Original Article

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The Impact of ^{18}F-FDG PET/CT and Related Parameters on Staging, Disease Management and Prognosis in Patients with Cholangiocarcinoma

Kolanjiyokarsinomlu Hastalarda ^{18}F-FDG PET/BT ve İlgili Parametrelerin Evreleme, Hastalık Yönetimi ve Prognoz Üzerine Etkisi

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Abstract

Objectives: We aimed to evaluate the relationship of ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) parameters with diagnostic efficacy, disease management and prognosis in patients with cholangiocarcinoma (CCA). The prognostic value of the spleen/liver ^{18}F-FDG uptake ratio was also investigated.

Methods: The clinical and imaging findings of 39 patients who met the diagnostic criteria and underwent ^{18}F-FDG PET/CT imaging for staging between 2013 and 2023 were retrospectively analysed.

Results: The tumour was intrahepatic in 34 patients and extrahepatic in 5 patients. PET/CT detected nodal involvement in 21 patients (53.8%) and distant metastases in 35 patients (89.7%). Fourteen cases (35.9%) had regional-distant metastases detected by PET/CT but not by magnetic resonance imaging/CT, and the stage of the disease changed accordingly. SUV_{max}, SUV_{mean}, metabolic tumor volume, tumour lesion glycolysis, tumor-to-liver ratio (tumour/liver parenchyma SUV_{max}), tumor-to-background ratio (tumour/blood pool SUV_{max}), tumor-stroma ratio (tumour/spleen parenchyma SUV_{max}), and standardized liver ratio (SLR) (spleen/liver SUV_{max}) did not differ based on tumour location. Recurrence occurred in 14 patients (35.9%), and 2 patients survived. When the cut-off values for the parameters were determined by the Youden index, progression-free survival (PFS) was significantly shorter in patients with an SLR value of less than 0.94 compared to the others (p=0.04). Nodal involvement, metastatic location, and other PET/CT parameters had no significant effect on PFS and overall survival.

Conclusion: Our results highlight the efficacy of ^{18}F-FDG PET/CT in staging nodal and distant metastases, similar to several studies in patients with CCA. Although SLR was found to have significant efficacy in PFS among the parameters we analysed, it is appropriate to evaluate the prognostic significance of these parameters in larger patient groups.

Keywords: Cholangiocellular carcinoma, ^{18}Fluorine-fluorodeoxyglucose, positron emission tomography/computed tomography, positron emission tomography, survival

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Öz

Amaç: Bu çalışmada, ^{18}Flor-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/BT) parametrelerinin kolanjiyokarsinom (CCK) hastalarında tanısal etkinlik, hastalık yönetimi ve prognoz ile ilişkisini değerlendirmeyi amaçladık. Ayrıca dalak/karaciğer ^{18}F-FDG tutulum oranının prognostik değerini de araştırdık.

Yöntem: 2013-2023 yılları arasında tanı kriterlerini karşılayan ve evreleme için ^{18}F-FDG PET/BT görüntülemesi yapılan 39 hastanın klinik ve görüntüleme bulguları retrospektif olarak analiz edildi.

Bulgular: Tümör 34 hastada intrahepatik, 5 hastada ise ekstrahepatikti. PET/BT ile 21 hastada (%53,8) nodal tutulum ve 35 hastada (%89,7) uzak metastaz tespit edildi. On dört olguda (%35,9) PET/BT ile bölgesel-uzak metastaz tespit edilirken manyetik rezonans görüntüleme/BT ile tespit edilemedi ve hastalığın evresi buna göre değişti. SUV_{maks}, SUV_{ort}, metabolik tümör volümü, tümör lezyon glikolizi, tümör/karaciğer oranı (tümör/karaciğer parankimi SUV_{maks}), tümör-arka plan oranı (tümör/kan havuzu SUV_{maks}), tümör-stroma oranı (tümör/dalak parankimi SUV_{maks}) ve standartlaştırılmış karaciğer oranı (SLR) (dalak/karaciğer SUV_{maks}) değerleri tümör yerleşimlerine göre farklılık göstermedi. Hastaların 14'ünde (%35,9) nüks gelişti ve 2 hastada sağkalım mevcuttu. Youden indeksi ile parametreler için cut-off değerleri belirlendiğinde, SLR değeri 0,94'ün altında olan hastalarda progresyonsuz sağkalım (PFS) diğerlerine kıyasla anlamlı olarak daha kısaydı (p=0,04). Nodal tutulum, metastatik yerleşim ve diğer PET/BT parametrelerinin PFS ve genel sağkalım üzerinde anlamlı bir etkisi yoktu.

Sonuç: Bulgularımız, ^{18}F-FDG PET/BT'nin nodal ve uzak metastaz evrelemesindeki etkinliğini vurgulamakta olup, CCK hastalarında yapılan birçok çalışmaya benzerdir. SLR, analiz ettiğimiz parametreler arasında PFS'de anlamlı etkinliğe sahip bulunsa da, bu parametrelerin prognostik öneminin daha büyük hasta gruplarında değerlendirilmesi uygun olacaktır.

Anahtar kelimeler: Kolanjiyoselüler karsinom, ^{18}Flor-florodeoksiglukoz, pozitron emisyon tomografisi/bilgisayarlı tomografi, pozitron emisyon tomografisi, sağkalım

Introduction

Cholangiocellular carcinoma is the second most common primary hepatobiliary tumour (5-30% of primary hepatobiliary tumours) and accounts for 3-5% of gastrointestinal cancers. It originates from the biliary epithelium and has an aggressive course and poor prognosis (1,2). Depending on the location of the tumour, cholangiocarcinoma (CCAs) are divided into 2 groups: intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA) (Klatskin tumour and distal pancreatic duct tumours). It is predominantly eCCA, and in two-thirds of cases, the focus is at the bifurcation of the hepatic ducts. Although the incidence of CCA is higher in Asia than in Western countries, there has been an increase in both incidence and mortality rates, particularly for iCCA, CCA (3,4). While the majority of patients have no identifiable risk factors, there are a number of well-defined risk factors, including primary sclerosing cholangitis, cirrhosis, viral hepatitis, diabetes, and alcohol consumption (5). Nearly 90% of cases are adenocarcinomas, which may show varying degrees of differentiation. Clinical presentation is characterised by predominantly non-specific symptoms, until the advanced stage, making diagnosis difficult. This finding is supported by 2/3 recurrence of cases and 5-year survival rates of 20-40% (6,7). The only curative approach is radical surgical resection with a clear surgical margin. Therefore, tumour-related local features (tumour location, margin, relationship to surrounding structures/degree of invasion), regional lymph node (LN) involvement and distant metastatic status are important markers in this approach (8). This procedure cannot be used due to locally advanced disease, the presence of distant metastases, or insufficient liver capacity, which is observed in approximately 2/3 of cases at the time of diagnosis (9). However, in cases of aggressive or recurrent disease, multidisciplinary treatment modalities including systemic chemotherapy and/or radiotherapy are also used to improve survival (8,10). Imaging plays a pivotal role in the diagