whole-body ^{18}F -FDG PET/CT and ^{68}Ga -FAPi PET/CT scans were performed using a PET scanner (Discovery PET/CT 710, General Electric Medical Systems, Milwaukee, WI, USA) with high resolution, time-of-flight function, and LYSO crystal and integrated with 64-slice CT scanner. The average activity of ^{18}F -FDG was 425 ± 64 MBq (range: 340-548 MBq) [11.5 ± 1.7 mCi (range: 9.2-14.8 mCi)], ^{68}Ga -FAPi was 243 ± 57 MBq (range: 122-312 MBq) [6.6 ± 1.5 mCi (range: 3.3-8.4 mCi)]. Patients were positioned supine on the PET scanner bed 60 minutes after intravenous injection of radiopharmaceuticals. CT and PET images were acquired from the vertex region to mid-thigh. ^{68}Ga -FAPi PET/CT scans were performed within 7 days after ^{18}F -FDG PET/CT.

Evaluation of ^{18}F -FDG and ^{68}Ga -FAPi PET/CT Images

The presence of primary breast lesions and metastatic lesions, as well as changes in disease stage, on ^{18}F -FDG and ^{68}Ga -FAPi PET/CT scans were noted. Uptake in the tumor was measured by maximum standardized uptake value (SUV_{max}) using circular regions of interest drawn around the lesions with focal uptake in transaxial slices and automatically adapted to a 3D voxel area.

The final disease status of PET-positive and PET-negative findings was determined using a predefined composite reference standard. Histopathological confirmation was used whenever clinically available. For lesions without histopathological confirmation, a ^{68}Ga -FAPi PET/CT-positive finding was accepted as true-positive only when all of the following criteria were fulfilled: anatomical/radiological correlation on diagnostic contrast-enhanced CT and/or magnetic resonance imaging (MRI); compatible findings on follow-up or correlative imaging performed at least 6 months after the index PET/CT, including ^{68}Ga -FAPi PET/CT, ^{18}F -FDG PET/CT, CT, and/or MRI; and confirmation by multidisciplinary tumor board assessment. Follow-up imaging findings were interpreted together with the clinical course and treatment status. PET findings were not used as the sole reference standard. All images were reviewed by consensus by three senior nuclear medicine physicians for confirmation.

For lesion-site-based detection analysis, the number of patients positive at each metastatic site was determined using a composite reference standard derived from all available patient data. This included histopathological confirmation when available, contrast-enhanced CT, MRI when clinically performed, other conventional imaging findings, follow-up imaging, tumor marker evolution, clinical course, and multidisciplinary consensus. Therefore, detection rates were not calculated solely from ^{18}F -FDG PET/CT and ^{68}Ga -FAPi PET/CT findings, but were correlated with the parameters mentioned above.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 25.0, IBM Inc.). Descriptive analyses were conducted to assess the characteristics of the patients and their tumors. The mean and standard deviation were calculated for normally distributed measurements, and the median and range for non-normally distributed measurements. The SUV_{max} of the primary tumor areas, axillary lymph nodes and metastases on the ^{18}F -FDG and ^{68}Ga -FAPi PET/CT images were recorded and statistically compared using the paired t-test. Chi-square test was used to evaluate the staging accuracy of ^{18}F -FDG PET/CT

and ⁶⁸Ga-FAPi PET/CT. A p value of less than 0.05 was considered statistically significant.

Results

Pathology reports from previous surgeries/biopsies were available for all patients; however, a documented histopathological subtype was available in 24 patients: lobular carcinoma in 16, ductal carcinoma in 6, signet-ring cell carcinoma in 1, and mucinous carcinoma in 1. In 5 patients, the pathology reports did not include a documented histopathological subtype. Thirteen patients (44.8%) were enrolled for staging purposes, and 16 (55.2%) were enrolled for restaging purposes.

⁶⁸Ga-FAPi PET/CT demonstrated positive findings in 22 patients, whereas ¹⁸F-FDG PET/CT revealed positive findings in only 12 patients. In seven patients (24.1%), neither ¹⁸F-FDG PET/CT nor ⁶⁸Ga-FAPi PET/CT detected any pathological findings. Among these patients, two were undergoing initial staging, while five were undergoing restaging. No pathological findings were detected in these patients by other imaging modalities or during follow-up.

On ⁶⁸Ga-FAPi PET/CT, the most frequently detected metastatic site was bone (41.4%, n=12), followed by axillary lymph nodes (34.5%, n=10), primary tumor lesions (34.5%, n=10), distant lymph nodes (24.1%, n=7), visceral metastases (20.7%, n=6), and peritoneal metastases (17.2%, n=5) (Table 1).

The detection of lymph nodes and distant metastases was higher with ⁶⁸Ga-FAPi PET/CT than with ¹⁸F-FDG PET/CT (Table 2). Furthermore, ⁶⁸Ga-FAPi PET/CT showed a higher SUV_{max} in primary tumor foci and metastases (p<0.05) (Table 3). The mean SUV_{max} of primary lesions was significantly higher on ⁶⁸Ga-FAPi PET/CT than on ¹⁸F-FDG PET/CT, 15.08±4.30 vs. 2.30±1.98, respectively, p<0.001. Axillary lymph node metastases also demonstrated significantly higher uptake on ⁶⁸Ga-FAPi PET/CT, with SUV_{max} of 23.54±16.46 compared with 5.30±11.22 on ¹⁸F-FDG PET/CT, p=0.032. For distant lymph node, visceral, peritoneal, and bone metastases, no ¹⁸F-FDG SUV_{max} comparison was possible because these sites were not detected on ¹⁸F-FDG PET/CT in our cohort. The mean SUV_{max} on ⁶⁸Ga-FAPi PET/CT were 14.07±6.50 for distant lymph node metastases, 10.66±4.50 for visceral metastases, 9.94±2.15 for peritoneal metastases, and 16.32±9.31 for bone metastases.

In 5 out of 13 patients (38.4%) referred for staging, the disease stage was higher on ⁶⁸Ga-FAPi PET/CT compared to ¹⁸F-FDG PET/CT. Following ⁶⁸Ga-FAPi PET/CT, one patient was upstaged from stage 1 to stage 2, one from stage 2 to stage 3, and another from stage 3 to stage 4 according to the American Joint Committee on

Table 1. Patient characteristics (n=29)

Characteristic	Value
Age, mean ± SD	57.7±11.6
Gender	
Female	29
Male	-
Histopathological subtype	Available in 24 patients
Lobular carcinoma	16
Ductal carcinoma	6
Signet ring cell carcinoma	1
Mucinous carcinoma	1
Primary surgery before scanning % (n)	
Yes	62.1% (18/29)
No	37.9% (11/29)
Lesion localization detected on ⁶⁸Ga-FAPi PET/CT, % (n)	
Primary lesion	34.5% (10/29)
Axillary lymph node metastasis	34.5% (10/29)
Distant lymph node metastasis	24.1% (7/29)
Visceral metastasis	20.7% (6/29)
Peritoneal metastasis	17.2% (5/29)
Bone metastasis	41.4% (12/29)
Indication for imaging, % (n)	
Staging	44.8% (13/29)
Restaging	55.2% (16/29)

SD: Standard deviation, ⁶⁸Ga-FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography

Table 2. Lesion detection rates for ¹⁸F-FDG and ⁶⁸Ga-FAPi PET/CT scans

Lesion site	Number of positive patients*	¹⁸ F-FDG	⁶⁸ Ga-FAPi
Primary lesion	11	8 (72.7%)	10 (90.9%)
Axillary LN metastasis	10	6 (60%)	10 (100%)
Distant LN metastasis	7	0	7 (100%)
Visceral metastasis	7	0	6 (85.7%)
Peritoneal metastasis	5	0	5 (100%)
Bone metastasis	12	0	12 (100%)

*: Number of positive lesion-sites were determined based on all known information about the patients, ¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose, ⁶⁸Ga-FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, LN: Lymph nodes

Cancer 8th edition. ⁶⁸Ga-FAPi PET/CT also revealed stage 4 disease in two patients where no findings were observed on ¹⁸F-FDG PET/CT. All patients who were upstaged to stage 4 (a total of 3 patients) were found to have bone

Table 3. SUV_{max} of ^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT according to lesion location

Lesion site	^{18}F -FDG	^{68}Ga -FAPI	p
Primary lesion	2.30±1.98	15.08±4.30	<0.001
Axillary LN metastasis	5.30±11.22	23.54±16.46	0.032
Distant LN metastasis	N/A	14.07±6.50	-
Visceral metastasis	N/A	10.66±4.50	-
Peritoneal metastasis	N/A	9.94±2.15	-
Bone metastasis	N/A	16.32±9.31	-

^{68}Ga -FAPI PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, LN: Lymph nodes, ^{18}F -FDG: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max} : Maximum standardized uptake value

metastases, as detected by ^{68}Ga -FAPI PET/CT, highlighting its superior sensitivity in identifying metastatic lesions compared to ^{18}F -FDG PET/CT.

Of the 21 patients referred to our clinic for restaging due to elevated tumor markers or suspected recurrence on conventional imaging during follow-up, ^{18}F -FDG PET identified recurrence in 8 patients, while ^{68}Ga -FAPI PET/CT detected recurrence in 16 patients (Figure 1). In 5 patients, no lesion was identified by either modality.

False-negative findings were observed in two patients: one had no uptake in the primary tumor, and the other had mucinous carcinoma with lung metastasis; these lesions were undetected by both ^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT.

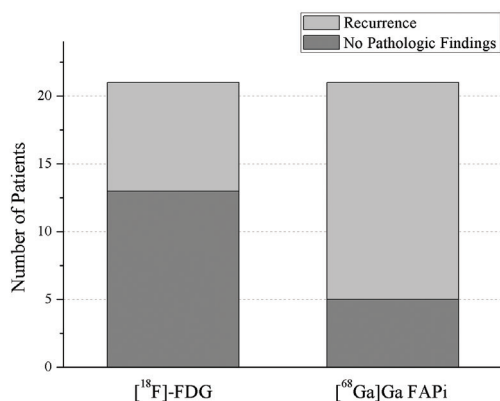


Figure 1. Recurrence detection numbers with ^{18}F -FDG and ^{68}Ga -FAPI PET/CT (n=21) in the restaging cohort. Among 16 patients referred for restaging, ^{18}F -FDG PET/CT identified recurrence in 3 patients, whereas ^{68}Ga -FAPI PET/CT detected recurrence in 11 patients. In 5 patients, no pathological finding was detected with either modality.

^{68}Ga -FAPI PET/CT: Gallium-68-fibroblast activation protein inhibitor positron emission/computed tomography, ^{18}F -FDG: ^{18}F -fluorodeoxyglucose

Discussion

Although ^{18}F -FDG PET/CT is a highly valuable method for the diagnosis and staging of breast cancer, it may yield negative findings in several histopathological subtypes of breast tumors, particularly in invasive lobular carcinoma and certain subtypes of ductal carcinoma (7). In such cases, both the diagnosis of the primary tumor and the staging of the disease can be compromised. ^{68}Ga -FAPI PET/CT stands out due to its low background uptake and high uptake in these tumor types (8). Recent studies have found that ^{68}Ga -FAPI PET/CT demonstrates generally high tumor uptake in breast cancer and shows a higher metastasis detection rate compared with ^{18}F -FDG PET/CT, particularly for bone and peritoneal metastases (9,10).

In our study, the lesion detection capabilities of both modalities across different regions are presented in Table 2. The reported detection rates were calculated using this composite reference standard. Accordingly, distant lymph node metastases were present in 7 patients and were detected by ^{68}Ga -FAPI PET/CT in all 7 patients. Visceral metastases were present in 7 patients and were detected by ^{68}Ga -FAPI PET/CT in 6 patients. Peritoneal metastases were present in 5 patients and were detected by ^{68}Ga -FAPI PET/CT in all 5 patients. These findings suggest that ^{68}Ga -FAPI PET/CT may provide additional diagnostic value in lesion sites that are often difficult to detect with ^{18}F -FDG PET/CT in low- ^{18}F -FDG-avidity breast cancer subtypes. According to these results, ^{68}Ga -FAPI was found to be highly effective, with detection rates of 100% for distant lymph nodes, 85.7% for visceral organ metastases, and 100% for peritoneal metastases. In contrast, ^{18}F -FDG PET/CT was unable to detect these lesions. In the literature, the detection rates of ^{18}F -FDG PET/CT for lobular breast carcinoma have been reported to vary between 50% and 90% (11). However, in our study, these rates were significantly lower. The key point emphasized in this study is that this group of tumors, for which ^{18}F -FDG has limited diagnostic value and often fails to detect, can be visualized with the novel molecular agent ^{68}Ga -FAPI.

While primary tumors and axillary lymph nodes can often be detected with the help of the CT component of ^{18}F -FDG PET/CT, distant lymph node, visceral organ, and peritoneal metastases are frequently missed in this patient group. In our study, the detection rates for axillary lymphadenopathy did not differ significantly between the two imaging modalities for staging. However, the number of lesions detected with ^{68}Ga -FAPI PET/CT was higher compared to ^{18}F -FDG PET/CT. Regarding the ability to detect the primary tumor, no significant difference was observed between the two modalities. The absence of a significant difference

between the two imaging modalities in detecting the primary tumor may be attributed to the limited sample size. On the other hand, the SUV_{max} of the primary tumors were found to be higher with ^{68}Ga -FAPi PET/CT. SUV_{max} for all localizations were significantly higher with ^{68}Ga -FAPi compared to ^{18}F -FDG (Table 3). Elboga et al. (12) performed a retrospective analysis involving 48 patients with invasive breast cancer, demonstrating that ^{68}Ga -FAPi PET/CT identified more primary breast lesions and additional metastatic lesions with greater uptake values compared to ^{18}F -FDG PET/CT. The effectiveness of ^{18}F -FDG PET/CT was notably reduced in the invasive lobular carcinoma subtype, emphasizing the necessity for a more efficient imaging modality, especially for this specific patient group in their study. Similarly, Ballal et al. (13) observed increased radiotracer uptake using ^{68}Ga -DOTA.SA.FAPi in lymph nodes corresponding to CT findings in the axillary region, where no uptake was detected with ^{18}F -FDG PET/CT. The findings of this prospective study highlight the significant impact of ^{68}Ga -FAPi PET/CT imaging on accurate staging of breast cancer, particularly in cases with lobular carcinoma.

According to our results, disease upstaging was observed in 44.8% of patients, emphasizing the diagnostic superiority of ^{68}Ga -FAPi PET/CT compared to ^{18}F -FDG PET/CT. This demonstrates the enhanced sensitivity of ^{68}Ga -FAPi PET/CT in detecting previously undetected metastases or disease extent. Notably, 50% of patients with lobular carcinoma were upstaged after ^{68}Ga -FAPi PET/CT imaging, emphasizing the potential of this modality to address the limitations of ^{18}F -FDG in this histological subtype, where lower glycolytic activity often leads to false negatives. The capability of FAPi to identify fibrotic or stromal components of tumors, which are prominent in lobular carcinoma, may account for this improvement. In the study conducted by Kratochwil et al. (14) it was reported that ^{68}Ga -FAPi PET/CT demonstrates high affinity for tumor stromal components, enabling high sensitivity even in tumors with low ^{18}F -FDG avidity. Our study findings are consistent with the literature and can be attributed to the ability of ^{68}Ga -FAPi PET/CT to effectively visualize the microscopic stromal and fibrotic components of tumors.

Of the 21 patients referred to our clinic for restaging due to elevated tumor markers or suspected recurrence on conventional imaging during follow-up, ^{18}F -FDG PET identified recurrence in 8 patients, while ^{68}Ga -FAPi PET/CT detected recurrence in 16 patients (Figure 2). In 5 patients, no lesion was identified with either modality. In our study, ^{18}F -FDG PET/CT failed to detect recurrence in 72.7% of patients who were later identified as having recurrent disease by ^{68}Ga -FAPi PET/CT. Studies in the literature have demonstrated the superiority of ^{68}Ga -FAPi PET/CT

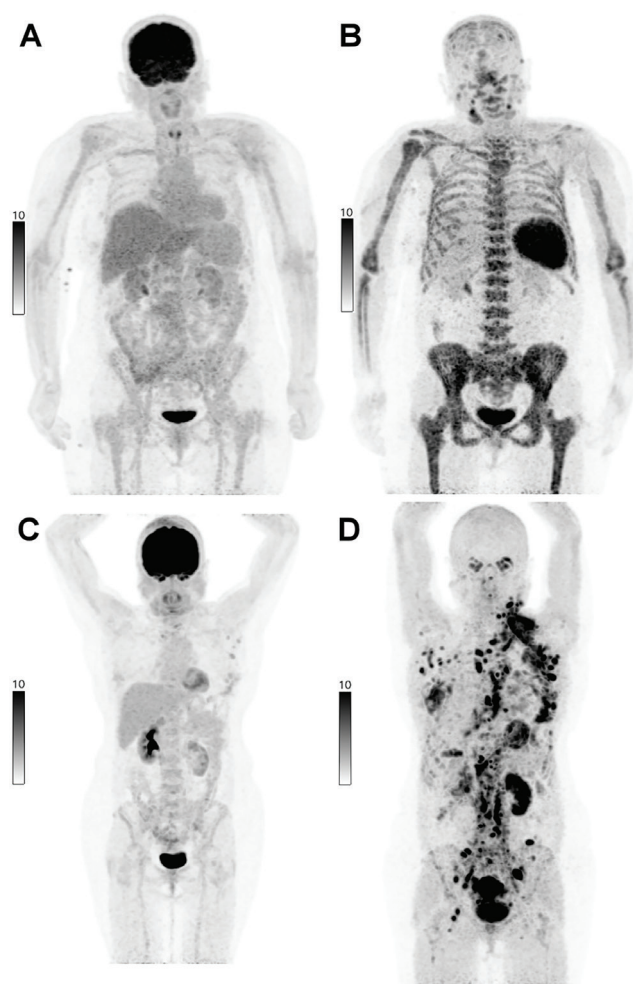


Figure 2. A 67-year-old female patient with invasive lobular breast carcinoma underwent ^{18}F -FDG PET/CT for restaging due to tumor marker progression. The ^{18}F -FDG PET/CT did not reveal any focal lesions to explain the tumor marker progression; it only showed mild, diffuse FDG uptake associated with bone marrow reactivation (A). However, ^{68}Ga -FAPi PET/CT images showed intense and widespread FAP expression suggestive of bone marrow infiltration (B). This finding was later confirmed by histopathological examination. The second patient was a 54-year-old woman with invasive lobular carcinoma of the left breast underwent ^{18}F -FDG PET/CT, which showed a mildly hypermetabolic primary mass and left axillary lymph nodes, and multiple sclerotic bone lesions without significant FDG uptake (C). ^{68}Ga -FAPi PET/CT detected nodular lesions in both breasts; metastatic lymph nodes in the left cervical, bilateral axillary, mediastinal, abdominal, and right femoral regions; suspicious activity along the greater curvature of the stomach; multiple bone metastases (D).

^{68}Ga -FAPi PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, ^{18}F -FDG: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography

over ¹⁸F-FDG PET/CT in detecting primary and metastatic lesions. Kömek et al. (15) showed that ⁶⁸Ga-FAPi-04 PET/CT detected more lesions compared to ¹⁸F-FDG PET/CT and exhibited higher tumor-to-background ratios. Similarly, a study highlighted the superiority of ⁶⁸Ga-FAPi PET/CT over ¹⁸F-FDG PET/CT, particularly in invasive lobular carcinoma (5). Additionally, the study conducted by Chen et al. (16) evaluated the potential use of ⁶⁸Ga-FAPi PET/CT in the detection, staging, and restaging of various cancer types and compared it with ¹⁸F-FDG PET/CT. The results demonstrated that ⁶⁸Ga-FAPi PET/CT offers higher sensitivity and specificity in various cancer types, particularly in breast cancer. While these studies emphasize the role of ⁶⁸Ga-FAPi PET/CT in the assessment of primary breast masses, axillary lymph nodes, and distant metastases, none have specifically focused on its utility in detecting breast cancer recurrence. Our study differs from prior investigations by not only validating the diagnostic superiority of ⁶⁸Ga-FAPi PET/CT in primary staging and metastasis detection, but also by revealing its extended capacity for restaging and recurrence identification.

Study Limitations

The main limitation of the present study is the relatively small sample size, particularly within each histopathological subgroup. Therefore, subgroup-based comparisons should be interpreted with caution, and the present findings should be considered preliminary and hypothesis-generating. Since the study specifically focused on breast cancer patients with low or limited ¹⁸F-FDG uptake, patient recruitment was inherently restricted. Larger multicenter prospective studies with standardized imaging protocols, pathological confirmation when feasible, and long-term clinical follow-up are required to validate these findings. This study demonstrates the diagnostic superiority of ⁶⁸Ga-FAPi PET/CT over ¹⁸F-FDG PET/CT, especially in invasive lobular carcinoma and challenging histological subtypes. However, the absence of long-term clinical outcome data in the study can be considered a limitation. Another limitation of the present study is the use of two FAP-targeting ligands, ⁶⁸Ga-DOTA-FAPi-46 and ⁶⁸Ga-DOTA-FAP-2286. Although both target the fibroblast activation protein, potential differences in pharmacokinetics, biodistribution, background activity, and lesion uptake may influence SUV-based measurements. Because the study was not designed as a head-to-head comparison and no patient underwent imaging with both tracers, the possible impact of ligand-related differences could not be formally assessed. Prospective studies using a single ligand or employing direct intraindividual comparison protocols are warranted. Another limitation is that histopathological

confirmation was not available for every ⁶⁸Ga-FAPi-positive metastatic lesion. Therefore, final lesion classification was based on a composite reference standard including histopathology when available, correlation with diagnostic contrast-enhanced CT and/or MRI, follow-up imaging for at least 6 months, clinical course, and multidisciplinary tumor board consensus. Future multicenter prospective studies with larger populations and subgroup analyses are needed to confirm its efficacy. Additionally, long-term survival and cost-effectiveness data will support its potential role in breast cancer management and inform personalized treatment strategies.

Conclusion

⁶⁸Ga-FAPi PET/CT was more effective than conventional ¹⁸F-FDG PET/CT in detecting and staging breast cancer in our cohort, especially invasive lobular carcinoma. The study findings support the use of ⁶⁸Ga-FAPi PET/CT as a complementary imaging tool not for all breast cancers, but particularly for low-¹⁸F-FDG-avidity histological subtypes, in whom ¹⁸F-FDG PET/CT has limited sensitivity for detecting extra-axillary and distant metastases. Larger multicenter studies with pathological confirmation of metastatic sites are warranted to validate these results and further define the clinical utility of FAPi imaging in this subset of patients.

Ethics

Ethics Committee Approval: This prospective study was approved by the Ethics Committee of Yeditepe University (decision no.: 1576, date: 02.03.2022).

Informed Consent: This is a single-center prospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G., N.K., S.Ç., B.B.Ö., Concept: N.A.S., Design: N.A.S., L.K., Data Collection or Processing: G.B., N.A.S., Analysis or Interpretation: G.B., N.A.S., Literature Search: N.A.S., Writing: G.B., N.A.S., K.A., B.B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Comparative Performance of ^{18}F -FDG PET/CT and ^{68}Ga -FAPI PET/CT in TENIS Syndrome in Treated Differentiated Thyroid Carcinoma

Tedavi Edilmiş Diferansiye Tiroid Karsinomunda TENIS Sendromunda ^{18}F -FDG PET/BT ve ^{68}Ga -FAPI PET/BT'nin Karşılaştırmalı Performansı

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Abstract

Objectives: Thyroglobulin-elevated negative iodine scintigraphy (TENIS) syndrome presents a significant diagnostic challenge in the management of differentiated thyroid carcinoma (DTC). Although ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) is the established imaging modality for detecting presence of structural disease, Gallium-68 (^{68}Ga)-fibroblast activation protein inhibitor (FAPI) PET/CT, which targets the tumor stroma, represents a promising new alternative. This study directly compared the lesion detection capabilities of both tracers in patients with TENIS.

Methods: In this prospective single-center study (2021-2024), 22 patients with TENIS syndrome underwent both ^{18}F -FDG and ^{68}Ga -FAPI PET/CT scans within a 7-day interval of each other. Lesion detectability and maximum standardized uptake values (SUV_{max}) were compared between the two modalities. Lesions were validated using histopathology or cytopathology, biochemical response to empirical ^{131}I therapy, imaging correlation or progression, and clinical progression methods.

Results: Among 22 patients (median age 43.5 years, 90% with papillary carcinoma), ^{18}F -FDG was positive in 23/33 cervical lymph nodes, whereas ^{68}Ga -FAPI was positive in 14/33 lymph nodes. Fourteen lymph nodes were positive on both modalities with comparable SUV_{max} (median ^{18}F -FDG 3.3 vs. ^{68}Ga -FAPI 3.6, $p=0.689$). All local recurrences in thyroid bed ($n=4$) were ^{18}F -FDG-positive, whereas only 3 of the local recurrences were ^{68}Ga -FAPI-positive. Distant metastases (lung and bone) showed similar detection rates.

Conclusion: ^{18}F -FDG PET/CT demonstrates superior lesion detectability, particularly for cervical lymph nodes, in TENIS syndrome. ^{68}Ga -FAPI PET/CT provides complementary information with comparable semiquantitative uptake in detected lesions but with lower overall detection. ^{18}F -FDG PET/CT remains the preferred imaging modality for comprehensive disease evaluation in patients with radioactive iodine-refractory DTC.

Keywords: TENIS syndrome, well differentiated thyroid carcinoma, ^{18}F -FDG PET, ^{68}Ga -FAPI PET, positron emission tomography computed tomography

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Öz

Amaç: Tiroglobulin yüksekliği olan negatif iyot sintigrafisi (TENIS) sendromu, diferansiye tiroid karsinomu (DTC) yönetiminde önemli bir tanısal zorluk oluşturmaktadır. Yapısal hastalığın varlığını saptamada ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸F-FDG PET/CT) yerleşik görüntüleme yöntemi olmakla birlikte, tümör stromasını hedefleyen Galyum-68 (⁶⁸Ga)-fibroblast aktivasyon proteini inhibitörü (FAPI) PET/CT umut vadeden yeni bir alternatif olarak öne çıkmaktadır. Bu çalışmada, TENIS hastalarında her iki izleyicinin lezyon saptama kapasiteleri doğrudan karşılaştırılmıştır.

Yöntem: Bu prospektif tek merkezli çalışmada (2021-2024), TENIS sendromu olan 22 hastaya, birbirinden 7 gün arayla ¹⁸F-FDG ve ⁶⁸Ga-FAPI PET/CT görüntülemeleri uygulanmıştır. İki yöntem arasında lezyon saptanabilirliği ve maksimum standartlaştırılmış tutulum değerleri (SUV_{max}) karşılaştırılmıştır. Lezyonlar; histopatoloji veya sitopatoloji, ampirik ¹³¹I tedavisine biyokimyasal yanıt, görüntüleme korelasyonu veya progresyonu ve klinik progresyon yöntemleri kullanılarak doğrulanmıştır.

Bulgular: Yirmi iki hasta arasında (ortanca yaş 43,5 yıl; %90'ı papiller karsinom), ¹⁸F-FDG 33 servikal lenf nodunun 23'ünde pozitif saptanırken, ⁶⁸Ga-FAPI 33 lenf nodunun 14'ünde pozitif saptanmıştır. On dört lenf nodu her iki yöntemde de pozitif bulunmuş ve SUV_{max} değerleri benzerlik göstermiştir (ortanca ¹⁸F-FDG: 3,3; ⁶⁸Ga-FAPI: 3,6; p=0,689). Tiroid yatağındaki tüm lokal nüksler (n=4) ¹⁸F-FDG pozitif iken, lokal nükslerin yalnızca 3'ü ⁶⁸Ga-FAPI pozitif bulunmuştur. Uzak metastazlarda (akciğer ve kemik) benzer saptama oranları gözlenmiştir.

Sonuç: ¹⁸F-FDG PET/CT, TENIS sendromunda özellikle servikal lenf nodları açısından daha üstün lezyon saptanabilirliği göstermektedir. ⁶⁸Ga-FAPI PET/CT, saptanan lezyonlarda karşılaştırılabilir yarı kantitatif tutulum değerleriyle tamamlayıcı bilgi sağlamakla birlikte, genel saptama oranı daha düşüktür. Radyoaktif iyoda refrakter diferansiye tiroid karsinomu olan hastalarda kapsamlı hastalık değerlendirmesi için ¹⁸F-FDG PET/CT tercih edilen görüntüleme yöntemi olmaya devam etmektedir.

Anahtar Kelimeler: TENIS sendromu, iyi diferansiye tiroid karsinomu, ¹⁸F-FDG PET, ⁶⁸Ga-FAPI PET, pozitron emisyon tomografisi/bilgisayarlı tomografi

Introduction

Thyroid cancer (TC) is the most prevalent endocrine malignancy, accounting for nearly 95% of endocrine neoplasms worldwide (1). Most cases are classified as differentiated thyroid carcinoma (DTC), including papillary and follicular subtypes (2). The standard management of DTC consists of total or near-total thyroidectomy, often followed by radioactive iodine (RAI) ablation and thyroid-stimulating hormone (TSH) suppression in intermediate- or high-risk patients, as recommended by the American Thyroid Association (ATA) guidelines (3,4). With appropriate management, patients with DTC frequently achieve a favorable prognosis, with reported 10-year disease-specific survival rates approaching 98% (5,6).

Nevertheless, a subset of patients encounters persistent or recurrent disease, manifested biochemically by elevated serum thyroglobulin (Tg ≥ 1 ng/mL while suppressed or ≥ 10 ng/mL after stimulation), with or without positive anti-Tg antibodies, even in the absence of structural evidence of disease (6,7). Approximately 20% of these patients eventually develop structural recurrence, which is associated with a worse prognosis (6). Moreover, between 5% and 15% of DTC and up to 50% of metastatic lesions evolve into radioiodine-refractory (RAIR) disease, characterized by loss of radioiodine avidity and more aggressive clinical behavior (8,9).

A clinically significant manifestation of RAIR-DTC is thyroglobulin-elevated, negative iodine scintigraphy (TENIS) syndrome, which is encountered in up to 27% of

post-treatment DTC cases (10). Patients with TENIS have elevated Tg levels despite negative radioiodine whole-body scans, implying iodine-non-avid, active disease (11). This scenario presents a diagnostic and management challenge because conventional radioiodine imaging fails to localize the disease (10,11).

The ATA guidelines recommend 2-¹⁸F-Fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) for patients with TENIS to localize metabolically active sites of recurrence/metastasis (3,4). The underlying rationale is the “flip-flop phenomenon,” i.e., the inverse relationship between iodine and glucose avidity in TC, in which dedifferentiated tumour cells lose iodine transport capacity but acquire increased glucose metabolism, rendering them detectable by ¹⁸F-FDG PET/CT (12,13). In well-differentiated, iodine-avid tumors, ¹⁸F-FDG uptake is low, but it increases in dedifferentiated and aggressive lesions (12,14). The sensitivity of ¹⁸F-FDG PET/CT in TENIS has been reported to be 68.8-87%, with false-negative rates of 8-21% depending on the disease burden and metabolic characteristics (12,15).

Recent advances have introduced fibroblast activation protein inhibitor (FAPI) labelled radiotracers that target cancer-associated fibroblasts abundant in the tumor stroma. Multiple FAPI compounds, such as FAPI-02, FAPI-04, and FAPI-46, are available, with Gallium-68 (⁶⁸Ga) labelling providing compatibility with clinical PET imaging (16). ⁶⁸Ga-FAPI PET/CT can detect lesions, irrespective of cellular differentiation or iodine avidity (16,17). Importantly, stroma and FAP expression are major features

of papillary and follicular thyroid carcinomas, particularly in dedifferentiated or aggressive disease, providing a rationale for ^{68}Ga -FAPI PET application in this setting (18,19).

While several studies have demonstrated strong ^{68}Ga -FAPI uptake in metastatic or thyroid bed recurrent RAI-DTC lesions, others have suggested variable results, especially in well-differentiated or low-stroma tumors (20). A recent head-to-head comparison in RAI-DTC showed that ^{68}Ga -FAPI detected additional lesions in approximately 20% of cases missed by ^{18}F -FDG, with higher target-to-background ratios (21). However, comprehensive comparative data on TENIS syndrome remain limited. Therefore, the comparison of ^{68}Ga -FAPI and ^{18}F -FDG PET/CT in TENIS remains an active area of clinical investigation.

Materials and Methods

Study Design and Patient Selection

This prospective, single-center study was conducted at a tertiary referral university-affiliated teaching hospital between 2021 and 2024. The study protocol was approved by the Amrita Institute of Medical Sciences and Research Institutional Clinical Research Ethics Committee, and written informed consent was obtained from all participating patients. This study conformed to the ethical guidelines of the 2013 revision of the Declaration of Helsinki.

Eligible patients were adults aged ≥ 18 years with histopathologically confirmed DTC who had previously undergone total or near-total thyroidectomy, received adjuvant ^{131}I ablation, and subsequently developed TENIS syndrome. The inclusion criteria required documented elevated serum Tg levels (stimulated Tg ≥ 10 ng/ml or further rising trend of stimulated Tg level in patients with previously documented stimulated Tg ≥ 2 ng/ml), and a negative diagnostic ^{131}I scan. The exclusion criteria were the presence of a second primary malignancy or refusal to provide informed consent.

PET/CT Acquisition Protocol

All PET/CT examinations were performed using a Siemens Biograph Horizon PET/CT system (Siemens Healthineers, Germany) equipped with lutetium oxyorthosilicate detectors and time-of-flight (TOF) reconstruction. Each patient underwent both ^{18}F -FDG and ^{68}Ga -FAPI PET/CT within seven days (median interval: 2 days). Patients fasted for at least six hours before ^{18}F -FDG PET/CT. Blood glucose was measured prior to radiotracer injection and was required to be <150 mg/dl. Intravenous ^{18}F -FDG was administered at a dose of 3.7 MBq/kg, followed by whole-body images (skull base to mid-thigh) acquired 45-60 min post-injection, with one minute per bed position. For FAPI

PET/CT, the patients received an intravenous injection of 1.8-2.2 MBq/kg ^{68}Ga -FAPI-04. Imaging was initiated 30-45 min post-injection, using the same anatomical range but with a two-minute acquisition per bed position. A low-dose, non-contrast CT scan (130 kV, 110-130 mAs, 3 mm slice thickness) was acquired for attenuation correction and anatomical localization, followed by a three-dimensional PET acquisition. Images were reconstructed using the ordered-subsets expectation-maximization + TOF algorithm (3 iterations $\times$ 10 subsets) with CT-based attenuation and scatter correction. The data were reviewed using the syngo MI Workplace software suite (Siemens Healthineers).

Image Analysis

The images were independently reviewed by two board-certified, experienced nuclear medicine physicians blinded to the clinical and laboratory information and each other's interpretations. Discrepancies were resolved through consensus. Lesions were considered positive on PET if they showed focal ^{18}F -FDG or ^{68}Ga -FAPI uptake exceeding the background without a physiological explanation. Semi-quantitative analysis involved manual delineation of regions of interest around each lesion to obtain the maximum standardized uptake value (SUV_{max}). Lesions on CT without PET positivity were considered pathological if they fulfilled CT criteria for disease involvement.

Lesion Confirmation and Validation

We employed a hierarchical multimodal approach for lesion validation. Whenever feasible, lesions were confirmed by surgical excision with histopathological examination, or by fine-needle aspiration cytology. This represents the gold standard for confirmation. For lesions that could not be biopsied, the biochemical response to empirical ^{131}I therapy was used as a surrogate marker. Decreases in stimulated Tg levels following therapy are considered supportive evidence of both disease presence and treatment response. Recurrent lesions in the thyroid bed were corroborated by correlative ultrasound imaging, which demonstrated the characteristic features of recurrent TC. Imaging features suggestive of metastatic disease were used to identify distant lesions. Serial follow-up imaging (PET/CT, CT, or magnetic resonance imaging) demonstrating interval growth or increased metabolic activity of the lesions was also considered confirmatory evidence. Clinical deterioration with new or worsening symptoms (e.g., bone pain and respiratory symptoms), corroborated by imaging findings, was used to validate lesion significance. This multimodal confirmation strategy provided validation despite the practical limitations of performing histopathological sampling in all patients with advanced diseases.

Data Collection

Clinical and laboratory data were systematically collected from electronic hospital medical records and included: patient demographics (age and sex), histopathological subtype and grade, initial surgical treatment, number of ¹³¹I therapy cycles, cumulative radioiodine dose, and serial stimulated serum Tg and anti-Tg antibody (TgAb) measurements (measured at initial diagnosis, at TENIS detection, and post-therapy). The imaging data included lesion location, lesion size on anatomical CT, and SUV_{max} on both ¹⁸F-FDG and ⁶⁸Ga-FAPI PET/CT. Follow-up data included subsequent management (surgery, empirical radioiodine therapy), histopathological confirmation results, serial imaging findings, biochemical response assessments, and clinical outcomes.

Statistical Analysis

Continuous variables are presented as medians (ranges), and categorical variables are presented as counts (percentages). Paired comparisons of SUV_{max} in lesions positive on both modalities were performed using the Wilcoxon signed-rank test. Statistical significance was set at p<0.05.

Results

Patient Characteristics

This study included 22 TENIS patients. The median age was 43.5 years (range, 21-79 years), and 63% were female. Most cases (90%) were identified as papillary thyroid carcinoma, while follicular and poorly differentiated/microcarcinoma accounted for the remaining 10%. Most patients (59%) underwent total thyroidectomy, while 37% also underwent lymph node dissection. Eleven patients (50%) received one cycle of ¹³¹I therapy, and the remaining 11 patients (50%) received two cycles; the median cumulative radioiodine dose was 118.5 mCi (range, 60-215 mCi). The initial median Tg and anti-TgAb levels were 50.48 ng/ml and 28.07 IU/ml, respectively. Most patients (86%) had Tg levels above 10 ng/mL, and most were at intermediate risk on initial assessment. Patient characteristics are shown in Table 1.

Lesion Confirmation

Lesion validation followed a hierarchical multimodal approach. The validation methods by lesion type are summarized in Table 2. Cervical lymph node involvement was confirmed by histopathology or cytopathology in 75% (9 of 12 patients), providing high confidence in nodal disease findings. Local recurrences and distant metastatic lesions were confirmed primarily by biochemical response, imaging findings, and clinical progression, reflecting

the practical challenges of invasive sampling at these anatomical sites.

Local thyroid bed recurrent lesions

CT imaging identified local recurrence in 4 of 22 patients. In all four patients, the lesions were ¹⁸F-FDG-avid, whereas in three patients the lesions were ⁶⁸Ga-FAPI-positive (Figure 1).

Table 1. Patient characteristics (n=22)

Characteristic	Value
Median age, years (range)	43.5 (21-79)
Sex, n (%)	
Female	14 (63%)
Male	8 (37%)
Histopathologic features	
Pathologic subtype, n (%)	
Papillary	20 (90%)
Follicular	1 (5%)
Poorly differentiated + microcarcinoma	1 (5%)
Initial treatment	
Initial surgery, n (%)	
Total thyroidectomy + LN dissection	8 (37%)
Total thyroidectomy only	13 (59%)
Subtotal thyroidectomy	1 (4%)
¹³¹ I therapy cycles, n (%)	
1 cycle	11 (50%)
2 cycles	11 (50%)
Cumulative ¹³¹ I dose, mCi (range)	118.5 (60-215)
Biochemical parameters	
Tg at initial diagnosis, ng/mL (range)	50.48 (0.8-925.9)
Tg-Ab at initial diagnosis, IU/mL (range)	28.07 (1.25-4000)
Tg at TENIS detection, ng/mL (range)	42.22 (0.04-274)
Tg-Ab at TENIS detection, IU/mL (range)	28.07 (1.25-4000)
Tg post-therapy (n=21), n (%)	
0-10 ng/mL	3 (14%)
>10 ng/mL	18 (86%)
Tg-Ab post-therapy (n=21), n (%)	
Positive	5 (24%)
Negative	16 (76%)
Risk stratification	
Initial risk stratification (n=21), n (%)	
Low	3 (14%)
Intermediate	16 (76%)
High	2 (10%)

LN: Lymph node, Tg: Thyroglobulin, Tg-Ab: Anti-thyroglobulin antibody, TENIS: Thyroglobulin-elevated negative iodine scintigraphy

One ¹⁸F-FDG-avid lesion (SUV_{max} 3.2) was negative on ⁶⁸Ga-FAPI PET/CT imaging. The median ¹⁸F-FDG SUV_{max} for local recurrence was 4.45 (range, 3.2-6.8), and the median ⁶⁸Ga-FAPI SUV_{max} was 2.9 (range, 2.4-10.5). The SUV metrics are presented in Table 3.

Lymph Node Metastases

Among the 33 lymph nodes identified on CT imaging, ¹⁸F-FDG was positive in 23 nodes (69.7%), whereas ⁶⁸Ga-FAPI was positive in 14 nodes (42.4%) (Figure 2). Fourteen nodes were positive on both modalities and analyzed in

Table 2. Lesion validation methods by lesion type		
Lesion type	Number of patients (n=)	Confirmation method
Cervical lymph nodes	n=12	Histopathology/FNAC (n=9), Tg changes post empirical ¹³¹ I (n=2), clinical progression (n=1)
Local recurrence	n=2	Tg changes post empirical ¹³¹ I (n=1), correlative ultrasound imaging (n=1)
Pulmonary nodules	n=4	Imaging progression on follow-up (n=2), imaging correlation (n=1), clinical progression (n=1)
Skeletal lesions	n=1	Clinical progression (n=1)

FNAC: Fine-needle aspiration cytology, Tg: Thyroglobulin

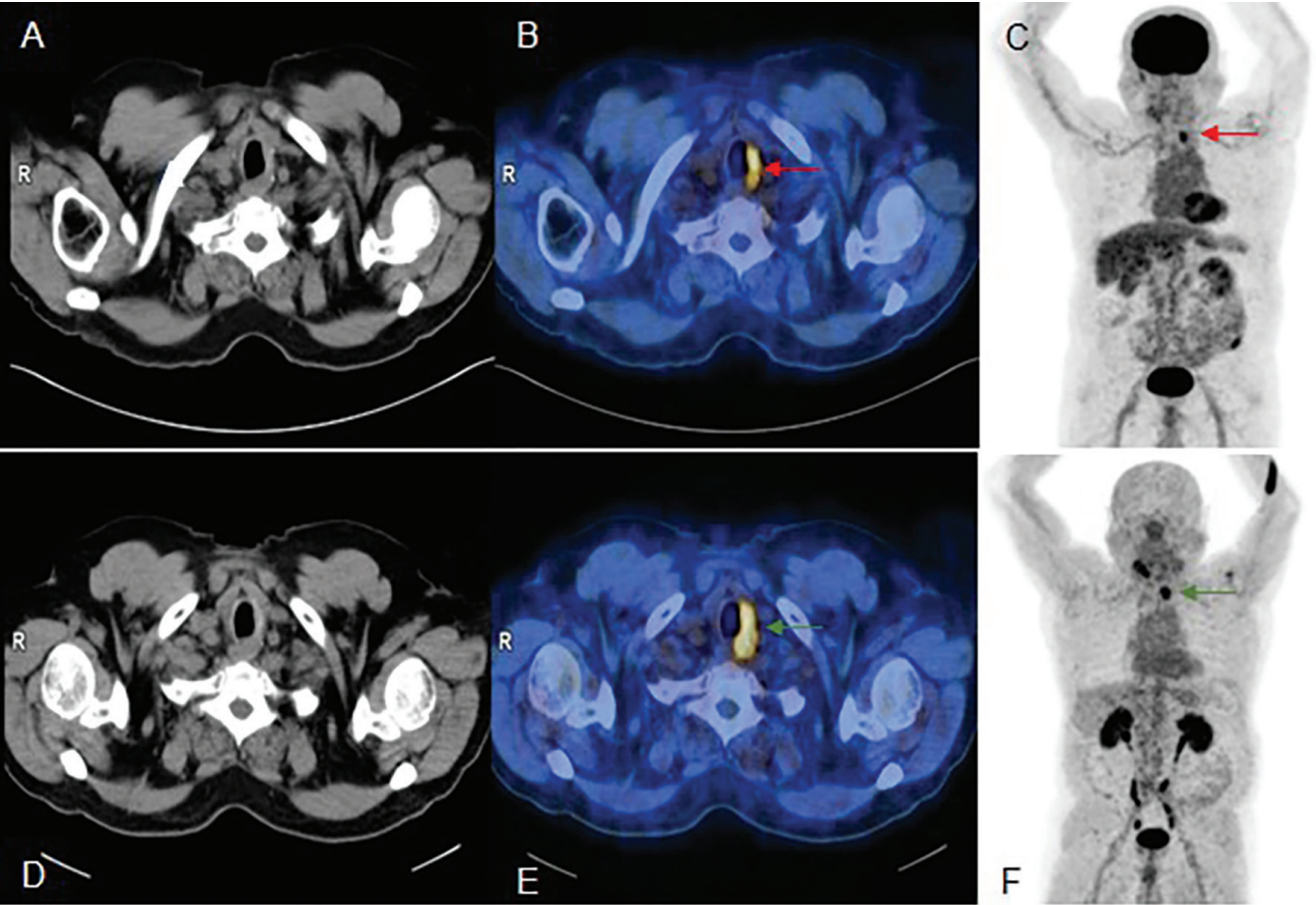


Figure 1. Detection of local recurrence in the thyroid bed. (A, D) axial non-contrast CT shows an ill-defined soft-tissue lesion in thyroid bed on left side. (B) Selected axial fused images demonstrating moderate ¹⁸F-FDG uptake (SUV_{max} 6.8) (red arrow). (E) ⁶⁸Ga-FAPI PET shows intense uptake (SUV_{max} 10.5) in the soft tissue lesion suggesting a prominent stromal reaction (green arrow). (C, F) MIP images of ¹⁸F-FDG PET and ⁶⁸Ga-FAPI PET whole body showing focal increased ¹⁸F-FDG and ⁶⁸Ga-FAPI in lower neck and physiological tracer distribution in rest of the whole body

¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose, CT: Computed tomography, ⁶⁸Ga-FAPI PET: Gallium-68-fibroblast activation protein inhibitor positron emission tomography, SUV_{max}: Maximum standardized uptake value, MIP: Maximum intensity projection

paired comparisons of SUV_{max}. The median SUV_{max} was 3.3 (range 2.2-16.8) for ¹⁸F-FDG and 3.6 (range 2.2-9.8) for ⁶⁸Ga-FAPI (Figure 3). The Wilcoxon signed-rank test showed no significant difference in SUV_{max} between ¹⁸F-FDG and ⁶⁸Ga-FAPI in paired lymph-nodal lesions (p=0.689). ¹⁸F-FDG PET/CT detected more lymph nodes overall than ⁶⁸Ga-FAPI PET/CT. The detailed metrics are presented in Table 4.

Distant Metastases

Five pulmonary lesions were identified on CT. ¹⁸F-FDG was positive in all five lesions, whereas ⁶⁸Ga-FAPI was positive in four lesions (Figure 4). The median SUV_{max} was 3.3 for ¹⁸F-FDG and 5.05 for ⁶⁸Ga-FAPI, respectively. Mean SUV_{max} was 5.72±5.75 for ¹⁸F-FDG and 5.95±4.13 for ⁶⁸Ga-FAPI.

Table 3. SUV _{max} values for local recurrence lesions		
Metric	¹⁸ F-FDG PET/CT	⁶⁸ Ga-FAPI PET/CT
n (lesions)	4	3
Median SUV _{max} (range)	4.45 (3.2-6.8)	2.9 (2.4-10.5)
Mean ± SD	4.73±1.69	5.27±4.54
FAPI: Fibroblast activation protein inhibitor, SUV _{max} : Maximum standardized uptake value, SD: Standard deviation, ¹⁸ F-FDG PET/CT: ¹⁸ F-fluorodeoxyglucose positron emission tomography/computed tomography		

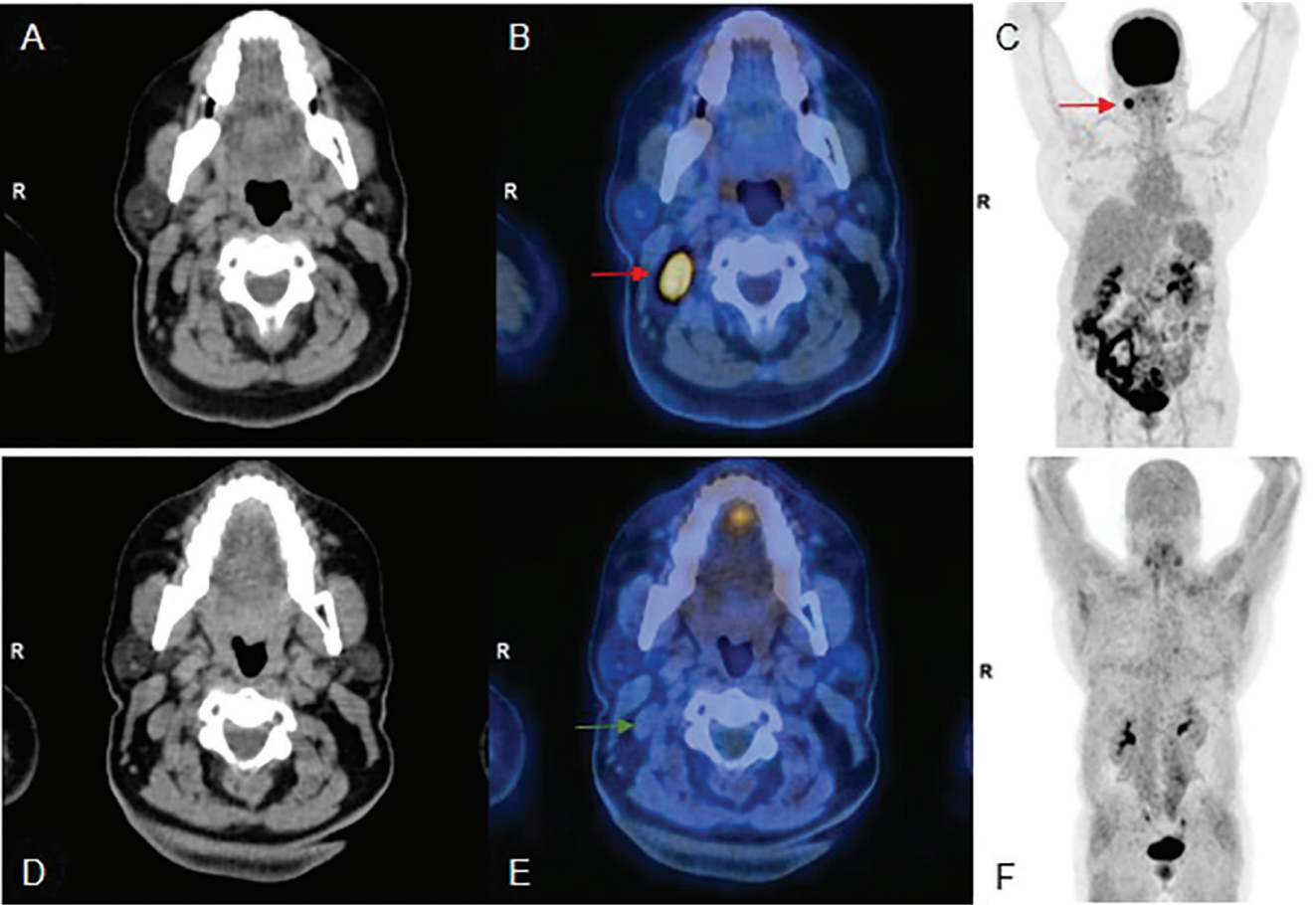


Figure 2. Superior lymph nodal detectability of ¹⁸F-FDG PET. (A, D) axial non-contrast CT showing an enlarged right level II cervical lymph node (B, E) selected axial fused images demonstrating ¹⁸F-FDG positive node (red arrow) that was ⁶⁸Ga-FAPI negative (green arrow). (C, F) MIP images of ¹⁸F-FDG PET and ⁶⁸Ga-FAPI PET Whole body PET showing focal increased ¹⁸F-FDG in lower neck with no ⁶⁸Ga-FAPI positivity and physiological tracer distribution in rest of the whole body
¹⁸F-FDG PET: ¹⁸F-fluorodeoxyglucose positron emission tomography, CT: Computed tomography, ⁶⁸Ga-FAPI PET: Gallium-68- fibroblast activation protein inhibitor positron emission tomography, MIP: Maximum intensity projection

Two bone lesions were identified, both detected by ¹⁸F-FDG and ⁶⁸Ga-FAPI PET/CT. The median SUV_{max} values were 4.75 for ¹⁸F-FDG and 3.5 for ⁶⁸Ga-FAPI. The mean SUV_{max} was 4.75±0.64 for ¹⁸F-FDG and 3.5±0.42 for ⁶⁸Ga-FAPI. The

Wilcoxon signed-rank test comparing paired lung and bone lesions (n=6) showed no statistically significant difference in SUV_{max} (p=1.0). The detailed metrics are presented in Table 5.

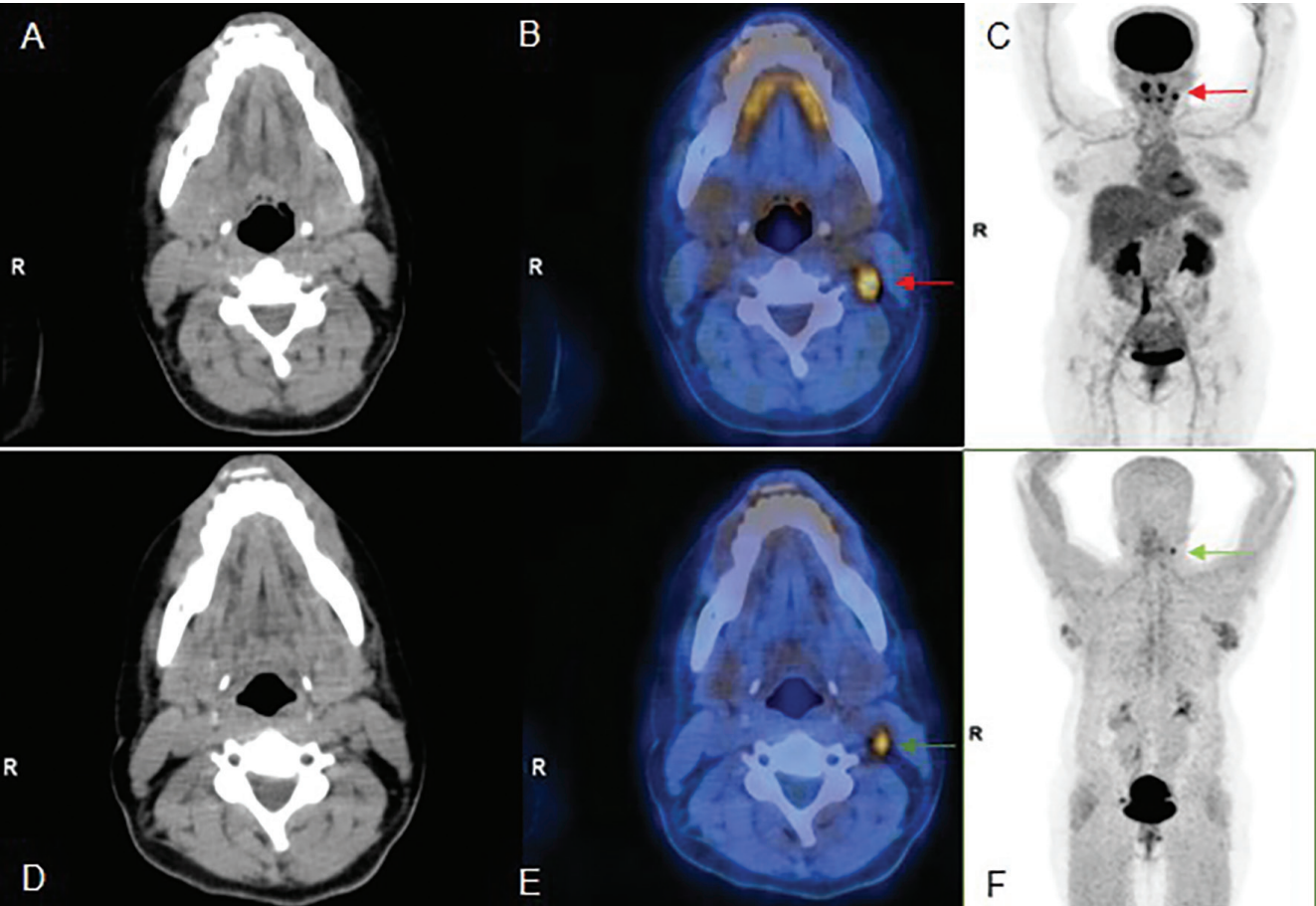


Figure 3. Lesser ⁶⁸Ga-FAPI avidity than ¹⁸F-FDG avidity in a metastatic cervical lymph node (A, D) axial CT image showing a metastatic left level II lymph node. (B) Corresponding fused ¹⁸F-FDG PET image demonstrating intense metabolic activity in the lymphnode (SUV_{max} 9.8) (red arrow). (E) Fused ⁶⁸Ga-FAPI PET image showing moderate uptake (SUV_{max} 6.1) in the same node (green arrow). Histopathological examination of the surgical resection specimen confirmed metastatic papillary thyroid carcinoma. (C, F) MIP images of ¹⁸F-FDG and ⁶⁸Ga-FAPI whole body PET showing focal increased ¹⁸F-FDG and ⁶⁸Ga-FAPI uptake in upper cervical region on left side and physiological tracer distribution in rest of the whole body

¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose, CT: Computed tomography, ⁶⁸Ga-FAPI PET: Gallium-68- fibroblast activation protein inhibitor positron emission tomography, SUV_{max}: Maximum standardized uptake value, MIP: Maximum intensity projection

Table 4. SUV _{max} values for lymph node metastases				
Metric	¹⁸ F-FDG PET/CT	⁶⁸ Ga-FAPI PET/CT	Paired lesions	Wilcoxon p-value
n (detected nodes)	23	14	14	—
Detection rate (%)	69.7%	42.4%	—	—
Median SUV _{max} (range)	3.3 (2.2-16.8)	3.6 (2.2-9.8)	—	0.689
Mean ± SD	4.48±2.87	4.06±1.92	—	—
FAPI: Fibroblast activation protein inhibitor, SUV _{max} : Maximum standardized uptake value, SD: Standard deviation, ¹⁸ F-FDG PET/CT: ¹⁸ F-fluorodeoxyglucose positron emission tomography/computed tomography				

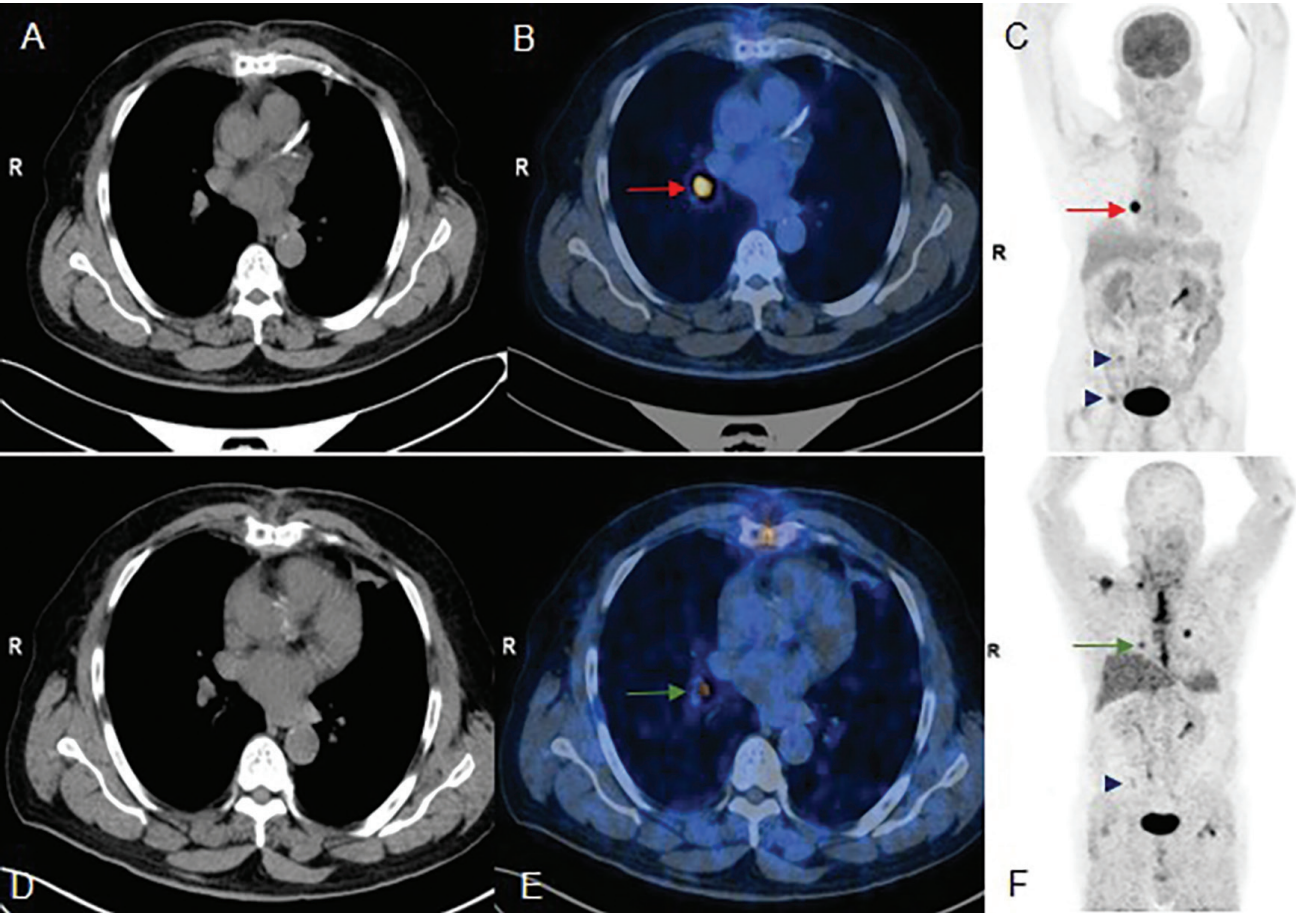


Figure 4. Representative images showing pulmonary metastases. (A, D) axial CT image showing a right lung nodule. (B) Corresponding fused ¹⁸F-FDG PET image demonstrate intense metabolic activity (SUV_{max} 15.9) in the lung nodule (red arrow). (E) Fused ⁶⁸Ga-FAPI-04 PET image show moderate uptake (SUV_{max} 7.3) in the same nodule (green arrow). (C, F) MIP images of ¹⁸F-FDG and FAPI whole body PET show additional foci of increased ¹⁸F-FDG and FAPI uptake in left lung and right lower cervical lymph node (more prominent on FAPI). Bone lesions in right iliac bone are better appreciable on ¹⁸F-FDG (blue arrow heads)

¹⁸F-FDG: ¹⁸F-fluorodeoxyglucose, CT: Computed tomography, ⁶⁸Ga-FAPI PET: Gallium-68- fibroblast activation protein inhibitor positron emission tomography, SUV_{max}: Maximum standardized uptake value

Table 5. SUV _{max} values for distant metastases			
	Metric	¹⁸ F-FDG PET/CT	⁶⁸ Ga-FAPI PET CT
Lungs	n (detected)	5	4
	Median SUV _{max}	3.3	5.05
	mean ± SD	5.72±5.75	5.95±4.13
Bones	n (detected)	2	2
	Median SUV _{max}	4.75	3.5
	Mean ± SD	4.75±0.64	3.5±0.42
Combined	Wilcoxon p-value	1.0 (not significant)	
FAPI: Fibroblast activation protein inhibitor, SUV _{max} : Maximum standardized uptake value, SD: Standard deviation, ¹⁸ F-FDG PET/CT: ¹⁸ F-fluorodeoxyglucose positron emission tomography/computed tomography, ⁶⁸ Ga-FAPI: Gallium-68- fibroblast activation protein inhibitor			

Discussion

This prospective comparative study of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT in a representative TENIS cohort demonstrated important differences in tracer performance, especially in nodal detection. ^{18}F -FDG was positive in a significantly higher number of lymph node metastases than ^{68}Ga -FAPI (23 vs. 14 nodes, 69.7% vs. 42.4% detection rate), reaffirming its established role as the preferred modality for the evaluation of TENIS (2,3,4). These findings are consistent with large meta-analyses and practice guidelines emphasizing the sensitivity of ^{18}F -FDG PET/CT for metabolically active, dedifferentiated recurrent disease (5,6).

Clinical Significance of Nodal Detection in Papillary Thyroid Carcinoma

Papillary thyroid carcinoma characteristically metastasizes to the cervical lymph nodes, with nodal involvement occurring in 30-80% of cases, depending on tumor size and histologic features (22,23). Accurate nodal detection is critical for staging, prognostication, and treatment planning. In this context, the superior nodal detectability of ^{18}F -FDG PET/CT (23 nodes detected vs. 14 by ^{68}Ga -FAPI) represents a clinically significant advantage that directly impacts patient management decisions regarding surgical intervention, empirical radioiodine therapy, or watchful waiting (24,25).

Lesion Confirmation and Validation

The multimodal lesion confirmation approach employed in this study reflects the real-world challenges of validating imaging findings in patients with advanced TC. While 75% (9 of 12) of cervical lymph node cases were confirmed by histopathology or cytopathology, which provided robust validation, the remaining nodal lesions and most distant lesions relied on biochemical response, imaging progression, or clinical correlation. This hierarchical validation strategy, although pragmatic and clinically appropriate, limits the ability to definitively establish false-negative rates. The high proportion of histopathologically confirmed cervical nodes strengthens confidence in our finding of superior nodal detectability with ^{18}F -FDG, as these represent the most rigorously validated lesions in our cohort. For distant lesions, reliance on imaging progression and clinical correlation may introduce uncertainty but remains consistent with accepted clinical practice in managing advanced DTC, where biopsy is often impractical (26,27).

Comparative Performance of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT

^{68}Ga -FAPI PET/CT, targeting fibroblast activation in the tumor microenvironment, demonstrated comparable

SUV_{max} values to those of ^{18}F -FDG in paired local, nodal, and distant lesions, but failed to detect several cervical lymph nodes with metastases. This is consistent with recent reports highlighting that, while ^{68}Ga -FAPI excels in certain stroma-rich or desmoplastic lesions (especially at the local recurrence site or in some distant metastases), it is less sensitive for varied nodal disease burden (16,18,28). The mechanism underlying this differential performance is likely related to heterogeneity in the composition of the tumor microenvironment. Lymph node metastases may have lower stromal FAP expression relative to their metabolic activity, which favors ^{18}F -FDG detection (29,30).

In our analysis, distant lesions in the lungs and bones were detected by both tracers at similar detection rates. One pulmonary lesion was negative for ^{68}Ga -FAPI. The SUV_{max} values showed no significant differences ($p=1.0$). However, these two tracers may have different strengths. ^{68}Ga -FAPI can outperform ^{18}F -FDG in fibrotic or cancer-associated fibroblast-rich metastatic foci, as shown in recent clinical trials (21); however, it is not uniformly superior across all lesion types. The occasional higher ^{68}Ga -FAPI SUV_{max} in some locally recurrent lesions (maximum 10.5 vs. 6.8 for ^{18}F -FDG) suggests that ^{68}Ga -FAPI may identify lesions with prominent stromal reactions that could be underestimated by FDG alone (31,32).

Semiquantitative Analysis

The lack of a significant difference in uptake intensity (SUV_{max}) between ^{18}F -FDG and ^{68}Ga -FAPI in paired lesions ($p=0.689$ for lymph nodes, $p=1.0$ for distant metastases) suggests that both tracers detect lesions and provide a comparable semiquantitative assessment. This finding indicates that ^{68}Ga -FAPI can be reliably used to characterize lesions. However, the clinical impact of missing lesions—particularly the nine additional lymph nodes detected only by ^{18}F -FDG (27% of all nodes) in our cohort—underscores the greater utility of ^{18}F -FDG for comprehensive restaging and treatment planning. Missed nodal disease can lead to understaging and inadequate treatment selection, potentially affecting long-term outcomes (33,34).

Comparison with Existing Literature

Our findings align with and extend those of recent comparative studies of ^{18}F -FDG and ^{68}Ga -FAPI PET/CT in TC. A recent study by Alevroudis et al. (21) reported that ^{68}Ga -FAPI detected additional lesions in approximately 20% of patients with RAIR-DTC with higher target-to-background ratios. However, that study included a broader RAIR-DTC population rather than focusing specifically on TENIS syndrome. Our study specifically addresses the TENIS population and demonstrates that, while ^{68}Ga -FAPI may

offer complementary information in select cases, ^{18}F -FDG provides superior overall lesion detection, particularly for nodal disease.

Clinical Implications and Future Directions

Based on our findings, ^{18}F -FDG PET/CT should remain the first-line imaging modality for TENIS syndrome evaluation. ^{68}Ga -FAPI PET/CT may serve as a complementary tool in specific scenarios, including when ^{18}F -FDG PET/CT is negative or equivocal despite high Tg levels; for evaluating local recurrence where stromal reaction may be prominent; in patients with poorly differentiated or dedifferentiated TC with suspected high stromal content; and for treatment planning when targeting stromal components with novel therapies.

Future research should focus on larger multicenter prospective studies to validate these findings and to establish clear clinical algorithms; to assess the correlation of ^{68}Ga -FAPI uptake with histopathologic FAP expression and stromal density; to explore ^{68}Ga -FAPI PET/CT for response assessment following targeted therapies; and to develop radiomic and artificial intelligence approaches that integrate multi-tracer PET data for improved diagnostic accuracy and prognostication.

Study Limitations

This study has a few limitations. First, the modest sample size ($n=22$) from a single center limits the generalizability and statistical power of the subgroup analyses. Technical factors, including different acquisition protocols for ^{18}F -FDG and ^{68}Ga -FAPI (1 vs. 2 min per bed position), may influence image quality and lesion detection, although these protocols reflect standard clinical practice for each tracer. The study was also limited by the heterogeneity of the validation methods. Finally, we did not perform a detailed analysis of the target-to-background ratios or assess the impact of lesion size on detectability, which could provide additional insights into the relative tracer performance.

Conclusion

^{18}F -FDG PET/CT remains the reference imaging modality for detecting structural disease in TENIS syndrome, while ^{68}Ga -FAPI PET/CT is a promising, currently supplementary tool when conventional imaging is inconclusive. The superior nodal detectability of ^{18}F -FDG PET/CT has direct clinical implications for the accurate staging and treatment planning of papillary thyroid carcinoma, the predominant histologic type in TENIS syndrome. The integration of both modalities, potentially in a dual-tracer protocol, could be explored to further enhance diagnostic yield and therapeutic guidance in challenging DTC cases.

Ethics

Ethics Committee Approval: The study protocol was approved by the Amrita Institute of Medical Sciences and Research Institutional Clinical Research Ethics Committee (approval number: ECASM-AIMS-2023-066, date: 24.02.2023).

Informed Consent: All patients participating in the study provided written informed consent.

Footnotes

Authorship Contributions

Concept: J.B.B., M.S., U.M., P.S., Design: J.B.B., M.S., U.M., S.S.P., Data Collection or Processing: J.B.B., P.P., A.S., S.S., B.R.R., P.S., Analysis or Interpretation: J.B.B., M.S., U.M., R.R., Literature Search: J.B.B., R.R., A.S., S.S., B.R.R., P.S., Writing: J.B.B., M.S., B.R.R., P.S.

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Papillary Thyroid Microcarcinomas Detected by Nuclear Medicine Imaging: Distinct Clinicopathological Features Compared with Conventional Modalities

Nükleer Tıp Görüntüleme Yöntemleriyle Saptanan Papiller Tiroid Mikrokarsinomlarının Klinikopatolojik Özellikleri: Konvansiyonel Yöntemlerle Karşılaştırma

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Abstract

Objectives: Papillary thyroid carcinomas detected by nuclear medicine imaging techniques may have a worse prognosis than those identified by conventional methods. However, it remains unclear whether this applies to papillary thyroid microcarcinomas (PTMCs).

Methods: Patients diagnosed with PTMC at Hacettepe University Faculty of Medicine between 2008 and 2020 were categorized into three groups: (1) incidental PTMCs (Inc-PTMC; n=249), (2) non-incidental PTMCs (NonInc-PTMC; n=134), and (3) PTMCs detected by nuclear medicine imaging methods (NM-PTMC; n=24). Tumor pathological characteristics, including multifocality, extrathyroidal extension, vascular invasion, and lymph node involvement, were analyzed. Logistic regression analysis was performed to assess the association between detection method and tumor aggressiveness while adjusting for potential confounders.

Results: Patients in NM-PTMC group were significantly older at diagnosis (54.7±11.2 years) than those in Inc-PTMC (51.1±11.3 years) and NonInc-PTMC (46.9±11.7 years, p=0.001) groups. Tumor size was larger in NM-PTMCs (4.8±2.5 mm) and NonInc-PTMCs (5.3±2.2 mm) compared to Inc-PTMCs (3.4±2.4 mm, p<0.0001). Multiple logistic regression analysis revealed that NM-PTMCs had a markedly higher risk of cervical lymph node metastasis compared with both Inc-PTMCs [odds ratio (OR): 36.04; 95% confidence interval (CI): 6.02-215.59, p=0.001] and NonInc-PTMCs (OR: 8.68; 95% CI: 1.15-65.22, p=0.036). NM-PTMC also had an increased risk of positive surgical margins compared with Inc-PTMC (OR: 5.08; 95% CI: 1.57-16.39, p=0.006), whereas only NonInc-PTMC had a higher risk of extrathyroidal extension (OR: 3.19; 95% CI: 1.48-8.84, p=0.003). The detection method was not associated with multifocality.

Conclusion: Nuclear medicine-detected PTMCs may differ in their clinicopathological profile from other PTMC subgroups and may represent an intermediate phenotype between Inc-PTMC and NonInc-PTMC.

Keywords: Papillary thyroid microcarcinoma, incidental, non-incidental, nuclear medicine, ¹⁸F-FDG PET/CT

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Öz

Amaç: Nükleer tıp görüntüleme yöntemleriyle saptanan papiller tiroid kansinomlarının, konvansiyonel yöntemlerle saptananlara kıyasla daha kötü prognoza sahip olabileceği düşünülmektedir. Ancak bu durumun papiller tiroid mikrokarsinomları (PTMK) için de geçerli olup olmadığı net değildir.

Yöntem: Hacettepe Üniversitesi Tıp Fakültesi'nde 2008-2020 yılları arasında PTMK tanısı alan hastalar üç gruba ayrıldı: (1) insidental PTMK'lar (Inc-PTMK; n=249), (2) non-insidental PTMK'lar (NonInc-PTMK; n=134) ve (3) nükleer tıp görüntüleme yöntemleriyle saptanan PTMK'lar (NM-PTMK; n=24). Multifokalite, ekstrasitroidal yayılım, vasküler invazyon ve lenf nodu tutulumu dahil olmak üzere tümörün patolojik özellikleri değerlendirildi. Saptama yöntemi ile tümör agresifliği arasındaki ilişkiyi, olası karıştırıcı faktörlere göre düzelterek değerlendirmek amacıyla lojistik regresyon analizi yapıldı.

Bulgular: NM-PTMK grubundaki hastalar tanı sırasında ($54,7 \pm 11,2$ yıl), Inc-PTMK ($51,1 \pm 11,3$ yıl) ve NonInc-PTMK ($46,9 \pm 11,7$ yıl; $p=0,001$) gruplarındaki hastalara göre anlamlı olarak daha yaşlıydı. Tümör boyutu, NM-PTMK ($4,8 \pm 2,5$ mm) ve NonInc-PTMK ($5,3 \pm 2,2$ mm) gruplarında, Inc-PTMK grubuna ($3,4 \pm 2,4$ mm; $p<0,0001$) kıyasla daha büyüktü. Çoklu lojistik regresyon analizinde, NM-PTMK'ların servikal lenf nodu metastazı açısından hem Inc-PTMK'lara [olasılık oranı (OR): 36,04; %95 güven aralığı (GA): 6,02-215,59; $p=0,001$] hem de NonInc-PTMK'lara (OR: 8,68; %95 GA: 1,15-65,22; $p=0,036$) kıyasla belirgin şekilde daha yüksek risk taşıdığı saptandı. NM-PTMK grubunda ayrıca Inc-PTMK grubuna göre pozitif cerrahi sınır riski daha yüksekti (OR: 5,08; %95 GA: 1,57-16,39; $p=0,006$). Buna karşılık, yalnızca NonInc-PTMK grubunda ekstrasitroidal yayılım riski daha yüksekti (OR: 3,19; %95 GA: 1,48-8,84; $p=0,003$). Saptama yöntemi ile multifokalite arasında ilişki bulunmadı.

Sonuç: Nükleer tıp yöntemleriyle saptanan PTMK'lar, klinikopatolojik profilleri açısından diğer PTMK alt gruplarından farklılık gösterebilir ve Inc-PTMK ile NonInc-PTMK'lar arasında ara bir fenotipi temsil edebilir.

Anahtar Kelimeler: Papiller tiroid mikrokarsinomu, insidental, non-insidental, nükleer tıp, ^{18}F -FDG PET/BT

Introduction

Incidental papillary thyroid microcarcinomas (Inc-PTMCs) generally have a favorable prognosis, with low recurrence and long-term mortality rates in large cohorts and meta-analyses, compared with non-Inc-PTMCs (NonInc-PTMCs) (1,2,3,4,5). One possible explanation is that the two groups have distinct clinicopathological characteristics, with NonInc-PTMC showing larger tumor size and higher rates of multifocality, cervical lymph node involvement, and capsular invasion (2,3,5).

Nuclear medicine modalities, including ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT), are increasingly used for indications ranging from malignancies to benign inflammatory conditions, and have become important methods in the detection of thyroid lesions, with papillary thyroid carcinoma (PTC) rates ranging from 20% to 30% (6,7,8,9). In addition, studies have shown that nuclear medicine imaging methods used for parathyroid imaging, such as $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile ($^{99\text{m}}\text{Tc}$ -MIBI) single-PET/CT (SPECT/CT) and ^{18}F -florokolin (^{18}F -FCH) PET/CT, have high specificity and accuracy for detecting concurrent thyroid carcinoma (10,11). Importantly, PTCs detected by ^{18}F -FDG PET/CT may exhibit more aggressive features than PTCs in general (12,13,14). Whether these observations extend to PTMCs, however, remains unknown. No studies to date have investigated whether PTMCs detected by nuclear medicine imaging show distinct clinical and pathological characteristics compared with those of Inc-PTMC and Non-Inc-PTMC. While many classification systems categorize

tumors detected on imaging performed for unrelated indications as "incidental," PTMCs detected by nuclear medicine may represent a functionally and metabolically distinct subgroup whose clinicopathological profile has not been characterized separately. PTMCs are increasingly managed with active surveillance protocols in selected patients, making accurate risk stratification at the time of detection particularly important. Clinicopathological features that indicate a higher likelihood of nodal involvement or aggressive histological variants may influence the decision between immediate surgery and observation. In this context, the modality through which a PTMC is first identified may carry prognostic implications that extend beyond those established for PTCs in general, and cannot be assumed to mirror findings derived from larger tumor cohorts. This study therefore aimed to compare the clinicopathological features of PTMCs detected by nuclear medicine imaging with those of Inc-PTMC and Non-Inc-PTMC to determine whether the method of detection may serve as an additional consideration in risk stratification.

Materials and Methods

This retrospective cohort study included 407 patients diagnosed with PTMC at Hacettepe University Faculty of Medicine, Ankara, Türkiye between January 2008 and December 2020, who were identified through a comprehensive review of thyroidectomy pathology reports. Only patients who underwent surgery at our institution were included; cases referred from external centers for pathological consultation were excluded. Tumors were classified and subtyped according to the

World Health Organization (WHO) criteria (15). Although the most recent WHO classification no longer uses the term PTMC, it remains widely used in clinical practice and contemporary literature; therefore, the term was retained for clarity and comparability. PTMC was defined as a PTC measuring <10 mm in greatest dimension, regardless of focality. Tumors were considered multifocal if two or more distinct tumor foci were identified in one or both lobes. Bilobar involvement was defined as the presence of tumor foci in both thyroid lobes. For multifocal tumors, the largest tumor focus was used for size-based analyses. Extrathyroidal extension was defined as microscopic or gross invasion beyond the thyroid capsule. Vascular invasion was recorded when tumor emboli were present within blood vessels located in the tumor capsule or in the adjacent thyroid parenchyma. Cervical lymph node metastasis was histologically confirmed in resected nodes. Positive surgical margins were identified in pathology reports and were defined as the presence of tumor cells at the inked margin or within <1 mm of the surgical margin. This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hacettepe University (approval no: SBA 25/813, date: 23.09.2025).

Patients were categorized into three groups according to the detection method:

Group 1 - Inc-PTMC

Tumors were incidentally detected in thyroidectomy specimens removed for benign thyroid disease (e.g., multinodular goiter) or for non-thyroidal head and neck pathology, with no preoperative suspicion of thyroid malignancy. These cases fulfilled all of the following criteria (n=249):

- The PTMC was not the index lesion leading to surgery.
- Surgery was not performed for suspected thyroid cancer or its metastasis.
- The surrounding thyroid tissue was histologically benign, except for the PTMC.

Group 2 - NonInc-PTMC

Tumors detected following preoperative suspicion of malignancy based on at least one of the following (n=134):

- Fine-needle aspiration biopsy showing malignant or suspicious cytology.
- Preoperative ultrasound suggestive of thyroid malignancy.
- Preoperative evidence or suspicion of regional lymph node or distant metastasis.

Group 3 - Nuclear medicine-detected PTMCs (NM-PTMC)

Tumors identified after a thyroid lesion was detected on nuclear medicine imaging performed for unrelated clinical indications, including (n=24):

- ^{18}F -FDG PET/CT (n=16): oncologic staging or surveillance in 15 patients, and evaluation of vasculitis in the remaining patient.
- ^{18}F -FCH PET/CT (n=2): evaluation of hyperparathyroidism.
- $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT (n=6): evaluation of hyperparathyroidism.

Representative examples of NM-PTMC are shown in Figures 1 and 2. All patients undergoing ^{18}F -FCH PET/CT or $^{99\text{m}}\text{Tc}$ -MIBI imaging also received a thyroid ultrasound during the same session as part of our institutional protocol. Given the small sample size, nuclear medicine imaging modalities were grouped a priori; post-hoc subgroup analyses were also performed.

For each patient, data were collected, including age at PTMC diagnosis, sex, tumor size (mm), multifocality, bilobar involvement, extrathyroidal extension, vascular invasion, cervical lymph node metastasis, concurrent lymphocytic thyroiditis, details of the surgical procedure and LND, the indication for surgery, and preoperative imaging results.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (range), as appropriate. Differences among the three groups were assessed using ANOVA for

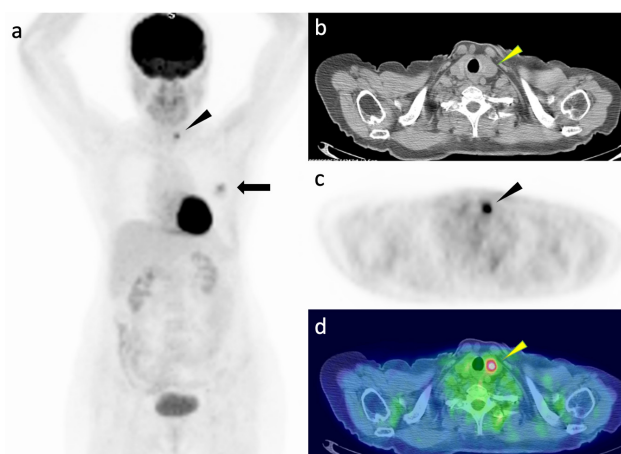


Figure 1. Maximum intensity projection image of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) (a); axial CT (b), PET (c), and fused PET/CT (d) slices at the level of the thyroid gland. The case represents a female patient who was referred for ^{18}F -FDG PET/CT for staging of left breast cancer (a, arrow). An incidental sub-centimetric thyroid nodule with intense FDG uptake was also identified and later confirmed as papillary thyroid carcinoma (a-d, arrowhead)

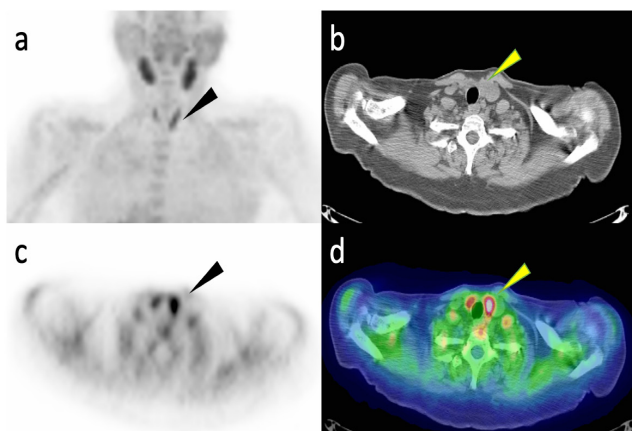


Figure 2. Maximum intensity projection image of ^{18}F -florokolin (^{18}F -FCH) PET (a); axial computed tomography (CT) (b), positron emission tomography (PET) (c), and fused PET/CT (d) slices at the level of the thyroid gland. This case concerns a female patient referred for ^{18}F -FCH PET/CT to evaluate hyperparathyroidism. An incidental sub-centimetric thyroid nodule with intense ^{18}F -FCH uptake was also detected and subsequently confirmed to be a 6-mm papillary thyroid carcinoma (a-d, arrowhead)

variables that were normally distributed. The Kruskal-Wallis test was used for non-normally distributed variables.

Categorical variables were summarized as frequencies and percentages, and group differences were compared using Pearson's chi-square test or Fisher's exact test, as appropriate.

To identify independent predictors of pathological tumor characteristics (extrathyroidal extension, positive surgical margins, multifocality, vascular invasion, and cervical lymph node metastasis), univariate logistic regression analyses were initially performed. Variables with a p -value <0.05 in univariate analyses and clinically relevant covariates (age at diagnosis, sex, tumor size, multifocality, and detection method) were included in multiple logistic regression models. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

All statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). A two-tailed p -value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The main characteristics of the patients are presented in Table 1. Patients in NM-PTMC group were the oldest on average (54.7 ± 11.2 years), significantly older than those in NonInc-PTMC but not significantly different from those in

Inc-PTMC group. In contrast, sex distributions were similar across cohorts, with no significant pairwise differences in the proportions of male patients.

Thyroid functional status differed markedly among the groups ($p < 0.001$ overall). The Inc-PTMC group had the highest proportion of hyperthyroid patients (21.3%), followed by the NonInc-PTMC group (5.2%) and the NM-PTMC group (4.2%). The remaining patients in each group were predominantly euthyroid (Inc-PTMC: 73.1%, NonInc-PTMC: 85.1%, NM-PTMC: 91.7%), with a small proportion hypothyroid (Table 1).

The extent of surgical treatment varied significantly according to detection method ($p < 0.001$ overall). Total thyroidectomy (with or without completion thyroidectomy) was the primary surgical procedure in the majority of cases in all groups. Concurrent central compartment lymph node dissection (LND) was markedly more common in the NM-PTMC group than in the NonInc-PTMC group. Only 2.0% of patients with Inc-PTMC had an initial cervical lymph node excision as part of a total thyroidectomy. The NM-PTMC group had a significantly higher LND rate than the NonInc-PTMC group.

A total of 145 patients received radioactive iodine following thyroid surgery: 62 in the incidental group (24.9%), 72 in the non-incidental group (53.7%), and 11 in the nuclear medicine group (45.8). These differences were statistically significant ($p < 0.001$). The median dose of RAI was 100 mCi (range, 21-175 mCi).

The prevalence of additional malignancies (synchronous non-thyroidal cancers) differed between groups. More than half of the patients in the NM-PTMC group had a concomitant malignancy (62.5%), a rate significantly higher than that in both the Inc-PTMC and NonInc-PTMC groups. The Inc-PTMC group also had a higher incidence of coexisting malignancy than the NonInc-PTMC group (12.9% vs 6.0%, $p = 0.036$). However, the presence of a non-thyroidal malignancy was not a risk factor for adverse tumoral characteristics in multiple regression analyses.

In the NM-PTMC group, all thyroidal uptakes identified on nuclear medicine imaging were focal. In patients detected by ^{18}F -FDG PET/CT, the median maximum standardized uptake value (SUV_{max}) was 3.3 (range, 1.2-21.2). Among patients undergoing ^{18}F -FCH PET/CT or $^{99\text{m}}\text{Tc}$ -MIBI imaging, suspicious sonographic features were identified in both patients who underwent ^{18}F -FCH PET/CT and in two of the six patients who underwent $^{99\text{m}}\text{Tc}$ -MIBI imaging.

Pathological Characteristics

The main pathological features of PTMCs across the three groups are presented in Table 2, while independent

predictors identified through multivariable analyses are shown in Table 3.

Mean tumor size differed significantly among the three groups ($p < 0.001$ overall). Tumors in NonInc-PTMC group were the largest, with a mean diameter of 5.35 ± 2.28 mm, followed by those in NM-PTMC group (4.82 ± 2.57 mm) and then Inc-PTMC group (3.43 ± 2.40 mm).

Histopathological subtypes also showed a distinct distribution (overall $p < 0.001$). The classical papillary subtype predominated in the Inc-PTMC and NonInc-PTMC groups, with smaller proportions of the follicular variant and other aggressive variants, including tall cell, diffuse sclerosing, hobnail, and columnar. The NM-PTMC group exhibited a more heterogeneous pattern, with classical,

Table 1. The main characteristics of papillary thyroid microcarcinoma (PTMC) patients

	Inc-PTMC (n=249)	NonInc-PTMC (n=134)	NM-PTMC (n=24)	p-value	p ¹	p ²	p ³
Age at diagnosis (years $\pm$ SD)	51.1 $\pm$ 11.3	46.9 $\pm$ 11.7	54.7 $\pm$ 11.2	0.001	0.001	0.14	0.003
Gender (M, %)	62 (24.9%)	26 (19.4%)	2 (8.3%)	0.11			
Type of thyroid surgery (n, %)							
Total thyroidectomy	211 (84.7%)	107 (79.9%)	12 (50.0%)				
Subtotal thyroidectomy	25 (10.0%)	4 (2.9%)	2 (8.3%)				
Subtotal thyroidectomy + completion thyroidectomy	8 (3.2%)	2 (1.5%)	2 (8.3%)				
Total thyroidectomy + cervical LND	5 (2%)	21 (15.6%)	8 (33.3%)				
Preoperative thyroid hormone status (n, %)							
Euthyroid	182 (73.1%)	114 (85.1%)	16 (66.7%)	<0.001	0.004	0.55	0.014
Hypothyroid	6 (2.4%)	4 (3.0%)	4 (16.7%)				
Hyperthyroid	53 (21.3%)	12 (9.0%)	4 (16.7%)				
Unknown	8 (3.2%)	4 (3.0%)	-				
Additional malignancy (n, %)	32 (12.9%)	8 (6%)	15 (62.5%)	<0.001	0.036	<0.001	<0.001

Inc-PTMC: Incidental PTMC, NonInc-PTMC: Non-incidental PTMC, NM-PTMC: PTMC detected by nuclear medicine imaging methods, SD: Standard deviation, LND: Lymph node dissection
p¹: Comparison between groups Inc-PTMC and NonInc-PTMC
p²: Comparison between groups Inc-PTMC and NM-PTMC
p³: Comparison between groups NonInc-PTMC and NM-PTMC

Table 2. The main pathological characteristics of PTMCs

	Inc-PTMC (n=249)	NonInc-PTMC (n=134)	NM-PTMC (n=24)	p-value			
				p	p ¹	p ²	p ³
Tumor size (mm $\pm$ SD)	3.43 $\pm$ 2.40	5.35 $\pm$ 2.28	4.82 $\pm$ 2.57	<0.001	<0.001	0.009	0.32
Variant (n, %)							
Classical	194 (78.2%)	102 (76.1%)	8 (33.3%)	<0.001	0.51	<0.001	<0.001
Follicular	44 (17.7%)	21 (15.7%)	8 (33.3%)				
Other	10 (4.0%)	11 (8.2%)	8 (33.3%)				
Multifocality (yes, %)	70 (28.1%)	66 (49.3%)	10 (41.7%)	<0.001	<0.001	0.16	0.49
Capsule invasion (yes, %)	2 (0.8%)	5 (3.7%)	2 (8.3%)	0.02	0.042	0.003	0.31
Extrathyroidal extension (yes, %)	13 (5.2%)	27 (20.1%)	3 (12.5%)	<0.001	<0.001	0.14	0.39
Surgical margins (positive, %)	18 (7.3%)	25 (18.7%)	7 (29.2%)	<0.001	0.001	0.001	0.36
Vascular invasion (yes, %)	1 (0.4%)	3 (2.2%)	0	0.19	0.09	0.76	0.47
Cervical LN involvement (yes, %)	4 (1.6%)	20 (14.9)	6 (25.0%)	<0.001	<0.001	<0.001	0.22
Lymphocytic thyroiditis (yes, %)	45 (18.1%)	43 (32.1%)	6 (25.0%)	0.008	0.002	0.40	0.49

PTMC: papillary thyroid microcarcinoma, Inc-PTMC: Incidental PTMC, NonInc-PTMC: Non-incidental PTMC, NM-PTMC: PTMC detected by nuclear medicine imaging methods, LN: Lymph node, Group 1: Incidental PTMCs, group 2: Non-incidental PTMCs, group 3: PTMCs detected by nuclear medicine imaging methods
p¹: Comparison between groups Inc-PTMC and NonInc-PTMC
p²: Comparison between groups Inc-PTMC and NM-PTMC
p³: Comparison between groups NonInc-PTMC and NM-PTMC

Table 3. Independent predictors of adverse pathological features in PTMC (multivariable logistic regression)

Outcome	Significant predictors	OR (95% CI)	p-value
ETE	Non-incidental vs. incidental PTMCs	3.19 (1.48-8.84)	0.003
	Tumor size	1.24 (1.07-1.43)	0.004
Multifocality	Tumor size	1.18 (1.08-1.30)	<0.001
Positive surgical margins	PTMCs detected by nuclear medicine imaging methods	5.08 (1.57-16.39)	0.006
	Multifocality	2.07 (1.03-4.15)	0.039
	Tumor size	1.32 (1.14-1.52)	<0.001
Cervical LN metastasis	PTMCs detected by nuclear medicine imaging methods vs. incidental PTMCs	36.04 (6.02-215.59)	0.001
	PTMCs detected by nuclear medicine imaging methods vs. non-incidental PTMCs	8.68 (1.15-65.22)	0.036
	Non-incidental vs. incidental PTMCs	5.64 (1.58-20.11)	0.004
	ETE	8.31 (2.40-28.81)	0.001
	Vascular invasion	74.91 (1.31-4285.91)	0.037
	Age	0.94 (0.90-0.99)	0.017
	Male gender	6.01 (2.00-18.01)	0.001

PTMC: Papillary thyroid microcarcinoma, ETE: Extrathyroidal extension, LN: Lymph node, OR: Odds ratio, CI: Confidence interval

follicular, and other aggressive variants each occurring in equal proportions (Table 2).

Tumor multifocality and bilaterality were more common in the NonInc-PTMC and NM-PTMC groups than in the Inc-PTMC group. However, in the multiple logistic regression analysis, the detection method for PTMC was not associated with multifocality; only tumor size was associated with multifocality (Table 3).

Several markers of local tumor invasion differed significantly between groups. Capsular invasion was rare in the Inc-PTMC group but more frequent in the NonInc-PTMC and NM-PTMC groups, with an overall group difference of $p=0.02$ (Table 2). However, the detection method was not identified as a risk factor for capsular invasion in the multiple logistic regression analysis. Extrathyroidal extension was more common in Inc-PTMC and Non-Inc-PTMC. This difference was mainly driven by the contrast between the NonInc-PTMC and Inc-PTMC groups. Multiple logistic regression analysis confirmed that Non-Inc-PTMCs had a significantly higher risk of extrathyroidal extension than Inc-PTMCs. Tumor size was also an independent risk factor for extrathyroidal extension, whereas multifocality was not an independent risk factor (Table 3). Positive resection margins were more common in the NonInc-PTMC and NM-PTMC groups (Table 2). Multiple logistic regression analysis confirmed that only the NM-PTMC group had a significantly increased risk of positive surgical margins compared with the Inc-PTMC group, whereas the NonInc-PTMC group showed no comparable increase in risk. In

addition, tumor size and multifocality were independent risk factors for positive surgical margins. Vascular invasion was exceedingly uncommon in all three groups, with no statistically significant differences among the groups.

Cervical lymph node metastasis differed markedly among groups, with the highest rates in the NM-PTMC group, followed by the NonInc-PTMC group, and very low rates in the Inc-PTMC group (Table 2). Both the NonInc-PTMC and NM-PTMC groups had significantly higher rates of lymph node involvement than the Inc-PTMC group, whereas the difference between the NonInc-PTMC and NM-PTMC groups was not significant (Table 2). Multiple logistic regression analysis revealed that patients in the NonInc-PTMC and NM-PTMC groups had a significantly increased risk of cervical lymph node metastasis compared with the Inc-PTMC group. The NM-PTMC group also had a significantly higher risk than the NonInc-PTMC group. Younger age, male sex, and features of invasive disease (extrathyroidal extension and vascular invasion) emerged as significant predictors of nodal involvement (Table 3). However, the wide CI for vascular invasion suggests limited precision of this estimate, likely due to the low number of cases.

Coexisting lymphocytic thyroiditis was most prevalent in Non-Inc-PTMCs, but was not associated with adverse pathological characteristics in multivariable models.

Patients in the NM-PTMC group were further subdivided according to whether they were detected incidentally via PET/CT or other nuclear medicine imaging modalities

because the likelihood of secondary malignant tumors is already higher in patients with known malignancies. No significant differences were observed between these subgroups with respect to age at diagnosis (53.81 ± 11.35 vs 56.63 ± 11.63 years, respectively), tumor size (5.06 ± 2.56 vs 4.28 ± 2.69 mm, respectively), or other pathological characteristics, including multifocality, cervical lymph node metastasis, and extrathyroidal extension (all $p > 0.1$).

Discussion

In this study, we demonstrated that NM-PTMC displayed distinct clinicopathological features compared with both Inc-PTMC and Non-Inc-PTMC. Patients in this group were older at diagnosis, had larger tumors, and had a disproportionately high prevalence of aggressive histological variants. They also underwent LND more frequently and had markedly higher rates of positive surgical margins and cervical lymph node metastases. In contrast, Non-Inc-PTMCs were characterized by larger tumor size and an increased risk of extrathyroidal extension, whereas Inc-PTMCs generally showed the most favorable pathological profile. Logistic regression confirmed that NM-PTMC were independently associated with a higher risk of positive margins and nodal metastasis, whereas extrathyroidal extension was more strongly linked to non-incidental tumors. Additional predictors of aggressiveness across the cohort included younger age, male sex, and the presence of extrathyroidal extension or vascular invasion, although the latter was rare and associated with imprecise estimates due to small numbers. Taken together, these findings suggest that the mode of detection may be an important determinant of the biological behavior of PTMCs.

Studies have shown that during ^{18}F -FDG PET/CT, the chance of detecting thyroid uptake is 2%-3%. Patients with focal uptake seem to be particularly at risk, and when cytopathological confirmation is available, a 20%-30% risk of thyroid malignancy has been reported (7,8,9,13). SUV_{max} has been investigated as a potential predictor of malignancy, but no consensus exists regarding an optimal cutoff value. In our cohort, the median SUV_{max} of incidental PTMCs was 3.3 (range, 1.2-21.2). Pagano et al. (16) proposed a cutoff of 5.0 (positive predictive value 50%, negative predictive value 92.3%), whereas Demir et al. (8) suggested 5.5 (sensitivity 82%, specificity 65%). Others have also reported higher SUV_{max} values in malignant than in benign lesions (17,18,19). Conversely, Makis et al. (20) and Toyoshima et al. (21) found no correlation, highlighting that subsequent thyroid ultrasound findings were more reliable. These findings further emphasize that incidental focal uptake should be corroborated by

dedicated thyroid ultrasonography, as metabolic activity alone may be insufficient to characterize malignancy risk. Notably, in our cohort, all patients undergoing ^{18}F -FCH PET/CT or $^{99\text{m}}\text{Tc}$ -MIBI imaging also received thyroid ultrasound during the same session (a "one-stop-shop" approach), which strengthens the reliability of lesion assessment.

PTCs detected by ^{18}F -FDG PET/CT may show less favorable pathological characteristics than PTCs in general. An earlier paper by Are et al. (12) suggested that PTCs detected by ^{18}F -FDG PET/CT showed aggressive features such as the tall cell variant and extrathyroidal extension, although no control group was included. Law and Lang (14) later compared Inc-PTMCs according to detection method (^{18}F -FDG PET/CT, $n=22$, and ultrasound, $n=11$) and found that multifocality, bilaterality, and cervical lymph node metastasis may be more frequent in the ^{18}F -FDG PET/CT group. Although this study included patients with PTMCs, the exact number was not specified. Piccardo et al. (22) reported that intense focal uptake in differentiated thyroid carcinomas detected by ^{18}F -FDG PET/CT ($\text{SUV}_{\text{max}} \geq 3$) was associated with persistent or progressive disease. On the other hand, Pak et al. (23) found no difference in multifocality, extrathyroidal extension, surgical margins, or cervical lymph node metastasis between Inc-PTMC patients detected by ^{18}F -FDG PET/CT ($n=48$) and those detected by other imaging methods ($n=48$), except that patient in the ^{18}F -FDG PET/CT group were older and had a higher tumor stage at diagnosis. Nonetheless, clinical and pathological data on PTCs detected by ^{18}F -FDG PET/CT remain limited, likely because patients undergoing ^{18}F -FDG PET/CT often have another primary malignancy, and not all individuals with thyroidal uptake proceed to fine-needle aspiration or thyroid surgery. Furthermore, prognosis and survival are predominantly determined by the primary malignancy rather than by the thyroid lesion itself. Regarding other modalities, including $^{99\text{m}}\text{Tc}$ -MIBI SPECT/CT and ^{18}F -FCH PET/CT, a limited number of studies have suggested that incidental focal thyroidal uptake may indicate malignancy (10,11). However, there are no data on their clinical or pathological significance.

PTMCs represent a different clinical context. Although previous studies have compared Inc-PTMC and Non-Inc-PTMC (4), the potential impact of detection by nuclear medicine imaging on PTMC clinicopathological features has not been investigated previously. Definitions of incidental thyroid carcinoma vary across studies. In many reports, thyroid cancers detected during imaging performed for unrelated indications, including nuclear medicine imaging, are also classified as incidental. However, in our study, we deliberately categorized NM-PTMC as a separate group

because their detection pathways, patient characteristics, and clinical contexts differ substantially from those of surgically incidental tumors.

NM-PTMC occupied an intermediate clinicopathological position between Inc-PTMCs and Non-Inc-PTMCs. Their mean tumor size resembled that of non-incidental PTMCs, and they displayed a higher frequency of aggressive histological variants, consistent with a previous report on PTC (12). In contrast, only Non-Inc-PTMCs were independently associated with extrathyroidal extension. A potential explanation for the larger tumor size and higher rate of positive surgical margins observed in NM-PTMCs is the limited spatial resolution of nuclear medicine imaging. Both PET and SPECT have substantially lower spatial resolution than high-resolution ultrasound, so lesions generally must reach a sufficient size or demonstrate significant radiotracer avidity to be detectable. Accordingly, the tumors in the NM-PTMC group may represent a biologically selected subset whose members have already achieved a size or metabolic activity threshold necessary for detection, rather than a random sample of all PTMCs. This detection threshold effect could enrich the nuclear medicine-detected group with tumors exhibiting more aggressive biological behavior, including tumors with higher proliferative activity or greater metabolic demand, features that may independently contribute to incomplete resection and positive margins.

The most prominent and clinically relevant finding was a significantly increased risk of cervical lymph node metastasis in NM-PTMC. This association persisted after adjustment for potential confounders. Notably, extrathyroidal malignancy had no significant impact on any clinicopathological characteristics. However, patients in the NM-PTMC group underwent LND at a significantly higher rate than those in the other groups, particularly the Inc-PTMC group, in which LND was performed in only 2.0% of cases. Because lymph node metastasis can only be confirmed histologically in dissected specimens, the higher LND rate in the NM-PTMC group may have increased the likelihood of identifying microscopic nodal involvement that would otherwise have remained undetected. This could have artificially inflated the observed nodal metastasis rate in the NM-PTMC group relative to the Inc-PTMC group and this should be considered when interpreting the large OR for lymph node metastasis in the NM-PTMC group. The decision to perform LND in the NM-PTMC group was likely influenced by preoperative suspicion of nodal disease based on imaging or intraoperative findings; nonetheless, the possibility of ascertainment bias cannot be excluded in this retrospective cohort.

We also evaluated pathology reports according to the presence of concomitant Hashimoto's thyroiditis (HT), as previous studies have suggested that coexisting HT may influence the clinicopathological features of both PTC and PTMC, either favorably (24,25) or unfavorably (26). In our series, HT was more prevalent in the non-incidental and nuclear medicine-detected groups than in incidental PTMCs. However, no significant association was observed between the presence of HT and tumor characteristics in our analysis.

This study has several strengths. It represents one of the largest series focusing exclusively on PTMCs and, to our knowledge, is the first to investigate their clinicopathological features by detection method. Second, all cases were evaluated within a single tertiary center, ensuring standardized pathological assessment and uniform reporting. Third, Inc-PTMC and Non-Inc-PTMCs were defined carefully to avoid misclassification and overlap between the groups. The inclusion of three distinct cohorts (Inc-PTMC and Non-Inc-PTMC, and NM-PTMC) facilitated a comprehensive comparative analysis.

Study Limitations

The study also has several limitations. The relatively small number of NM-PTMC (n=24) and the retrospective design should be acknowledged as limitations. Although only 24 patients in the nuclear medicine-detected PTMC group underwent surgery and were included in the analysis, the total number of PTMCs identified by nuclear medicine imaging is likely to be higher, as not all such lesions necessarily proceed to surgery. In clinical practice, thyroid foci identified on imaging performed for non-thyroid malignancies are often not investigated further, leading to possible underdiagnosis, rather than true rarity, in this subgroup. Therefore, our findings should be interpreted as indicating a strong association rather than as a precise estimate of effect size; this is reflected by the large ORs and wide CIs resulting from the limited number of events in the nuclear medicine-detected group. Furthermore, long-term data on overall survival and disease-free survival were not available. An additional limitation warranting explicit discussion is the potential for detection bias in assessing cervical lymph node metastasis (see above).

Conclusion

In this retrospective cohort, PTMCs detected by nuclear medicine imaging were associated with less favorable pathological features than Inc-PTMCs and Non-Inc-PTMCs identified through conventional diagnostic methods. Despite their small size, these tumors showed a significantly higher frequency of cervical lymph node metastasis. While

the underlying mechanisms remain uncertain and selection bias cannot be excluded, our findings suggest that NM-PTMC may differ in their clinicopathological profiles from other PTMC subgroups. Accordingly, the context in which a PTMC is detected may provide additional information during risk assessment. Further prospective multicenter studies are required to validate these observations and clarify their potential implications for clinical decision-making.

Ethics

Ethics Committee Approval: This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hacettepe University (approval no: SBA 25/813, date: 23.09.2025).

Informed Consent: This retrospective cohort study included 407 patients diagnosed with PTMC at Hacettepe University Faculty of Medicine, Ankara, Türkiye between January 2008 and December 2020, who were identified through a comprehensive review of thyroidectomy pathology reports.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.S., Concept: S.H.O., G.K., J.K., M.F.B., A.G., Design: A.G., Data Collection or Processing: İ.Ç., B.E., G.K., Analysis or Interpretation: J.K., M.F.B., A.G., Literature Search: S.H.O., Writing: S.H.O., A.G.

Conflict of Interest: Murat Fani Bozkurt is the Editor-in-Chief of Molecular Imaging and Radionuclide Therapy. However, he was not involved in any stage of the editorial evaluation or decision-making process for this manuscript. The manuscript was evaluated by editors from institutions different from those of the authors. The remaining authors declared no conflicts of interest.

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Separation of ^{90}Y Microspheres and Imaging with PET/CT: Phantom Study

^{90}Y Mikrosferlerinin Ayrılması ve PET/BT ile Görüntülenmesi: Fantom Çalışması

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Abstract

Objectives: Yttrium 90 (^{90}Y) microspheres are utilized in the treatment of liver tumors. This study aimed to prepare ^{90}Y suitable for experimental studies by separating it from within the microspheres and imaging it cartographically in positron emission tomography/computed tomography (PET/CT).

Methods: ^{90}Y microspheres were incubated for 2 hours in a solution containing 5.5 molar sodium chloride (NaCl) and 6 molar hydrochloric acid at pH 5. After this period, separation was achieved by passing through a 0.22 μm pore size polytetrafluoroethylene filter. A liver phantom, mimicking human liver equivalent dimensions and containing two simulated tumors, was filled with ^{90}Y and imaged scintigraphically in PET/CT.

Results: The true ^{90}Y ratios between the large simulated tumor and the small simulated tumor compared to normal liver tissue were approximately 10:1 and 2:1, respectively. PET/CT images yielded these ratios as 11.3 and 2.13 for the large and small tumors, respectively. Homogeneous distribution of ^{90}Y within the simulated liver tissue was observed.

Conclusion: The separation technique enabled preparation of a homogeneous ionic ^{90}Y solution suitable for quantitative PET/CT phantom imaging and may facilitate future phantom-based dosimetric studies.

Keywords: Yttrium 90 (^{90}Y), microspheres, separation processes, PET/CT imaging

Öz

Amaç: İtiryum-90 (^{90}Y) mikroküreler karaciğer tümörlerinin tedavisinde kullanılmaktadır. Bu çalışmanın amacı, ^{90}Y 'yi mikrokürelerden ayırarak deneysel çalışmalara uygun hale getirmek ve pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) ile kartografik olarak görüntülemektir.

Yöntem: ^{90}Y mikroküreler, pH 5'te 5,5 molar sodyum klorür (NaCl) ve 6 molar hidroklorik asit içeren bir çözelti içerisinde 2 saat inkübe edildi. Bu sürenin ardından, 0,22 μm gözenek çapına sahip politetrafluoroetilen filtreden geçirilerek ayırma işlemi gerçekleştirildi. İnsan karaciğerine eşdeğer boyutları taklit eden ve iki simüle tümör içeren bir karaciğer fantomu ^{90}Y ile dolduruldu ve PET/BT'de sintigrafik olarak görüntüldü.

Bulgular: Büyük simüle tümör ve küçük simüle tümörün normal karaciğer dokusuna kıyasla gerçek ^{90}Y oranları sırasıyla yaklaşık 10:1 ve 2:1 olarak belirlendi. PET/BT görüntülerinde bu oranlar büyük ve küçük tümörler için sırasıyla 11,3 ve 2,13 olarak elde edildi. Simüle karaciğer dokusu içerisinde ^{90}Y 'nin homojen dağılım gösterdiği gözlemlendi.

Sonuç: ^{90}Y mikroküre kompleksinden elde edilen saflaştırılmış ^{90}Y çözeltisi, deneysel çalışmalarda kullanılabilecek bir forma dönüştürülmüştür.

Anahtar Kelimeler: İtiryum-90 (^{90}Y), mikrosferler, ayırım işlemleri, PET/BT görüntüleme

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Introduction

Selective internal radiation therapy using yttrium-90 (^{90}Y)-loaded microspheres is an effective treatment modality for liver tumors. In this method, high radiation doses are delivered directly to the tumor via the hepatic artery using catheter-based techniques (1,2,3,4,5). Radioembolization is a targeted technique involving the administration of ^{90}Y -containing microspheres into specific branches of the hepatic artery. After intrahepatic arterial infusion, ^{90}Y microspheres become trapped within the microvascular bed. When ^{90}Y decays, it emits beta (β) radiation with an average energy of 0.93 MeV and a maximum energy of 2.26 MeV. Electrons at these energies can generate Bremsstrahlung (deceleration X-rays) when interacting with tissue. Gamma camera imaging utilizes these X-rays. In addition, ^{90}Y emits low-yield annihilation photons at a rate of approximately 32 per million decays, enabling positron emission tomography (PET) imaging (6).

In liver tumor treatment, two commonly used dosimetry approaches exist: pre- and post-treatment dosimetry.

Pre-treatment dosimetry is performed using $^{99\text{m}}\text{Tc}$ -MAA-based scintigraphic imaging with a gamma camera. The first step in dosimetric calculations is the determination of the lung shunt fraction, which reflects the fraction of activity shunted from the liver to the lungs. In addition, the radiation tolerance of normal liver tissue and the intended tumor absorbed dose can be calculated for treatment planning (7,8,9,10). After calculations performed with $^{99\text{m}}\text{Tc}$ -MAA, the determined dose is administered to the patient using ^{90}Y microspheres (11). It is well known that the intrahepatic distribution of $^{99\text{m}}\text{Tc}$ -MAA microspheres differs from that of ^{90}Y microspheres. Therefore, post-treatment dosimetric studies using ^{90}Y microspheres are also performed (12,13). For this purpose, some studies have used phantoms simulating the human liver and lungs labeled with ^{99}Tc (14). However, due to technical limitations, no pre-dosimetric phantom studies using ^{90}Y microspheres have been reported. In contrast, post-dosimetric studies using ^{90}Y microspheres in patient imaging do exist. One such study was performed by D'Arienzo et al. (15) using a phantom with ^{90}Y chloride. In that study, ^{90}Y was used in chloride form without microspheres, allowing a homogeneous distribution of ^{90}Y in PET/computed tomography (CT) imaging and enabling dosimetric analysis. Partial volume effect (PVE) is a phenomenon that complicates scintigraphic differentiation in small liver tumors, as in all nuclear medicine imaging. PVE is a complex process influenced by several factors, including tumor size and shape, background activity in surrounding tissues,

spatial resolution of the imaging system, voxel size, and imaging modality. Chiesa et al. (16) reported that lesions smaller than 3 cm are affected by PVE, and particularly tumors smaller than 2 cm cannot be reliably corrected for PVE and therefore should be excluded from evaluation. These investigators studied PVE both in phantoms and in patients using $^{99\text{m}}\text{Tc}$. Further phantom studies are required for PET imaging of small liver tumors using pure ^{90}Y , as tumor diameter cannot be adequately characterized.

Before separation, ^{90}Y -labeled microspheres contain a partially cross-linked cation-exchange polymer matrix composed of polystyrene resin. During labeling, $^{90}\text{Y}^{3+}$ replaces sodium ions (Na^+) via ion exchange and binds to the resin matrix, thereby attaching to the microspheres. Subsequently, ^{90}Y is immobilized on the microspheres by precipitation in the form of a phosphate salt. The ^{90}Y -microsphere complex is maintained together by physical forces rather than chemical bonds, resulting in a relatively weak association that may be disrupted in highly ionic environments. SIR-Spheres consist of biocompatible resin microspheres radiolabeled with ^{90}Y . During ion exchange, sodium ions (Na^+) are replaced by $^{90}\text{Y}^{3+}$, which binds to the polystyrene cation-exchange resin layer. Subsequently, ^{90}Y is immobilized on the resin microspheres by phosphate precipitation (17).

Although previous phantom studies have used ^{90}Y chloride solutions, studies investigating the extraction of ^{90}Y from commercial resin microspheres and its subsequent use in phantom imaging are extremely limited. The ability to obtain a homogeneous ionic ^{90}Y solution from microspheres may provide a significant advantage for cost-effective phantom-based dosimetric research and imaging studies. The aim of this study is to separate ^{90}Y from microspheres into ionic form, optimize the preparation of ^{90}Y solution for experimental studies, and validate its accuracy using PET/CT imaging and quantitative analysis.

Material and Methods

No live data were used in this study, and all data were produced from phantom studies. Due to the harmful effects of radiation on living organisms, experimental studies involving radiation are often conducted using organ-mimicking phantoms. In this study, we used a phantom resembling the human liver, containing two simulated tumors with known volumes. The study was planned in two stages: the first stage involved filtration of solutions with microspheres, and the second stage involved imaging and quantification of the phantom using PET/CT. The imaging was performed both when the phantom was

labeled with microspheres and after the microspheres were separated from the ⁹⁰Y.

⁹⁰Y Microspheres Characteristics and Separation Technique

Commercially available resin-based ⁹⁰Y microspheres were used as the radionuclide source in this study. The microspheres consist of a polystyrene resin matrix with an average diameter of $32 \pm 10 \mu\text{m}$ and a specific gravity of approximately 1.6 g/dL (15,16). The association between ⁹⁰Y and the resin matrix can be disrupted under highly ionic conditions, allowing the radionuclide to be separated from the microspheres. To separate the ⁹⁰Y isotope from this resin, the microspheres were treated with a solution composed of a mixture of 5.5 M NaCl and 6 M HCl at pH 5 [NaCl (pKa: 7.15), HCl (pKa: -6.3), and Y+3 (pKa: 10.64)]. After incubation at room temperature for 2 hours, the solution containing ionic ⁹⁰Y was separated from the resin particles by passing it through a $0.22 \mu\text{m}$ PTFE filter. Since the initial trial was successful, further experimental replication was not performed. The microspheres within the ⁹⁰Y complex have dimensions ranging from 20 to 60 microns (with an average of 32 ± 10 microns), which prevented them from passing through sterilizing filters due to their size. Consequently, when these microspheres were transferred into the product vial in their free form, they became trapped within the vial. Meanwhile, the ⁹⁰Y radionuclide remained in its free form within the product vial, completing the separation process. The separated ionic form of ⁹⁰Y radionuclide was then utilized in the second phase of phantom imaging studies.

Liver Phantom and Water Tank

The liver model used in this study consists of three main sections: normal liver tissue, a large tumor, and a small tumor. Collaboration with the chemical engineering department was employed to determine the materials for the phantom. The liver phantom was fabricated from filament material called polylactic acid using fused deposition modeling on 3D printers. The model was designed to have a specific gravity similar to human tissue ($d=1.24 \text{ g/cm}^3$). The dimensions of the liver phantom are 112 mm x 191 mm with an empty mass of 350 grams, and it includes three caps for filling with radiopharmaceutical solution.

The leftmost cap is used to fill the 690 cm^3 volume representing the hepatic parenchyma (normal liver) with liquid radioactive material. The other caps, designed as cylindrical structures with volumes of 9.5 cm^3 and 202 cm^3 respectively, are used to fill liquid radioactive material into two separate and independently designed tumors

of different sizes (Figure 1). These tumor sizes represent commonly encountered small and relatively large volumes. Scintigraphic imaging of the liver phantom was conducted using a tank made of plexiglass that matches the dimensions of a normal human abdominal area and can be filled with water.

Measurement of ⁹⁰Y Radioactivity, Imaging Protocol and Quantification

Radioactivity measurements were performed using a dose calibrator (Biodex Atom lab 300 dose calibrator). Accuracy tests of the dose calibrator were performed with a Cs-137 calibration source prior to measurement. The activities of ⁹⁰Y in ionic form, to be injected into the simulated tumors and empty spaces representing normal liver tissue in the phantom, were drawn into syringes and measured in the dose calibrator. Subsequently, the ⁹⁰Y radionuclide was diluted with water, and activities of 684 MBq, 2025 MBq, and 18.70 MBq were respectively filled into the locations representing normal liver, large tumor, and small tumor in the phantom. Empty syringes were measured again for background correction. This process allowed the determination of the net activity amounts deposited into the phantoms.

The PET/CT images of the phantom were acquired using a Siemens Horizon Biograph model scanner with the subject positioned on a single bed for a duration of 20



Figure 1. View of the liver phantom inside the water tank. The figure shows the liver phantom placed inside a water tank. The filling caps, from left to right, correspond to the normal liver, small tumor, and large tumor compartments, respectively

minutes. The imaging process was carried out in two stages: in the initial stage, imaging was performed using the radiopharmaceutical labeled with ^{90}Y microspheres. In the second stage, following separation from the ^{90}Y microspheres, the phantom was filled with the microspheres, and imaging was repeated under identical conditions using the same PET/CT scanner.

The image reconstruction was performed according to routine clinical protocol using the OSEM 3D algorithm with 16 subsets and 8 iterations. Quantification PET/CT images was carried out using the OsiriX Dicam Viewer program. In the first stage, after filling the phantom with a solution of ^{90}Y microspheres into the tumor-simulating regions and empty spaces representing normal liver tissue, PET/CT imaging

was performed. The PET images showed the settling of ^{90}Y microspheres towards the bottom. Volumes of interest (VOIs) were drawn around the areas where microspheres settled and named as VOI_1 and VOI_2 . in accordance with conventional use. Similarly, the entire liver (including tumors) was named VOI_3 (Figure 2). Subsequently, the counts for $\text{VOI}_3 - (\text{VOI}_1 + \text{VOI}_2)$ were calculated to determine the ratio of settled ^{90}Y microspheres. The ratio of settled ^{90}Y microspheres $[(\text{VOI}_1 + \text{VOI}_2) / \text{VOI}_3]$ was determined using the equation.

In the second stage, the actual values of the ^{90}Y activity per unit volume (MBq/mL) for normal liver (N) and tumor (T) were calculated based on the amounts of ^{90}Y activity filled into the phantom. PET images were used to draw 10 VOIs of the same size over the normal liver and separately over the tumors to determine the counts.

Statistical Analysis

The T/N ratios in the ^{90}Y microsphere PET/CT images and the T/N ratios in the ^{90}Y PET/CT images were evaluated using the Mann-Whitney U test. A significance level of $p < 0.05$ was used to indicate a statistically significant difference.

Results

After filling the phantom with the solution of ^{90}Y microspheres into the tumor-simulating regions and empty spaces representing normal liver tissue, PET/CT imaging was conducted. VOIs were drawn around the areas where microspheres settled. These regions were named VOI_1 and VOI_2 , and their total counts were determined (Figure 2). The total count for VOI_1 was 82484 and for VOI_2 it was 62039. The total count for the entire liver (including tumors) was determined by drawing the VOI around the area of interest, resulting in a count of 151204 for VOI_3 . Using these counts, the ratio of settled microspheres $[(\text{VOI}_1 + \text{VOI}_2) / \text{VOI}_3]$ was calculated as $(82484 + 62039) / 151204 = 0.95858$ (95.58%).

The actual ^{90}Y unit activity amounts Mega Becquerel/cm³ (MBq/cm³) placed into the phantom were 1 MBq/cm³ for normal liver (N), 9.9 MBq/cm³ for the large tumor (Ltm), and 4.73 MBq/cm³ for the small tumor (Stm), considering the volumes of the tumors. The T/N ratios for Ltm and Stm were determined to be 1/10 and 1/2, respectively. After separating the microspheres and filling pure ^{90}Y into the phantom and tumor-simulating regions, PET/CT imaging was performed. The obtained images showed that the ^{90}Y microspheres did not settle at the bottom but distributed relatively homogeneously. VOIs were drawn around the outer boundaries of the tumors on the images. The large and small tumors were labeled as Ltm and

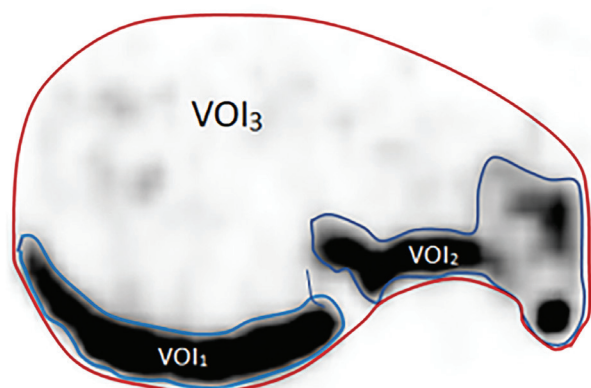


Figure 2. VOIs drawn on the PET/CT Image of ^{90}Y microspheres filled in the phantom. VOIs were delineated on the PET/CT image of the phantom filled with ^{90}Y
VOI: Volume of interest, PET/CT: Positron emission tomography/computed tomography, ^{90}Y : Yttrium-90

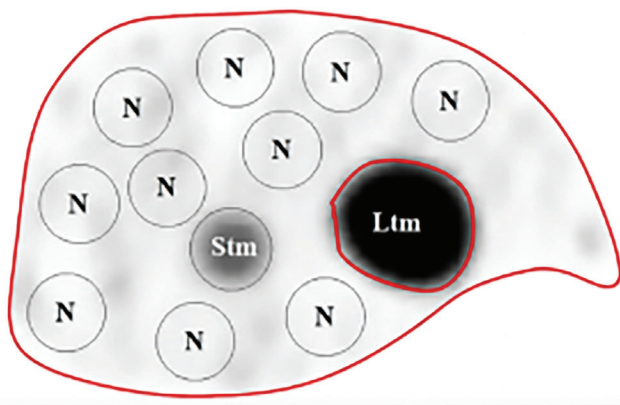


Figure 3. VOIs Drawn on the PET/CT Image of ^{90}Y Filled in the Phantom. VOIs were delineated on the PET/CT image of the phantom filled with ^{90}Y
VOI: Volume of interest, PET/CT: Positron Emission tomography/computed tomography, ^{90}Y : Yttrium-90; Ltm: Large tumor, Stm: Small tumor, N: Normal liver

Stm, respectively. Additionally, 10 VOIs were drawn from different regions corresponding to normal liver tissue (N) on the cross-sectional image (Figure 3). The average VOI counts were 70120 for Ltm and 13848 for Stm. The T/N ratios were calculated by dividing the average VOI counts of Stm and Ltm by the VOI counts of N separately (Table 1).

Data distribution was assessed and non-parametric statistics were therefore applied. Statistical Comparison of Ltm and Stm T/N Values Using Mann-Whitney U Test Revealed a Highly Significant Difference at the $p=0.00018$ Level.

Discussion

The present study demonstrated that ⁹⁰Y can be successfully separated from commercially available resin microspheres and converted into an ionic solution suitable for phantom-based PET/CT imaging studies. When the separated ionic ⁹⁰Y solution was introduced into the phantom, it exhibited a homogeneous distribution, thereby enabling reliable quantitative PET analysis.

The differences between the two preparation methods before and after separation of the particulate resin microspheres were demonstrated both visually and quantitatively in Figures 2 and 3. Approximately 95.6% of the detected activity from the intact microspheres accumulated in the dependent (lower) regions of the phantom, confirming that gravitational sedimentation dominates the distribution of resin microspheres under static phantom conditions. Such sedimentation renders phantom studies unsuitable for quantitative imaging

and dosimetric validation because the intended activity distribution cannot be maintained. In contrast, following separation of ⁹⁰Y from the microspheres, the activity was distributed throughout the phantom without visible sedimentation, resulting in PET images that more accurately reflected the intended activity concentrations.

An important finding of this study was the close agreement between the prepared activity concentrations and the quantitative measurements obtained from PET imaging. The planned tumor-to-normal liver (T/N) activity concentration ratio was 10:1 for the large tumor and 2:1 for the small tumor. PET imaging yielded mean T/N ratios of 11.3 ± 0.8 and 2.26 ± 0.17 , respectively. Although minor deviations were observed, these differences were within the expected range attributable to the PVE, the spatial resolution of PET, image reconstruction, VOI delineation, and counting statistics. Furthermore, the Mann-Whitney U test demonstrated a highly significant difference between the T/N ratios of the two tumor models ($p=0.00018$). These findings confirm that the prepared phantom successfully generated two distinct activity concentrations that were quantitatively distinguishable by PET/CT.

Most phantom studies reported in the literature have used commercially available ⁹⁰Y chloride (⁹⁰YCl₃) solutions because of their inherently homogeneous distribution (15). Son et al. (18) used ⁹⁰Y chloride in a phantom dosimetry study and demonstrated that its homogeneous activity distribution was suitable for quantitative PET imaging. Similarly, Mille et al. (19) performed phantom experiments using a homogeneous ⁹⁰YCl₃ solution. They emphasized the usefulness of this approach for image-based dosimetry while also recommending that future studies investigate more realistic heterogeneous activity distributions. In contrast, the present study demonstrates that by separating ionic ⁹⁰Y from residual resin microspheres obtained from clinical applications, a homogeneous mixture exceeding 95% uniformity can be achieved for phantom studies. This approach therefore provides an alternative radionuclide source for phantom preparation without requiring commercially available ⁹⁰Y chloride.

Clinical studies have shown that ⁹⁰Y resin microspheres do not sediment under the influence of gravity but instead become distributed throughout the hepatic arterial microvasculature. Gulec et al. (11) reported consistent tumor-to-normal liver uptake ratios following radioembolization, demonstrating that the microspheres become physiologically embolized within the hepatic arterioles. Likewise, Son et al. (18) reported good agreement between dosimetric estimates obtained using ^{99m}Tc-MAA single photon emission computed tomography (SPECT)/CT and post-treatment

Table 1. T/N ratios calculated from VOIs drawn on the PET/CT image showing relatively homogeneous distribution of ⁹⁰Y in the phantom

N	VOI (Counts)	T/N (Stm)	T/N (Ltm)
1	6623	2.09	10.6
2	6568	2.10	10.7
3	6459	2.14	10.9
4	6123	2.26	11.5
5	6425	2.16	10.9
6	5523	2.50	12.7
7	6610	2.10	10.6
8	5423	2.54	12.9
9	5887	2.34	11.9
10	5968	2.32	11.7
Mean $\pm$ SD	6203 $\pm$ 447	2.26 $\pm$ 0.17	11.3 $\pm$ 0.8

T/N: Tumor-to-normal tissue ratio, VOI: Volume of interest, PET/CT: Positron emission tomography/computed tomography, ⁹⁰Y: Yttrium-90, SD: Standard deviation, Stm: Small tumor, Ltm: Large tumor

⁹⁰Y PET/CT findings. Furthermore, Elschot et al. (20) demonstrated that PET/CT provides more accurate post-treatment activity quantification than Bremsstrahlung SPECT imaging. These clinical observations fundamentally differ from static phantom experiments because, under in vivo conditions, the microspheres are retained within the tumor microvasculature rather than freely settling under gravity. Consequently, the sedimentation observed in our initial phantom experiment should not be interpreted as a limitation of clinical radioembolization but rather as a phenomenon specific to the static phantom model. For phantom applications requiring homogeneous activity distribution, separation of ⁹⁰Y from the microspheres therefore appears to be necessary.

Although the separated ionic solution produced a substantially more homogeneous activity distribution, minor count differences were still observed among the VOIs representing N tissue (Table 1). These small variations are more likely attributable to the intrinsic characteristics of PET imaging, including image noise, positron range, limited spatial resolution, and VOI placement, rather than incomplete mixing of the radionuclide. In addition, because image acquisition and reconstruction were performed using a routine clinical PET/CT protocol, no recovery coefficient or partial volume correction was applied, ensuring that the results reflected standard clinical imaging conditions.

Study Limitations

This study has several limitations. First, only a single separation protocol employing a 0.22 µm sterile membrane filter was evaluated, and alternative separation techniques were not investigated. Second, only PET/CT imaging was assessed, whereas other quantitative imaging modalities, such as SPECT/CT, were not examined. Finally, the experiments were performed using a static phantom, which cannot fully reproduce the complex vascular trapping mechanisms and heterogeneous microsphere distribution encountered during clinical radioembolization. Future studies should evaluate alternative separation methods, different phantom geometries, and multimodal imaging approaches to provide a more comprehensive validation of this technique.

Conclusion

In conclusion, when used under static phantom conditions, ⁹⁰Y resin microspheres tend to sediment because of their particulate nature and higher density. To achieve a homogeneous distribution of ⁹⁰Y in any medium, appears to be necessary for phantom studies requiring homogeneous activity distribution. In this study, it was demonstrated that

ionic ⁹⁰Y radionuclide can be successfully obtained from ⁹⁰Y resin microspheres by filtration through a sterile 0.22 µm membrane filter (Merck Millipore).

Ethics

Ethics Committee Approval: Since it is not a live study, ethics committee approval is not required.

Informed Consent: N/A.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Author Contributions: Concept: Ö.D., E.K., Design: Ö.D., Data Collection or Processing: Ö.D., E.K., Analysis or Interpretation: Ö.D., E.K., Literature Search: Ö.D., E.K.; Writing: Ö.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial.

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Combined Maximum Tolerated Activity and Lesion-based Dosimetry for Personalized Radioiodine Therapy in Metastatic Differentiated Thyroid Carcinoma: An Early Institutional Experience

Metastatik Diferansiye Tiroid Karsinomunda Kişiselleştirilmiş Radyoiyot Tedavisi için Maksimum Tolere Edilen Aktivite ve Lezyon Bazlı Dozimetrinin Kombine Edilmesi: Kurumumuzun Erken Dönem Deneyimi

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Abstract

Objectives: Empirical fixed-activity radioiodine (RAI) therapy remains widely used in differentiated thyroid carcinoma (DTC), despite substantial inter-patient variability in iodine kinetics. Pre-therapeutic dosimetry offers a personalised approach by estimating radiation exposure to organs at risk as well as to tumour lesions. To describe our institutional experience with combined maximum tolerated activity (MTA) and lesion-based dosimetry in patients with metastatic or recurrent DTC, and to evaluate its impact on clinical decision-making.

Methods: A retrospective case series of six DTC patients undergoing pre-therapeutic Iodine-131 dosimetry over two years was recorded. Whole-body and blood-based dosimetry were used to calculate MTA, while lesion-based dosimetry was calculated via estimated absorbed lesion-based dose per administered activity (LDpA). Treatment decisions were made following multidisciplinary discussion.

Results: Five patients completed the dosimetric evaluation. In one patient with high tumour burden, MTA and LDpA provided complementary safety and efficacy data, although facility constraints had limited the final administered activity. In three patients with small-volume inoperable cervical nodal disease, LDpA was <5 Gy/GBq, predicting a limited therapeutic benefit thus preventing further ineffective RAI therapy administration. In another patient with osseous metastases, prior high cumulative RAI exposure as well as low LDpA indicated limited benefit in further high dose RAI therapy, highlighting the importance of early dosimetric assessment.

Conclusion: Personalised dosimetry with combined safety-based and lesion-based approach may enhance the therapeutic precision in patients with advanced DTC. However, careful patient selection is essential in maximising clinical utility.

Keywords: Dosimetry, metastatic differentiated thyroid carcinoma, MTA, lesion-based dosimetry

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Öz

Amaç: Ampirik sabit aktiviteli radyoaktif iyot (RAI) tedavisi, iyot kinetiğinde hastalar arası belirgin değişkenlik bulunmasına rağmen diferansiye tiroid karsinomunda (DTK) yaygın olarak kullanılmaya devam etmektedir. Tedavi öncesi dozimetri, risk altındaki organların yanı sıra tümör lezyonlarının maruz kalacağı radyasyon dozunu tahmin ederek kişiselleştirilmiş bir yaklaşım sunmaktadır. Bu çalışmanın amacı, metastatik veya rekürren DTK'li hastalarda maksimum tolere edilebilir aktivite (MTA) ile lezyon bazlı dozimetrenin birlikte kullanımına ilişkin kurum deneyimimizi sunmak ve bu yaklaşımın klinik karar verme süreci üzerindeki etkisini değerlendirmektir.

Yöntem: İki yıllık bir süre boyunca tedavi öncesi iyot-131 dozimetresi uygulanan altı DTK hastasının retrospektif olgu serisi değerlendirildi. MTA'nın hesaplanmasında tüm vücut ve kan bazlı dozimetri kullanılırken, lezyon bazlı dozimetri, uygulanan aktivite başına tahmini absorbe lezyon dozu (LDpA) üzerinden hesaplandı. Tedavi kararları multidisipliner değerlendirme sonrasında verildi.

Bulgular: Beş hasta dozimetri değerlendirmesini tamamladı. Yüksek tümör yüküne sahip bir hastada MTA ve LDpA, güvenlik ve etkinlik açısından birbirini tamamlayan veriler sağladı; ancak tesisin fiziksel kısıtlılıkları uygulanabilecek nihai aktiviteyi sınırladı. Küçük hacimli, opere edilemeyen servikal nodal hastalığı bulunan üç hastada LDpA <5 Gy/GBq olarak saptandı ve bunun sınırlı terapötik yarar öngördüğü değerlendirildi. Böylece, etkisiz olması beklenen ilave RAI tedavilerinin uygulanmasından kaçınıldı. Kemik metastazları bulunan başka bir hastada ise daha önce alınmış yüksek kümülatif RAI aktivitesi ve düşük LDpA değeri, ilave yüksek aktiviteli RAI tedavisinden elde edilecek yararın sınırlı olacağını gösterdi ve erken dönemde dozimetri değerlendirmesinin önemini ortaya koydu.

Sonuç: Güvenlilik temelli ve lezyon bazlı yaklaşımların birlikte kullanıldığı kişiselleştirilmiş dozimetri, ileri evre DTK'li hastalarda tedavinin hassasiyetini artırabilir. Bununla birlikte, klinik yararın en üst düzeye çıkarılabilmesi için uygun hasta seçimi büyük önem taşımaktadır.

Anahtar Kelimeler: Dozimetri, metastatik farklılaşmış tiroid karsinomu, MTA, lezyon bazlı dozimetri

Introduction

Thyroid cancer is the ninth most common malignancy worldwide, with approximately 586,000 new cases reported globally (1). Over recent decades, the incidence of thyroid cancer has risen substantially, increasing from 4.9 per 100,000 population in 1975 to 14.3 per 100,000 in 2015. This trend is largely attributed to earlier detection and improved diagnostic modalities, particularly due to the widespread use of high-resolution imaging (2). Thyroid cancer demonstrates a marked female predominance, with incidence rates approximately three times higher in women than in men, estimated at 10.1 per 100,000, and accounting for nearly 1 in every 20 cancers diagnosed among women worldwide (1). Established risk factors for thyroid cancer include exposure to ionising radiation, as well as excess body weight, increased height, hormonal influences, and certain environmental pollutants (1). The vast majority of thyroid malignancies with more than 90% are classified as differentiated thyroid carcinoma (DTC), encompassing papillary, follicular, and oncocytic (Hürthle cell) carcinoma (2).

The standard management of DTC consists of surgical resection, followed by radioiodine (RAI) therapy and thyroid stimulating hormone (TSH) suppression. In cases of RAI-refractory DTC, alternative treatment modalities such as external beam radiotherapy or systemic targeted therapies, including multikinase inhibitors may be considered (2). RAI therapy is administered with the intent of thyroid remnant ablation, adjuvant treatment, or for treatment of known residual or metastatic disease. In patients with DTC who present with known distant metastases at initial diagnosis, RAI therapy is routinely recommended following

total thyroidectomy. Two principal strategies for activity prescription are typically employed; most commonly practiced being empirical fixed-activity administration, with the latter being dosimetry-based therapy (2).

Despite its widely preferred strategy of therapy due to its ease of use and generally favourable outcomes, the RAI empirical fixed activity unfortunately does not account for inter-patient variability. Variability among patients in iodine biodistribution and clearance is influenced largely by multiple factors such as individual renal function, tumour burden, metastatic pattern and prior treatments (2). As a result, fixed-dose strategies may lead to under-treatment in patients with rapid iodine clearance or extensive disease, or conversely excessive radiation exposure in patients with prolonged whole-body retention. This variability is particularly relevant in patients with extensive metastatic disease or diffuse lung metastases, in whom high administered activities are associated with an increased risk of bone marrow suppression, radiation pneumonitis, and pulmonary fibrosis (2).

On the other hand, pre-therapeutic RAI dosimetry offers individualised administered activity by estimating patient-specific radiation exposure to critical organs and target tissues. This is performed through the calculation of iodine kinetics via serial measurements, selecting the administered activity that maximises therapeutic efficacy while maintaining exposure within established safety limits. Therefore, in this era of precision medicine, dosimetry has emerged as an important tool in the management of selected patients with DTC, particularly those with metastatic disease, unusual iodine kinetics, or elevated risk of treatment-related toxicity (2).

The pre-therapeutic RAI dosimetry can be broadly categorised into maximum tolerated activity (MTA) and lesion-based dosimetry. MTA as recommended by the European Association of Nuclear Medicine (EANM) are bound to the basic principle of dose-limiting organs (3). They rely on the administration of a tracer activity of iodine, followed by serial whole-body counting and blood sampling to model iodine kinetics and estimate radiation exposure to the bone marrow and lungs, the principal dose-limiting organs. This approach allows calculation of the highest safely administrable therapeutic activity while maintaining radiation exposure below established toxicity thresholds. Lesion-based dosimetry, in contrast, focuses on quantifying the absorbed dose delivered to metastatic or residual tumour tissue using serial planar imaging and single photon emission computed tomography/computed tomography (SPECT/CT)–time-based activity measurements. Although lesion dosimetry provides valuable insight into tumour dose–response relationships and may better predict therapeutic efficacy, its routine clinical application remains limited by methodological complexity, multiple time point imaging requirements, and the lack of standardised absorbed dose targets for tumour control. This study describes our institutional experience using combined MTA and lesion-based dosimetry in selected patients with metastatic or recurrent DTC and evaluates its clinical impact.

Materials and Methods

Study Design and Patient Selection

This retrospective case series included six patients with DTC, referred for pre-therapeutic Iodine-131 (I-131) dosimetry between 2023 and 2025. Patients were selected following multidisciplinary team discussion based on following indications:

Concern for organ-at-risk toxicity with high-risk of bone marrow suppression, as well as pulmonary and renal toxicity

High tumour burden including extensive metastasis or large tumour size

Inoperable recurrent disease

Prior high cumulative RAI exposure

Dosimetry Protocol

All patients received 5 mCi of I-131 after adequate patient preparation with either one month duration of thyroxine withdrawal or injection of the recombinant human TSH (rhTSH). Serial whole-body scans (WBS) and blood sampling were performed at 2, 4, 24, 48, and 120 hours

post-administration for MTA calculation. WBS and regional SPECT/CT imaging were obtained at 1, 4, 24, 48, and 120 hours post I-131 administration for lesion-based dosimetry. MTA was calculated based on established bone marrow dose limits (≤ 200 cGy) and whole-body retention for lung toxicity. Critical lung activity at 48 hours whole-body retention is based on the Benua criterion, calculated using OLINDA 1.1 with this formula:

$$ctivity(t)=A*\exp(-at)+B*\exp(-bt)+C*\exp(-ct)$$

(uptake % all time point)

LDpA was calculated using time–activity curves as well as from lesion-based dosimetry using the HERMES software, which was derived from serial imaging (Table 1). Details of the HERMES software were as below:

Hermes Medical Solutions, Stockholm, Sweden: HybridRecon-Oncology 3.2.0

Fitting model: Mono-exponential, bi-exponential (for voxel–trapezoidal)

Algorithm: Phantom-based (OLINDA /EX 1.1) ORNL adult phantom

Assumptions: Physical half-life correction

There is no uncertainty calculation for the LDpA value in our study. However, the LDpA value was estimated using organ-based dosimetry–Medical Internal Radiation Dose (MIRD), following Walter Jentzen calculation:

Projected ^{131}I residence time (RC-corrected)

$$\frac{LDpA}{\text{Gy/GBq}} = 1.573 \cdot \frac{(\tau_L/\text{min})}{(m/\text{g})} \cdot (1 + 0.136 \cdot \sqrt[3]{m/\text{g}})$$

Lesion mass (using common tissue densities)

Comparison was also made with voxel-based dosimetry using Hermes Voxel Dosimetry.

This retrospective case series has been submitted to the National Medical Research Register (Advancing Medical Research in Malaysia) with the research ID RSCH 1D-26-01243-NC0 for ethical approval on 26 February 2026.

Results

Five patients completed dosimetry protocol. One patient did not complete the protocol due to an intercurrent event.

Patient 1 : High Tumour Burden Case

A 65-year-old gentleman had initially presented with pathological right humeral fracture, and was treated with surgical plating and biopsy. The histopathology of the right humerus biopsy was confirmed to be metastatic follicular

thyroid carcinoma, which he subsequently underwent total thyroidectomy. Histopathology of the thyroid tissue was proven to be widely invasive follicular thyroid carcinoma. Magnetic resonance imaging of the spine demonstrated expansile bone lesions with soft tissue components involving T9 and L4 vertebrae, suggestive of bone metastasis. He then received RAI twice (Figure 1), with a cumulative dose of 300 mCi I-131. WBS post second RAI demonstrated multiple skeletal metastases involving the left scapula, distal right humerus, vertebrae (T9 and L4) as well as proximal right femur. With the persistently high suppressed serum thyroglobulin [2088ng/mL ^{18}F -fluorodeoxyglucose positron emission tomography/CT (^{18}F -FDG PET/CT)] was arranged, revealing ^{18}F -FDG-avid skeletal metastases at the left scapula, vertebrae and pubic bone. Correlating both images, there were presence of mixed iodine- and ^{18}F -FDG-avid metastasis at multiple bones with predominant iodine-avidity.

We proceeded with the calculation of MTA and LDpA targeting the T9 and L4 vertebrae lesions with 5 mCi I-131 after two doses of rhTSH injection. Subsequently, the patient received his third RAI therapy with 300 mCi I-131 (total cumulative dose of 600 mCi I-131) under rhTSH stimulation and steroid cover, which was then tapered down post therapy. Post treatment whole body scan

showed stable I-131 skeletal metastasis in the left scapula, distal right humerus, vertebrae (T9 and L4) as well as proximal right femur, some with lesser intensity of uptake. Repeated ^{18}F -FDG PET/CT done due to persistently high serum thyroglobulin levels showed similar ^{18}F -FDG-avid skeletal metastasis in the left scapula, vertebrae and pubic bone. He was then referred to the oncologist as he was considered as RAI refractory disease, and was started on T. Lenvatinib 14mg OD. Suppressed serum thyroglobulin levels were monitored and showed good response to Lenvatinib, reducing significantly from 36851ng/mL to 1172ng/mL. ^{18}F -FDG PET/CT done a year after the RAI and Lenvatinib initiation showed interval reduction in ^{18}F -FDG-avid skeletal metastasis in the spine of left scapula, vertebral body and left pubic ramus with latest suppressed serum thyroglobulin of 223.00 ng/mL.

Patient 2: Small-volume Inoperable Cervical Disease

A 76-year-old lady with a history of undergoing thyroidectomy in 2003 with no documented histopathology had presented again in 2019 with a complaint of right sided neck swelling. She then underwent right hemithyroidectomy, and the histopathology was consistent with widely invasive follicular carcinoma with extrathyroidal extension. Two years later, she developed recurrent neck swelling and underwent a tumour debulking surgery.

Table 1. Table summary of MTA and LDpA of patients

Patient	MTA			LDpA		
	48-h retention value (%)	Bone marrow toxicity (Gy/GBq)	MTA (mCi)	Calculated LDpA (Gy/GBq)	Estimated activity (mCi)	Estimated absorbed dose (Gy)
Patient 1	4.14	0.0760	711	L1 (T9): 9.18	500	169.90
					400	135.92
					300	101.94
				L2 (L4): 6.10	500	112.86
					400	90.28
					300	67.71
Patient 2	3.17	0.1185	456	1.17	500	21.64
					400	17.32
					300	12.99
Patient 3	5.44	0.0942	574	0.19	500	7.21
					400	5.77
					300	4.33
Patient 4	8.4	0.0750	721	0.38	400	5.59
Patient 5	2.31	0.0526	1028	0.19	500	3.59
					400	2.87
					300	2.15

MTA: Maximum tolerated activity, LDpA: Lesion dose per administered activity

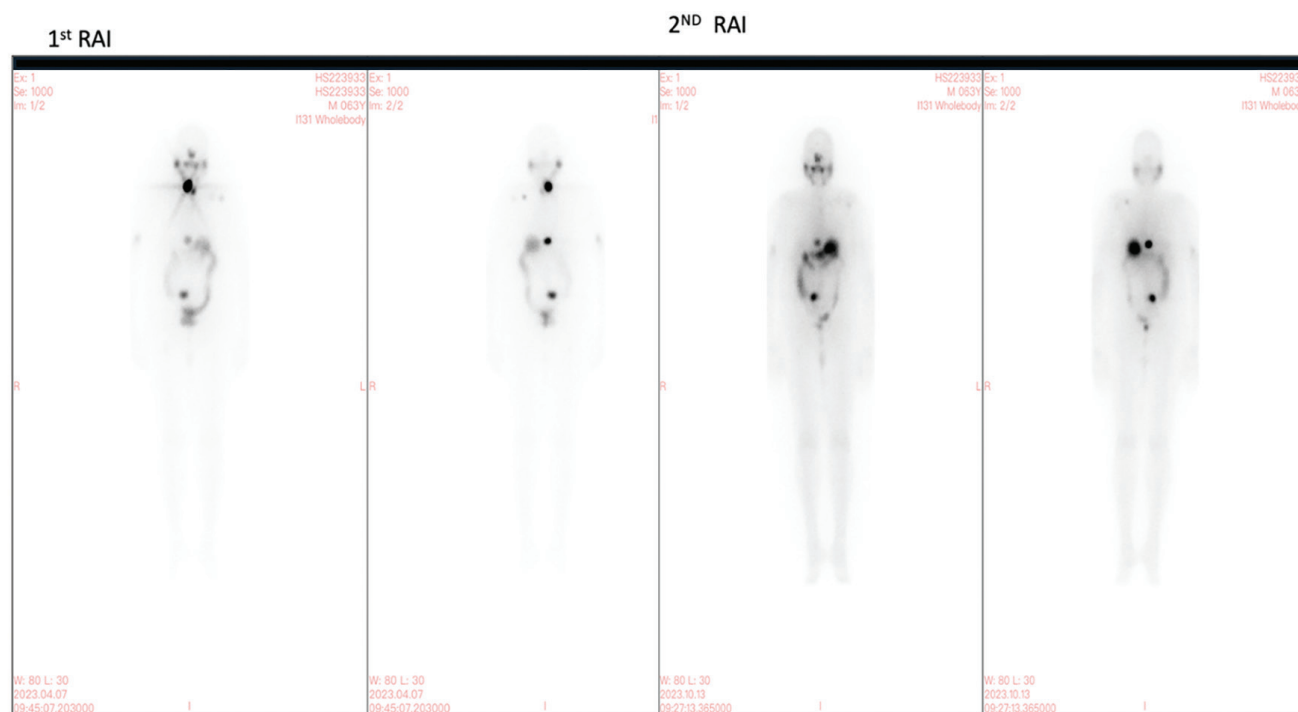


Figure 1. Serial I-WBS of patient 1 who received two times of RAI. I-WBS post second ablation demonstrated multiple skeletal metastases involving the left scapula, distal right humerus, vertebrae (T9 and L4) as well as proximal right femur
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

The histopathology showed recurrent follicular thyroid carcinoma with presence of right internal jugular vein tumour thrombus. The stimulated serum thyroglobulin level was more than 5000ng/mL, thus ^{18}F -FDG PET/CT was arranged, demonstrating ^{18}F -FDG-avid mass in the right thyroid bed measuring up to 4.4cm (maximum standardized uptake value 17.4). This patient received 6 courses of RAI treatment over a period of 4 years (cumulative dosage received was 870 mCi of I-131). During this period, she also underwent her fourth surgical intervention, which was debulking of tumour procedure. Multiple WBS post therapy showed a persistent solitary iodine-avid disease at the lower neck region with consistently raised stimulated thyroglobulin reading of 520ng/mL (Figure 2). Correlating both images, there was a solitary mixed iodine- and ^{18}F -FDG-avid disease at the soft tissue lesion in the right thyroid bed.

We proceeded with calculation of MTA and LDpA with of 5 mCi of I-131 after two doses of rhTSH injection. WBS showed focal increased tracer uptake at the neck corresponding to soft tissue lesion at the right thyroid bed measuring 1.3 x 0.9 cm. LDpA calculation showed extremely low lesion absorbed dose (LDpA 1.17 Gy/GBq). Based on this, it was inferred that the patient would not

benefit from further RAI treatment, and the patient opted for surveillance and TSH suppression therapy.

She was originally on active surveillance with only TSH suppression therapy, and first surveillance ^{18}F -FDG PET/CT done at 1 year interval showed stable disease at the neck. However, serial serum thyroglobulin monitoring showed persistently increasing levels up to 1720ng/mL after 2 years duration. Repeated ^{18}F -FDG PET/CT at 2 years after the last RAI treatment dose demonstrated progressive ^{18}F -FDG-avid disease in the neck with the presence of new ^{18}F -FDG-avid nodal and lung metastases. She subsequently received a trial course of RAI therapy with 150 mCi of I-131, which demonstrated iodine-avid disease in the neck and nodal regions, along with newly identified metastatic involvement of the lungs, liver, and bones. In view of the documented disease progression and retained iodine avidity at the new disease sites, she was scheduled for another RAI ablative therapy.

Patient 3: Small-volume Inoperable Cervical Disease

A 37-year-old lady initially presented with neck swelling for 6 years in duration, which was gradually increasing in size. She underwent total thyroidectomy on 16/6/2022 which showed papillary thyroid carcinoma with pretracheal

nodal metastasis. She received RAI therapy three times between 2021 and 2024, with a total cumulative dose of 340 mCi I-131. The latest post therapy WBS showed similar focal increased uptake in the superior mediastinum, corresponding to the subcentimeter left upper paratracheal node (Figure 3). Stimulated serum thyroglobulin reading was 24.8ng/mL.

We proceeded with calculation of MTA and LDpA calculation after 5 mCi of I-131 on 16/12/2024 under thyroxine withdrawal. WBS done 48 hours post-administration of I-131 showed only faint uptake in the left lower neck region. Lesion-based dosimetry calculation revealed a very low absorbed dose in this lesion (LDpA 0.39 Gy/GBq). In view of the low LDpA, we explained to the patient that there was no benefit in further RAI treatment for such a small volume disease, and the patient was then placed on TSH suppression therapy.

Patient 4: Small-volume Inoperable Cervical Disease With Fertility Issue

38-year-old male, with a history of left sided neck swelling in 2019. He was investigated for suspicious thyroid nodules and eventually underwent total thyroidectomy with left modified radical neck dissection. Histopathology confirmed the diagnosis of papillary thyroid carcinoma with

lymph node metastasis. He has received a total of 7 RAI treatments between the years of 2019 and 2024, totalling 870 mCi I-131. He also underwent right modified radical neck dissection in between RAI therapy in 2022. WBS post 7th RAI treatment demonstrated persistent uptake in the lower neck corresponding to pretracheal lymph node measuring 1.0x1.4cm (Figure 4). Stimulated serum thyroglobulin showed a reduction in trend from the initial figure of 105.4 ng/mL to the latest reading of 11.0 ng/mL.

We proceeded with calculation of MTA and lesion dose per administered activity calculation using 5 mCi of I-131 on 17/3/2025 under thyroxine withdrawal, which showed very poor iodine retention and lesion absorbed dose in the lower neck lesion (LDpA 0.38 Gy/GBq). Subsequently, it was concluded that patient would likely have no significant benefit from continuing with further RAI treatment. This enabled the patient who had been struggling with fertility issues to opt for surveillance and TSH suppression therapy, and to proceed for active fertility assessment and treatment.

Patient 5: Osseous Metastases With High Prior Cumulative RAI

A 41-year-old lady with underlying history of right hemithyroidectomy for multinodular goitre, presented

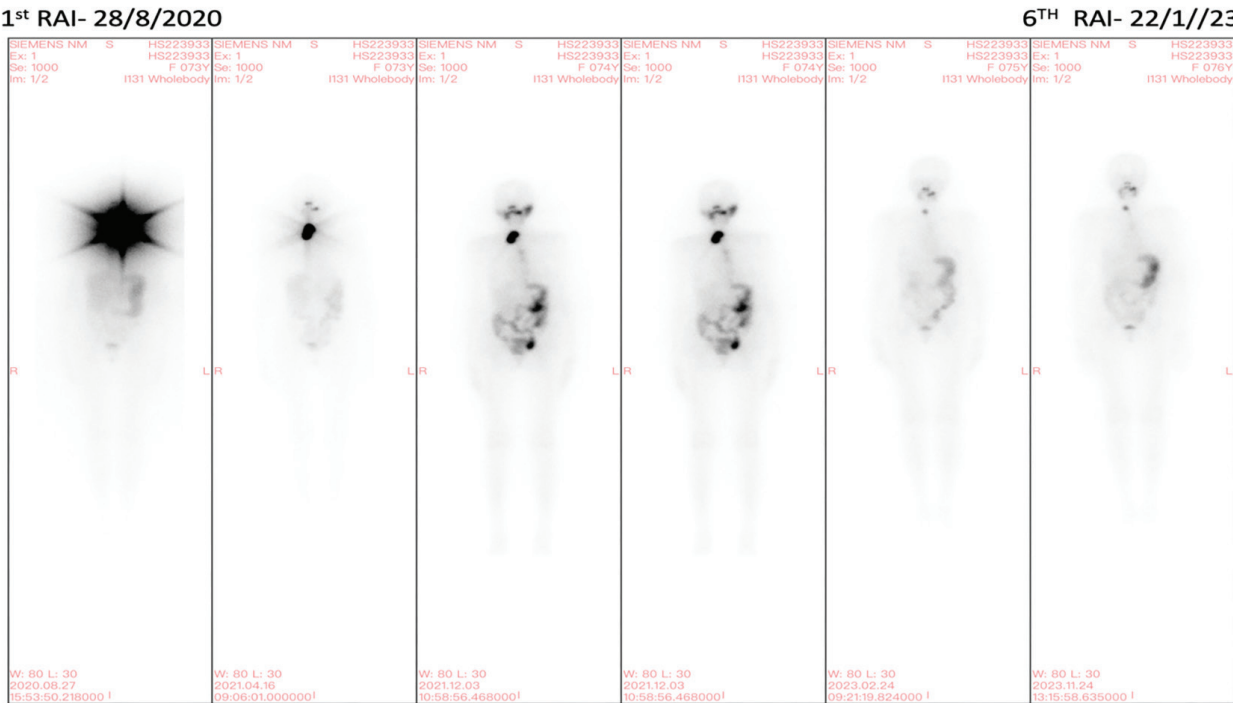


Figure 2. Serial I-WBS of patient 2 who received six times of RAI. I-WBS post six ablation demonstrated persistent solitary iodine-avid disease at the lower neck region
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

with incidental pulmonary nodules on CT during follow-up. Biopsy of the lung nodules was consistent with metastatic follicular carcinoma. Left hemithyroidectomy was performed and the histopathology was consistent with the follicular variant of micropapillary thyroid carcinoma. First few post therapy WBS showed iodine avid disease in the cervical nodes, lungs and bone. She underwent a total of 8 RAI treatments over seven years (cumulative dose 1330 mCi), with the latest WBS post 150 mCi of I-131 showing persistent tracer uptake anterior to the hyoid bone, at L1

vertebra and left proximal femur lytic lesions (Figure 5). Subsequent ^{18}F -FDG PET-CT showed non- ^{18}F -FDG avid lytic bone lesions in the vertebra, right acetabulum and left femur.

We proceeded with calculation of MTA and LDpA with 5 mCi of I-131 after two doses of rhTSH injection. WBS performed showed mild iodine avid metastatic disease at the left femur. LDpA calculation showed significantly low lesion absorbed dose at left proximal femur lesion (LDpA 0.19Gy/GBq). Since monitoring of stimulated serum

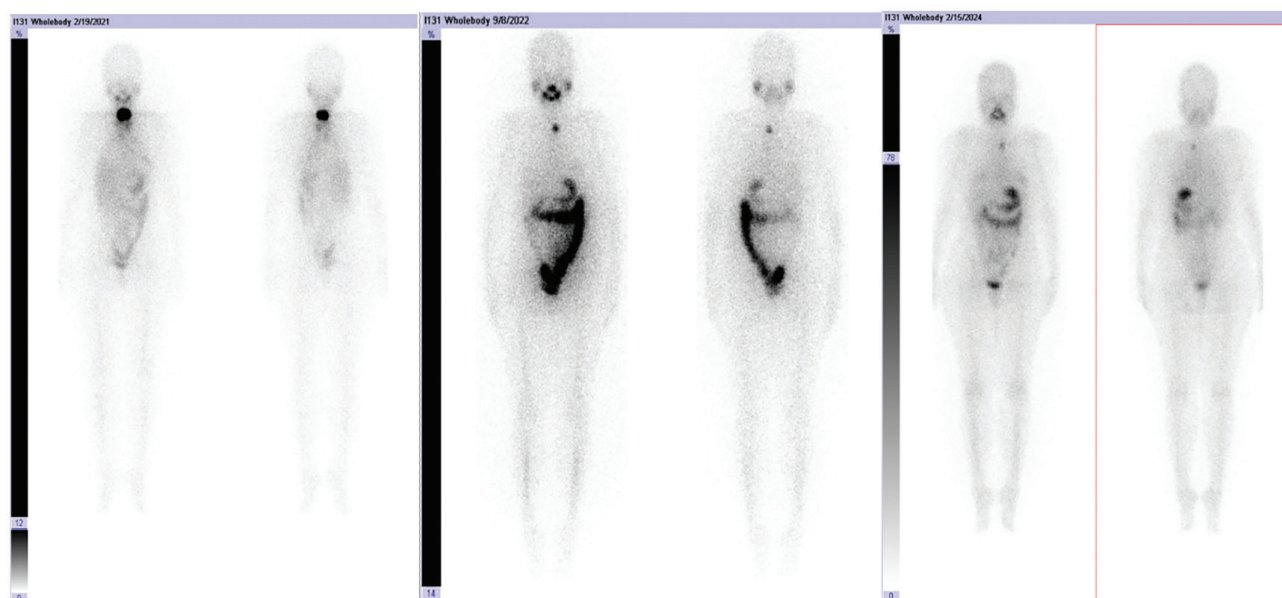


Figure 3. Serial I-WBS of patient 3 who received total of three ablation. I-WBS post ablation demonstrated focal increased uptake in the superior mediastinum, corresponding to left upper paratracheal node
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

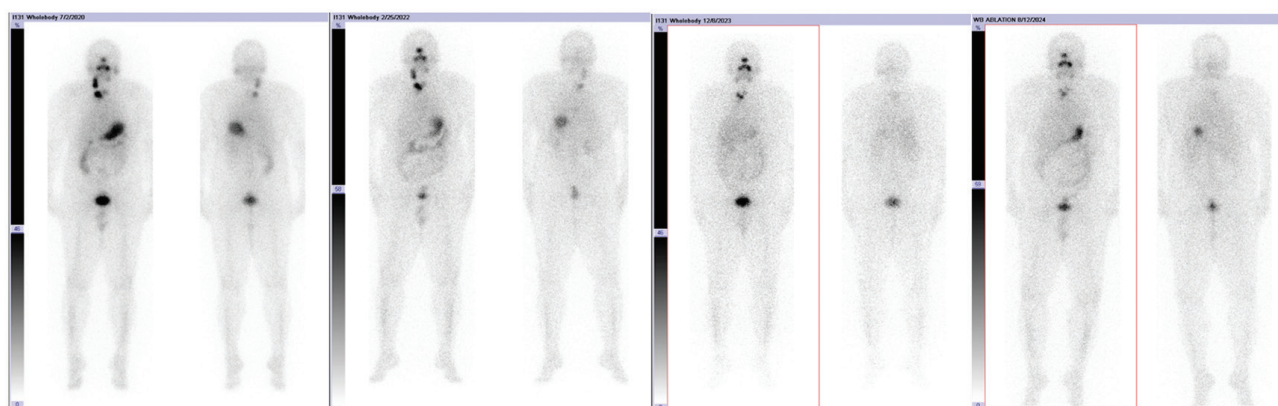


Figure 4. Serial I-WBS of patient 4 who received total of eight ablation (images above are the last 4 I-WBS post ablation). I-WBS post ablation demonstrated persistent uptake in the lower neck corresponds to pretracheal lymph node measuring 1.0 x 1.4 cm
I-WBS: Iodine whole-body scan

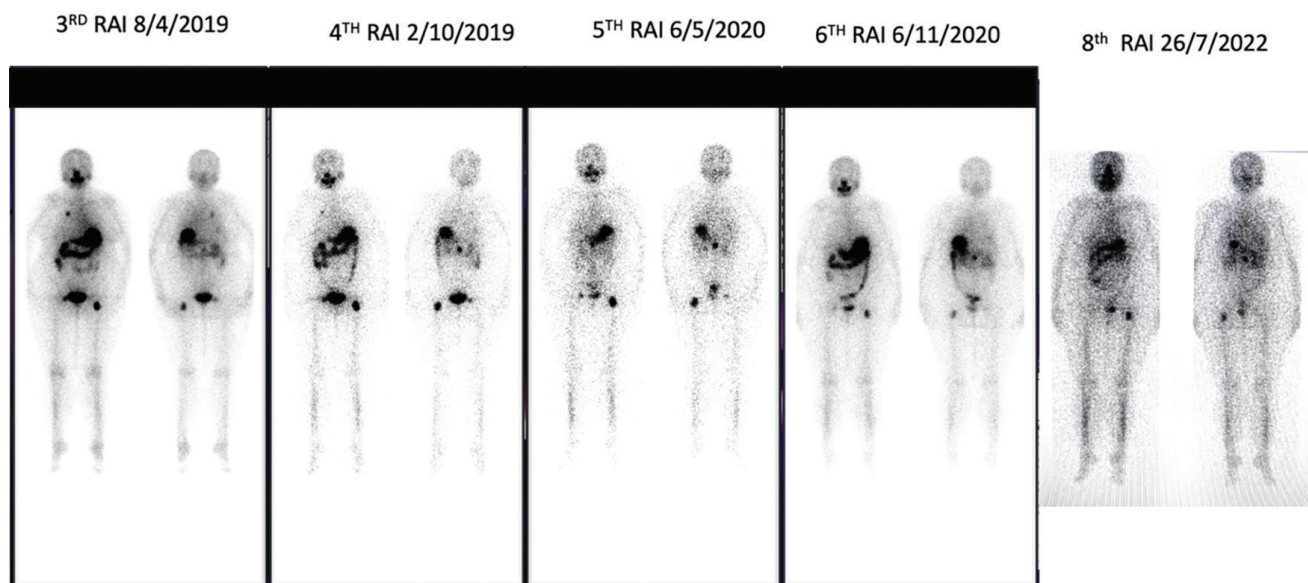


Figure 5. Serial I-WBS of patient 5 who received eight RAI. I-WBS post eight ablation demonstrated persistent tracer uptake anterior to the hyoid bone, at L1 vertebra and left proximal femur lytic lesions
RAI: Radioactive iodine, I-WBS: Iodine whole-body scan

thyroglobulin had been stable over the past few years, with the latest serum thyroglobulin reading of 31.2 ng/mL and minimal benefit for further RAI treatments as evidenced by low iodine retention time, the patient opted for TSH suppression therapy and close surveillance with 6 monthly serum thyroglobulin and anti-thyroglobulin monitoring.

Discussion

A total of six patients with DTC underwent pre-therapeutic dosimetry over a two-year period at our center. One patient was unable to complete the procedure due to a low-impact fall at home during the study period, resulting in abandonment of the dosimetric assessment. The remaining five patients successfully completed the protocol. For these patients, both the MTA method and the LDpA calculations were performed.

The primary objective of pre-therapeutic dosimetry is to administer an adequate radiation dose to the target lesions to achieve therapeutic efficacy (curative, disease stabilisation, or palliative intent), while minimising radiation exposure to critical organs in order to reduce the risk of acute and long-term toxicities. In our institution, patient selection for dosimetric evaluation was determined following multidisciplinary team discussion, taking into

consideration patient's disease burden, concern for toxicity to vital organs, and also patient's cumulative RAI treatments and exposure, especially for those with repeated RAI therapy.

Nagarajah et al. (4) demonstrated a correlation between absorbed dose thresholds and complete response rates in metastatic lesions and thyroid remnants. The authors emphasised that different metastatic sites require different absorbed dose targets to optimise therapeutic response. Specifically, bone metastases require an absorbed dose exceeding 85 Gy to achieve approximately 46% response rates, whereas substantially higher absorbed doses (350-650 Gy) are associated with response rates of 70-80% (4). Our first patient presented with high tumour burden with multiple osseous metastases, which were both ^{18}F -FDG and iodine avid. Based on whole-body and blood-based dosimetry, the calculated MTA, without exceeding bone marrow and pulmonary safety thresholds, was 711 mCi of I-131. However, LDpA calculations demonstrated that an administered activity of approximately 400 mCi would only be able to achieve a target absorbed dose of approximately 135 Gy for both T9 and L4 vertebral metastases. This information allows the treating physician to understand that curative intent of treatment may not be attainable as

less than 50% of patients with bone metastasis achieve remission with estimated absorbed doses of 85 Gy (5). However, due to logistical and facility limitations during treatment of our first patient, the maximum administrable activity was restricted to 300 mCi and he was ultimately given the maximum dose at that time which was below the calculated MTA (711 mCi) and below the estimated activity required to achieve optimal absorbed dose for bone metastases. In this patient, although we were able to give a higher than empirical dose of RAI therapy (300 mCi), the LDpA enabled us to adjust our expectations from curative to palliative intent as complete remission might not be achievable in this patient. An early referral to the oncology department was made, and this patient has been doing well after the initiation of systemic therapy (Lenvatinib) which is evidenced by pain reduction and reducing serum Thyroglobulin levels.

The case above highlights the difference between organ-at-risk-limited activity (MTA approach) and LDpA, which is personalised to each individual. These findings also demonstrate the importance of individualised lesion-based dosimetry in patients with high tumour burden, particularly in skeletal metastases where higher absorbed doses may be necessary for optimal therapeutic outcomes. Nagarajah et al. (4) also reported that a target absorbed dose of 85 Gy is associated with treatment response rates of approximately 75% in lymph node metastases and 95% in pulmonary metastases. In contrast, thyroid remnants require substantially higher absorbed doses, exceeding 300 Gy, to achieve response rates of approximately 91%. These findings further support the concept that absorbed dose thresholds vary according to lesion type and anatomical location.

Our second and third patients both who had undergone multiple rounds of RAI treatment initially underwent pre-therapeutic dosimetry with curative intent. Both patients demonstrated persistent RAI uptake in inoperable soft tissue lesions within the neck. Despite visible iodine avidity on previous high dose post therapy whole body scans, lesion-based dosimetry using I-131 of 5 mCi revealed low absorbed dose per administered activity (<5 Gy/GBq) in these subcentimeter lesions, indicating limited therapeutic efficacy from further RAI administration. Jentzen et al. (5), in earlier studies, categorised metastatic lesions into three groups according to LDpA, correlating with probability of therapeutic response. Lesions were stratified into low (<5 Gy/GBq), intermediate (5-10 Gy/GBq), and high (>10 Gy/

GBq) LDpA groups (5). Clinically meaningful response rates were significantly higher when LDpA exceeded 5 Gy/GBq (5). Based on this classification, both the two patient's lesions fell under the low LDpA category, suggesting a low likelihood of achieving curative benefit with additional I-131 therapy. These findings highlight the clinical value of lesion-based dosimetry in identifying patients unlikely to benefit from further RAI treatment, thereby facilitating earlier transition to alternative therapeutic strategies.

Similar to the second and third patients, our fourth patient presented with persistent solitary RAI uptake in the lower neck region corresponding to inoperable cervical nodal metastasis. His previous RAI treatments have demonstrated a concurrent reduction in stimulated serum Thyroglobulin levels, indicating partial success in treatment. However, due to the prolonged and recurrent RAI treatments, he had delayed his family planning despite being married for more than five years. He was verbally informed that there was suspicion of oligospermia. Following multidisciplinary team discussion, lesion-based dosimetry was performed with curative intent. However, the calculated LDpA was markedly low (<5 Gy/GBq), indicating a low probability of achieving meaningful therapeutic response with additional RAI therapy. Consequently, a watchful waiting strategy was adopted with serial serum Thyroglobulin level monitoring. In this patient, findings of the lesion based dosimetry enabled the patient to make an informed decision whereby the patient could make the choice not for further RAI rience of the second, third, and fourth patients, we observed that lesion size appears to play a significant role in dosimetric outcomes. Subcentimeter or small-volume lesions consistently demonstrated low LDpA values, suggesting limited radiation delivery despite visible iodine avidity. This observation highlights an important clinical consideration - that RAI uptake alone does not necessarily translate into sufficient absorbed dose for therapeutic efficacy. From a technical perspective, small-volume disease also presents additional challenges. Accurate tumour delineation during image-based dosimetry is more challenging as it is susceptible to partial volume effects and contouring inaccuracies, potentially leading to under or overestimation of lesion size and inaccuracies in absorbed dose calculation. Even so, there could be underestimation of calculations of LDpA due to the small lesion size, leading to markedly reduced estimated absorbed dose. Partial volume effects in LDpA estimation can be corrected by performing Recovery Coefficients. However, due to the unavailability of a suitable phantom, recovery coefficient measurements

could not be performed at our center during this study period. Consequently, partial-volume correction using recovery coefficients was not incorporated into the current LDpA estimations. As part of future work, phantom-based recovery coefficient determination will be implemented to improve the accuracy and reliability of LDpA estimates in subsequent patients. We also believe that close collaboration between the nuclear medicine physician and medical physicist is essential to ensure precise tumour mapping which will in turn translate into reliable dosimetric assessment.

Our fifth patient presented with three osseous metastases that were delineable on CT imaging. All lesions demonstrated RAI avidity on post ablation WBS without corresponding uptake on ^{18}F -FDG PET/CT, suggesting well-differentiated disease biology and a favorable prognosis for RAI-based therapy. However, as the patient had already received a high cumulative administered activity of RAI well as increased risk of secondary malignancy. Lesion-based dosimetry demonstrated only mild tracer uptake in the left femoral lesion with low LDpA, indicating insufficient radiation delivery to achieve therapeutic benefit. Based on these findings, further RAI therapy was deemed unlikely to provide meaningful clinical response. This case proposes the importance of early dosimetric assessment in patients with potentially curable metastatic disease. Timely implementation of lesion-based dosimetry may help optimise therapeutic strategy before cumulative RAI exposure limits treatment options, thereby maximising the likelihood of achieving adequate absorbed dose to target lesions while minimising unnecessary radiation burden, in which higher cumulative RAI exposure dosage may lead to increased risk of leukaemia or secondary malignancies in short and long-terms (8).

Our dosimetry-based approach is consistent with contemporary guidance from the American Thyroid Association (ATA) and the EANM, which recognises the role of individualised RAI activity selection in selected patients with differentiated thyroid cancer. The ATA guidelines suggests the use of empiric fixed-activity regimens for remnant ablation and many intermediate-risk cases, and proposes the use of whole-body and blood-based dosimetry in metastatic disease to limit bone marrow exposure (≤ 200 cGy) and to avoid excessive whole-body retention (2). Similarly, EANM guidance emphasises the value of personalised absorbed dose estimation in advanced or recurrent disease (3). Earlier study in dosimetry suggested the application of five-point protocol, which is time-

consuming and complex thus making it less favourable among physicians. Although this 5-point protocol is certainly the most accurate, few studies have suggested the use of adapted 24-96 hour approach (5). This two point protocol is recommended when clinical workload is particularly heavy, to reduce logistical and time demands for patients and caregivers as well as the clinical costs (5). A more recent study has validated the use of a simplified dosimetry model to determine the %48-hour fractional whole body retention thus the MTA (6). This simplified dosimetry allows us to calculate the maximum dose activity for the marrow in a more practical method, although it is currently not being advocated as a replacement for full patient-specific dosimetry. Rather, its use is proposed when a more comprehensive dosimetry is not feasible, which this approach could be used to guide the therapist in selecting the I-131 prescribed activity in treating patients with metastatic DTC (7).

Although worldwide I-124 PET/CT is preferred as it is considered superior for thyroid cancer dosimetry due to its higher spatial resolution and improved quantitative accuracy, I-131 was selected as the radiotracer in our centre because of its greater availability and cost-effectiveness. Even though previous studies have demonstrated that I-124 PET provides more accurate quantification for dosimetric purposes (8), emerging evidence has supported the feasibility of I-131 as a diagnostic tracer for pre-therapeutic dosimetry in differentiated thyroid cancer (4). All of our patients had the five time points serial whole body and blood count obtained at 2, 4, 24, 48, and 120 hours following administration of 5 mCi of I-131. In addition, WBS with regional SPECT/CT imaging were performed at 1, 4, 24, 48, and 120 hours post-administration to enable lesion-based dosimetric analysis.

Apart from this, the potential thyroid stunning effect associated with the administration of 5 mCi I-131 during MTA assessment should also be considered. Several studies have reported that diagnostic doses of 5 mCi I-131 may induce clinically significant thyroid stunning, particularly during the early post-diagnostic period, thereby reducing subsequent therapeutic RAI uptake. These reports have suggested a waiting interval of approximately 2-3 months before definitive RAI therapy to allow recovery of iodine-trapping function (9). In consideration of this potential phenomenon, our department elected to schedule RAI ablation therapy approximately three months after MTA calculation to permit gradual recovery of iodine-trapping ability and optimise therapeutic uptake.

This case series demonstrates that although RAI dosimetry is time consuming and requires close collaboration among nuclear medicine physicians, medical physicists, radiopharmacists and technologists, it provides meaningful clinical value in the management of DTC patients. Individualised dosimetric assessment influenced therapeutic decision-making in our cohort by identifying patients likely to benefit from RAI therapy, while sparing others from ineffective and potentially burdensome treatment. Careful patient selection remains crucial to maximise the clinical utility of dosimetry. In our experience, patients with high tumour burden, pulmonary metastases, renal impairment, or high prior cumulative RAI exposure derive the greatest potential benefit from personalised activity planning. Conversely, routine application in low-risk or small-volume disease may not yield significant therapeutic advantage. Overall, personalised RAI dosimetry represents a precision-medicine approach that may optimise therapeutic efficacy while minimising unnecessary radiation exposure. With continued refinement of technique and appropriate patient selection, dosimetry has the potential to play an increasingly important role in the individualised management of advanced thyroid cancer.

Study Limitations

This study is limited by small sample size, retrospective design, heterogeneity in disease presentation, and limited long-term outcome. Larger prospective studies are recommended to validate the LDpA thresholds and to define the standardised tumour absorbed dose targets.

Another limitation of this study is the absence of formal uncertainty quantification for the estimated LDpA values. Although dosimetric calculations were performed using the MIRD organ-based methodology, uncertainties associated with image quantification, ROI delineation, system calibration, and time–activity curve fitting were not propagated into the final dose estimates. Furthermore, partial volume correction was not applied, as recovery coefficients could not be determined due to the unavailability of a suitable calibration phantom at our institution during the study period. As a result, the reported LDpA values may be affected by residual quantification errors, particularly for small lesions. Nevertheless, comparison with voxel-based dosimetry using Hermes Voxel Dosimetry demonstrated comparable dose estimates, providing supportive evidence for the robustness of the findings. Future studies incorporating phantom-derived recovery coefficients and comprehensive uncertainty analyses are warranted to further improve the accuracy and reliability of LDpA estimation.

Conclusion

Pre-therapeutic dosimetry, with combined application of MTA and lesion-based dosimetry in selected patients with advanced DTC strongly influenced the clinical decision making process, leading to change in clinical strategy in many of the cases. Careful patient selection is vital in ensuring maximum benefit for the patients undergoing personalised dosimetry.

Ethics

Ethics Committee Approval: This retrospective case series has been submitted to the National Medical Research Register (Advancing Medical Research in Malaysia) with the research ID RSCH 1D-26-01243-NC0 for ethical approval.

Informed Consent: Six patients with DTC underwent pre-therapeutic I-131 dosimetry between 2023 and 2025 after multidisciplinary team selection.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A.R., H.M.,J.L., A.M., S.Z.A.H., H.H., Concept: N.A.R., H.M.,J.L., S.Z.A.H., Design: N.A.R., S.Z.A.H., Data Collection or Processing: N.A.R., A.M., H.H., Analysis or Interpretation: N.A.R., A.M., H.H., Literature Search: N.A.R., Writing: N.A.R., H.M.,J.L., A.M.

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Prognostic Value of Primary Tumor and Immune Organ Metabolic Parameters Derived from Pretreatment ¹⁸F-FDG PET/CT in Gastric Adenocarcinoma: A Retrospective Survival Analysis

Mide Adenokarsinomunda Tedavi Öncesi ¹⁸F-FDG PET/BT ile Elde Edilen Primer Tümör ve İmmün Organ Metabolik Parametrelerinin Prognostik Değeri: Retrospektif Sağkalım Analizi

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Abstract

Objective: To investigate the association of primary tumor volume-based parameters and immune organ (liver, spleen, bone marrow) metabolic parameters and their derived ratios [spleen-to-liver ratio (SLR), bone marrow-to-liver ratio (BLR), spleen-to-bone marrow ratio (SBR)], measured on pretreatment ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT), with overall survival in gastric adenocarcinoma.

Methods: 127 patients with histopathologically confirmed gastric adenocarcinoma who underwent pretreatment ¹⁸F-FDG PET/CT were retrospectively evaluated. Maximum standardized uptake value, mean standardized uptake value, metabolic tumor volume, total lesion glycolysis (TLG) and immune-organ SUVs were measured and the ratios calculated. Survival analyses used the Kaplan-Meier method, log-rank test, and Cox regression.

Results: There were 91 death events (71.7%); the Kaplan-Meier median overall survival was 16.56 months, with 1-, 3-, and 5-year survival rates of 58.3%, 33.1%, and 28.1%, respectively. No significant independent association with overall survival was demonstrated for any of the primary-tumor or immune-organ PET/CT parameters; the SBR was lower in deceased patients ($p=0.041$) and showed a non-significant protective trend at the univariate level [hazard ratio (HR)=0.802 per 1 standard deviation (SD); 95% confidence interval (CI) 0.621–1.038; $p=0.093$], which was not supported by cut-off-based or multivariable analyses. In the primary multivariable model, distant metastasis independently increased the hazard of death (HR=1.798; 95% CI 1.187–2.723; $p=0.006$), whereas TLG SLR, and BLR showed no independent significance. In the stage-adjusted model, advanced stage remained independently associated with OS (HR=4.403; $p=0.001$).

Conclusion: In this gastric adenocarcinoma cohort with a high proportion of advanced-stage disease, no independent association with overall survival was demonstrated for any of the evaluated tumor- or immune-organ PET/CT parameters; established clinicopathological factors showed stronger prognostic associations than the PET-derived parameters. The prognostic role of immune organ metabolism in gastric cancer should be evaluated in large prospective studies.

Keywords: Stomach neoplasms, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography prognosis, spleen, bone marrow

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Öz

Amaç: Mide adenokarsinomlu hastalarda tedavi öncesi ^{18}F -florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (^{18}F -FDG PET/BT) ile ölçülen primer tümör volüm-tabanlı parametrelerinin (maksimum standartlaştırılmış tutulum değeri, ortalama standartlaştırılmış tutulum değeri, metabolik tümör hacmi, total lezyon glikolizi (TLG) ve immün organ (karaciğer, dalak, kemik iliği) metabolik parametreleri ile bunlardan türetilen oranların (dalak/karaciğer [SLR], kemik iliği/karaciğer [BLR]) genel sağkalım (GS) ile ilişkisinin araştırılması amaçlandı.

Yöntem: Histopatolojik olarak doğrulanmış gastrik adenokarsinomu bulunan ve tedavi öncesi ^{18}F -FDG PET/BT yapılan 127 hasta retrospektif olarak değerlendirildi. Maksimum standartlaştırılmış tutulum değeri, ortalama standartlaştırılmış tutulum değeri, metabolik tümör hacmi, total lezyon glikolizi (TLG) ve immün organların standartlaştırılmış tutulum değerleri ölçüldü ve ilgili oranlar hesaplandı. Sağkalım analizlerinde Kaplan–Meier yöntemi, log-rank testi ve Cox regresyonu kullanıldı.

Bulgular: Toplam 91 ölüm (%71,7) gerçekleşti. Kaplan–Meier yöntemiyle hesaplanan medyan genel sağkalım 16,56 ay olup 1, 3 ve 5 yıllık sağkalım oranları sırasıyla %58,3, %33,1 ve %28,1 idi. Primer tümör veya immün organ PET/BT parametrelerinin hiçbirinin genel sağkalımla anlamlı bağımsız ilişkisi gösterilemedi. SBR, yaşamını yitiren hastalarda daha düşüktü ($p=0,041$) ve tek değişkenli analizde istatistiksel olarak anlamlı olmayan koruyucu yönde bir eğilim gösterdi [bir standart sapma (SD) artış başına hazard oranı (HR)=0,802; %95 güven aralığı (GA): 0,621–1,038; $p=0,093$]. Ancak bu bulgu, eşik değere dayalı veya çok değişkenli analizlerle desteklenmedi. Birincil çok değişkenli modelde uzak metastaz, ölüm hazardını bağımsız olarak artırırken (HR=1,798; %95 GA: 1,187–2,723; $p=0,006$), TLG, SLR ve BLR bağımsız istatistiksel anlamlılık göstermedi. Evreye göre düzeltilmiş modelde ileri evre, genel sağkalımla bağımsız olarak ilişkili olmaya devam etti (HR=4,403; $p=0,001$).

Sonuç: İleri evre hastalığın yüksek oranda temsil edildiği bu mide adenokarsinomu kohortunda değerlendirilen tümör ve immün organ PET/BT parametrelerinin hiçbirisi için bu kohortta genel sağkalımla bağımsız bir ilişki gösterilemedi; yerleşik klinikopatolojik faktörler, PET-türevi parametrelerden daha güçlü prognostik ilişkiler gösterdi. İmmün organ metabolizmasının mide kanserindeki prognostik rolü, geniş serili prospektif çalışmalarla değerlendirilmelidir.

Anahtar Kelimeler: Mide neoplazileri, ^{18}F -florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi, z prognoz, dalak, kemik iliği

Introduction

Gastric cancer is the fifth most common malignancy worldwide and remains a leading cause of cancer-related death; a substantial proportion of patients are diagnosed at an advanced stage and prognosis is poor (1). ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) is widely used for staging and the assessment of distant metastases in gastric cancer. The prognostic value of semiquantitative metabolic parameters of the primary tumor maximum standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) remains controversial; although high tumor uptake has been suggested to be associated with worse survival, considerable heterogeneity exists across individual studies. A recent study from our center likewise showed that distant metastasis, local invasion, and vascular invasion were associated with primary tumor metabolism regardless of HER2 status, while the prognostic role of PET parameters remained unresolved (2).

Meanwhile, ^{18}F -FDG uptake in the organs of the reticuloendothelial system has been proposed as a non-invasive surrogate of the host systemic inflammatory/immune response to the tumor. In gastric cancer, the bone marrow-to-liver $\text{SUV}_{\text{ratio}}$ bone marrow-to-liver ratio (BLR) was reported to be an independent predictor of recurrence-free and overall survival (OS) after curative resection (3). A high spleen-to-liver $\text{SUV}_{\text{ratio}}$ spleen-to-liver ratio (SLR) has been associated with poor survival after ipilimumab in metastatic

melanoma (4), bone marrow uptake predicted distant recurrence in resected breast cancer (5), and bone marrow and spleen uptake were prognostic in colorectal cancer (6). Associations of secondary lymphoid organ metabolism with survival have also been reported in advanced lung cancer patients treated with immune checkpoint inhibitors (7,8), and similar findings have been shown in lymphoma (9,10), cervical cancer (11), and breast cancer (12). In gastric cancer, reticuloendothelial system uptake has been linked to the tumor immune microenvironment and prognosis (13), and diffuse splenic uptake to poor prognosis (14). These observations are consistent with growing evidence for the central role of systemic immunity in tumor progression (15,16,17,18). However, the prognostic value of these parameters in predominantly advanced-stage gastric adenocarcinoma has not been adequately investigated.

The aim of this study was to investigate the association of primary tumor volume-based parameters and immune organ (liver, spleen, bone marrow) metabolic parameters and their derived ratios, measured on pretreatment ^{18}F -FDG PET/CT, with OS in patients with gastric adenocarcinoma.

Materials and Methods

Patient Characteristics

This study consisted of 127 consecutive patients with histopathologically confirmed gastric adenocarcinoma referred to the Nuclear Medicine Clinic of University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Türkiye, for baseline ^{18}F -FDG PET/CT

prior to treatment. Patients with complete pretreatment PET/CT data, physiological liver, spleen, and bone marrow measurements, and available survival follow-up were included; clinical and pathological variables were extracted when available. Between March 2015 and November 2024, 884 patients who underwent PET/CT with a diagnosis or suspicion of gastric adenocarcinoma at our hospital were retrospectively reviewed. The inclusion criterion was a pathological diagnosis of gastric adenocarcinoma confirmed at our center; all patients had endoscopic biopsy results, pathology specimens obtained at external centers were re-evaluated at our institution, and a subset also had pathological results from total resection material, in which perineural invasion, vascular invasion, local invasion (T stage), nodal status, and tumor size were evaluated.

Patients were excluded for the following reasons: absence of a pathological diagnosis of gastric adenocarcinoma confirmed at our center, prior or synchronous malignancy, PET/CT performed after the initiation of any oncological treatment, incomplete or poor-quality PET/CT data, and unavailable survival follow-up. To ensure that the reference-organ measurements reflected physiological uptake, patients with focal or diffuse liver, spleen, or bone marrow metastases, active infection or inflammatory disease, or known hematological disorders at the time of PET/CT were also excluded. After application of these criteria, 757 patients were excluded and the final study cohort comprised 127 patients; the patient selection process is summarized in Figure 1.

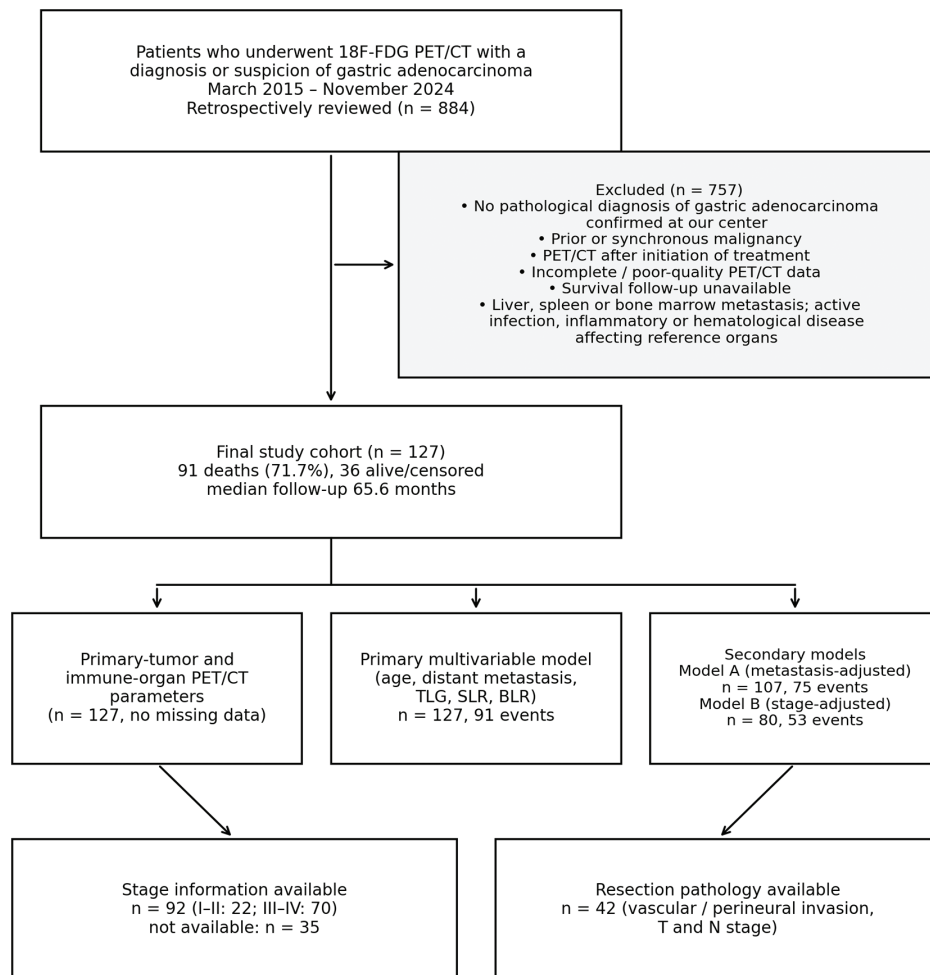


Figure 1. Flow diagram of patient selection. Of 884 patients who underwent ^{18}F -FDG PET/CT with a diagnosis or suspicion of gastric adenocarcinoma between March 2015 and November 2024, 127 met the inclusion criteria and formed the final study cohort

^{18}F -FDG: Fluorine-18 fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography

Retrospective data, covering the period from March 2015 to November 2024, were collected from institutional records, the hospital information system, and PACS. Data collection encompassed patient demographics (age, sex), tumor characteristics, including primary tumor location and histological subtype (Lauren classification), HER2 status, regional lymph node and distant metastatic status, serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9)], and documented therapeutic interventions. Total resection material was available in 42 patients, while the remaining 85 patients had only biopsy material. Tumor location was divided into four groups: esophagogastric junction (EGJ)-cardia, corpus-fundus, antrum, and diffuse; patients with tumors involving more than one region were classified as diffuse. Tumors involving the EGJ with an epicenter located >2 cm into the proximal stomach were staged as esophageal carcinomas and were not included, whereas cancers within the gastric cardia not involving the EGJ were staged as gastric carcinomas. The classification of tumor location was based on the region in which the tumor was pathologically proven, not solely on the areas of FDG uptake. The American Joint Committee on Cancer (AJCC) staging system was used to stage the tumor. The patient pool and imaging protocol were drawn from the gastric adenocarcinoma series previously published from our center (2). The treatment data was obtained through patient files and an electronic treatment archive system. OS was determined by calculating the months between the date of diagnosis and the date of death registered in the death notification system; surviving patients were censored at the date of last follow-up. The date of histopathological diagnosis was retained as the primary time origin for all survival analyses, in keeping with the conventional definition of OS in gastric cancer and to allow comparison with previous studies; because PET/CT was performed in close temporal proximity to the biopsy, the choice of origin was not expected to affect the results materially. The interval between the biopsy date and the PET/CT date was recorded for each patient, and, because the investigated parameters were derived from PET/CT, a sensitivity analysis in which OS was calculated from the date of PET/CT was additionally performed. Among treatment variables, surgical resection of the primary tumor (n=42) could be reliably ascertained from the pathology records and was used as the treatment covariate; detailed systemic treatment data were not available in the analysis dataset. Median follow-up (65.6 months) was estimated using the reverse Kaplan-Meier method. This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki following approval by the Clinical Research Ethics Committee of University of Health Sciences

Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no: 19, date: 09.01.2023). Owing to the retrospective design, the requirement for individual informed consent was waived.

¹⁸F-FDG PET/CT Imaging Protocol

Imaging was conducted after a six-hour fast, provided patients' blood glucose level was ≤ 150 mg/dL. An intravenous dose of ¹⁸F-FDG (0.09-0.14 mCi/kg, or 3.33-5.18 MBq/kg) was subsequently administered. Post-injection, patients rested in a quiet environment for 60 minutes before whole-body PET/CT imaging. Studies were acquired on either a GE Discovery MI 3-Ring system (GE Healthcare, Milwaukee, WI, USA) or a Siemens Biograph 6 LSO HI-REZ scanner (Siemens Medical Solutions, Chicago, IL, USA) employing LYSO and LSO crystal detectors, respectively. Low-dose CT was used for attenuation correction and anatomical localization, with acquisition parameters of 40–60 mAs, 140 kV, and 5 mm slice thickness on both systems. Of the 127 examinations, 53 were performed on the GE Discovery MI and 74 on the Siemens Biograph 6 system, using the manufacturers' standard iterative reconstruction protocols. Both systems employed manufacturer-standard ordered-subset expectation-maximization (OSEM) iterative reconstruction with CT-based attenuation correction and standard corrections for scatter, random coincidences, and decay; SUV values were normalized to body weight. Because acquisitions spanned a nine-year period, the exact reconstruction settings (number of iterations, number of subsets, and post-reconstruction Gaussian filtering) were not uniformly retrievable for every examination. The two systems were used in parallel over the study period without a formal cross-calibration or harmonization procedure. Because per-patient scanner assignment was not recorded in the study database, individual patients could not be linked to a specific scanner, and a scanner-stratified sensitivity analysis of the PET-derived parameters could not be performed. Imaging and SUV measurements were performed in accordance with the recommendations of the EANM procedure guidelines for tumour imaging (19).

Image Analysis

A specialized workstation (GE Advanced Workstation, version 3.2, with the PET VCAR quantification module; GE Healthcare) was used to analyze the images. Maximum-intensity projection images were used to first locate the primary gastric tumor, and then the fused axial, sagittal, and coronal planes were employed for a thorough evaluation. Two experienced nuclear medicine physicians independently reviewed all PET/CT images; any discrepancies were resolved by consensus. Both readers reviewed all studies independently for lesion identification;

quantitative measurements were obtained from a single consensus VOI after joint review, and manual adjustment of the semiautomatic VOI was limited to excluding adjacent physiological or inflammatory uptake. Interobserver reproducibility of the quantitative measurements was not formally assessed. Both readers were blinded to the quantitative PET-derived measurements but had access to the relevant clinical information and cross-sectional imaging findings required for routine interpretation.

Primary-tumor volume of interest (VOI) delineation was performed semiautomatically on fused PET/CT images and manually adjusted in three orthogonal planes to encompass the whole metabolically active tumor while excluding adjacent physiological FDG uptake (gastric wall, bowel), non-tumoral inflammatory uptake, and unrelated hypermetabolic foci, with CT morphology used to confirm the anatomical extent of the lesion. Primary tumors with low or absent FDG uptake, in which the lesion could not be visually distinguished from physiological gastric wall activity, were delineated with reference to the CT-defined (mural thickening) extent of the tumor ($n=10$); no patient was excluded on the basis of low tumor FDG avidity. SUV_{max} and SUV_{mean} were extracted from the final VOI. MTV was defined as the volume of all voxels within the primary-tumor VOI exceeding a fixed threshold of 40% of SUV_{max} , and total TLG was computed as the product of MTV and SUV_{mean} .

Physiological FDG uptake in immune-related organs was additionally measured to characterize the systemic immune-metabolic response. A spherical VOI of fixed diameter was placed in the right hepatic lobe (5 cm) and in the spleen (3 cm), avoiding focal lesions, vessels, and organ margins, to obtain the SUV_{max} values for the liver (SUV_{liver}) and spleen (SUV_{spleen}). For bone marrow uptake, separate spherical volumes of interest were placed in each of the L3, L4, and L5 vertebral bodies, avoiding degenerative or focal lesions; SUV_{BM} was defined as the highest of the SUV_{max} values measured across these three vertebrae. All organ measurements were thus consistently based on SUV_{max} , so that the numerator and denominator of each derived ratio relied on the same SUV metric. The liver was used as the reference tissue, owing to its relatively stable physiological FDG uptake, and the following ratios were derived: the SLR ($SLR = SUV_{spleen} / SUV_{liver}$), the BLR ($BLR = SUV_{BM} / SUV_{liver}$), and the spleen-to-bone-marrow ratio ($SBR = SUV_{spleen} / SUV_{BM}$). Although both SUV_{max} - and SUV_{mean} -based reference-organ measurements have been used in the literature, a uniform SUV_{max} -based approach was adopted to avoid mixing different SUV metrics within a single ratio.

Statistical Analysis

Data were analyzed using the Jamovi 2.6.19.0 program. Categorical variables are reported as frequency and percentage, and continuous variables as mean $\pm$ standard deviation (SD) or median [(range/interquartile range (IQR))], as appropriate to their distribution. Differences in PET/CT parameters between patients who died during follow-up and those who remained alive were assessed using the independent-samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using the Pearson chi-square test, or Fisher's exact test when expected cell frequencies were low. Relationships between primary-tumor and immune-organ PET/CT metabolic parameters were assessed using Spearman's rank correlation coefficient.

Overall survival was estimated using the Kaplan-Meier method, with group comparisons by the log-rank test at both the median value and a data-optimized (maximally selected) cut-off for each parameter; p-values from the latter were corrected for multiple cut-point testing using a permutation procedure to avoid inflation of type-I error. One-, three-, five-, seven-, and nine-year OS estimates were reported with 95% confidence intervals (CIs). The association between each continuous PET/CT parameter and OS was evaluated using univariate Cox proportional-hazards regression. In the univariate analyses, hazard ratio (HR), 95% CIs, and p values were calculated. To test the independent prognostic value of the PET parameters, the pre-specified primary multivariable Cox model included age, distant metastasis, and the selected PET parameters (TLG, SLR, and BLR). TLG was selected as the representative volumetric tumor-burden metric, whereas SLR and BLR were selected a priori as the principal liver-referenced immune-organ ratios based on previous literature (2,3); the SBR was not part of this pre-specified model. A metastasis-adjusted model extended with additional clinical covariates (sex, CEA, CA19-9) (Model A) and a stage-adjusted model in which the AJCC stage group replaced distant metastasis (Model B) were constructed as secondary (exploratory) analyses in smaller complete-case subsets. To limit model complexity in these smaller subsets, the secondary models included TLG and SLR as representative tumor- and immune-organ PET parameters. The proportional hazards assumption of the Cox models was assessed based on the association of scaled Schoenfeld residuals with time. In the univariate analyses and in the primary multivariable model, continuous PET/CT parameters were evaluated per 1 SD increase. In the secondary models (Models A and B), TLG, CEA, and CA19-9 were $\log_2$ -transformed owing to their right-skewed distributions; in these models, the HR

values for these variables were interpreted as the change in hazard per doubling of the respective parameter. Complete-case analysis was used for missing data. Two pre-specified sensitivity analyses were performed: (i) all survival analyses were repeated with OS calculated from the date of PET/CT instead of the date of diagnosis, and (ii) the primary multivariable model was additionally adjusted for surgical resection of the primary tumor (yes vs. no) as the available treatment covariate.

The discriminatory performance of the parameters for OS was evaluated at 1, 3, and 5 years using inverse-probability-of-censoring-weighted (IPCW) cumulative/dynamic time-dependent ROC analysis, which accounts for censoring; 95% CIs for the time-dependent area under the curve (AUC) values were obtained by bootstrapping (400 resamples). The time-dependent ROC analysis was defined as a secondary (exploratory) analysis. Correlations between primary-tumor and immune-organ metabolic parameters were assessed using Spearman's rank correlation coefficient. A two-sided p value <0.05 was considered statistically significant.

Results

A total of 127 patients were included in the analysis [median age 62.0 years (IQR 55.0-72.0); range 26-89]; advanced-stage disease was highly represented in the cohort (76% of patients with known stage were stage III-IV). There were 91 death events (71.7%) and 36 (28.3%) alive/censored observations. The median follow-up estimated by the reverse Kaplan-Meier method was 65.6 months. Baseline patient, tumor, and treatment characteristics are summarized in Table 1. Forty-two patients (33.1%) underwent surgical resection of the primary tumor, whereas 85 (66.9%) had endoscopic ($n=74$) or external-center ($n=11$, re-evaluated at our institution) biopsy material only. The interval between the date of histopathological diagnosis and PET/CT did not exceed one month in any patient. The Kaplan-Meier median OS was 16.56 months, and the 1-, 3-, 5-, 7-, and 9-year survival probabilities were estimated at 58.3%, 33.1%, 28.1%, 28.1%, and 28.1%, respectively (Figure 2).

For the primary tumor, the median SUV_{max} was 8.86 (IQR 5.69-15.29), SUV_{mean} 4.44 (2.94-7.16), MTV 30.64 cm^3 (16.61-54.40), and TLG 146.28 g (56.28-298.74). For the immune organs, the median liver SUV_{max} was 2.81, spleen SUV_{max} 2.38, and bone marrow SUV_{max} 2.65; the median SLR was 0.83, BLR 0.93, and SBR 0.85. Organ metabolisms were strongly and significantly inter-correlated: liver-spleen $r=0.72$, spleen-bone marrow $r=0.55$, liver-bone marrow $r=0.54$ (all $p<0.001$).

Apart from the SBR, no PET/CT parameter differed significantly between survivors and deceased patients; the SBR was significantly lower in deceased patients ($p=0.041$), with a borderline trend for the SLR ($p=0.089$). In univariate Cox models, primary-tumor SUV_{max} , SUV_{mean} , MTV, and TLG; liver, spleen, and bone marrow SUV_{max} values; and the SLR, BLR, and SBR were not significantly associated with OS; the SBR showed a non-significant protective trend (HR=0.802 per 1 SD; 95% CI 0.621-1.038; $p=0.093$) (Table 2). This trend was likewise not supported by the median cut-off analysis ($p=0.112$), the permutation-corrected maximally selected cut-off analysis (corrected $p=0.32$), or a multivariable model including the SBR (HR=0.805; 95% CI 0.613-1.056; $p=0.117$); permutation-corrected cut-off analyses were non-significant for all parameters (lowest corrected $p=0.086$, for spleen SUV_{max}) (Figure 3). In the secondary, time-dependent (IPCW) ROC analysis, discriminatory performance was low at all time points; the highest time-dependent AUC values (oriented so that values >0.50 indicate discrimination in the direction of the observed association) were obtained for the SBR at 3 years (0.594; 95% CI 0.475-0.691) and for MTV at 5 years (0.595; 95% CI 0.461-0.734), and the CIs, included 0.50 for all parameters. In the primary multivariable Cox model (age, distant metastasis, TLG, SLR, BLR; $n=127$, 91 events), distant metastasis independently increased the hazard of death (HR=1.798; 95% CI 1.187-2.723; $p=0.006$), whereas TLG, SLR, and BLR entered into the model showed no independent significance; a borderline protective trend was observed for the SLR (HR=0.813; 95% CI 0.644-1.026; $p=0.081$) (Table 3). In contrast, advanced stage (III-IV), distant metastasis, and elevated CEA and CA19-9 were significantly associated with survival (Table 2); these findings support the internal clinical validity of the dataset. In Kaplan-Meier subgroup analyses, advanced stage ($p<0.001$) and distant metastasis (median 9.6 vs. 22.0 months; $p=0.007$) were associated with markedly shorter survival, whereas non-intestinal Lauren type ($p=0.125$) and HER2 positivity ($p=0.184$) did not reach statistical significance (Figure 4).

In the subgroup with available resection pathology ($n=42$), the presence of vascular invasion was associated with markedly shorter survival (log-rank $p=0.004$; univariate Cox HR=3.596; 95% CI 1.407-9.189; $p=0.008$). Borderline trends were observed for perineural invasion ($p=0.077$), T3-T4 local invasion ($p=0.094$), and nodal positivity ($p=0.189$) (Figure 5).

In the secondary, extended multivariable models, clinical variables and PET parameters were evaluated together (Figure 6). In the metastasis-adjusted Model A ($n=107$,

Table 1. Baseline patient, tumor, and treatment characteristics (n=127)	
Characteristic	n=127
Age, years, median (IQR); range	62.0 (55.0-72.0); 26-89
Sex, male/female, n (%)	89 (70.1)/38 (29.9)
PET/CT indication, n (%)	
Initial staging	96 (75.6)
Diagnostic work-up	31 (24.4)
Primary tumor location, n (%)	
EGJ-cardia	28 (22.0)
Corpus-fundus	40 (31.5)
Antrum	38 (29.9)
Diffuse (more than one region)	21 (16.5)
Lauren classification, n (%)	
Intestinal	94 (74.0)
Diffuse	8 (6.3)
Indeterminate	2 (1.6)
Not available	23 (18.1)
Histological differentiation, n (%)	
Well	8 (6.3)
Moderate	47 (37.0)
Poor	35 (27.6)
Signet ring cell/mucinous/mixed	7 (5.5)/5 (3.9)/2 (1.6)
Not available	23 (18.1)
HER2 status, positive/negative, n (%)	19 (15.0)/108 (85.0)
Pathological material, n (%)	
Total resection of primary tumor	42 (33.1)
Endoscopic biopsy only	74 (58.3)
External-center material (re-evaluated at our institution)	11 (8.7)
AJCC stage group, n (%)	
I-II	22 (17.3)
III	14 (11.0)
IV	56 (44.1)
Not available	35 (27.6)
Distant metastasis, present / absent, n (%)	57 (44.9)/70 (55.1)
CEA, ng/mL, median (IQR)	4.35 (1.87-22.71); available n=110
CA19-9, U/mL, median (IQR)	21.8 (7.8-89.3); available n=113
Treatment, n (%)	
Surgical resection of primary tumor	42 (33.1)
Systemic treatment	Not uniformly available in the analysis dataset
PET/CT scanner, n (%)	
GE Discovery MI	53 (41.7)
Siemens Biograph 6	74 (58.3)
Diagnosis-to-PET/CT interval	≤1 month in all patients
Follow-up, months, median (reverse Kaplan-Meier)	65.6
Death events, n (%)	91 (71.7)
IQR: Interquartile range, PET/CT: Positron emission tomography/computed tomography, EGJ: Esophagogastric junction, HER2: Human epidermal growth factor receptor 2, AJCC: American Joint Committee on Cancer, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, GE: General electric	

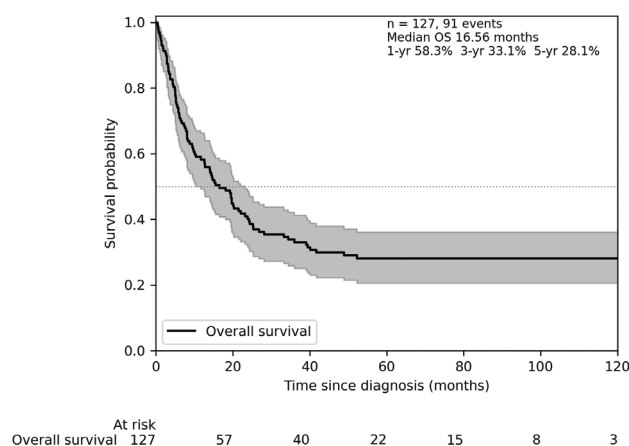


Figure 2. Kaplan-Meier overall survival curve for the entire cohort (n=127; 91 events) with numbers at risk. Survival was calculated from the date of histopathological diagnosis (biopsy date); the median overall survival was 16.56 months

75 events), no covariate retained independent statistical significance (distant metastasis: HR=1.384, $p=0.262$; CA19-9: HR=1.063, $p=0.116$; male sex: HR=1.577, $p=0.090$) (Table 4). In the stage-adjusted Model B (n=80, 53 events), advanced stage was the only variable independently associated with OS (HR=4.403; 95% CI 1.781-10.890; $p=0.001$) (Table 5); CEA ($p=0.513$) and CA19-9 ($p=0.291$) showed no independent significance. The PET parameters (TLG and SLR) remained non-significant in both secondary models. In the assessment based on Schoenfeld residuals, no evidence of violation of the proportional hazards assumption was found for any covariate in the primary model or in Models A and B (all $p>0.05$). The variable-level distribution of missing data is summarized in Table 6; there were no missing observations for the PET/CT parameters. In both models, TLG and SLR provided no independent prognostic contribution. In the sensitivity analysis using the PET/CT date as the time origin (n=127, 91 events), the median OS was 15.93 months and the 1-, 3-, and

Table 2. Univariate Cox regression analysis of PET metabolic and clinical parameters (n=127; events=91)

Parameter	Median (IQR)	Deceased vs. alive, median (p)	HR (95% CI)	p	Optimal cut-off (corrected p)
Primary tumor					
SUV _{max}	8.86 (5.69-15.29)	8.25 vs. 10.00 (0.514)	0.947 (0.770-1.166)	0.609	12.27 (0.678)
SUV _{mean}	4.44 (2.94-7.16)	4.37 vs. 4.70 (0.465)	1.006 (0.811-1.248)	0.956	3.59 (0.773)
MTV (cm ³)	30.64 (16.61-54.41)	33.87 vs. 28.00 (0.128)	1.137 (0.940-1.375)	0.187	35.01 (0.235)
TLG (g)	146.28 (56.28-298.74)	150.15 vs. 130.45 (0.526)	1.151 (0.941-1.407)	0.170	31.81 (0.780)
Immune organs					
Liver SUV _{max}	2.81 (2.41-3.33)	2.83 vs. 2.80 (0.991)	0.958 (0.774-1.185)	0.690	2.27 (0.182)
Spleen SUV _{max}	2.38 (2.01-2.74)	2.34 vs. 2.41 (0.441)	0.862 (0.696-1.068)	0.175	1.29 (0.086)
Bone marrow SUV _{max}	2.65 (1.98-3.29)	2.61 vs. 2.66 (0.716)	1.002 (0.825-1.218)	0.983	3.37 (0.896)
SLR	0.83 (0.71-0.93)	0.81 vs. 0.85 (0.089)	0.862 (0.696-1.067)	0.173	0.78 (0.383)
BLR	0.93 (0.76-1.16)	0.93 vs. 0.95 (0.558)	1.084 (0.887-1.325)	0.429	1.23 (0.391)
SBR	0.85 (0.71-1.07)	0.80 vs. 0.94 (0.041)	0.802 (0.621-1.038)	0.093	1.00 (0.317)
Clinical variables					
Distant metastasis (yes vs. no)	–	–	1.748 (1.157-2.640)	0.008	–
Stage (III-IV vs. I-II)	–	–	4.585 (2.081-10.104)	<0.001	–
CEA (per doubling)	–	–	1.095 (1.009-1.188)	0.029	–
CA19-9 (per doubling)	–	–	1.098 (1.023-1.179)	0.009	–
Sex (male vs. female)	–	–	1.398 (0.876-2.229)	0.160	–
Lauren (non-intestinal vs. intestinal)	–	–	1.717 (0.853-3.457)	0.130	–
HER2 (positive vs. negative)	–	–	0.664 (0.361-1.220)	0.187	–

For the continuous PET/CT parameters, HRs are per 1 standard deviation increase; for distant metastasis, yes vs. no; for stage, III-IV vs. I-II; for CEA and CA19-9, per doubling (log₂-transformed). Deceased vs. alive comparison by Mann-Whitney U test. Optimal cut-off: maximally selected log-rank statistic (cut-points between the 10th and 90th percentiles) with permutation-corrected p (1000 permutations). HR: Hazard ratio; CI: Confidence interval; IQR: Interquartile range; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis; SLR: Spleen-to-liver SUV_{rat}; BLR: Bone marrow-to-liver SUV ratio; SBR: Spleen-to-bone-marrow SUV ratio

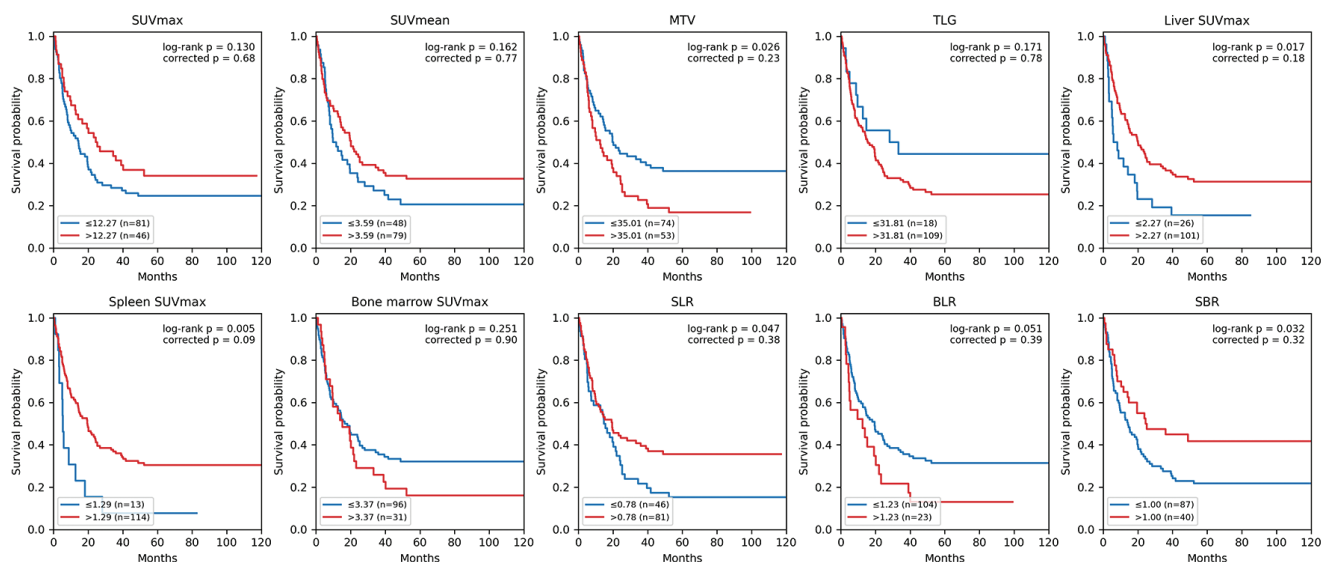


Figure 3. Kaplan-Meier overall survival curves according to maximally selected cut-offs of the primary-tumor (SUV_{max} , SUV_{mean} , MTV, TLG) and immune-organ (liver, spleen, and bone marrow SUV_{max} ; SLR, BLR, SBR) PET/CT parameters. Uncorrected log-rank p values and permutation-corrected p values are given in each panel; none of the comparisons remained significant after correction for multiple cut-point testing

SUV_{max} : Maximum standardized uptake value, SUV_{mean} : Mean standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, BLR: Bone marrow-to-liver ratio, SBR: Spleen-to-bone marrow ratio, PET/CT: Positron emission tomography/computed tomography

Table 3. Primary multivariable Cox model (age, distant metastasis, TLG, SLR, BLR; n=127; events=91)

Variable	Unit	HR	95% CI	p
Age	10 years	1.068	0.901-1.266	0.449
Distant metastasis	Yes/No	1.798	1.187-2.723	0.006
TLG	1 SD	1.137	0.915-1.413	0.245
SLR	1 SD	0.813	0.644-1.026	0.081
BLR	1 SD	1.140	0.908-1.432	0.260

Pre-specified primary model; all variables were entered jointly. For the PET parameters, HRs are per 1 standard deviation (SD) increase; for age, per 10-year increase. Proportional hazards assumption (scaled Schoenfeld residuals): all $p > 0.05$. HR: Hazard ratio, CI: Confidence interval, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, BLR: Bone marrow-to-liver ratio, SD: Standard deviation

5-year survival rates were 58.3%, 33.9%, and 28.0%, respectively; no PET/CT parameter was significantly associated with OS in univariate Cox models (all $p > 0.11$; SBR HR=0.816 per 1 SD; 95% CI 0.633–1.052; $p=0.117$), and in the primary multivariable model distant metastasis remained independently associated with OS (HR=1.845; 95% CI 1.218–2.795; $p=0.004$), whereas TLG ($p=0.246$), SLR (HR=0.818; $p=0.092$), and BLR ($p=0.320$) did not. In the treatment-adjusted sensitivity model (age, distant metastasis, surgical resection, TLG, SLR, BLR; n=127), surgical resection of the primary tumor was strongly associated with longer survival (HR=0.310; 95% CI 0.176–0.547; $p < 0.001$) and distant metastasis lost independent significance (HR=1.085; 95% CI 0.682–1.725; $p=0.730$); in this model the SLR showed a protective association

(HR=0.729 per 1 SD; 95% CI 0.582–0.913; $p=0.006$) and the BLR a nominal adverse association (HR=1.282; 95% CI 1.023–1.606; $p=0.031$), while TLG remained non-significant (HR=1.217; $p=0.085$). Because surgical resection is closely linked to stage and metastatic status, and these PET associations were not observed in the pre-specified models, they should be regarded as exploratory.

Discussion

In this cohort of 127 gastric adenocarcinoma patients with a high proportion of advanced-stage disease, no independent association with OS was demonstrated for either primary tumor volume-based parameters or immune organ metabolic parameters measured on pretreatment ^{18}F -FDG PET/CT, whereas the clinical prognostic signal

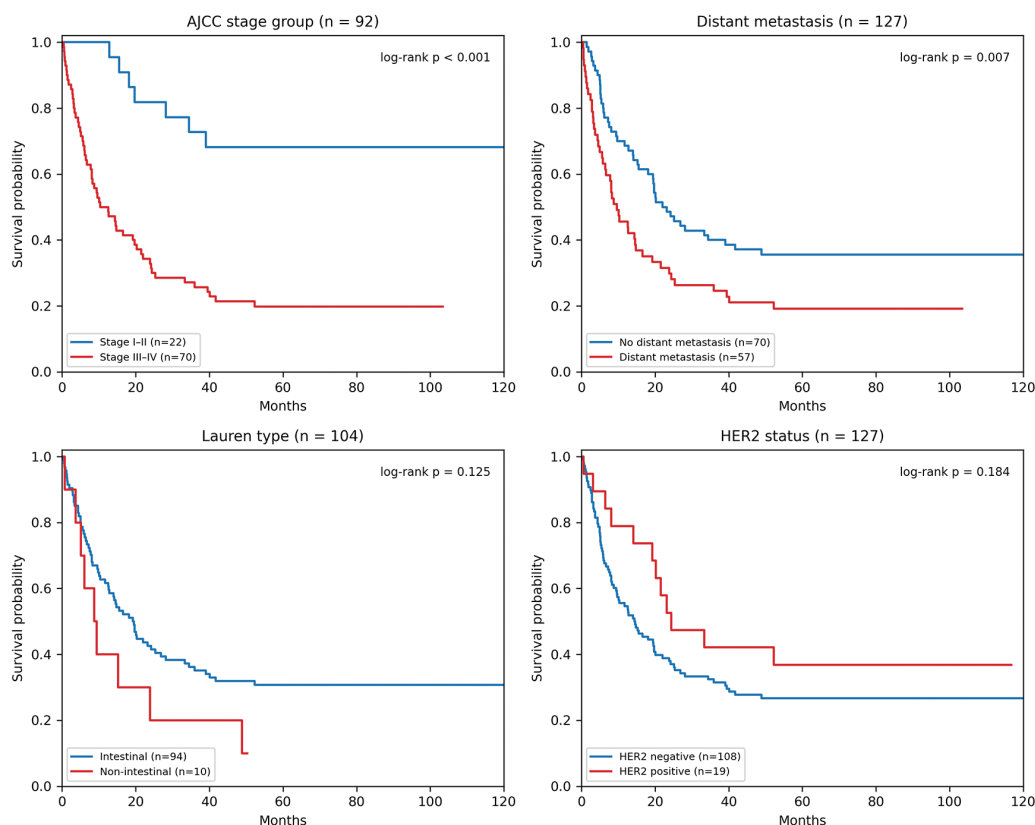


Figure 4. Kaplan-Meier overall survival curves according to AJCC stage group (I-II vs. III-IV; $n=92$), distant metastasis status ($n=127$), Lauren classification (intestinal vs. non-intestinal; $n=104$), and HER2 status ($n=127$)

AJCC: American Joint Committee on Cancer, HER2: Human epidermal growth factor receptor 2

was preserved: distant metastasis was an independent prognostic factor in the primary multivariable model ($HR=1.798$; $p=0.006$), while advanced stage remained independently associated with OS in the subset with available stage information ($HR=4.403$; $p=0.001$). In Model A, extended with additional covariates, no single variable retained significance; this attenuation may partly reflect the smaller complete-case sample, fewer events, and covariance among clinical predictors. The significant associations observed for established clinical prognostic factors support the internal clinical validity of the dataset; however, they do not exclude the possibility that modest prognostic effects of PET-derived parameters could have remained undetected.

Our findings regarding primary tumor parameters are consistent with the heterogeneity of the literature. Although high tumor FDG uptake has been suggested to be associated with poor prognosis, this association has not been consistent across studies; the low FDG avidity of signet ring cell and mucinous subtypes is a well-recognized

factor weakening the link between uptake and biological aggressiveness in gastric cancer. In our center's previous HER2 series, metabolic parameters were cross-sectionally associated with distant metastasis and invasion, but their independent prognostic role remained unresolved (2); the present study tested this question directly, with a survival endpoint, in the same center's patient pool and found no independent association between these parameters and OS.

The negative finding for immune organ metabolism contrasts with parts of the literature. Lee et al. (3) reported that BLR was an independent predictor of recurrence-free and OS in 309 gastric cancer patients after curative resection, and diffuse splenic uptake has been associated with poor prognosis in gastric cancer (14). Similarly, immune-organ parameters have been found prognostic in melanoma (4), breast cancer (5,12), colorectal cancer (6), cervical cancer (11), and aggressive lymphoma (9,10). The most plausible explanation for this discrepancy is cohort composition: positive findings have largely been obtained

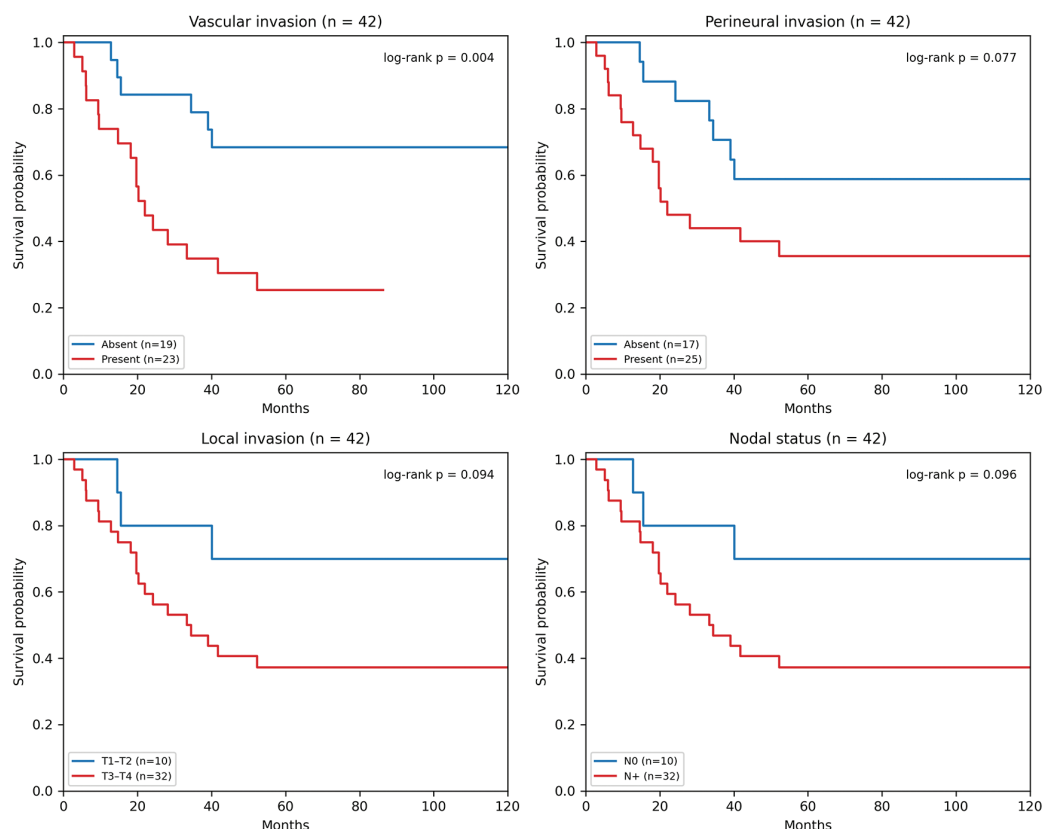


Figure 5. Kaplan-Meier overall survival curves in the resection-pathology subgroup (vascular invasion, perineural invasion, T stage, and N stage; n=42)

Table 4. Metastasis-adjusted clinical-PET multivariable Cox model (Model A; n=107; events=75)

Variable	Unit	Adjusted HR	95% CI	p
Age	10 years	1.089	0.899-1.318	0.384
Male sex	Male/Female	1.577	0.931-2.670	0.090
Distant metastasis	Yes/No	1.384	0.785-2.439	0.262
CEA	Per doubling	1.041	0.937-1.157	0.456
CA19-9	Per doubling	1.063	0.985-1.148	0.116
TLG	Per doubling	1.009	0.877-1.161	0.901
SLR	1 SD	0.889	0.686-1.153	0.377

Model A jointly includes age, sex, distant metastasis, CEA, CA19-9, TLG, and SLR. The analysis was conducted on complete cases. Because CEA, CA19-9, and TLG were log2-transformed, their HRs are interpreted per doubling; the SLR HR is per 1 SD increase. Proportional hazards assumption: all $p > 0.05$. HR: hazard ratio; CI: confidence interval, PET: Positron emission tomography, HR: Hazard ratio, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, SD: Standard deviation,

in early-stage, curatively resected (3) or immunotherapy-treated (4,7,8) populations. In our cohort, with its high proportion of advanced/metastatic disease, the prognostic impact of tumor burden and metastatic spread may have obscured the comparatively subtle signal of the host inflammatory response.

Moreover, the lack of independent significance of TLG, SLR, and BLR in the multivariable model was consistent with the lack of significant associations observed in the univariate analyses. The SBR was lower in deceased patients and showed a protective trend at the univariate level, but this trend did not reach statistical significance and was not supported by alternative analytical approaches; it

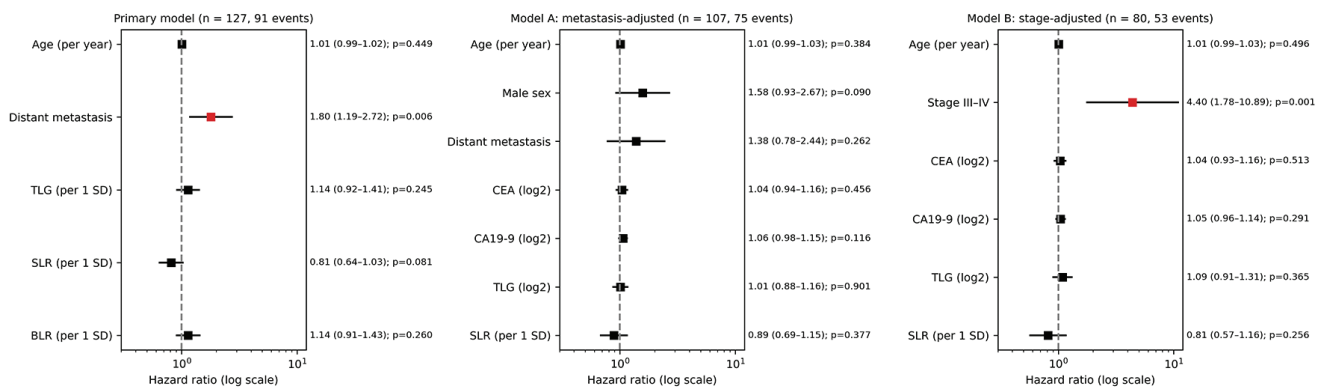


Figure 6. Forest plots of the primary pre-specified multivariable Cox model (age, distant metastasis, TLG, SLR, BLR), the metastasis-adjusted Model A, and the stage-adjusted Model B (hazard ratios with 95% confidence intervals, log scale; red squares indicate p<0.05)
TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, BLR: Bone marrow-to-liver ratio, SD: Standard deviation, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9

Table 5. Stage-adjusted clinical-PET multivariable Cox model (Model B; n=80; events=53)				
Variable	Unit	Adjusted HR	95% CI	p
Age	10 years	1.080	0.865-1.349	0.496
Stage III-IV	III-IV/I-II	4.403	1.781-10.890	0.001
CEA	Per doubling	1.037	0.930-1.155	0.513
CA19-9	Per doubling	1.048	0.961-1.143	0.291
TLG	Per doubling	1.088	0.906-1.306	0.365
SLR	1 SD	0.814	0.571-1.161	0.256

Model B jointly includes age, stage group, CEA, CA19-9, TLG, and SLR. The analysis was conducted on complete cases with all model variables, including stage, available. Stage I-II is the reference group. Because CEA, CA19-9, and TLG were log₂-transformed, their HRs are interpreted per doubling; the SLR HR is per 1 SD increase. Proportional hazards assumption: all p>0.05. HR: Hazard ratio, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, TLG: Total lesion glycolysis, SLR: Spleen-to-liver ratio, SD: Standard deviation

should therefore be considered hypothesis-generating. Methodological concerns about the type I error risk introduced by data-driven cutoffs have likewise been raised, and similar methodological concerns have been raised in lymphoma series (10). This observation underscores the importance of predefined cutoff values and multiple-testing corrections in prognostic biomarker studies.

Several biological mechanisms may underlie the protective trend observed for a higher SBR, although this signal did not reach statistical significance in the univariate analysis, was absent in the multivariable models, and should be interpreted with caution. Splenic FDG uptake reflects the metabolic activity of the white-pulp lymphoid compartment and of red-pulp macrophages and monocytes, whereas bone marrow uptake predominantly reflects granulopoietic activity and tumor-driven emergency myelopoiesis (15,16). In cancer, systemic release of interleukin-6, granulocyte- and granulocyte-macrophage colony-stimulating factors, and other tumor-derived mediators expands the myeloid compartment, mobilizes myeloid-derived suppressor cells

and neutrophils from the marrow, and is accompanied by contraction of adaptive lymphoid populations; this myeloid-skewed, immunosuppressive systemic state has been linked to disease progression (17,18) and to reticuloendothelial FDG uptake in gastric cancer (13). Within this framework, a relatively higher splenic than marrow uptake (higher SBR) may indicate a comparatively preserved lymphoid/reticuloendothelial immune activity relative to marrow myelopoiesis, whereas a lower SBR may reflect dominance of tumor-driven myelopoiesis over splenic immune activity, which would be consistent with the protective direction of the trend observed here. The absence of a comparable signal for the bone marrow parameters may be explained by several factors. First, lumbar bone marrow FDG uptake is influenced by non-immune determinants that are common in gastric cancer, such as chronic gastrointestinal blood loss and anemia with reactive erythroid hyperplasia, age-related changes in marrow cellularity, recent hemorrhage, and degenerative vertebral changes, which add measurement variability unrelated

Table 6. Variable-level distribution of missing data

Variable	Available (n)	Missing (n)	Missing %
Age	127	0	0.0
Sex	127	0	0.0
Biopsy type	127	0	0.0
HER2 status	127	0	0.0
Distant metastasis	127	0	0.0
AJCC stage	92	35	27.6
CEA	110	17	13.4
CA19-9	113	14	11.0
Lauren classification	104	23	18.1
Histological grade/type	104	23	18.1
Tumor size	42	85	66.9
Perineural invasion	42	85	66.9
Vascular invasion	42	85	66.9
T stage	42	85	66.9
N stage	42	85	66.9
PET/CT parameters (all)	127	0	0.0

Percentages were calculated over the total of 127 patients. No imputation was applied to missing values; the corresponding analyses were conducted on complete cases. Resection-pathology variables (tumor size, invasion, T and N stage) were available only in the 42 patients with total resection material, HER2: Human epidermal growth factor receptor 2, AJCC: American Joint Committee on Cancer, CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9, T stage: Primary tumor stage, N stage: Regional lymph node stage, PET/CT: Positron emission tomography/computed tomography.

to antitumor immunity. Second, the spleen and the bone marrow respond to tumor-derived signals with different kinetics and cell populations: the spleen acts as a reservoir and site of extramedullary myelopoiesis and lymphoid activation, whereas the marrow response is dominated by granulopoiesis, so that the two organs may carry partly independent prognostic information (6,9,10,13). Third, the positive findings for BLR reported by Lee et al. (3) were obtained in a curatively resected, predominantly early-stage population; in our cohort dominated by advanced and metastatic disease, tumor burden and metastatic spread may have overwhelmed the comparatively subtle marrow signal. Finally, the SBR normalizes the two immune organs to each other rather than to the liver, thereby removing inter-patient variation in hepatic FDG uptake, which may have rendered it more sensitive to the balance between splenic and marrow activity than the liver-referenced ratios. Notably, the protective direction of the spleen-related ratios was also observed for the SLR in the exploratory resection-adjusted model, lending some internal consistency to this hypothesis, although the strong link between resectability and stage precludes causal interpretation. These considerations are hypothesis-generating and require confirmation in prospective studies incorporating concurrent hematological and immunological markers.

Study Limitations

Our study has several limitations. First, its retrospective, single-center design carries a risk of selection bias and limits external validity. Second, two PET/CT systems were used without formal cross-calibration; the exact reconstruction settings and the per-patient scanner assignment were not retrievable, so scanner-adjusted modeling was not possible and residual scanner-related SUV variability cannot be excluded. Third, treatment was heterogeneous over the 2015-2024 period; only surgical resection could be included as a treatment covariate, whereas systemic treatment data were not uniformly documented, so treatment-stratified analyses and adjustment for era-related changes in treatment were not possible. Fourth, resection-pathology variables were available in only 42 patients and stage information was missing in approximately 28%, limiting the power of the subgroup and stage-adjusted analyses. Fifth, concurrent inflammatory markers such as CRP and the neutrophil-to-lymphocyte ratio were not available, and interobserver reproducibility of the PET measurements was not formally assessed. Sixth, the findings have not been externally validated, and the high proportion of advanced-stage disease limits generalizability to early-stage disease. Finally, the absence of a statistically significant association does not establish that the evaluated PET parameters

lack prognostic value; modest effects may have remained undetected owing to the sample size, number of events, and cohort composition.

Conclusion

In this gastric adenocarcinoma cohort with a high proportion of advanced-stage disease, no independent association with OS was demonstrated for either primary-tumor or immune-organ metabolic PET/CT parameters. This finding does not establish the absence of prognostic value; rather, it indicates that no independent effect could be demonstrated in a cohort dominated by advanced-stage disease. In contrast, established clinical indicators, particularly distant metastasis and advanced AJCC stage, retained prognostic relevance. The prognostic role of immune-organ metabolism warrants evaluation in larger, stage-stratified prospective cohorts using predefined cutoffs.

Ethics

Ethics Committee Approval: This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki following approval by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no: 19, date: 09.01.2023).

Informed Consent: Owing to the retrospective design, the requirement for individual informed consent was waived.

Declaration on the Use of Artificial Intelligence: Artificial intelligence-assisted tools were used solely for language editing and formatting support during the preparation of this manuscript. All study design, data collection, statistical analyses, interpretation of the results, and the final content were performed, verified, and approved by the authors, who take full responsibility for the manuscript.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ö., M.Ö.T., Concept: H.Ö., M.Ö.T., Design: H.Ö., Data Collection or Processing: M.N.A.T., M.Ö.T., H.Ö., Analysis or Interpretation: H.Ö., Literature Search: M.N.A.T., M.Ö.T., Writing: H.Ö., M.Ö.T.

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Multimodal Functional Imaging in Tumor-induced Osteomalacia: ⁶⁸Ga-DOTATATE, ¹⁸F-FDG, and ⁶⁸Ga-FAPI PET/CT Findings

Tümör Kaynaklı Osteomalazide Multimodal Fonksiyonel Görüntüleme: ⁶⁸Ga-DOTATATE, ¹⁸F-FDG ve ⁶⁸Ga-FAPI PET/BT Bulguları

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Abstract

Tumor-induced osteomalacia, resulting from tumoral overproduction of fibroblast growth factor 23, is a rare paraneoplastic syndrome clinically characterized by muscle weakness, bone pain, and pathological fractures. Fewer than 1,000 cases have been reported in the literature. Laboratory findings typically include hypophosphatemia, normal or decreased levels of 1.25-dihydroxy vitamin D, and normal or elevated levels of FGF23. Functional imaging methods, particularly somatostatin receptor imaging, play an important role in the localization of the tumor. In this case of tumor-induced osteomalacia, we presented the findings from gallium-68 (⁶⁸Ga)-DOTATATE, ⁶⁸Ga-fibroblast, and ¹⁸F-fluorodeoxyglucose positron emission tomography imaging modalities used for tumor localization.

Keywords: Tumor-induced osteomalacia, phosphaturic mesenchymal tumors, ⁶⁸Ga-DOTATATE PET/CT, ⁶⁸Ga-FAPI PET/CT, ¹⁸F-FDG PET/CT

Öz

Fibroblast büyüme faktörü 23'ün tümöral üretimine bağlı gelişen tümör kaynaklı osteomalazi, kas güçsüzlüğü, kemik ağrısı ve patolojik kırıklarla seyreden, nadir görülen bir paraneoplastik sendromdur. Literatürde bildirilen olgu sayısı 1000'in altındadır. Laboratuvar bulguları, hipofosfatemi, normal veya düşük düzeyde 1.25-dihidroksi vitamin D ve normal ya da artmış FGF23 düzeyleri ile karakterizedir. Tümörün lokalizasyonunda somatostatin reseptör görüntüleme başta olmak üzere fonksiyonel görüntüleme yöntemleri önemli bir rol oynamaktadır. Tümör kaynaklı osteomalazi olgusunda, tümör lokalizasyonunu belirlemek amacıyla kullanılan galyum-68 (⁶⁸Ga)-DOTATATE, ⁶⁸Ga-fibroblast ve ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi görüntüleme yöntemlerinin bulgularını sunduk.

Anahtar Kelimeler: Tümör kaynaklı osteomalazi, fosfatürik mezenkimal tümörler, ⁶⁸Ga-DOTATATE PET/BT, ⁶⁸Ga-FAPI PET/BT, ¹⁸F-FDG PET/BT

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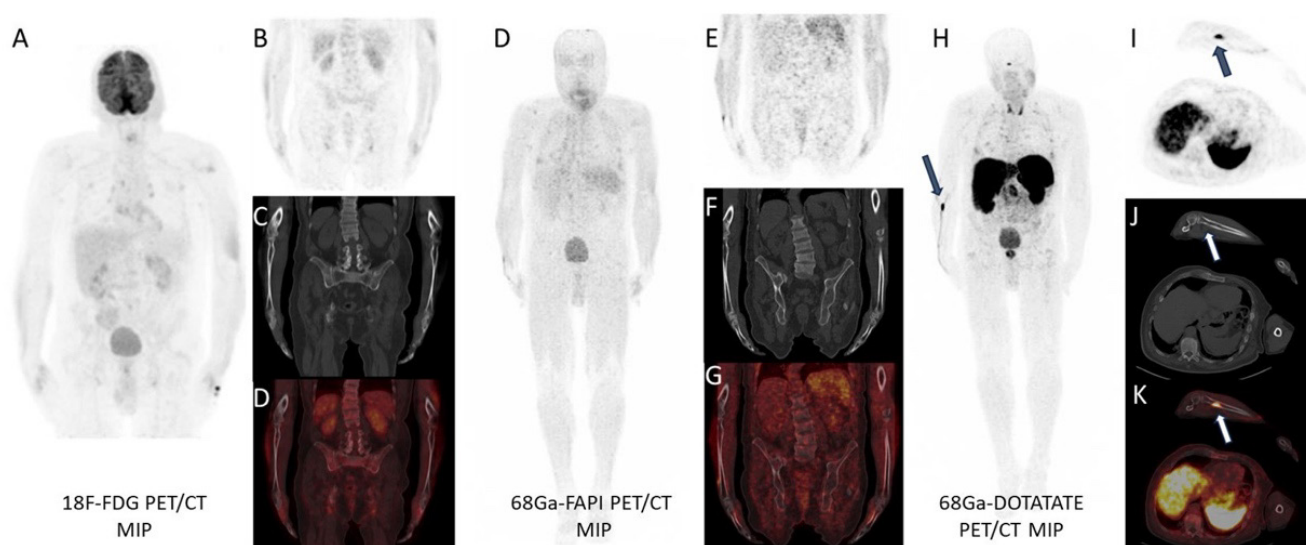


Figure 1. A 65-year-old man with a history of bilateral hip fractures treated with prosthetic hip replacements presented with diffuse bodily pain and muscle weakness. The man, who was ambulatory with the aid of a cane, had chronic hypophosphatemia. Laboratory tests revealed a serum phosphate level of 0.8 mg/dL (reference range: 2.5-4.5 mg/dL), a parathyroid hormone level of 70 pg/mL (reference range: 15-65 pg/mL), and a calcitriol (1.25-dihydroxy vitamin D) level of 23 pg/mL (reference range: 20-80 pg/mL). Serum FGF23 levels were elevated. Urinary phosphate excretion was also elevated (1960 mg/day; reference: 400-1300 mg/day). Assessment of bone mineral density by dual-energy X-ray absorptiometry showed T-scores of -1.4 in the lumbar spine and -1.6 in the hip region. Genetic analysis revealed a heterozygous mutation in the *FGF23* gene. With the patient's consent, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) and ^{68}Ga -fibroblast (^{68}Ga -FAPI) PET/CT imaging were performed to determine lesion localization; however, no abnormal tracer uptake was observed (A, D). Subsequently, a ^{68}Ga -DOTATATE PET/CT scan was conducted. Axial PET and fused PET/CT images (I, K) revealed a focal tracer-avid lesion measuring approximately 2.5×1.2 cm at the proximal end of the right radius (maximum standard uptake value: 39.9). Corresponding CT images (J) revealed a mild increase in density within the medullary bone marrow area. The maximum intensity projection image (H) confirmed the localization of the primary lesion in the proximal right radius. Contrast-enhanced magnetic resonance imaging of the right forearm showed a lesion corresponding to the area of ^{68}Ga -DOTATATE uptake that appeared hyperintense on T2-weighted images, hypointense on T1-weighted images, and exhibited homogeneous contrast enhancement. The patient with additional comorbidities did not consent to histopathological examination. The patient is currently under follow-up and receiving vitamin D and oral phosphate supplementation.

Tumor-induced osteomalacia (TIO) typically originates from phosphaturic mesenchymal tumors, which are usually small, slow-growing, and benign, and can be located in soft tissue or bone throughout the body from the skull to the feet (1,2). These tumors are most commonly localized in the lower extremities and the head and neck region, whereas the upper extremities are the least frequently affected sites (3). Due to their typically small and solitary nature, identifying the exact location of these tumors is often challenging (4). Localization generally begins with functional imaging techniques, including somatostatin receptor (SSTR) imaging (^{68}Ga -DOTATATE or octreotide scan) and ^{18}F -FDG PET/CT (5). In a recent meta-analysis, SSTR-PET/CT demonstrated a higher detection rate for culprit tumors in TIO patients compared to ^{18}F -FDG PET/CT (6). Fibroblast activation protein inhibitor (FAPI) is known to accumulate in various benign and malignant conditions (7,8). Although only a limited number of TIO cases have been evaluated with FAPI imaging in the literature, some of these have shown uptake at the tumor site (9). We evaluated the contribution of ^{68}Ga -FAPI PET/CT, alongside ^{68}Ga -DOTATATE PET/CT and ^{18}F -FDG PET/CT, to tumor localization in a man with TIO. Our findings demonstrate the superiority of ^{68}Ga -DOTATATE PET/CT over ^{18}F -FDG and ^{68}Ga -FAPI PET/CT for lesion localization.

Ethics

Informed Consent: Written informed consent was obtained from all patients before imaging.

Footnotes

Authorship Contributions

Concept: Z.T., U.E.S., İ.Ö., M.Y., B.E.A., Design: U.E.S., İ.Ö., M.Y., B.E.A., E.A., Data Collection or Processing: U.E.S., İ.Ö., M.Y., B.E.A., E.A., Analysis or Interpretation: U.E.S., İ.Ö., M.Y., B.E.A., E.A., Literature Search: U.E.S., İ.Ö., M.Y., B.E.A., E.A., Writing: Z.T., U.E.S., E.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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⁶⁸Ga-DOTATATE Uptake in Rare Metastatic/Inoperable Mediastinal Paraganglioma with Anomalous Coronary Supply

Anormal Koroner Beslenmeye Sahip Nadir Metastatik/İnoperabl Mediastinal Paragangliomada ⁶⁸Ga-DOTATATE Tutulumu

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Abstract

Mediastinal paragangliomas (PGLs) are extremely rare neuroendocrine tumors. Clinical presentation varies and tumor resection can be challenging due to bleeding and risk of catecholamine surges in functional tumors. We report on a case 68 with a DOTATATE avid mediastinal mass which was histopathologically confirmed as a PGL that was fed by the coronary artery in whole-body positron emission tomography/computed tomography imaging using gallium-68-DOTATATE.

Keywords: Paraganglioma, neuroendocrine tumor, ⁶⁸Ga-DOTATATE, ¹⁷⁷Lu-DOTATATE, PET/CT

Öz

Mediastinal paragangliomalar (PGLs) son derece nadir görülen nöroendokrin tümörlerdir. Klinik tablo değişkenlik gösterir ve fonksiyonel tümörlerde kanama ve katekolamin artışı riski nedeniyle tümör rezeksiyonu zor olabilir. Bu yazıda, galyum-68-DOTATATE kullanılarak yapılan tüm vücut pozitron emisyon tomografisi/bilgisayarlı tomografi görüntülemesinde koroner arter tarafından beslenen bir PGL olarak histopatolojik olarak doğrulanan, DOTATATE tutulumu gösteren bir mediastinal kitle olgusunu sunuyoruz.

Anahtar Kelimeler: Paraganglioma, nöroendokrin tümör, ⁶⁸Ga-DOTATATE, ¹⁷⁷Lu-DOTATATE, PET/BT

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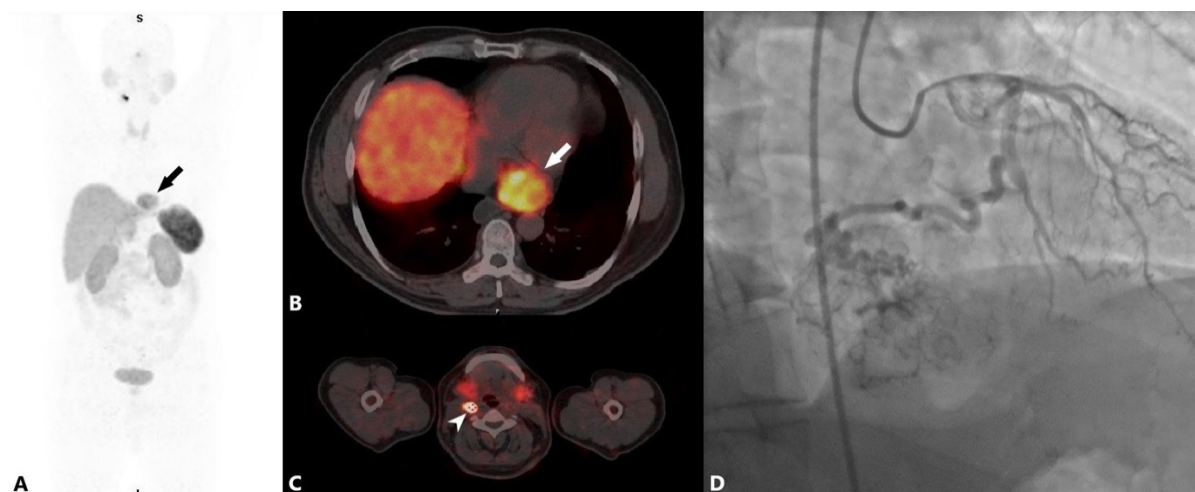


Figure 1. A 52-year-old male patient with significantly elevated normetanephrine level presenting with headache and hypertension was referred for gallium-68 DOTATATE positron emission tomography/computed tomography (PET/CT) for further evaluation. The maximum intensity projection (A) and axial PET/CT (B and C) images revealed a high DOTATATE uptake in the mediastinal mass (black and white arrows; maximum [standard uptake values (SUV_{max}): 18.34] and lymph node at right level 2 (arrowhead; SUV_{max} : 56.56). A thoracotomy was performed to remove the mass, which was determined to be a paraganglioma by histopathology, but it was deemed inoperable because of proximity to major thoracic structures and fed by the coronary artery (D).

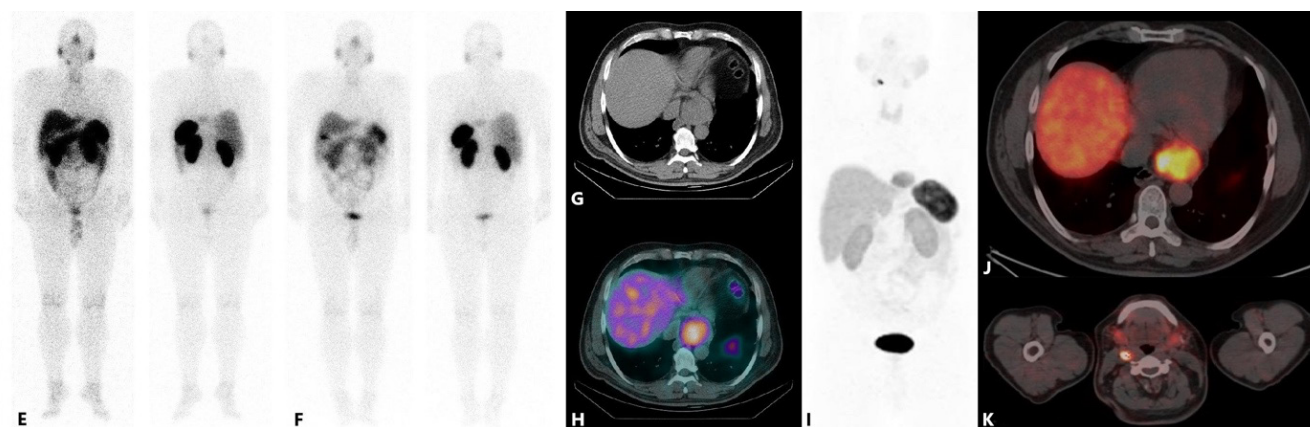


Figure 2. Following embolization of the feeder branch using particles and four cycles of peptide receptor radionuclide therapy (PRRT) with lutetium-177 DOTATATE (^{177}Lu -DOTATATE) [whole-body scans after PRRT, (E) for first cycle and (F) for fourth cycle]. After 4 cycles of ^{177}Lu -DOTATATE, computed tomography (CT) (G) and single photon emission tomography/CT axial fusion (H) images of mediastinal mass. After treatment uptake of cervical lesion was decrease while mediastinal mass uptake was stable. Post-PRRT gallium-68 DOTATATE positron emission tomography/CT [^{68}Ga -DOTATATE PET/CT] maximum intensity projection (I) and axial fusion (J and K) images of mediastinal mass and cervical lymph node. ^{68}Ga -DOTATATE PET/CT imaging in March 2025, 9 months following to fourth cycle, showed partial decreased in tracer avidity with in cervical lymph node [maximum standard uptake values (SUV_{max}): decreased from 56.56 to 33.19; Krenning score of 4 to a score of 3]. Mediastinal mass was stable (SUV_{max} minimal decreased from 18.34 to 17.49; Krenning score of 3 to a score of 3). According to PERCIST criteria, the patient classified stable disease. The serum norepinephrine decreased from 432 to 282 nmol/L after 4 cycles. The patient's symptoms were improved during follow-up. Mediastinal paragangliomas (PGLs) are extremely rare, accounting for approximately 1% to 2% of all PGLs. In patients with inoperable or metastatic PGL, symptomatic or progressive disease is usually treated with chemotherapy, radionuclide therapy, external radiotherapy or tyrosine kinase inhibitors. Functional mediastinal PGLs with anomalous coronary considered high-risk surgically. ^{177}Lu -DOTATATE therapy is safe modality for inoperable and metastatic mediastinal PGLs. ^{68}Ga -DOTA-coupled peptides can be used for imaging because PGLs, which are neuroendocrine tumors arising from pluripotent neural crest stem cells, express somatostatin receptors. Since neuroendocrine tumors overexpress somatostatin receptor like PGLs, ^{68}Ga -DOTATATE PET/CT has a high specificity in detecting them. With the use of DOTATATE's theranostic qualities, patients who may be suitable for PRRT can be chosen using ^{68}Ga -DOTATATE PET/CT (1-7). This report highlights the role of DOTA-coupled peptides in the diagnostic and therapeutic applications of a rare patient with a mediastinal PGL with an unusual coronary artery supply, which poses a high surgical risk.

Ethics

Informed Consent: The written informed consent was obtained from the patient.

Authorship Contributions

Concept: B.O., Design: B.O., Data Collection or Processing: R.Y., M.Ö., Analysis or Interpretation: R.Y., M.Ö., Literature Search: B.O., R.Y., Writing: B.O.

Conflict of Interest: The authors declare no conflicts of interest.

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Persistent ^{18}F -FDG Uptake in a Post-treatment Hodgkin's Lymphoma: Not Always Residual Disease

Hodgkin Lenfomada Tedavi Sonrası Kalıcı ^{18}F -FDG Tutulumu: Her Zaman Rezidü Hastalık Değildir

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Abstract

We report the case of a 31-year-old woman with osseous Hodgkin's lymphoma who underwent post-therapeutic ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography. The scan revealed a hypermetabolic lesion in the pubic symphysis and iliac crests, initially suggestive of residual disease. Multimodal evaluation, including $^{99\text{m}}\text{Tc}$ -methoxy-isobutyl-isonitrile scintigraphy, laboratory tests revealed primary hyperparathyroidism, and biopsy confirmed a brown tumor. This case highlights the importance of integrating multimodal imaging and pathology to avoid misinterpretation of ^{18}F -FDG-avid lesions.

Keywords: Hodgkin's lymphoma, brown tumor, primary hyperparathyroidism, ^{18}F -FDG PET/CT, $^{99\text{m}}\text{Tc}$ -MIBI scintigraphy

Öz

Osseöz Hodgkin lenfoması olan 31 yaşındaki bir kadının, tedavi sonrası ^{18}F -florodeoksiglukoz (^{18}F -FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) incelemesi sunulmaktadır. Görüntülemeye pubik simfiz ve iliak krestlerde hipermetabolik bir lezyon saptanmış ve başlangıçta rezidüel hastalık olarak değerlendirilmiştir. Ancak $^{99\text{m}}\text{Tc}$ -metoksi-izobütil-izonitril ($^{99\text{m}}\text{Tc}$ -MIBI) sintigrafisi ve laboratuvar testlerini içeren multimodal değerlendirme sonucunda primer hiperparatiroidizm saptanmış, biyopsi ise kahverengi tümörü doğrulamıştır. Bu olgu, ^{18}F -FDG tutulumu gösteren lezyonların yanlış yorumlanmasını önlemek için multimodal görüntüleme ve patolojik değerlendirmenin birlikte ele alınmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Hodgkin lenfoması, kahverengi tümör, primer hiperparatiroidizm, ^{18}F -FDG PET/BT, $^{99\text{m}}\text{Tc}$ -MIBI sintigrafisi

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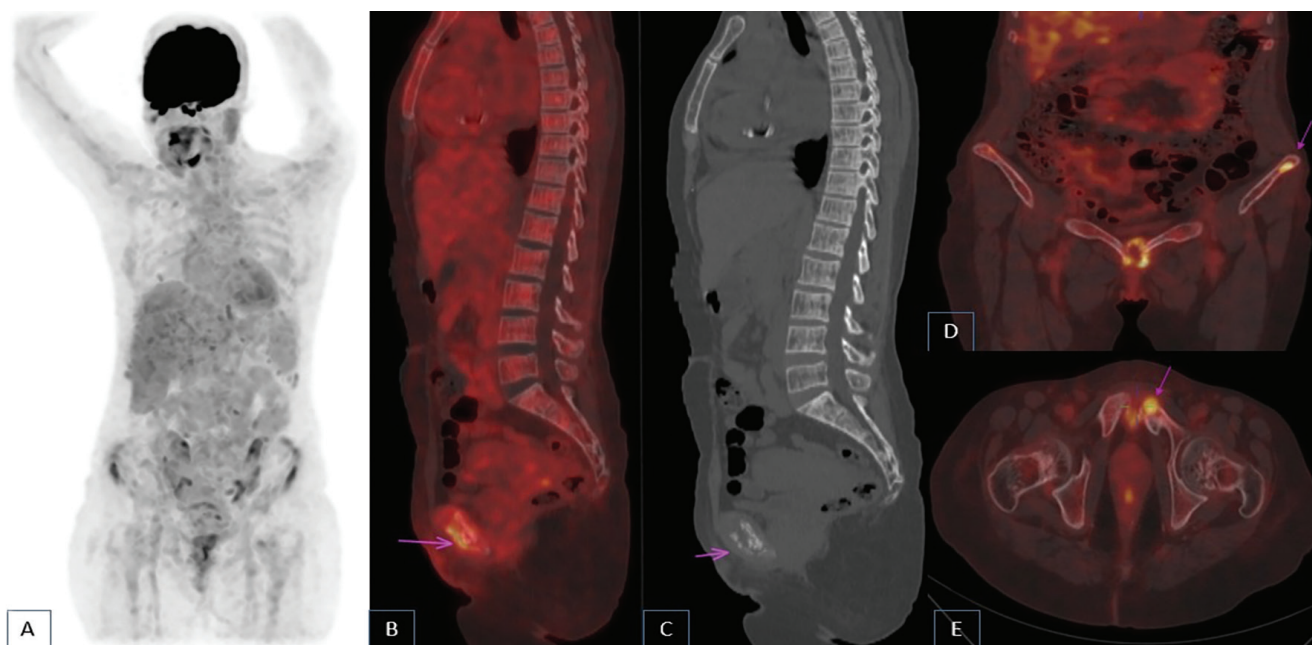


Figure 1. A young woman being followed for stage IV osseous Hodgkin's lymphoma was referred for post-therapeutic morpho-metabolic evaluation. A positron emission tomography/computed tomography scan using ^{18}F -fluorodeoxyglucose (^{18}F -FDG) was performed, showing the physiological and pathological distribution of the radiopharmaceutical (maximum intensity projection; A). The examination demonstrated a complete metabolic response in the initial tumoral sites and a persistent focal uptake in the pubic symphysis and left iliac crest maximum standard uptake values of 4.6 (fusion and computed tomography images in sagittal projection and fusion images in coronal and axial projection; arrow; B, C, D, E). Further investigations were performed, as ^{18}F -FDG-avid benign bone lesions, including brown tumors, can mimic residual malignancy (1), particularly when the location is atypical for residual lymphoma.

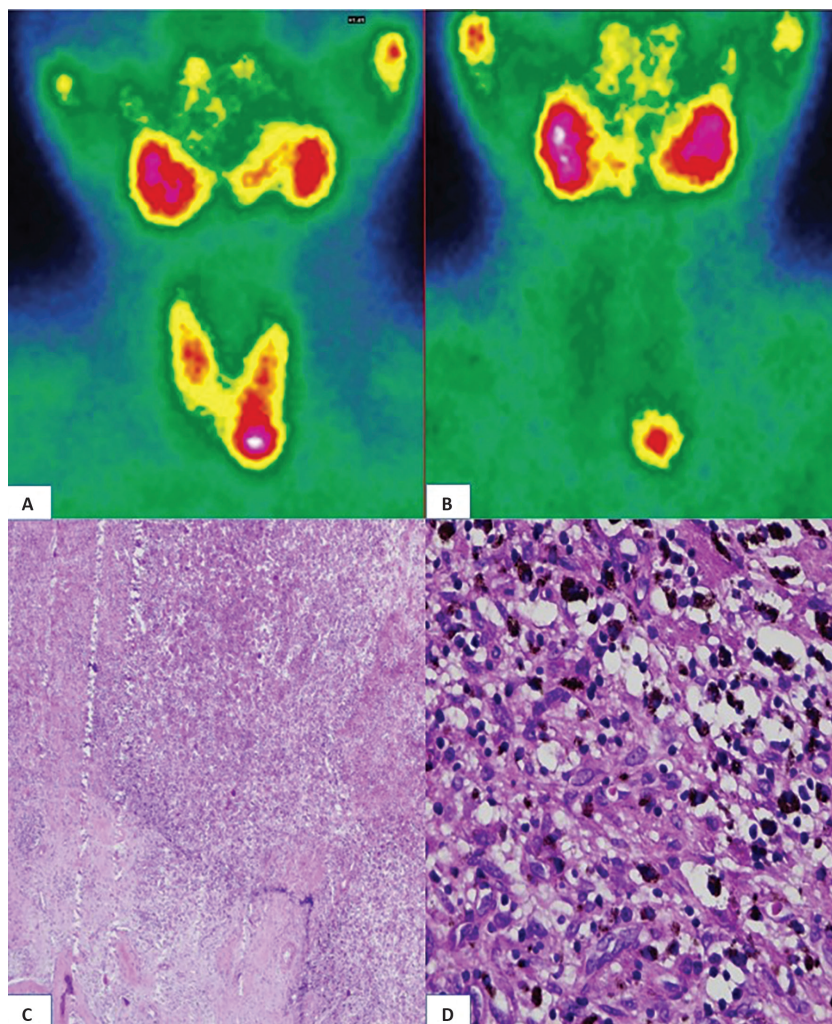


Figure 2. Laboratory tests revealed elevated parathyroid hormone (PTH) at 123 pg/mL, suggesting that primary hyperparathyroidism is the underlying cause of the bone abnormalities and ^{18}F -fluorodeoxyglucose (^{18}F -FDG) uptake. $^{99\text{m}}\text{Tc}$ -methoxy-isobutyl-isonitrile scintigraphy parathyroid scintigraphy was performed, revealing a persistent focal radiotracer uptake located in the inferior left thyroid lobe on both early and delayed planar images, consistent with a parathyroid adenoma (early images showing tracer uptake in both thyroid lobes and a focal area of increased activity inferior to the left thyroid lobe; A and delayed images demonstrating persistent focal uptake at the same site; B). Histopathological examination of the pubic symphysis biopsy revealed multinucleated giant cells with eosinophilic cytoplasm, intermingled with mononuclear cells and hemosiderin deposits, consistent with a brown tumor, confirming a benign process (low- and high-magnification microscopic sections showing a lobulated bone lesion; panels C and D). These findings underscore the importance of integrating metabolic imaging with biochemical and histological assessments to avoid misinterpretation of benign ^{18}F -FDG-avid lesions during post-therapeutic lymphoma evaluation (2,3).

On ^{18}F -FDG positron emission tomography/computed tomography, brown tumors may demonstrate intense metabolic activity and closely mimic malignant bone lesions. This increased ^{18}F -FDG uptake reflects their high cellularity and increased osteoclastic activity, both of which are driven by excessive PTH stimulation. The resulting bone resorption leads to an accumulation of metabolically active fibroblasts and multinucleated giant cells with elevated glucose metabolism, explaining their strong ^{18}F -FDG avidity. Similar diagnostic pitfalls have been reported, in which ^{18}F -FDG-avid skeletal lesions were initially misinterpreted as metastases or giant-cell tumors before being correctly identified by biochemical assays and parathyroid scintigraphy (1,2). Although the coexistence of Hodgkin lymphoma and brown tumor is rare, previous reports have described benign ^{18}F -FDG-avid bone lesions persisting after lymphoma remission, including giant cell tumor and fibrous dysplasia (4,5). Therefore, brown tumors and giant cell tumors should be considered in the differential diagnosis of ^{18}F -FDG-avid bone lesions, particularly in the absence of biochemical or histopathological correlation.

Ethics

Informed Consent: The informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Concept: D.N., A.M., S.M., I.G., H.G., Design: D.N., A.M., S.M., I.G., H.G., Data Collection or Processing: D.N., Analysis or Interpretation: D.N., A.M., H.G., Literature Search: D.N., Writing: D.N.

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Diffuse Gastric Uptake and Metabolic Superscan in the Patient with Multiple Myeloma

Multipl Miyelomlu Hastada Yaygın Gastrik Tutulum ve Metabolik Superscan

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Abstract

Metastatic calcification is characterized by abnormal deposition of calcium in extraosseous tissues resulting from disruption of calcium-phosphorus homeostasis. It occurs without tissue damage and is usually seen in normal organs. It is most commonly observed in patients with chronic renal failure, paraneoplastic hypercalcemia, and vitamin D intoxication. Metabolic superscan is characterized by diffusely increased skeletal activity with suppressed renal visualization, often without soft-tissue involvement. This pattern reflects altered radiotracer biodistribution secondary to severe metabolic bone turnover. We report a case of multiple myeloma in which diffuse ^{99m}Tc-MDP uptake was observed in the stomach on a metabolic superscan.

Keywords: Multiple myeloma, metabolic superscan, gastric uptake, hypercalcemia, methylene diphosphonate, bone scan

Öz

Metastatik kalsifikasyon, kalsiyum-fosfor homeostazının bozulması ile kemik dışı dokularda anormal kalsiyum birikimiyle karakterize durumdur. Dokuda hasar olmaksızın meydana gelir ve genellikle organ fonksiyonu normal olan dokularda görülür. Sıklıkla kronik böbrek yetmezliği, paraneoplastik hiperkalsemi ve D vitamini intoksikasyonu durumlarına eşlik eder. Metabolik superscan ise kemik sintigrafisinde renal aktivitenin kaybıyla giden diffüz artmış kemik tutulumunu ile karakterize durumdur. Genellikle kemik dışı organ tutulumu görülmemektedir. Bu patern, yoğun metabolik kemik döngüsüne bağlı bozulmuş radyoizotop biyodağılımını yansıtmaktadır. Bu çalışmada, metabolik superscan zemininde midede yaygın ^{99m}Tc-MDP tutulumu gösteren multiple myelom hastası sunulmaktadır.

Anahtar Kelimeler: Multiple myelom, metabolik superscan, gastrik tutulum, hiperkalsemi, metilen difosfonat, kemik sintigrafisi

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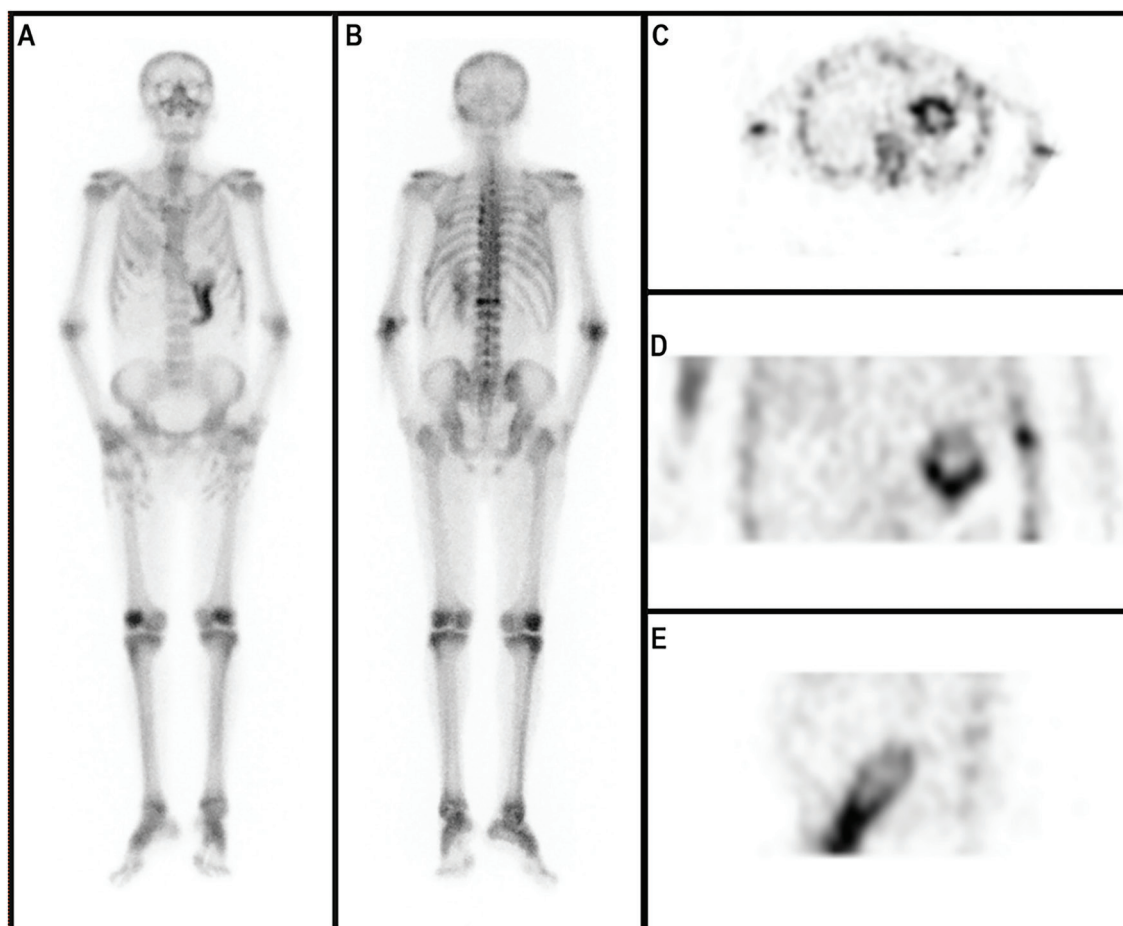


Figure 1. A sixty-seven-year-old man was referred for bone scintigraphy to evaluate a suspected paraneoplastic compression fracture of the lumbar vertebrae. The patient had advanced renal failure during the past year. In the tests conducted one day prior to imaging, calcium was 14.3 mg/dL (normal range: 8.5-10.5 mg/dL), albumin was 2.8 g/L, and his haemoglobin was 9.9 g/dL. The patient had widespread bone pain, predominantly involving the lumbar region. Bone scintigraphy revealed linear accumulation of activity in the first lumbar vertebra and focal increased uptake in various ribs on planar images (A, B) and diffuse increased ^{99m}Tc -MDP uptake in the gastric wall on SPECT axial, coronal, and sagittal images (C, D, E). There was no renal retention; the findings were consistent with the metabolic superscan. Written informed consent for the anonymized publication of clinical data and images was obtained from the patient prior to the initiation of the study.

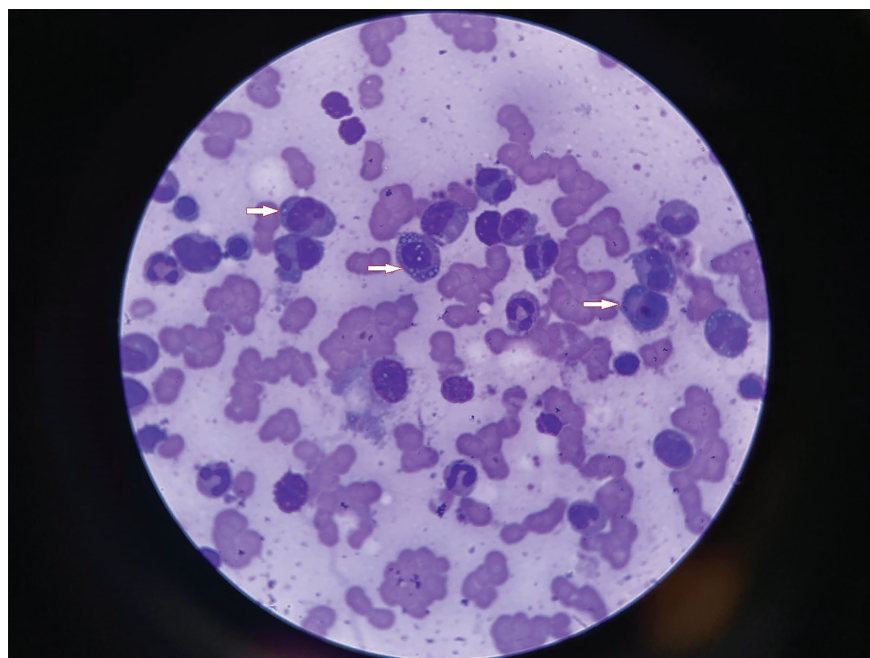


Figure 2. A bone biopsy was performed during vertebroplasty surgery, and atypical plasma cells were detected, which led to further investigation for multiple myeloma. Free kappa light chain was 22 mg/L, free lambda light chain was 4,550 mg/L, and the involved/uninvolved ratio was higher than 100. Bone marrow aspiration and biopsy were performed; more than 20% plasma cells (mostly bizarre forms and plasmablasts) were noted (Figure 2, arrows), and the amyloid stain was negative. The concurrent gastric mucosal biopsy was also negative for amyloid staining. The patient was diagnosed with lambda light-chain multiple myeloma. Free lambda light-chain concentration declined to 38 mg/L at the four-month follow-up after treatment. In the present case, diffuse gastric ^{99m}Tc -MDP uptake was observed in association with severe hypercalcemia and a metabolic superscan pattern in a patient with newly diagnosed multiple myeloma. Radionuclide bone scans are not routinely recommended in multiple myeloma since the disease usually progresses with osteolytic lesions (1). The disease is characterized by systemic amyloid deposits or hypercalcemia; cases of extraosseous tracer uptake have rarely been reported, including gastric uptake (2,3,4,5). Kanoh et al. (6) performed gastric biopsies in a patient with myeloma who demonstrated amyloid deposits, and hypothesized that this was the cause of the observed activity. In our case, amyloid staining of the gastric mucosa was negative. Cases showing gastric uptake have been reported in the literature; however, the unique feature of our case was diffuse gastric involvement occurring concomitantly with a metabolic superscan, which has not been observed in other cases (7,8).

Ethics

Informed Consent: Written informed consent for the anonymized publication of clinical data and images was obtained from the patient prior to the initiation of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.B.B., Ö.Ş., G.B., H.A., F.T., Concept: G.B.B., G.B., E.B., Design: G.B.B., H.A., E.B., Data Collection or Processing: G.B.B., H.A., E.B., Analysis or Interpretation: Ö.Ş., H.A., Literature Search: G.B.B., F.T., Writing: G.B.B., Ö.Ş., F.T., E.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Follicular Thyroid Carcinoma with Cavernous Sinus Metastasis and Perineural Spread: A Rare Manifestation of Radioiodine-refractory Disease

Kavernöz Sinüs Metastazı ve Perinöral Yayılım Gösteren Foliküler Tiroid Karsinomu: Radyoiyot Tedavisine Dirençli Hastalığın Nadir Bir Belirtisi

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Abstract

Cavernous sinus metastasis from follicular thyroid carcinoma (FTC) is exceedingly rare and typically indicates advanced, radioiodine-refractory disease. We report a 37-year-old man with minimally invasive FTC who was treated with total thyroidectomy, neck dissection, and cumulative radioiodine therapy totaling 720 mCi for persistent iodine-avid disease. Four years later, he developed progressive left-sided palsies of cranial nerves III, IV, and VI. Imaging revealed a cavernous sinus mass with orbital apex extension and perineural spread. Serum thyroglobulin was markedly elevated (>500 ng/mL), whereas diagnostic radioiodine scintigraphy demonstrated no uptake, a finding consistent with dedifferentiated disease. Biopsy confirmed metastatic FTC. The patient received external beam radiotherapy and systemic therapy with lenvatinib; however, the disease progressed, and he died 16 months after the diagnosis of cavernous sinus metastasis. This case highlights the aggressive potential of FTC, the limitations of radioiodine imaging in dedifferentiated disease, and the poor prognosis associated with skull-base metastases despite multimodal therapy.

Keywords: Follicular thyroid cancer, cavernous sinus metastasis, iodine-131 whole-body scintigraphy, ¹⁸F-FDG PET/CT

Öz

Foliküler tiroid karsinomundan (FTC) kaynaklanan kavernoöz sinüs metastazı son derece nadirdir ve tipik olarak ilerlemiş, radyoiyot tedavisine dirençli hastalığı gösterir. Bu yazıda, minimal invaziv FTC'si olan ve total tiroidektomi, boyun diseksiyonu ve kalıcı iyot tutulumu nedeniyle 720 mCi kümülatif radyoiyot tedavisi uygulanan 37 yaşında bir erkek hastayı bildiriyoruz. Dört yıl sonra, ilerleyici, sol üçüncü, dördüncü ve altıncı kraniyal sinir felçleri gelişti. Görüntüleme, orbital apeks uzantısı olan ve perinöral yayılım gösteren bir kavernoöz sinüs kitlesi saptandı. Serum tiroglobulin düzeyi belirgin yüksekti (>500 ng/mL), tanısal radyoiyot sintigrafisi ise dediferansiyasyon hastalığıyla uyumlu olarak tutulum göstermedi. Biyopsi, metastatik FTC'yi doğruladı. Hastaya eksternal radyoterapi ve lenvatinib ile sistemik tedavi uygulandı; ancak hastalık ilerledi ve kavernoöz sinüs metastazı tanısından 16 ay sonra hayatını kaybetti. Bu olgu, foliküler tiroid kanserinin agresif potansiyelini, dediferansiyasyon hastalığında radyoiyot görüntülemenin sınırlılıklarını ve çok yönlü tedaviye rağmen kafa tabanı metastazlarıyla ilişkili kötü prognozu vurgulamaktadır.

Anahtar Kelimeler: Foliküler tiroid kanseri, kavernoöz sinüs metastazı iyot-131 tüm vücut sintigrafisi, ¹⁸F-FDG PET/CT

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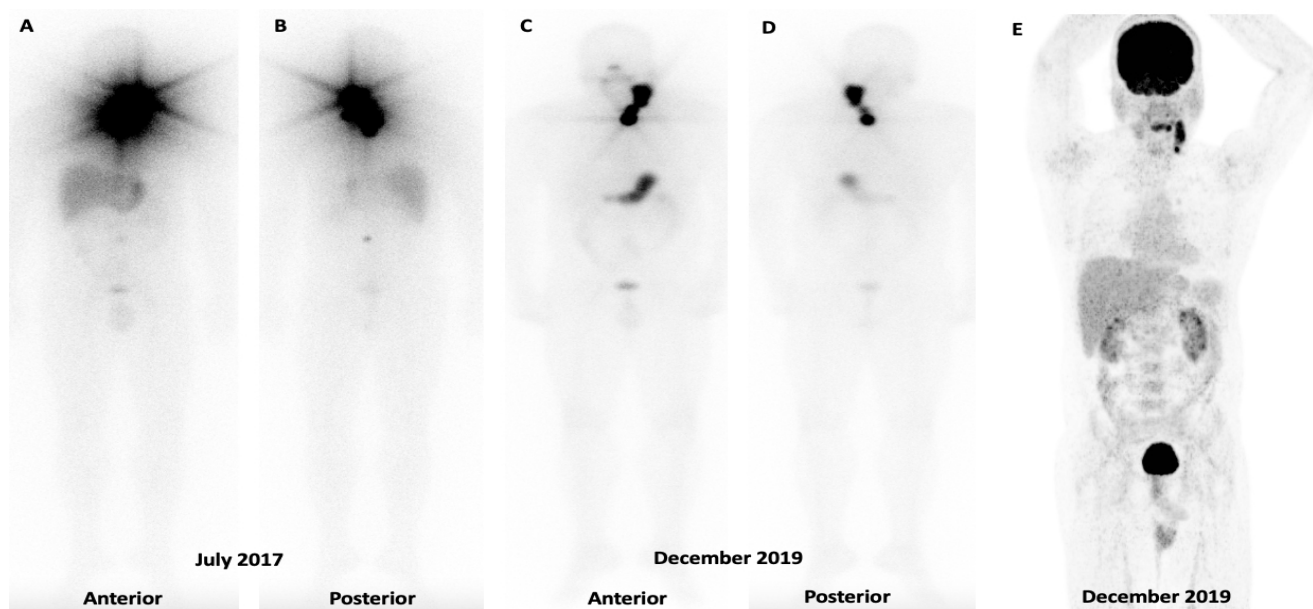


Figure 1. A 37-year-old man with minimally invasive follicular thyroid carcinoma (FTC) presented with a left thyroid nodule and underwent hemithyroidectomy, followed by completion thyroidectomy and left cervical lymph node dissection, which confirmed metastatic disease (pT3aN1bM0). He subsequently received multiple courses of adjuvant radioiodine therapy (a cumulative dose of 720 mCi) for persistent iodine-avid disease in the thyroid bed, cervical region, and upper mediastinum (A, B). Despite repeated treatment, serial imaging demonstrated residual disease (C, D), and stimulated serum thyroglobulin levels progressively rose to >500 ng/mL, indicating ongoing tumor activity. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography demonstrated metabolically active left cervical lymphadenopathy (E), which was followed by locoregional recurrence requiring further surgical resection.

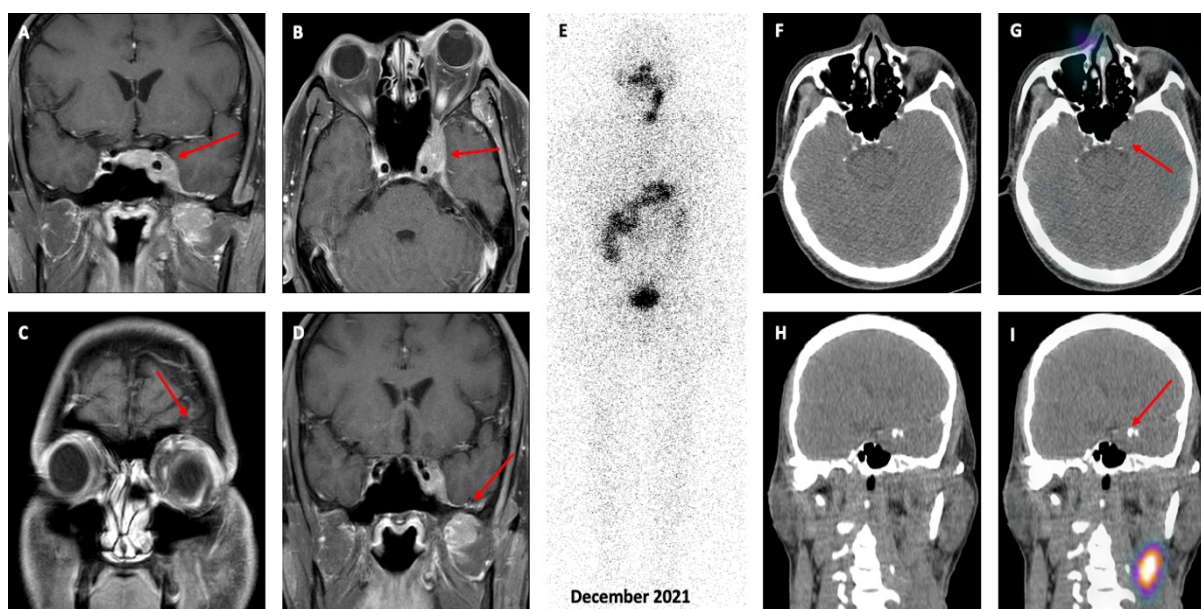


Figure 2. Four years after initial diagnosis, the patient developed progressive left-sided ptosis and ophthalmoplegia, corresponding to palsies of cranial nerves III, IV, and VI. Contrast-enhanced computed tomography (CT) and T1-weighted magnetic resonance imaging revealed an enhancing mass centered in the left cavernous sinus (A, B), measuring approximately 3.6 cm and extending into the orbital apex (C). Perineural spread was present along the mandibular and auriculotemporal nerves, with involvement of the deep lobe of the parotid gland, pterygopalatine fossa, and adjacent masticator space (D). Diagnostic iodine-131 whole-body scintigraphy (E) and SPECT/CT (F-I), performed following recombinant thyroid-stimulating hormone stimulation, demonstrated no abnormal uptake in the cavernous sinus region, confirming loss of iodine avidity.

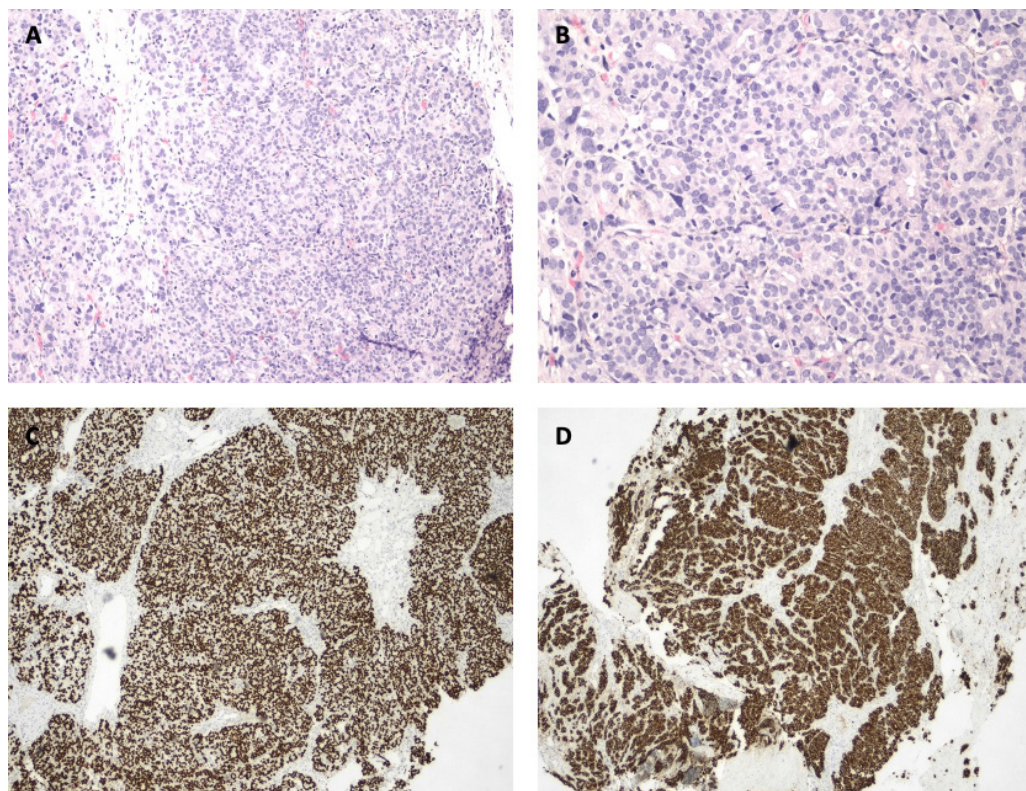


Figure 3. Biopsy demonstrated histopathological and immunohistochemical features of metastatic follicular thyroid carcinoma (FTC). (A) low-power view (x4) showing follicular and nested architecture; (B) high-power view (x20) demonstrating pleomorphic nuclei and mitotic figures; (C) positive nuclear staining for TTF-1; (D) positive cytoplasmic staining for CK7. These findings confirm metastatic FTC and are consistent with radioiodine-refractory disease.

FTC characteristically spreads via hematogenous dissemination, most commonly to the lungs and bones, whereas intracranial metastases are rare (1,2). Cavernous sinus involvement represents an uncommon manifestation of advanced disease and often presents with cranial neuropathies due to its proximity to critical neurovascular structures (3). Tumor spread may occur via the valveless vertebral venous plexus or, less commonly, lymphatic pathways (1). In this case, perineural spread represents an additional route of extension and is associated with aggressive tumor biology and poorer outcomes (4). Loss of radioactive iodine (RAI) avidity reflects tumor dedifferentiation with reduced sodium-iodide symporter expression, signifying transition to radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC), which carries a poorer prognosis and limited therapeutic options (5,6). Further RAI therapy is ineffective, and management shifts toward alternative strategies. Given the inoperable skull-base location, external beam radiotherapy was administered for local control, in line with recommendations from the American Head and Neck Society (7). Systemic therapy with lenvatinib was initiated but required modification due to tolerability issues. Despite multimodal treatment, the disease progressed, and the patient died 16 months after diagnosis of cavernous sinus metastasis, reflecting the poor prognosis associated with intracranial involvement in RAIR-DTC (2,6). This case highlights a delayed aggressive transformation in FTC, emphasizes the recognition of atypical metastatic patterns such as cavernous sinus involvement and perineural spread, and underscores the limitations of radioiodine imaging in dedifferentiated disease.

Ethics

Informed Consent: The patient provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.L., M.F.M.R., S.Z.A.H.,
Concept: H.L., M.F.M.R., Design: H.L., M.F.M.R., Data

Collection or Processing: H.L., M.F.M.R., R.G., Analysis or Interpretation: H.L., M.F.M.R., J.J., R.G., S.Z.A.H., Literature Search: H.L., M.F.M.R., J.J., R.G., S.Z.A.H., Writing: H.L., M.F.M.R., J.J., R.G., S.Z.A.H.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Pearls and Pitfalls of ^{18}F -FDG PET/CT for Suspected Alzheimer's Disease in Patient with Down Syndrome

Alzheimer Hastalığından Şüphelenilen Down Sendromlu Olgunun Beyin ^{18}F -FDG PET/CT'sindeki İnciler ve Tuzaklar

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Abstract

Dementia in individuals with Down syndrome (DS) is the leading cause of early-onset cognitive decline occurring before the age of 50. However, establishing an accurate diagnosis remains particularly challenging due to pre-existing intellectual disability, variability in baseline cognitive function, and the limited reliability of standard neuropsychological assessments. ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) plays a critical role in identifying underlying neurodegenerative processes and supporting the diagnosis. We present a case of DS with multiple known and unknown pathologies identified on brain ^{18}F -FDG PET and a confirmed diagnosis of early-onset mild Alzheimer's disease.

Keywords: ^{18}F -FDG, dementia, Alzheimer, Down syndrome

Öz

Down sendromlu (DS) bireylerde demans, 50 yaş altındaki erken başlangıçlı bilişsel gerilemenin en sık nedenidir. Ancak, önceden var olan entelektüel yetersizlik, başlangıç bilişsel düzeyindeki bireysel farklılıklar ve standart nöropsikolojik testlerin sınırlı güvenilirliği nedeniyle doğru tanı koymak oldukça güçtür. ^{18}F -florodeoksiglukoz pozitron emisyon tomografisi (^{18}F -FDG PET) altta yatan nörodejeneratif süreçlerin ortaya konulmasında ve tanının desteklenmesinde kritik bir rol oynamaktadır. Burada, beyin ^{18}F -FDG PET incelemesinde hem bilinen hem de atipik patolojilerin saptandığı ve erken başlangıçlı hafif Alzheimer hastalığı tanısı konulan DS'li bir olguyu takdim ediyoruz.

Anahtar Kelimeler: ^{18}F -FDG, demans, Alzheimer, Down sendromu

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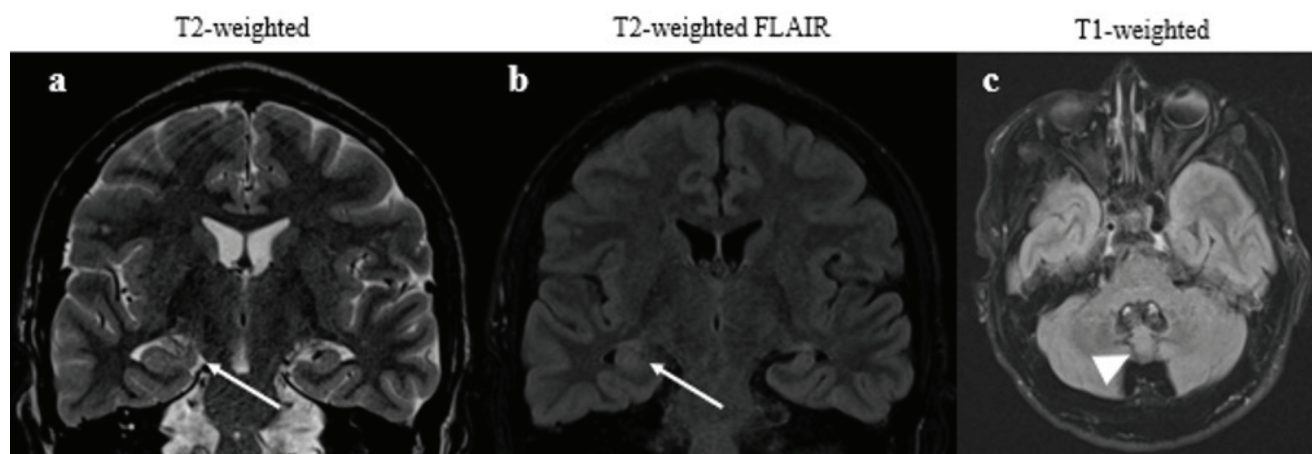


Figure 1. Thirty-five-year-old man patient with Down syndrome admitted to hospital with forgetting tasks, decrease in expression of wants/desires. After an episode leading to a fall/presumed seizure 5 years ago, his cognition and demeanor have changed. Electroencephalography revealed stiffening behaviors that are inconsistent with seizures. The Montreal Cognitive Assessment score was 6/30. Brain magnetic resonance imaging revealed mild volume loss of both hippocampi without abnormal T2/FLAIR signal, which likely represents degenerative changes associated with Trisomy-21 (a and b; arrows). Vermian hypoplasia with prominent extra-axial spaces was detected (c; arrowhead).

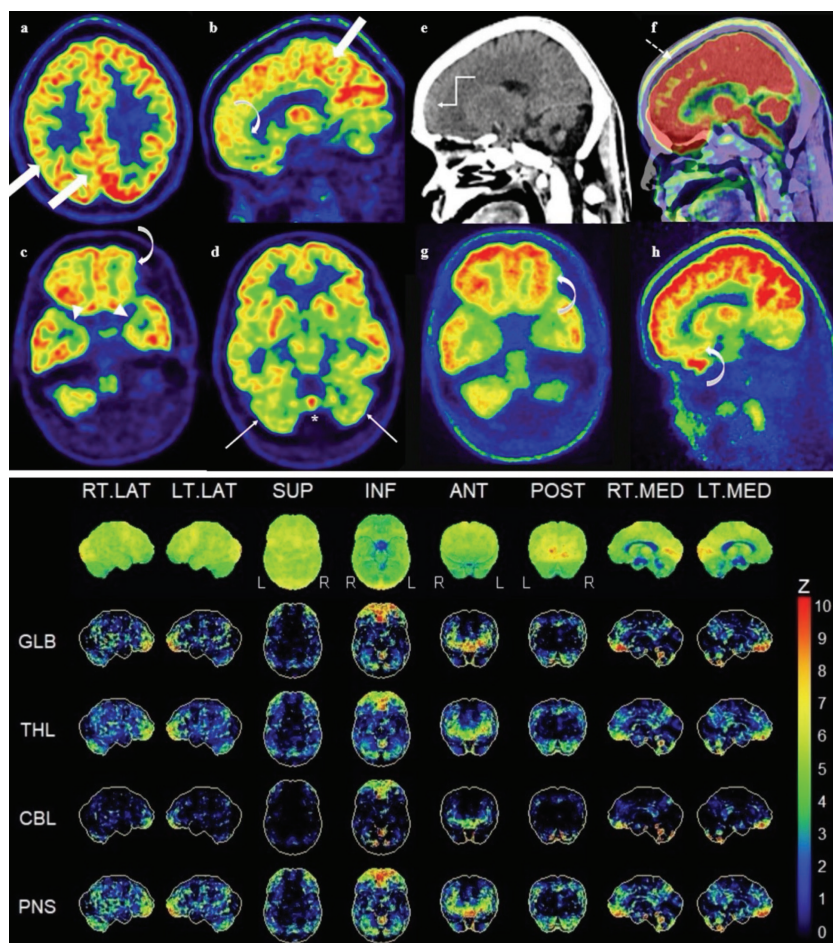


Figure 2. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) scan revealed mildly decreased uptake in the parieto-temporal lobes and precuneus bilaterally which were consistent with Alzheimer's disease (AD) (a and b; thick arrows). Markedly decreased uptake was detected bilaterally in the anteromedial temporal lobes, secondary to mild hippocampal atrophy (c; arrowheads). Because of cerebellar verian hypoplasia, uptake was decreased in the cerebellar hemispheres (d; thin arrows) and in the midline cerebellum (d; asterisk).

Decreased uptake was detected bilaterally in the anterior-inferior frontal lobes (b and c; right-curved arrow) without lobar atrophy on CT images (e; elbow-arrow). In the fused images, approximately 5 mm of head motion in the axial plane was detected between the CT and PET scans (f; dashed-arrow). Hypometabolism in the frontal lobes may have been an attenuation-correction artefact, but, in the light of non-attenuation-corrected (NAC) images, it is probably indicative of true hypometabolism (g and h; left-curved arrow).

The three-dimensional Stereotactic Surface Projections (3D-SSP) demonstrate the AD-related hypometabolic pattern by projecting stereotactically normalized ^{18}F -FDG PET data onto a standardized cortical surface and displaying deviations from an age-matched normative database. Unfortunately, no biomarker test was performed.

DS dementia is the most common form of dementia under the age of 50-years (1). Diagnosing dementia in Down syndrome (DS) could be challenging because of learning disabilities, unknown accuracy of cognitive tests, difficulties performing mental tests, and heterogeneity of intellectual functions. Similar pattern of hypometabolism in AD diagnosed cases either sporadic or DS, suggesting similar neurodegeneration processes (2). Although the diagnosis of AD was not confirmed with biomarker tests in our cases, a strong association between metabolic changes with biomarker levels was already reported (2). 3D-SSP analysis which was proved to be useful in objectively revealing early metabolic changes confirmed AD (3,4,5).

Neuroimaging presents some limitations in DS. Impaired communication may produce artifacts resulting from movement during acquisition. It has been reported that a spatial mismatch of 5-10 mm may result in errors of approximately 10-25% in measured ^{18}F -FDG PET activity (6,7,8). In our cases, we confirmed hypometabolism in the frontal lobes on NAC images. As a reflection difference in brain development, DS participants with or without dementia show lower metabolic rate and gray matter volume in frontal regions (9). Besides, larger involvement of frontal regions in DS cases with AD than sporadic AD cases was also reported (2).

^{18}F -FDG PET was critical not only because it revealed metabolic changes in anatomical pathologies that had already been detected by magnetic resonance imaging, but also because it clarified the AD diagnosis relevant to his current complaints. However, possible artefacts and variations must be well known in this specific patient group.

Ethics

Informed Consent: The written and verbal informed consent was obtained from the patient and his custodian.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.A., Concept: E.A., S.M., Design: E.A., S.M., Data Collection or Processing: E.A., Analysis or Interpretation: E.A., S.M., Literature Search: E.A., Writing: E.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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PET/CT Identifies Pubic Melorheostosis with High ⁶⁸Ga-PSMA Uptake in a Patient with Prostate Cancer

Prostat Kanserli Bir Hastada PET/BT ile Yüksek ⁶⁸Ga-PSMA Tutulumu Gösteren Meloreostosis Saptanması

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Abstract

Melorheostosis, a rare benign bone disorder marked by cortical thickening and irregular hyperostosis, typically affects peripheral bones but can also involve the axial skeleton. Though various molecular imaging radiotracers have been used to evaluate this condition, there are no previous reports of positive ⁶⁸Ga-prostate-specific membrane antigen positron emission tomography/computed tomography (⁶⁸Ga-PSMA PET/CT) findings in melorheostosis. This case presents a 70-year-old man with metastatic prostate cancer whose ⁶⁸Ga-PSMA PET/CT scan revealed intense ⁶⁸Ga-PSMA uptake in pubic melorheostosis seen on magnetic resonance imaging. The case highlights the possibility of ⁶⁸Ga-PSMA-avid melorheostosis and suggests ⁶⁸Ga-PSMA PET/CT may have a role in the evaluation of melorheostosis.

Keywords: Melorheostosis, ⁶⁸Ga-PSMA, diagnostic challenge, PET/CT, prostate cancer, false positive

Öz

Melorheostosis, kortikal kalınlaşma ve düzensiz hiperostosis ile karakterize nadir görülen benign bir kemik hastalığıdır. Genellikle periferik kemikleri etkiler, ancak aksiyal iskeleti de tutabilir. Bu hastalığın değerlendirilmesinde çeşitli moleküler görüntüleme radyofarmasötikleri kullanılmış olsa da, melorheostoziste pozitif ⁶⁸Ga-prostat spesifik membran antijeni pozitron emisyon tomografisi/bilgisayarlı tomografi (⁶⁸Ga-PSMA PET/BT) bulgularına dair daha önce herhangi bir bildirim bulunmamaktadır. Bu olguda, metastatik prostat kanseri olan 70 yaşındaki bir erkek hastada, manyetik rezonans görüntülemeye saptanan pubik melorheostosis alanında ⁶⁸Ga-PSMA PET/BT incelemesinde yoğun ⁶⁸Ga-PSMA tutulumu gösterilmiştir. Bu olgu, ⁶⁸Ga-PSMA tutulumu gösteren melorheostosis olasılığını vurgulamakta ve ⁶⁸Ga-PSMA PET/BT'nin melorheostosisin değerlendirilmesinde rol oynayabileceğini düşündürmektedir.

Anahtar kelimeler: Melorheostosis, ⁶⁸Ga-PSMA, tanısal zorluk, PET/BT, prostat kanseri, yanlış pozitif

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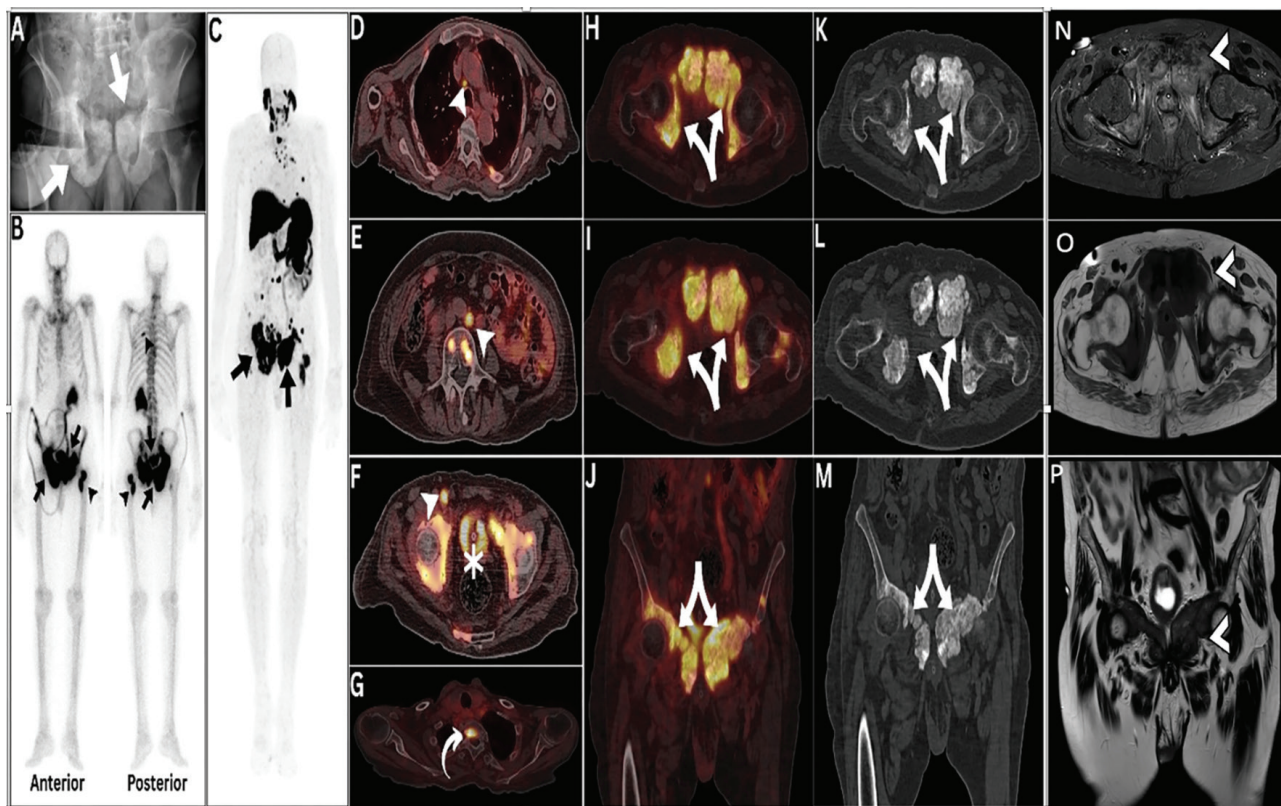


Figure 1. A 70-year-old man with metastatic hormone-sensitive prostate adenocarcinoma, treated with abiraterone and goserelin, developed progressive bilateral pubic pain. The patient provided written informed consent. Lab studies showed significantly elevated prostate-specific antigen and alkaline phosphatase levels. Pelvic X-ray revealed bony expansion with increased bone density and thickened cortex in both pubic bones (A, pelvic radiograph; arrows), which corresponded to an area of increased radiotracer uptake on skeletal scintigraphy (B, anterior and posterior planar skeletal scintigraphy; arrows). Other radiotracer-avid bone lesions were noted on skeletal scintigraphy, raising suspicion for new-onset skeletal metastases (B, anterior and posterior planar skeletal scintigraphy; arrowheads). ^{68}Ga -prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga -PSMA PET/CT), revealed diffuse ^{68}Ga -PSMA-avid prostatic involvement, and extensive ^{68}Ga -PSMA-avid lymphadenopathy and bone involvement [C, maximum intensity projection (MIP) PET image, D-G, axial fused images; annotations]. The pubic bones, which corresponded to areas of severe pain, displayed pronounced hyperostosis and a “dripping candlewax” sign consistent with melorheostosis; they also showed intense ^{68}Ga -PSMA uptake, with a maximum standardized uptake value of 20.2 (C, MIP PET image; H-J, axial and coronal fused PET/CT images; K-M, axial and coronal CT images; arrows). Magnetic resonance imaging further characterized these lesions (arrowheads), demonstrating bilateral cortical and subcortical hyperostosis of the pubic bones with uniformly low signal intensity on T1-weighted images (O) and predominantly low signal intensity on T2-weighted images (P), consistent with dense sclerotic bone. STIR sequences (N) revealed superimposed hyperintensity of the marrow and adjacent soft tissues, indicating associated edema and suggesting metabolically active disease. The patient was diagnosed with metastatic castration-resistant prostate cancer, was started on taxane chemotherapy, and received symptomatic therapy for melorheostosis, which led to rapid relief of pubic bone pain.

In our case, melorheostosis is located in the axial skeleton, more specifically in the pubic bones, which is a rare site of such entity (1,2). It also had increased ^{68}Ga -PSMA activity, which can be misdiagnosed as bone metastases in patients with prostate cancer (3). The observed expression pattern could be attributable to pronounced hypervascularization within melorheostotic lesions, consequently resulting in increased ^{68}Ga -PSMA expression (3,4). Also, it can be attributable to the proposition that the RAS signaling pathway, which is implicated in melorheostosis, may interact with other pathways such as TGF- β and PI3K/AKT2 (5). These pathways are known to regulate cellular processes like proliferation and differentiation, suggesting they could influence ^{68}Ga -PSMA expression in this condition (5). The differential diagnosis encompasses various osseous pathologies, including Paget’s disease, heterotopic ossification, and metastatic lesions (6,7,8). Radiological findings showing a dripping candle wax appearance indicated melorheostosis in the patient (4), highlighting the need for clinical follow-up and radiological correlation for accurate diagnosis. To the best of our knowledge, this case describes ^{68}Ga -PSMA-avid melorheostosis, reported here for the first time, and highlights its relevance as a pitfall in ^{68}Ga -PSMA PET/CT interpretation, with the aim of preventing false upstaging of prostate cancer and avoiding unwarranted treatment.

Ethics

Informed Consent: The patient provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.A.S., A.S.A., A.A-I., Concept: D.A.S., A.S.A., A.A-I., Design: D.A.S., A.S.A., A.A-I., Data Collection or Processing: D.A.S., A.S.A., A.A-I., Literature Search: D.A.S., A.S.A., A.A-I., Writing: D.A.S., A.S.A., A.A-I.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Immune Checkpoint Inhibitor-associated Periaortitis Detected on ¹⁸F-FDG PET/CT: A Rare Case of Nivolumab Toxicity

¹⁸F-FDG PET/BT'de Tespit Edilen İmmün Kontrol Noktası İnhibitörüyle İlişkili Periaortit: Nadir Bir Nivolumab Toksisitesi Olgusu

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Abstract

We report a case of a 64-year-old male with metastatic non-small-cell lung carcinoma who was undergoing neoadjuvant chemoimmunotherapy with cisplatin, pemetrexed, and nivolumab. Restaging ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) demonstrated segmental, linear ¹⁸F-FDG uptake along the abdominal aortic wall with corresponding crescentic soft-tissue thickening. Differential diagnoses included intramural hematoma, focal aortitis, atherosclerotic plaque, and tumor thrombus. CT angiography revealed a mildly enhancing periaortic soft-tissue rim involving a 5 cm infrarenal aortic segment, consistent with isolated periaortitis, likely induced by immunotherapy. Steroid therapy was initiated. Follow-up ¹⁸F-FDG PET/CT showed complete metabolic resolution, supporting an immune-related etiology. ¹⁸F-FDG PET/CT played a crucial role in early recognition of this immune-related adverse event by sensitively detecting vascular inflammation and guiding further evaluation with CT angiography. Early PET-based detection enabled timely initiation of steroid therapy, preventing potential vascular complications.

Keywords: ¹⁸F-FDG PET/CT, immune checkpoint inhibitors, periaortitis, immune-related adverse events, anti-programmed-death-receptor-1 (PD-1) antibody

Öz

Sisplatin, pemetrexed ve nivolumab neoadjuvan kemoimmünoterapisi gören metastatik küçük hücreli olmayan akciğer kanserli 64 yaşında bir erkek hastayı bildiriyoruz. Yeniden evreleme için yapılan ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸F-FDG PET/BT), abdominal aort duvarı boyunca segmental, doğrusal ¹⁸F-FDG tutulumu ve buna karşılık gelen hilal şeklinde yumuşak doku kalınlaşmasını gösterdi. Ayırıcı tanıları arasında intramural hematoma, fokal aortit, aterosklerotik plak ve tümör trombusu yer alıyordu. BT anjiyografi, muhtemelen immünoterapiye bağlı izole periaortit ile uyumlu, 5 cm'lik infrarenal aort segmentini içeren hafif kontrast tutan periaortik yumuşak doku kılıfını ortaya çıkardı. Steroid tedavisine başlandı. Takip amaçlı yapılan ¹⁸F-FDG PET/BT incelemesi, metabolik sorunların tamamen ortadan kalktığını göstererek immün sistemle ilişkili bir etiyolojiyi destekledi. ¹⁸F-FDG PET/BT, vasküler enflamasyonu hassas bir şekilde tespit ederek ve BT anjiyografi ile daha ileri değerlendirmeye rehberlik ederek, bu immün sistemle ilişkili advers olayın erken teşhisinde kritik bir rol oynadı. Erken PET tabanlı tespit, zamanında steroid tedavisine başlanmasını sağlayarak potansiyel vasküler komplikasyonları önledi.

Anahtar kelimeler: İmmün kontrol noktası inhibitörleri, periaortit, immün sistemle ilişkili advers olaylar

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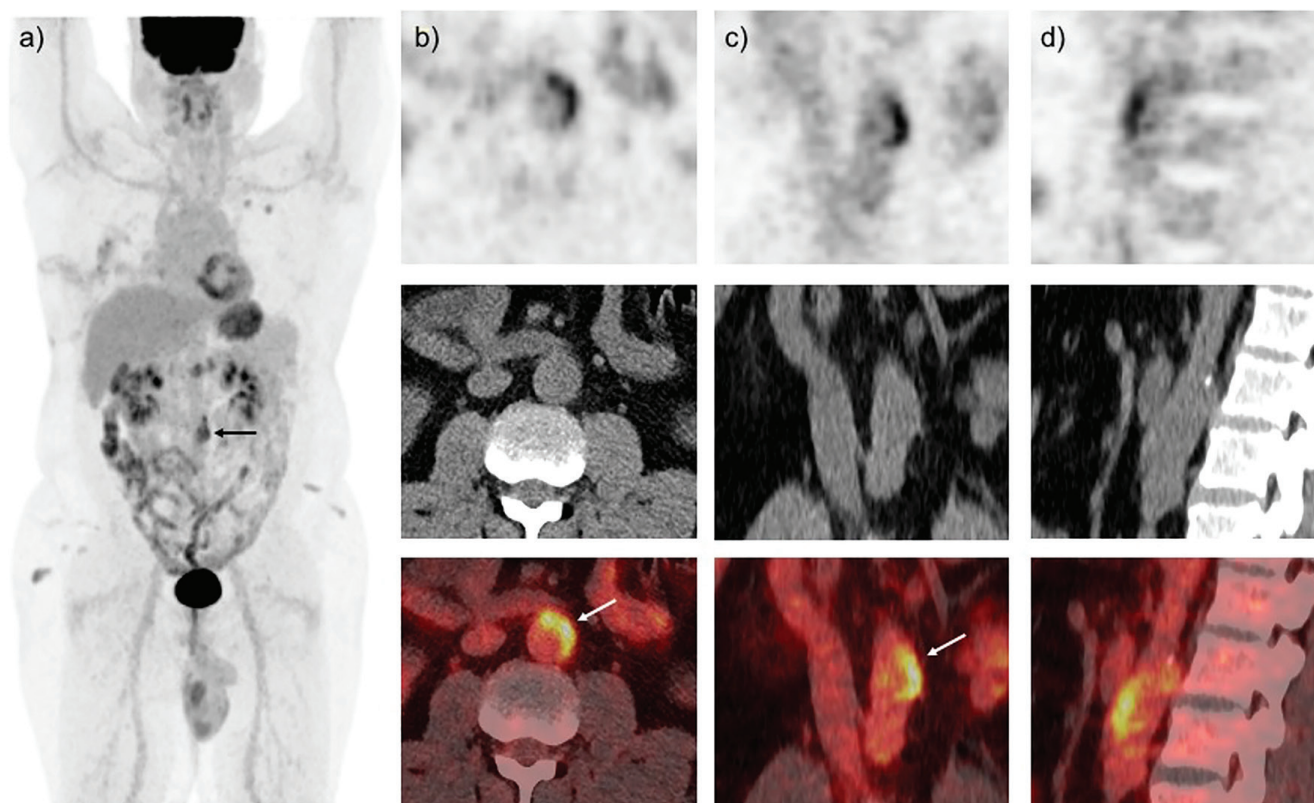


Figure 1. A 64-year-old male is a known case of metastatic non-small-cell lung carcinoma. On neoadjuvant chemoimmunotherapy with cisplatin/pemetrexed/ nivolumab. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) is performed for restaging. a) ^{18}F -FDG PET maximum intensity projection image and b-d) cross-sectional PET/CT images show segmental ^{18}F -FDG uptake in a continuous linear pattern of the abdominal aortic wall with maximum standard uptake values of 7.6, correlating to a crescentic soft-tissue thickening. Findings could represent an intramural hematoma, focal aortitis, or, less likely, an atherosclerotic plaque and tumor thrombus.

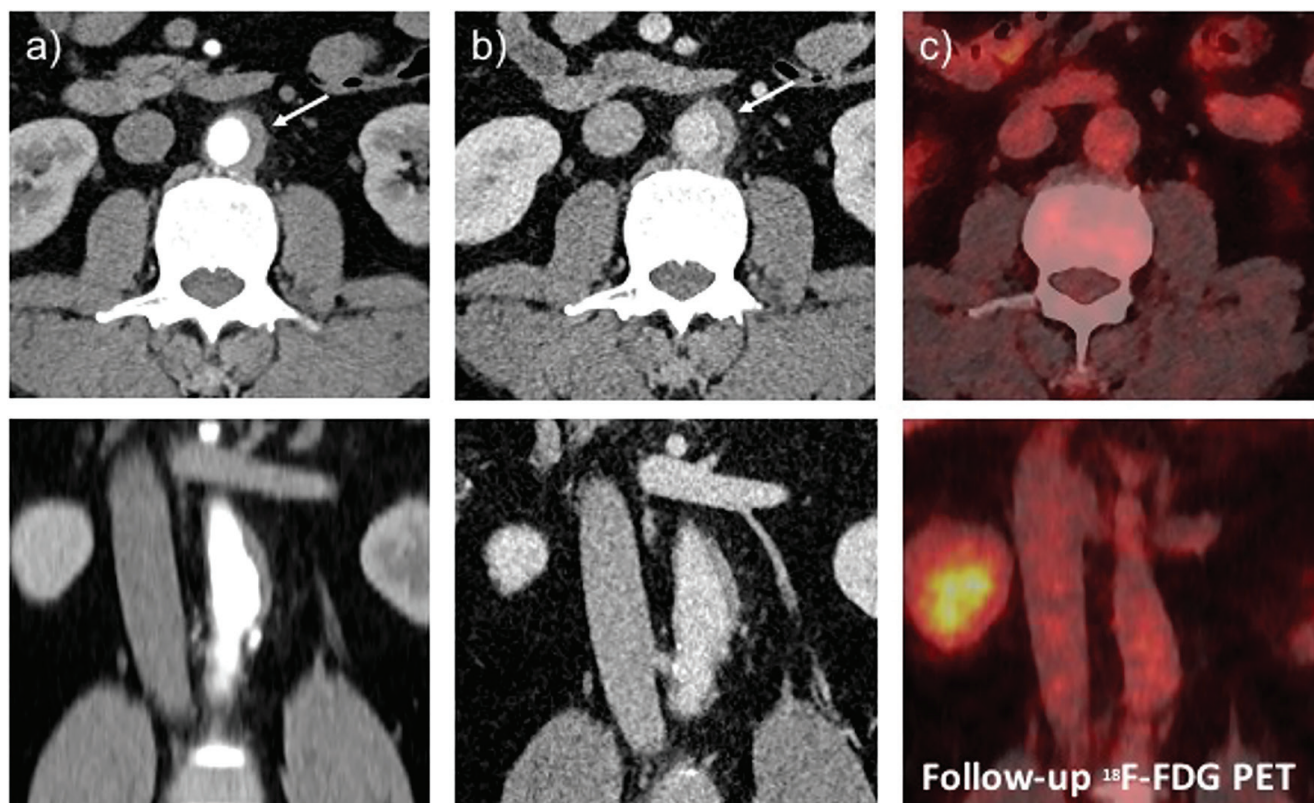


Figure 2. Computed tomography (CT) angiography in the a) arterial and b) delayed phases shows an irregular rim of soft-tissue density around the infra-renal portion of the abdominal aorta, which shows mild enhancement. Length of involvement is ~5 cm. Findings can suggest isolated periaortitis, likely induced by chemo-immunotherapy. The patient was started on steroids. c) Follow-up positron emission tomography (PET)/CT images show metabolic resolution of the previously seen eccentric uptake along the descending thoracic aorta. Immune checkpoint inhibitors (ICIs), including the PD-1 inhibitor nivolumab, have significantly improved outcomes in advanced malignancies such as non-small-cell lung carcinoma (1). However, when they remove inhibitory signals from T-cells, they may provoke a broad spectrum of immune-related adverse events (irAEs). While dermatologic, gastrointestinal, and endocrine toxicities are the most common, vascular irAEs particularly aortitis or periaortitis are increasingly recognized, but remain rare and potentially underdiagnosed. The pathophysiology is attributed to immune activation against vascular wall antigens, leading to T-cell-mediated inflammation, medial destruction, and soft-tissue thickening surrounding the vessel. The overall incidence of irAEs with either CTLA-4 or PD1/PDL1 inhibitors is approximately 15-30% (2).

^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET is widely utilized for diagnostic staging and restaging, assessing disease extent, monitoring treatment response, and supporting prognostic evaluation (3,4). ^{18}F -FDG PET/CT serves not only as a tool for staging and treatment response assessment but also as a crucial modality for identifying clinically silent irAEs in patients undergoing chemoimmunotherapy (5,6). Recognizing these imaging patterns allows timely initiation of immunosuppressive therapy, helps prevent serious vascular complications, and supports the safer use of ICIs in oncology practice. This is particularly important in vascular irAEs, as untreated aortitis can progress to aneurysm formation, dissection, or even life-threatening rupture. Because clinical manifestations are often vague or absent, imaging becomes indispensable, and in this setting, ^{18}F -FDG PET/CT assumes a key diagnostic role. ^{18}F -FDG uptake corresponds to activated macrophages and lymphocytes within the inflamed aortic wall, allowing ^{18}F -FDG PET/CT to identify active vasculitis even before structural changes develop. Several case series and imaging reviews have highlighted the role ^{18}F -FDG PET/CT for detecting large-vessel inflammation in ICI-treated patients, outperforming contrast-enhanced CT when the inflammatory component is subtle and non-occlusive (7,8). This case highlights a rare but clinically significant presentation of nivolumab-induced periaortitis detected incidentally on ^{18}F -FDG PET/CT during routine restaging. The characteristic linear aortic wall uptake prompted further evaluation with CT angiography, enabling early diagnosis and timely initiation of corticosteroid therapy. Complete metabolic resolution on follow-up PET/CT confirmed the immune-mediated nature of the process. As the use of ICIs continues to expand, awareness of vascular irAEs and the role of ^{18}F -FDG PET/CT in their early detection is essential for preventing potentially serious complications.

Ethics

Informed consent: The consent was obtained for image use.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.U., S.P.N., Concept: S.U., N.A., Design: S.U., A.J., K.A.R., A.A.B., N.A., S.P.N., Data Collection or Processing: S.U., A.J., K.A.R., N.A., Analysis or Interpretation: S.U., K.A.R., S.P.N., Literature Search: S.U., Writing: S.U., S.P.N.

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An Exceptional Presentation of Hutch Diverticulum on Bone Scintigraphy

Kemik Sintigrafisinde Hutch Divertikülünün İstisnai Bir Görünümü

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Abstract

Hutch diverticulum (HD) is a rare congenital condition characterized by the herniation of the bladder's mucosa and submucosa through the detrusor muscle fibers, encountered more commonly in children. An association between HD and situs inversus totalis (SIT) in an elderly patient has not been reported previously in the literature. We present the case of a 70-year-old male referred for routine bone scintigraphy as part of staging for lung carcinoma; thoraco-abdomino-pelvic computed tomography confirmed the staging and revealed a total transposition of the thoracic and abdominal organs, confirming SIT. This case highlights the exceptional association of HD and SIT, which was discovered incidentally in an elderly patient during metastatic staging for lung cancer. It underscores the importance of careful interpretation of scintigraphic findings, particularly when unusual radiotracer uptake is observed.

Keywords: Bone scintigraphy, Hutch diverticulum, situs inversus totalis

Öz

Hutch divertikülü (HD), mesane mukozasının ve submukozasının detrüsrör kas liflerinden fıtıklaşmasıyla karakterize nadir bir doğuştan gelen durumdur ve daha çok çocuklarda görülür. Yaşlı bir hastada HD ve situs inversus totalis (SIT) birlikteliği literatürde daha önce hiç bildirilmemiştir. Bu yazıda, torako-abdomino-pelvik bilgisayarlı tomografi ile doğrulanmış akciğer karsinomu evrelemesi kapsamında rutin kemik sintigrafisi için sevk edilen ve torasik ve abdominal organların tam transpozisyonu saptanarak SIT tanısı konulan 70 yaşındaki bir erkek hasta sunulmaktadır. Bu olgu, akciğer kanserinin metastatik evrelemesi sırasında tesadüfen saptanan, yaşlı bir hastada HD ve SIT'nin istisnai birlikteliğini vurgulamaktadır. Ayrıca, özellikle olağandışı radyofarmasötik tutulumu gözlemlendiğinde sintigrafik bulguların dikkatli yorumlanmasının önemini altını çizmektedir.

Anahtar Kelimeler: Kemik sintigrafisi, Hutch divertikülü, situs inversus totalis

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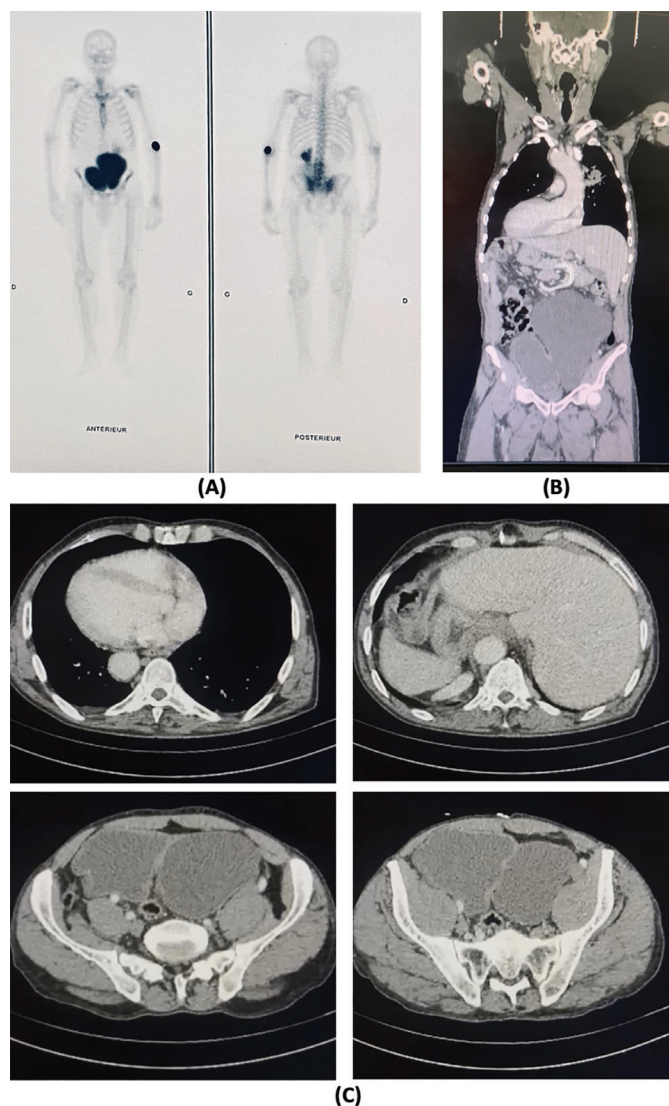


Figure 1. Hutch diverticulum (HD) is a rare congenital bladder diverticulum caused by herniation of the mucosa and submucosa through weakened detrusor muscle fibers, related to a congenital defect of Waldeyer's fascia (1). HD is typically diagnosed in childhood and is uncommon in adults, accounting for approximately 34% of reported cases (2,3). It may remain asymptomatic or present with complications such as urinary tract infection, lithiasis, rupture, or malignant transformation (2). We report the case of a 70-year-old man who was referred to our department for routine bone scintigraphy as part of lung carcinoma staging. Whole-body bone scintigraphy, acquired two hours after intravenous injection of 740 MBq of ^{99m}Tc -MDP, shows no abnormal skeletal uptake suggestive of bone metastasis. An incidental, intense radiotracer accumulation is observed in the left paravesical region, suggestive of a bladder diverticulum (A). Contrast-enhanced thoraco-abdomino-pelvic computed tomography showed a large bladder diverticulum arising from the left posterolateral wall, supporting the diagnosis of HD (C). Additionally, it revealed a total transposition of abdominal and thoracic viscera with a mirror image of internal organs attesting the diagnosis of situs inversus totalis (SIT) (B) and representing an exceptional association which was never reported in the literature. Single photon emission computed tomography/computed tomography can be considered an alternative imaging modality for diagnosis. The patient was then referred to the urology department for appropriate treatment. SIT is a rare congenital condition resulting from abnormal left-right axis determination during embryogenesis and associated with mutations in genes affecting ciliary function, such as *DNAH5* and *DNAI1*. HD has been reported in association with several congenital and connective tissue disorders, including Ehlers-Danlos, Williams-Beuren, Menkes, occipital horn, and cutis laxa syndromes (4). Only one pediatric case describing the association of HD and SIT has been previously reported (5). To our knowledge, no case was reported in the literature about this association in adult patients. Indeed, HD occurs in children with male predominance and only 34% incidence in adult patient (3); while HD and SIT are distinct entities, differential diagnoses should be considered before concluding this rare association. Bladder diverticula may arise secondary to chronic bladder outlet obstruction, neurogenic bladder dysfunction, or acquired structural abnormalities. Similarly, misinterpretation of abdominal situs in cross-sectional imaging could result from malrotation syndromes rather than true SIT (6). This case suggests that particular attention should be given by the nuclear physician when interpreting scintigraphic examinations, particularly when there is an unusual uptake of the radiotracer.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Concept: L.E.A., I.G., Design: L.E.A., I.G., Data Collection or Processing: L.E.A., I.G., Analysis or Interpretation: L.E.A., H.G., A.M., I.G., Literature Search: L.E.A., I.G., Writing: L.E.A.

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Extremely Rare Primary Gastric Alveolar Rhabdomyosarcoma in an Adult: ¹⁸F-FDG PET/CT Findings

Bir Erişkinde Son Derece Nadir Primer Gastrik Alveolar Rabdomyosarkom: ¹⁸F-FDG PET/BT Bulguları

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Abstract

Approximately 85-90% of all rhabdomyosarcoma (RMS) cases occur in children and adolescents. In adults, RMS accounts for only 2-5% of all soft tissue sarcomas. The annual incidence in adults is 0.3-0.5 per 1,000,000 and is classified as a "very rare tumor." More than 95% of RMSs are extragastric. Primary gastric RMS is reported extremely rarely in adults, and the estimated incidence is <0.01/1,000,000/year. This rate is <0.01% of all gastric malignancies and <1% of all adult RMSs. We report the ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography findings in an adult with primary gastric alveolar RMS, highlighting the metabolic characteristics of this extraordinarily rare malignancy.

Keywords: Rhabdomyosarcoma, alveolar rhabdomyosarcoma, ¹⁸F-FDG PET/CT, primary gastric rhabdomyosarcoma, rare malignancy

Öz

Rabdomyosarkom (RMS) olgularının yaklaşık %85-90'ı çocukluk ve adölesan dönemde görülür. Erişkinlerde ise RMS, tüm yumuşak doku sarkomlarının yalnızca %2-5'ini oluşturur. Erişkinlerde yıllık insidansı milyonda 0,3-0,5 olup "çok nadir tümör" olarak sınıflandırılır. RMS olgularının %95'ten fazlası ektragastriktir. Primer gastrik RMS erişkinlerde son derece nadir olup tahmini insidansı <0,01/1.000.000/yıl'dır. Bu oran tüm gastrik maligniteler arasında %0,01'den, tüm erişkin RMS'ler arasında ise %1'den azdır. Bu yazıda, primer gastrik alveolar RMS tanısı alan bir erişkin hastanın ¹⁸F-fluorodeoksiglukoz pozitron emisyon tomografi/bilgisayarlı tomografi bulguları sunularak bu son derece nadir malignitenin metabolik özellikleri vurgulanmaktadır.

Anahtar Kelimeler: Rabdomyosarkom, alveolar rabdomyosarkom, ¹⁸F-FDG PET/BT, primer gastrik rabdomyosarkom, nadir malignite

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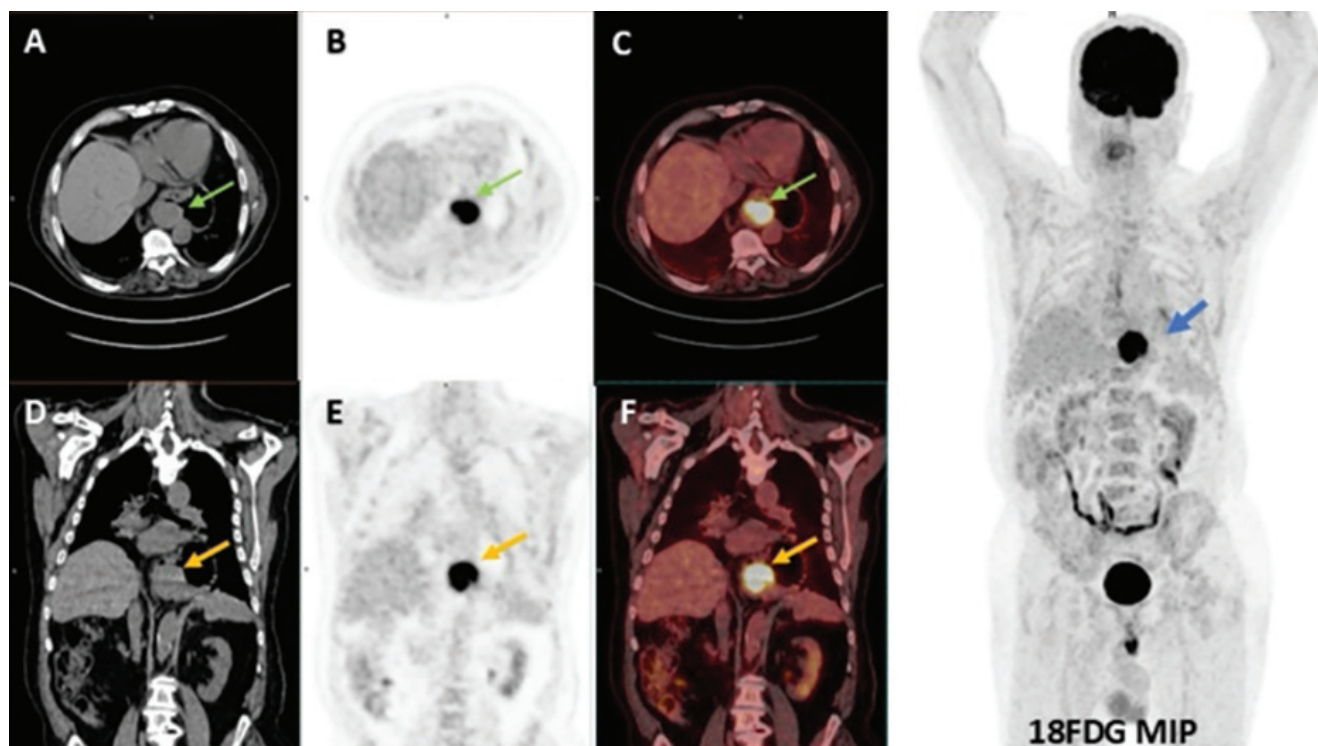


Figure 1. An 85-year-old male was evaluated for anemia. Endoscopic examination revealed a malignant-looking vegetative mass located distal to the Z line. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F FDG PET/CT) was performed for metabolic characterization and staging. Transaxial CT (A), PET (B), and PET/CT (C) images (green arrows); corresponding coronal CT (D), PET (E), and combined PET/CT (F) images (yellow arrows); and the maximum intensity projection (MIP) projection (blue arrow) show the lesion. It showed irregular wall thickening in the gastric cardia, reaching up to 16 mm at its thickest point, and intense ^{18}F -FDG uptake [maximum standardized uptake values (SUV_{max}): 19.90]. Histopathology confirmed the diagnosis of alveolar-type rhabdomyosarcoma (RMS). Primary gastric RMS is extremely rare in adults. Although RMS is the most common soft tissue sarcoma in children, it is rare in adults and rarely affects the gastrointestinal system (1). We highlight the metabolic features of this rare malignancy by reporting the ^{18}F -FDG PET/CT findings in an adult patient with primary gastric alveolar RMS. Although RMS is the most common soft tissue sarcoma in childhood, it is quite rare in adults, and gastrointestinal involvement is rare at all ages; primary gastric RMS—especially the alveolar subtype—is extremely rare, with very few documented cases (1,2,3,4,5). Gastric RMS is highly aggressive and may present with anemia, abdominal pain, or gastrointestinal bleeding, and in many cases, lymph node or lung metastases are present at the time of diagnosis (6). Treatment outcomes differ significantly between pediatric and adult RMS: multimodal treatment provides cure rates of over 70% in localized pediatric disease, while the situation is significantly worse in adults, with 5-year overall survival ranging from approximately 20% to 43% (7,8). ^{18}F -FDG PET/CT is an important imaging tool in RMS and demonstrates high metabolic activity, consistent with the significantly elevated SUV_{max} in this case. Gastric adenocarcinoma, which accounts for approximately 90% of gastric malignancies, also typically shows ^{18}F -FDG-avidity and should be prioritized in differential diagnosis when extensive gastric involvement is observed (2). This case highlights an extremely rare presentation of primary gastric alveolar RMS in an adult and emphasizes the role of ^{18}F -FDG PET/CT in metabolic characterization, staging, and clinical decision-making in unusual gastric malignancies. Primary gastric RMS should also be considered in the differential diagnosis of ^{18}F -FDG-avid gastric lesions. Written informed consent was obtained from the patient for the ^{18}F -FDG PET/CT examination.

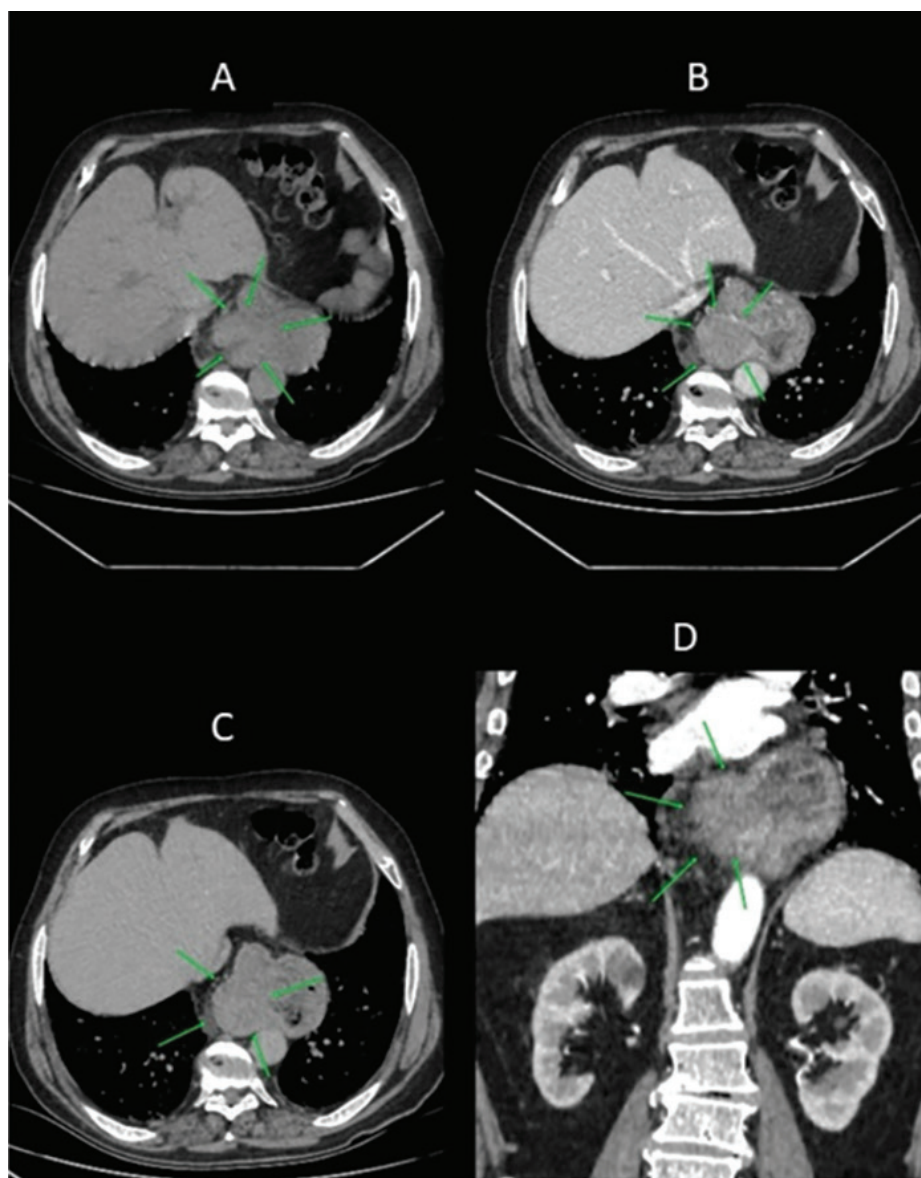


Figure 2. Dynamic contrast-enhanced upper abdominal computed tomography demonstrates a 28 × 41 mm hypovascular mass (green arrows) located in the portion of the stomach herniated into the thoracic cavity in a patient with a sliding hiatal hernia, on images obtained in the axial anterior contrast (A), portal venous (B), and delayed (C) phases, and on coronal reconstructed images (D).

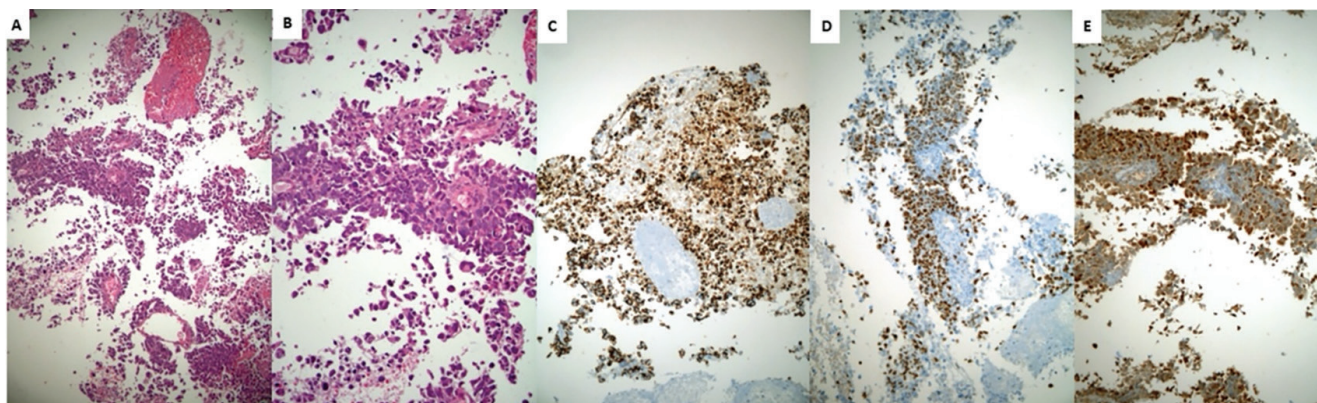


Figure 3. (A) Hematoxylin-eosin (H&E ×200) staining shows widespread layers of small, round tumor cells with sparse cytoplasm on a necrobiotic background. (B) H&E ×400 shows monomorphic tumor cells with hyperchromatic, angular nuclei, indistinct nucleoli, and evenly distributed chromatin. (C) Cytoplasmic desmin positivity in tumor cells immunohistochemistry (IHC ×200). (D) Strong nuclear MyoD1 positivity in tumor cells (IHC ×400). (E) Nuclear myogenin positivity in tumor cells (IHC ×400).

Ethics

Informed Consent: Written informed consent was obtained from the patient for the ^{18}F -FDG PET/CT examination.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar., Concept: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar., Design: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar., Data Collection or Processing: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar., Analysis or Interpretation: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar., Literature Search: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar., Writing: B.Y.B., İ.B., C.L., İ.T.R., E.A., G.A., E.Ar.

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⁶⁸Ga-FAPI Avidity in Fat Necrosis and Adrenal Adenoma: Expanding the Spectrum of Benign Pitfalls in Oncologic Imaging

Yağ Nekrozu ve Adrenal Adenomda ⁶⁸Ga-FAPi Tutulumu: Onkolojik Görüntülemelerde Benign Tuzakların Spektrumunu Genişletmek

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Abstract

Fat necrosis, a benign postoperative process related to tissue injury and repair, may demonstrate variable findings on functional imaging. We report a case of postoperative fat necrosis following pancreaticoduodenectomy showing intense ⁶⁸Ga-FAPI uptake in the absence of significant ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) avidity. Surveillance ¹⁸F-FDG positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) demonstrated only mild activity within the surgical bed maximum standard uptake value (SUV_{max} 2.4), while subsequent ⁶⁸Ga-FAPI PET/CT revealed marked uptake corresponding to fat necrosis SUV_{max} 9.9, consistent with pronounced fibroblast activation during postoperative healing. Additionally, a benign left adrenal adenoma showed low ¹⁸F-FDG uptake and only minimal ⁶⁸Ga-FAPI avidity (SUV_{max} 2.3), reflecting minimal stromal activation. This case highlights the tracer discordance between ¹⁸F-FDG and ⁶⁸Ga-FAPI in fat necrosis and underscores the importance of correlating ⁶⁸Ga-FAPI findings with surgical history and anatomic imaging to ensure accurate interpretation.

Keywords: ⁶⁸Ga-FAPI, ¹⁸F-FDG, fibroblast activation protein, fat necrosis, adrenal adenoma, pitfalls

Öz

Yağ nekrozu, doku hasarı ve onarımıyla ilgili iyi huylu bir postoperatif süreçtir ve fonksiyonel görüntülemelerde değişken bulgular gösterebilir. Pankreatikoduodenektomi sonrası postoperatif yağ nekrozunda belirgin ¹⁸F-florodeoksiglukoz (¹⁸F-FDG) tutulumu olmaksızın yoğun ⁶⁸Ga-FAPI tutulumu gözlenen bir olgu sunulmuştur. Takip amaçlı yapılan ¹⁸F-FDG pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸F-FDG PET/CT), cerrahi alanda yalnızca hafif aktivite maksimum standart tutulum değeri (SUV_{max} 2,4) gösterirken, daha sonraki ⁶⁸Ga-FAPI PET/CT, postoperatif iyileşme sırasında belirgin fibroblast aktivasyonuna uygun olarak yağ nekrozuna karşılık gelen belirgin bir tutulum (SUV_{max} 9,9) ortaya koymuştur. Ek olarak, benign sol adrenal adenom düşük ¹⁸F-FDG tutulumu ve yalnızca minimal ⁶⁸Ga-FAPI tutulumu (SUV_{max} 2,3) göstermiş olup, bu da minimal stromal aktivasyonu yansıtmaktadır. Bu olgu, yağ nekrozunda ¹⁸F-FDG ve ⁶⁸Ga-FAPI arasındaki tracer uyumsuzluğunu vurgulamakta ve doğru yorumlama sağlamak için ⁶⁸Ga-FAPI bulgularının cerrahi öykü ve anatomik görüntüleme ile ilişkilendirilmesinin önemini altını çizmektedir.

Anahtar kelimeler: ⁶⁸Ga-FAPI, ¹⁸F-FDG, fibroblast aktivasyon proteini, yağ nekrozu, adrenal adenom, tuzaklar

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Introduction

Fat necrosis is a benign pathological process resulting from injury to adipose tissue, most commonly caused by trauma, surgery, ischemia, infection, or exposure to digestive enzymes (1). Histopathologically, fat necrosis is characterized by necrotic adipocytes, release of free fatty acids, infiltration by lipid-laden macrophages and chronic inflammatory cells, and varying degrees of fibrosis and calcification. Over time, this reparative process may evolve into fibrotic or mass-like lesions (2). Fat necrosis is frequently encountered in postoperative settings, particularly after abdominal and pancreatic surgery, where surgical manipulation, vascular compromise, or pancreatic enzyme leakage can damage surrounding fat. Although its exact incidence is variable and likely underreported, fat necrosis is considered a relatively common benign postoperative finding in oncologic patients undergoing imaging surveillance (1).

On computed tomography (CT), fat necrosis exhibits a wide range of appearances depending on its stage, including fat stranding, ill-defined inflammatory changes, and mass-like soft-tissue lesions with fibrotic components. These features can closely mimic tumor recurrence or metastatic disease, especially in oncologic patients undergoing surveillance imaging, often necessitating further evaluation with functional imaging modalities (3).

^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET)/CT is commonly used to characterize indeterminate postoperative findings; however, ^{18}F -FDG uptake in fat necrosis is variable and may be minimal or absent, particularly in chronic or fibrosis-dominant lesions (2). More recently, fibroblast activation protein inhibitor (^{68}Ga -FAPI) PET/CT has emerged as a novel imaging modality, targeting activated fibroblasts involved in tissue repair and fibrosis, and has shown uptake in both malignant and benign conditions (4).

We report a case of postoperative fat necrosis following pancreaticoduodenectomy demonstrating intense ^{68}Ga -FAPI uptake in the absence of ^{18}F -FDG avidity, highlighting a potential diagnostic pitfall in postoperative oncologic imaging.

Case Report

A 53-year-old male presented in July 2025 with a 3-week history of severe, progressively worsening abdominal pain. The pain was predominantly epigastric and in the right upper quadrant, described as constant, dull, and pressure-like, with intermittent exacerbations following meals. It was associated with abdominal bloating, early satiety, nausea, and dark-colored urine, but without hematemesis or melena. The patient also reported pale

stools over the preceding days. On physical examination, the patient appeared ill and visibly jaundiced. Vital signs were stable. Scleral icterus and generalized jaundice were evident. Abdominal examination revealed distension with right upper quadrant tenderness; however, Murphy's sign was negative. Laboratory investigations demonstrated a cholestatic pattern of liver dysfunction, with markedly elevated total and direct bilirubin levels (10 mg/dL and 4 mg/dL, respectively), consistent with obstructive jaundice. Carbohydrate antigen 19-9 (CA 19-9) was elevated to 152 U/mL, suggesting a malignant biliary or periampullary process.

Given the clinical presentation of obstructive jaundice, a transabdominal ultrasound was performed as the first-line imaging modality. Ultrasound examination revealed marked intrahepatic and extrahepatic biliary dilatation, with the common bile duct measuring approximately 10 mm. The gallbladder was distended without wall thickening or gallstones; no acoustic-shadowing calculi were identified. The pancreatic head region appeared mildly heterogeneous, though visualization was limited by overlying bowel gas. These findings suggested a distal biliary obstruction and prompted further cross-sectional imaging. A contrast-enhanced CT scan demonstrated an ill-defined, enhancing, soft-tissue lesion measuring approximately 11×3.5 mm in the periampullary region and involving the distal common bile duct. This lesion was associated with significant upstream biliary dilatation, including the common bile duct, cystic duct, common hepatic duct, and right and left hepatic ducts. No definite evidence of liver metastases, ascites, or distant lymphadenopathy was identified. However, it showed a left adrenal lesion (3.3 cm), consistent with a benign adenoma.

The patient subsequently underwent endoscopic retrograde cholangiopancreatography with biliary decompression and tissue sampling on July 15, 2025. Endoscopic biopsy revealed a poorly differentiated adenocarcinoma. Following discussion at the multidisciplinary tumor board, the patient underwent definitive surgical management.

On July 29, 2025, the patient underwent a pancreaticoduodenectomy (Whipple procedure). Histopathological analysis confirmed a poorly differentiated signet-ring cell adenocarcinoma (poorly cohesive carcinoma) of the ampulla of Vater, staged as pT3bN0M0. The surgical resection margins were free of tumor, indicating an R0 resection.

As part of routine postoperative surveillance, a contrast-enhanced CT scan performed in November 2025 demonstrated no evidence of local recurrence or distant metastatic disease. The examination identified a small left paracolic lymph node measuring up to 0.7 cm, an area

within the surgical bed suggestive of fat necrosis, and a stable left adrenal lesion with imaging features consistent with an adenoma (Figure 1). However, these findings were considered indeterminate in the postoperative setting.

For further characterization of the paracolic lymph node, an ^{18}F -FDG PET/CT was performed in December 2025. The paracolic lymph node showed no ^{18}F -FDG uptake, favoring a benign or reactive etiology. A focal area within the surgical bed demonstrated mild metabolic activity maximum standard uptake value (SUV_{max} 2.4), suggestive of postoperative inflammatory changes. The left adrenal mass measured 3.3 cm, remained hypodense, and exhibited no significant ^{18}F -FDG uptake, findings consistent with a benign adrenal adenoma (Figure 2). Nevertheless, given the known limitations of ^{18}F -FDG in differentiating low-grade malignancy from postoperative or inflammatory changes, diagnostic uncertainty persisted.

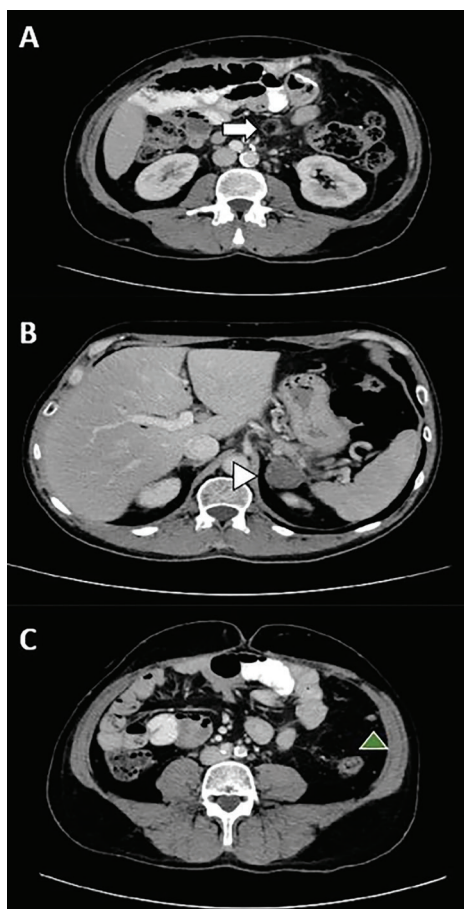


Figure 1. Contrast-enhanced CT scan (November 2025). (A) axial image demonstrating a focal area of fat necrosis within the surgical bed (white arrow) (B) axial image demonstrating a left adrenal adenoma (white arrowhead) (C) axial image demonstrating a small paracolic lymph node (green arrowhead)

CT: Computed tomography

Therefore, ^{68}Ga -FAPI PET/CT was subsequently performed for additional assessment. This study revealed diffuse ^{68}Ga -FAPI uptake within the pancreatic remnant, most consistent with postoperative fibro-inflammatory or reparative changes, while the previously identified paracolic lymph node remained non-avid. Notably, the focal fat necrosis in the surgical bed demonstrated markedly increased ^{68}Ga -FAPI uptake compared to ^{18}F -FDG uptake, with an SUV_{max} of 9.9, significantly higher than on the ^{18}F -FDG study. The left adrenal lesion exhibited minimal ^{68}Ga -FAPI avidity (SUV_{max} 2.3), a finding interpreted in the context of its benign imaging characteristics (Figure 3).

Overall, the absence of focal ^{68}Ga -FAPI-avid lesions suggestive of local recurrence or metastatic disease, particularly within the surgical bed and paracolic lymph nodes, supported a conservative management strategy with continued imaging surveillance. Written informed consent for publication of the clinical information and accompanying images was obtained from the patient.

Discussion

In this case, postoperative fat necrosis following pancreaticoduodenectomy demonstrated intense ^{68}Ga -FAPI PET/CT uptake but only mild ^{18}F -FDG avidity, indicating clear tracer discordance. The lesion was located within the surgical bed and showed imaging features suggestive of fat necrosis, with no clinical or biochemical evidence of disease recurrence. The low-level ^{18}F -FDG uptake likely reflects limited inflammatory activity, whereas the marked ^{68}Ga -FAPI avidity is more consistent with fibroblast activation related to postoperative tissue repair and fibrosis (4).

From an imaging perspective, fat necrosis typically appears on CT as a fat-density lesion with surrounding inflammatory stranding or soft tissue components, which may simulate tumor recurrence in the postoperative setting (5). On ^{18}F -FDG PET/CT, uptake is usually mild to moderate and reflects inflammatory activity (5), whereas ^{68}Ga -FAPI PET/CT may demonstrate intense uptake due to fibroblast activation associated with tissue repair and fibrosis, as presented in this case. In contrast, adrenal adenomas characteristically demonstrate low attenuation on CT (often <10 Hounsfield units) and are stable over time, and typically show absent or minimal uptake on both ^{18}F -FDG and ^{68}Ga -FAPI PET imaging (6). The differential diagnosis of postoperative fat-containing lesions includes local tumor recurrence, peritoneal metastasis, and postoperative inflammatory or fibrotic changes (7). Similarly, adrenal lesions may raise concern for adrenal metastasis, pheochromocytoma, or primary adrenal malignancy, particularly when imaging findings are atypical or equivocal (8). Therefore, careful integration of morphologic CT findings, functional PET imaging, and clinical context is essential for accurate interpretation.

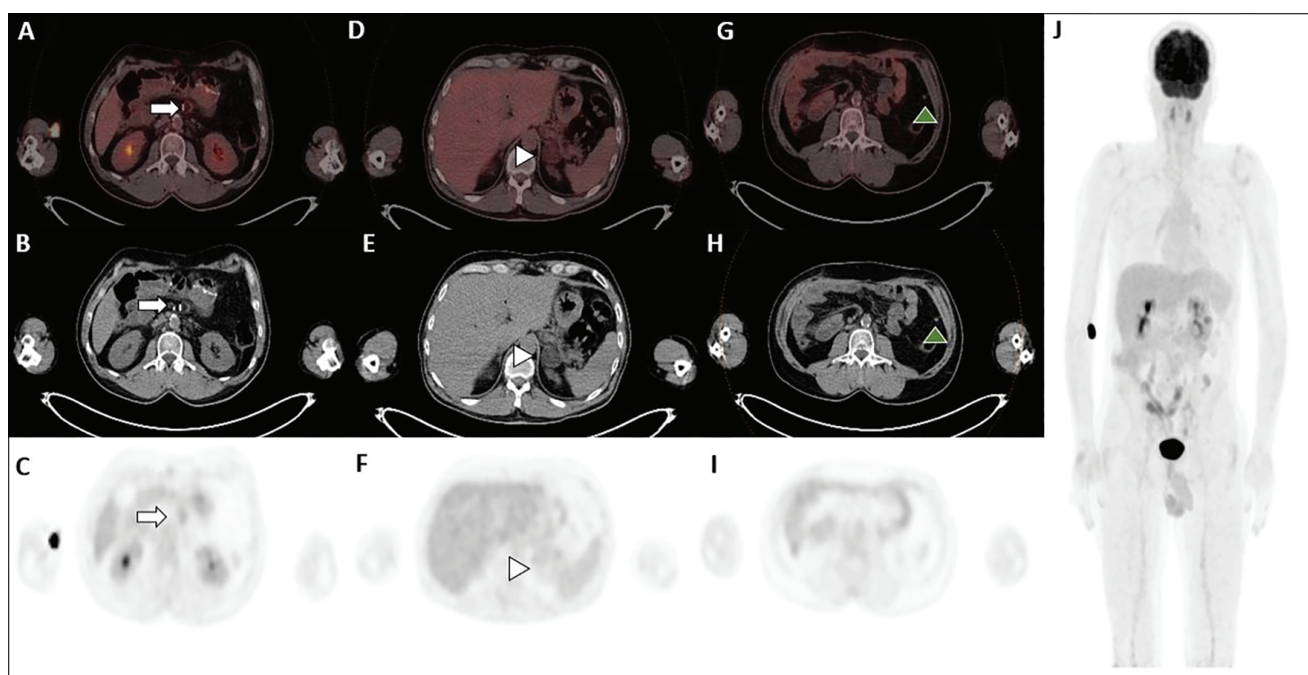


Figure 2. ^{18}F -FDG PET/CT scan (A-C) axial fused PET/CT, CT, and PET images demonstrate a focal area of fat necrosis within the surgical bed, showing mild ^{18}F -FDG uptake (SUV_{max} 2.4) (white arrow) (D-F) corresponding images demonstrate a left adrenal adenoma without ^{18}F -FDG uptake (white arrowhead) (G-I) images demonstrate a small paracolic lymph node without ^{18}F -FDG uptake, favoring a benign or reactive etiology (green arrowhead) (J) the maximum intensity projection image shows no abnormal hypermetabolic uptake
 ^{18}F -FDG PET/CT: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography, SUV_{max} : Maximum standard uptake value

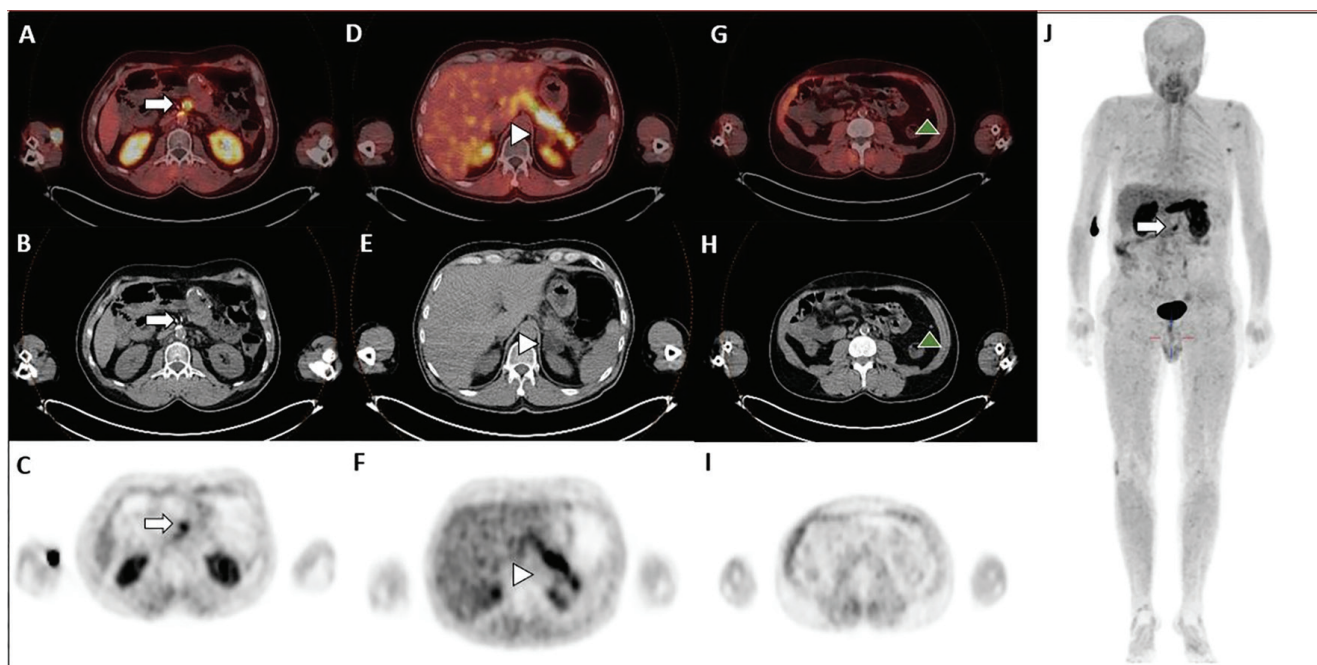


Figure 3. ^{68}Ga -FAPI PET/CT scan (A-C) axial fused PET/CT, CT, and PET images demonstrate a focal area of fat necrosis within the surgical bed that shows intense FAPI uptake (SUV_{max} 9.9) (white arrow) corresponding images (D-F) demonstrate a left adrenal adenoma with minimal FAPI uptake, indicated by the white arrowhead (G-I) images demonstrate a small paracolic lymph node without FAPI uptake, which favors a benign or reactive etiology (green arrowhead) (J) MIP image demonstrates a focal increase in FAPI uptake in the upper mid-abdomen, corresponding to fat necrosis (white arrow)
 PET/CT: Positron emission tomography/computed tomography, MIP: Maximum intensity projection, SUV_{max} : Maximum standard uptake value, FAPI: Fibroblast activation protein inhibitor

Several studies have shown that ^{68}Ga -FAPI PET/CT uptake is not specific to malignancy and may be observed in a range of benign conditions characterized by fibroblast activation, including postoperative changes, inflammatory lesions, and fibrotic processes (9). Activated fibroblasts play a central role in wound healing and tissue remodeling after surgery, which can lead to prominent ^{68}Ga -FAPI uptake even in the absence of a viable tumor (9). In contrast, ^{18}F -FDG uptake in such postoperative or fibro-inflammatory settings is frequently mild or variable, as metabolic activity is often limited once acute inflammation subsides and fibrosis predominates (10). This fundamental difference in tracer biology explains why lesions with minimal ^{18}F -FDG avidity may nevertheless appear conspicuous on ^{68}Ga -FAPI PET/CT and underscores the potential for false-positive interpretations when ^{68}Ga -FAPI uptake is assessed without careful correlation to clinical history and anatomic imaging. To date, only a single case report has described ^{68}Ga -FAPI uptake in fat necrosis, to which our case adds both confirmatory and novel observations. In that report, Maliha et al. (11) described CT-diagnosed intra-abdominal fat necrosis demonstrating mild ^{68}Ga -FAPI uptake slightly greater than ^{18}F -FDG uptake ($\text{SUV}_{\text{max}} \sim 2.9$ vs. 2.0) on ^{68}Ga -FAPI PET/CT, supporting the concept that fibroblast activation can persist in benign necrotic adipose tissue even years after surgery. In contrast, our patient's fat necrosis showed marked ^{68}Ga -FAPI avidity ($\text{SUV}_{\text{max}} 9.9$) alongside only mild ^{18}F -FDG uptake ($\text{SUV}_{\text{max}} 2.4$), indicating a more pronounced fibroblastic reparative process detectable by ^{68}Ga -FAPI imaging but with limited glycolytic activity on ^{18}F -FDG PET. This larger disparity between ^{68}Ga -FAPI and ^{18}F -FDG uptake underscores the heterogeneity of fibro-inflammatory responses in fat necrosis. It suggests that ^{68}Ga -FAPI PET/CT may be more sensitive to activated fibroblasts in certain postoperative lesions than ^{18}F -FDG PET/CT, while also highlighting the risk of overestimating benign postoperative changes as potential malignancy without careful clinical and morphologic correlation.

A similar principle applies to adrenal lesions. Adrenal adenomas are common benign adrenal cortical tumors and, on ^{18}F -FDG PET/CT, typically demonstrate low or only mild ^{18}F -FDG uptake because of their low glycolytic activity, although hormonally active adenomas and lipid-poor lesions may occasionally show moderate uptake, creating diagnostic overlap with malignant adrenal neoplasms and metastases (6). In contrast, ^{68}Ga -FAPI PET imaging targets fibroblast activation protein expressed by cancer-associated fibroblasts and stromal remodeling rather than tumor metabolism, and benign adrenal adenomas are therefore expected to show absent or minimal ^{68}Ga -FAPI uptake (12). To date, only a single published case has

specifically documented ^{68}Ga -FAPI findings in an adrenal cortical adenoma, in which a hormonally active adrenal adenoma did not demonstrate significant uptake on ^{68}Ga -FAPI PET/magnetic resonance imaging ($\text{SUV}_{\text{max}} \sim 1.8$), with postoperative histopathology confirming a benign adrenal cortical adenoma (12). The absence of ^{68}Ga -FAPI avidity in adrenal adenoma supports the concept that ^{68}Ga -FAPI PET may help distinguish benign adrenal cortical lesions from adrenal metastases, which are more likely to demonstrate prominent fibroblast-rich tumor stroma and, consequently, higher ^{68}Ga -FAPI uptake (13). However, broader clinical validation remains necessary given the very limited current evidence base.

Conclusion

This case demonstrates that postoperative fat necrosis can show intense ^{68}Ga -FAPI uptake despite minimal or absent ^{18}F -FDG avidity, reflecting fibroblast activation related to tissue repair rather than malignancy. Importantly, the ^{68}Ga -FAPI-avid lesion did not mimic tumor recurrence when interpreted in the context of surgical history, anatomic imaging, and clinical follow-up. Minimal ^{68}Ga -FAPI uptake in a benign adrenal adenoma further illustrates that low-level ^{68}Ga -FAPI avidity may occur in non-malignant adrenal lesions with limited stromal remodeling. This report adds to the growing body of evidence on ^{68}Ga -FAPI PET/CT pitfalls, expanding current knowledge of benign entities that may demonstrate increased tracer uptake and helping refine interpretive awareness in postoperative oncologic imaging.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M., R.M.A-H., B.A., A.A-I., Concept: S.M., A.A-I., Design: S.M., R.M.A-H., A.A-I., Data Collection or Processing: S.M., R.M.A-H., B.A., A.A-I., Analysis or Interpretation: S.M., R.M.A-H., B.A., A.A-I., Literature Search: S.M., R.M.A-H., B.A., A.A-I., Writing: S.M., R.M.A-H., B.A., A.A-I.

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Atypical Skull Base Metastasis from Pediatric Extremity Chondroblastic Osteosarcoma Detected by Surveillance ¹⁸F-FDG PET/CT: A Case Report with Focused Literature Review

Pediatric Ekstremitte Kondroblastik Osteosarkomunda Takip ¹⁸F-FDG PET/CT ile Saptanan Atipik Kafa Tabanı Metastazı: Olgu Sunumu ve Literatür Derlemesi

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Abstract

A 15-year-old girl who had previously undergone surgery and chemotherapy for non-metastatic chondroblastic osteosarcoma of the left fibula was evaluated with ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) during routine follow-up while in clinical remission. Imaging demonstrated a 36 × 17 mm hypermetabolic lesion in the right occipital condyle maximum standard uptake value [(SUV_{max}): 16.5], with adjacent bone and soft-tissue extension, together with a concurrent ¹⁸F-FDG-avid pulmonary nodule (SUV_{max}: 3.4). Shortly after imaging, the patient developed mild neck discomfort and right-sided tongue deviation, suggesting hypoglossal nerve involvement. Biopsy of the skull base lesion and histopathological evaluation of the pulmonary nodule confirmed metastatic chondroblastic osteosarcoma with concordant morphology and immunophenotype. The patient underwent biopsy of the occipital lesion, surgical excision, radiotherapy, and wedge resection of the pulmonary metastasis. Skull base involvement from osteosarcoma arising in the extremities is exceptional and is particularly rare in pediatric patients. This case highlights the complementary role of whole-body ¹⁸F-FDG PET/CT in detecting atypical metastatic sites that may not be routinely assessed by conventional surveillance strategies. In addition, the focused literature review underscores the exceptional rarity of skull base involvement in pediatric chondroblastic osteosarcoma and supports the need for heightened awareness of uncommon metastatic patterns.

Keywords: Chondroblastic osteosarcoma, pediatric osteosarcoma, skull base metastasis, ¹⁸F-FDG PET/CT, surveillance imaging

Öz

Daha önce sol fibulada non-metastatik kondroblastik osteosarkom nedeniyle cerrahi ve kemoterapi uygulanmış 15 yaşındaki kız hasta, klinik remisyonda iken rutin takip kapsamında ¹⁸F-florodeoksiglukoz pozitron emisyon tomografisi/bilgisayarlı tomografi (¹⁸F-FDG PET/CT) ile değerlendirildi. Görüntülemeye sağ oksipital kondilde, komşu kemik ve yumuşak dokuya uzanım gösteren, maksimum standart tutulum değeri [(SUV_{max}): 16,5], olan 36 × 17 mm boyutunda hipermetabolik bir lezyon ile eş zamanlı olarak ¹⁸F-FDG tutulumu gösteren bir pulmoner nodül (SUV_{max}: 3,4) saptandı. Görüntülemeye kısa süre sonra hastada hafif boyun rahatsızlığı ve sağa doğru dil deviasyonu gelişmesi hipoglossal sinir tutulumunu düşündürdü. Kafa tabanı lezyonundan alınan biyopsi ve pulmoner nodülün histopatolojik değerlendirmesi, uyumlu morfoloji ve

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immünofenotip ile metastatik kondroblastik osteosarkomu doğruladı. Hastaya oksipital lezyon biyopsisi, cerrahi eksizyon, radyoterapi ve pulmoner metastaza yönelik wedge rezeksiyon uygulandı. Ekstremité kökenli osteosarkomlarda kafa tabanı tutulumu son derece nadirdir ve özellikle pediatrik hastalarda oldukça seyrekir. Bu olgu, konvansiyonel izlem stratejileriyle rutin olarak değerlendirilmeyebilecek atipik metastatik odakların saptanmasında tüm vücut ^{18}F -FDG PET/BT'nin tamamlayıcı rolünü vurgulamaktadır. Ayrıca, odaklanmış literatür incelemesi pediatrik kondroblastik osteosarkomda kafa tabanı tutulumunun olağanüstü nadirliğini ortaya koymakta ve alışılmadık metastatik paternler konusunda farkındalığın artırılması gerektiğini desteklemektedir.

Anahtar Kelimeler: Kondroblastik osteosarkom, pediatrik osteosarkom, kafa tabanı metastazi, ^{18}F -FDG PET/BT, takip görüntüleme

Introduction

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, typically arising in the metaphyseal regions of long bones such as the distal femur, proximal tibia, and proximal humerus. Chondroblastic osteosarcoma, a histologic subtype characterized by the production of cartilaginous matrix in addition to malignant osteoid, accounts for a minority of cases and generally shares a clinical behavior similar to conventional osteosarcoma.

Osteosarcoma is characterized by hematogenous dissemination, with the lungs representing the predominant site of metastasis, whereas extrapulmonary spread is distinctly less frequent. Accordingly, standard surveillance strategies primarily focus on local limb magnetic resonance imaging (MRI) and chest computed tomography (CT) to detect local recurrence and pulmonary metastases. These protocols are designed to monitor the most common patterns of relapse and are not routinely intended to evaluate anatomically distant or clinically silent skeletal sites (1).

Although primary craniofacial osteosarcomas may involve the skull base through direct local extension, these tumors arise from the craniofacial skeleton itself and constitute a distinct clinical entity. In contrast, metastatic spread from an extremity osteosarcoma to the skull base is exceptionally uncommon, particularly in pediatric patients (2). Because the skull base is not considered a routine surveillance region in extremity osteosarcoma, metastatic involvement of this anatomically complex area may remain clinically unsuspected, particularly when early symptoms are minimal or nonspecific.

Whole-body ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT offers the advantage of comprehensive metabolic assessment, enabling simultaneous evaluation of both common and unexpected sites of disease involvement within a single examination. In this context, we present a pediatric case of chondroblastic osteosarcoma of the fibula with unexpected metastatic involvement of the occipital condyle detected on routine

surveillance PET/CT prior to the development of significant neurological symptoms. By illustrating a rare metastatic pattern outside conventional follow-up fields, this case suggests the complementary role of whole-body metabolic imaging in selected clinical contexts.

Case Report

A 15-year-old female with a history of non-metastatic chondroblastic osteosarcoma of the left proximal fibula was initially diagnosed in 2021. At presentation, the tumor measured approximately 6.5 cm in greatest dimension and showed cortical destruction with soft-tissue extension; surgical margins were intact. She underwent neoadjuvant chemotherapy followed by surgical resection and completed adjuvant treatment in August 2022, achieving clinical remission, after which she was followed with routine surveillance.

In December 2023, during routine oncologic surveillance, whole-body ^{18}F -FDG PET/CT was performed for restaging. The examination demonstrated a 36×17 mm hypermetabolic lesion in the right occipital condyle maximum standard uptake value (SUV_{max} : 16.5) (Figure 1), extending to the clivus and right hemi-C1 vertebra with adjacent soft-tissue infiltration. In the same study, a solitary ^{18}F -FDG-avid pulmonary nodule was identified in the anterior basal segment of the right lower lobe (SUV_{max} : 3.4), suggestive of concurrent metastatic disease.

At the time of PET/CT, the patient had no significant focal neurological deficit. Shortly thereafter, she developed mild neck discomfort and rightward deviation of the tongue on examination, consistent with hypoglossal nerve involvement. Cranial MRI was subsequently performed for detailed anatomical assessment. Contrast-enhanced T1-weighted sequences confirmed a heterogeneously enhancing mass centered in the right occipital condyle with destructive osseous changes, extension into the prevertebral and paravertebral soft tissues, and partial involvement of the right hypoglossal canal. Diffusion-weighted imaging demonstrated restricted diffusion with corresponding low ADC values, consistent with high tumor cellularity (Figure 2).

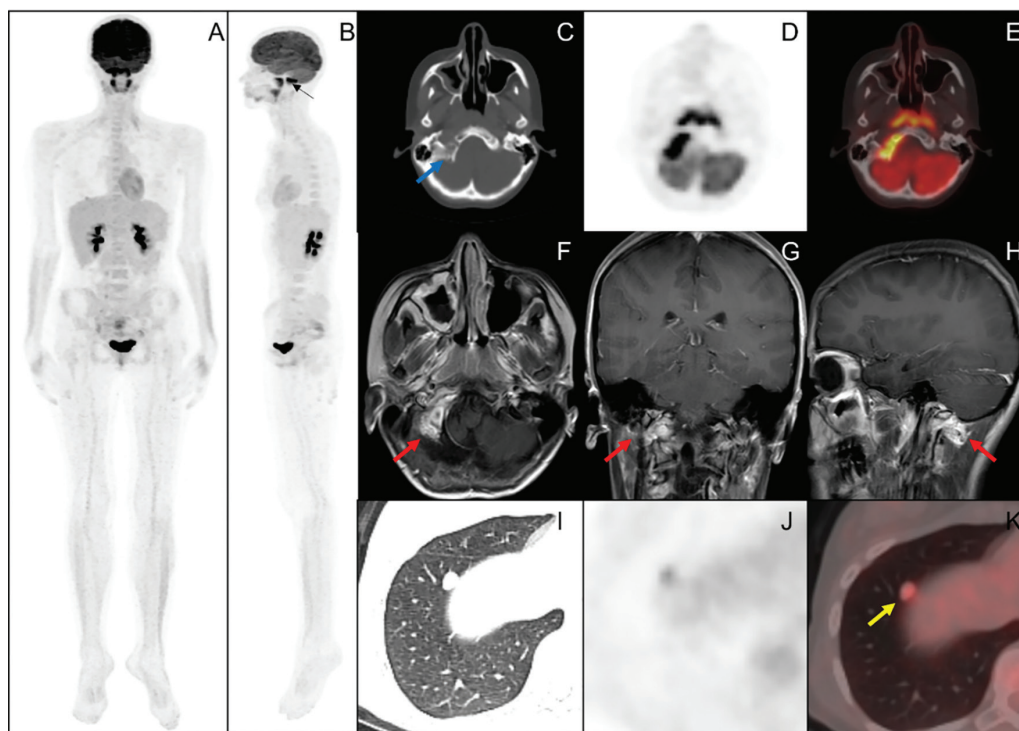


Figure 1. ^{18}F -FDG PET/CT and MRI of a 15-year-old girl with metastatic chondroblastic osteosarcoma

(A, B) MIP images show a hypermetabolic occipital condyle lesion (SUV_{max} : 16.5). (C-E) Axial CT (C, blue arrow), PET (D), and fused PET/CT (E) demonstrate the destructive skull base lesion. (F-H) Post-contrast T1-weighted MRI (red arrows) demonstrates a heterogeneously enhancing mass centered in the right occipital condyle, extending into prevertebral soft tissues and partially involving the hypoglossal canal, correlating with osseous destruction demonstrated on CT. (I-K) CT (I), PET (J), and fused PET/CT (K, yellow arrow) show an ^{18}F -FDG-avid right lower lobe pulmonary metastasis (SUV_{max} : 3.4)

MIP: Maximum intensity projection, SUV_{max} : Maximum standardized uptake value, CT: Computed tomography. PET: Positron emission tomography, MRI: Magnetic resonance imaging, ^{18}F -FDG: ^{18}F -Fluorodeoxyglucose

Following multidisciplinary evaluation, surgical management was planned and preceded by a diagnostic biopsy of the skull base lesion, which histopathologically confirmed metastatic chondroblastic osteosarcoma. Definitive surgical excision of the occipital condyle mass was subsequently performed in March 2024. Adjuvant radiotherapy was administered to the skull base region following surgery as part of local disease control. In April 2024, the patient underwent wedge resection of the right lower lobe pulmonary metastasis. Histopathological examination of the primary fibular tumor had demonstrated neoplastic osteoid formation with prominent cartilaginous matrix production. Immunohistochemistry showed SATB2 positivity, low p53 expression, and a Ki-67 proliferation index of approximately 10%. Analysis of paraffin blocks from the occipital lesion confirmed metastatic chondroblastic osteosarcoma with identical morphology and immunophenotype (Figure 3). The pulmonary nodule exhibited concordant histopathological features, confirming systemic metastatic dissemination. At the latest follow-up, 26 months after

detection of metastatic relapse, the patient remained without evidence of disease.

Discussion

Osteosarcoma is the most common primary malignant bone tumor in childhood and adolescence, with pulmonary metastases representing the predominant pattern of dissemination. In contrast, cranial or skull base involvement is distinctly uncommon and is more frequently described in the setting of primary craniofacial osteosarcomas rather than metastatic disease.

Most published reports of chondroblastic osteosarcoma involving the skull describe primary tumors arising from cranial bones or maxillofacial structures. Uysal et al. (3) reported a pediatric craniofacial chondroblastic osteosarcoma involving the maxillary, ethmoid, and sphenoid bones, emphasizing diagnostic challenges but again describing a primary cranial origin rather than metastatic spread. Similarly, Vasquez et al. (4) reported

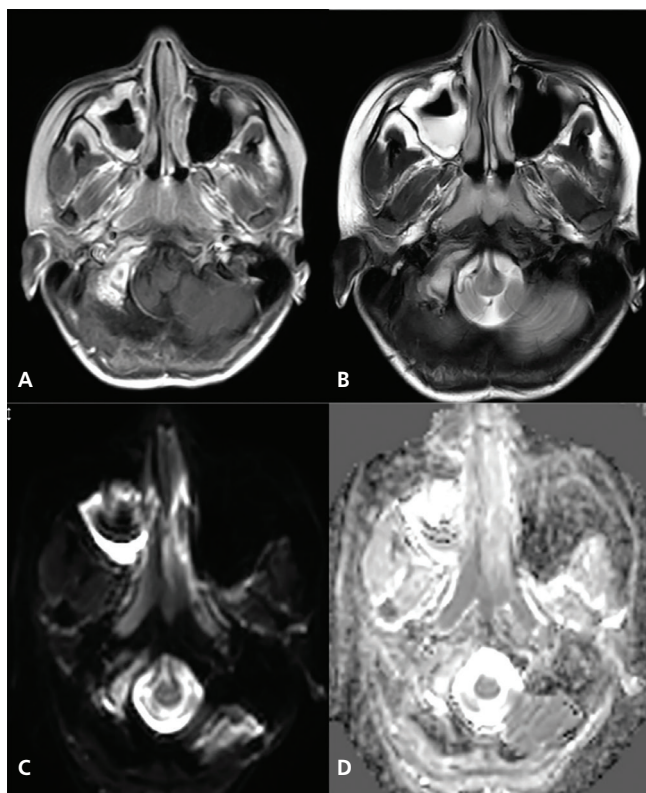


Figure 2. Axial MRI sequences of the right skull base lesion

(A) Contrast-enhanced T1-weighted image demonstrates a heterogeneously enhancing mass centered in the right occipital condyle, with cortical disruption and replacement of normal marrow signal. (B) T2-weighted image shows heterogeneous high signal intensity within the lesion. (C) Diffusion-weighted imaging (b800) reveals focal hyperintensity within the solid portions of the mass. (D) Corresponding apparent diffusion coefficient map demonstrates low signal intensity in the same region, confirming true diffusion restriction consistent with hypercellular malignant tissue

MRI: Magnetic resonance imaging

a pediatric primary skull osteosarcoma presenting as a parieto-occipital lesion without distant metastasis at presentation. He et al. (5) detailed imaging characteristics of primary occipital chondroblastic osteosarcoma with CT and MRI correlation, also without evidence of distant primary disease. Mamachan et al. (6) reported an anterior maxillary chondroblastic osteosarcoma limited to the craniofacial region without systemic dissemination. Almeida et al. (7) reported a rapidly progressive primary maxillary chondroblastic osteosarcoma in a young adult patient, further reinforcing the predominance of craniofacial origin in skull-related presentations. Adwani et al. (8) described a massive recurrent chondroblastic osteosarcoma of the maxilla in an adolescent patient, highlighting the aggressive behavior of primary maxillary tumors but not metastatic dissemination from an appendicular source.

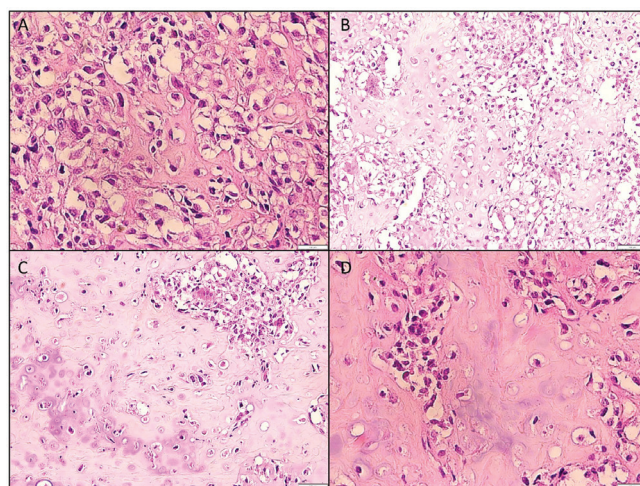


Figure 3. Histopathologic features of the occipital lesion

(A) Highly atypical polyhedral and spindle cells producing immature osteoid in a lace-like pattern (H&E, $\times 200$). (B) Chondroid matrix blending into eosinophilic osteoid with hyperchromatic oval to spindle cells and scattered multinucleated giant cells (H&E, $\times 100$). (C) High-grade malignant cartilage admixed with atypical oval to spindle cells and multinucleated giant cells (H&E, $\times 100$). (D) Cartilaginous component with high-grade stromal cells in areas with relatively scant osteoid production (H&E, $\times 200$) H&E: Hematoxylin and eosin

In contrast, Dumpala et al. (9) documented a rare case of mandibular gingival metastasis from a rib chondroblastic osteosarcoma; however, the metastatic involvement was limited to the oral cavity and did not extend to the skull base. Meningeal chondroblastic osteosarcoma represents an even rarer entity, typically presenting as a dura-based mass mimicking meningioma (10) (Table 1).

Importantly, across these reports, skull involvement consistently represents a primary cranial tumor rather than metastatic dissemination from an appendicular skeleton origin. To our knowledge, skull base metastasis arising from a pediatric extremity chondroblastic osteosarcoma has not been previously documented in the available literature.

The biological basis of atypical metastatic patterns in osteosarcoma remains incompletely understood. Although hematogenous dissemination explains the predominance of pulmonary metastases, the mechanisms underlying rare extrapulmonary skeletal involvement, particularly at the skull base, remain uncertain. In the present case, the unusual site of relapse is best interpreted as an uncommon manifestation of metastatic spread rather than evidence of a distinct biological pathway.

From an imaging standpoint, ^{18}F -FDG PET/CT plays an established role in staging, response assessment, and selected surveillance settings in osteosarcoma. Although most osteosarcomas demonstrate high ^{18}F -FDG avidity,

Table 1. Summary of reported cases of skull chondroblastic osteosarcoma

Author-year	Age-sex	Pediatric	Primary vs metastatic	Location	Imaging modality	PET/CT	Treatment	Outcome
Uysal et al. (3)	17-M	Y	Primary	Maxilla/ethmoid/sphenoid	Cranial X-ray, CT, MRI	N	Surgery + RT	No relapse (46 months)
Romeo et al. (10)	51-M	N	Primary	Meningeal	CT, MRI, cerebral angiography	N	Pre-operative embolization + surgery + ChT + RT	No relapse (43 months)
Dumpala et al. (9)	24-M	N	Metastatic (4 th rib)	Mandibular gingiva	CT, OPG	N	Surgery + ChT + RT	Poor outcome
Adwani et al. (8)	17-M	Y	Primary (recurrent)	Maxilla	CT	N	Surgery + ChT + RT	Deceased
Almeida et al. (7)	27-F	N	Primary	Maxilla	Panoramic radiography, CT	N	NACT	Not reported (short follow-up)
He et al. (5)	9-M	Y	Primary	Occipital	CT, MRI (CE + DWI)	N	Surgery (subtotal) + RT + ChT	Deceased (6 months after local recurrence)
Orunmuyi et al. (11)	32-M	N	Primary	Frontal	¹⁸ F-FDG PET/CT, ⁶⁸ Ga-RGD PET/CT	Y	Surgery + RT + ChT	Recurrent setting
Mamachan et al. (6)	58-M	N	Primary	Anterior maxilla	CT, ¹⁸ F-FDG PET/CT	Y	Surgery	No recurrence (asymptomatic at 1 year)
Mamachan et al. (6)	17-M	Y	Primary	Parietal-occipital	MRI, CT, bone scan	N	NACT + surgery + RT	Deceased (15 months)
Present Case - 2026	15-F	Y	Metastatic	Occipital	¹⁸ F-FDG PET/CT, CT, MRI	Y	Surgery + RT + ChT	No relapse; NED at 26 months follow-up

CT: Computed tomography, MRI: Magnetic resonance imaging, RT: Radiotherapy, ChT: Chemotherapy, OPG: Orthopantomography, NACT: Neoadjuvant chemotherapy, CE: Contrast-enhanced, DWI: Diffusion-weighted imaging, ¹⁸F-FDG PET/CT: ¹⁸F-Fluorodeoxyglucose positron emission tomography/computed tomography, ⁶⁸Ga-RGD PET/CT: Gallium-68-labeled arginine-glycine-aspartic acid PET/CT

variability in metabolic behavior has been reported. In a skull chondroblastic osteosarcoma case, ¹⁸F-FDG PET failed to demonstrate uptake while Gallium-68-labeled arginine-glycine-aspartic acid PET provided superior tumor visualization (11). In contrast to that report, our case demonstrated marked hypermetabolic activity within the occipital condyle on routine surveillance ¹⁸F-FDG PET/CT, enabling detection of a clinically occult skull base relapse prior to the development of significant neurological deficits.

Standard surveillance strategies for extremity osteosarcoma are primarily structured to detect local recurrence and pulmonary metastases, typically through limb MRI and chest CT. As a result, anatomically complex skeletal regions such as the skull base are not systematically evaluated in the absence of focal neurological symptoms. In the present case, routine surveillance with whole-body ¹⁸F-FDG PET/CT enabled simultaneous identification of both pulmonary and skull base metastatic sites within a single examination,

revealing an unexpected pattern of relapse that would not have been encompassed by conventional follow-up imaging fields.

Although this single case does not warrant modification of established surveillance algorithms, it illustrates that metastatic dissemination in osteosarcoma may occasionally extend beyond anticipated anatomical territories. By documenting skull base involvement arising from a pediatric extremity chondroblastic osteosarcoma, this report adds to the limited literature on atypical metastatic presentations and suggests that whole-body ¹⁸F-FDG PET/CT may help identify clinically unsuspected relapse in selected patients.

Conclusion

This case illustrates the potential utility of whole-body ¹⁸F-FDG PET/CT for identifying both typical and atypical relapse sites within a single examination and suggests

a complementary role for metabolic imaging beyond conventional surveillance protocols in selected clinical settings.

Ethics

Informed Consent: Written informed consent was obtained from the patient's legal guardian for publication of this case and accompanying images.

Availability of Data and Material: All data and materials are available from the corresponding author upon reasonable request.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.B., Concept: S.B., E.A., Design: S.B., H.G.S., İ.K., E.A., Data Collection or Processing: S.B., H.G.S., İ.K., U.Y., Analysis or Interpretation: S.B., H.G.S., İ.K., U.Y., Literature Search: S.B., H.G.S., Writing: S.B., U.Y., E.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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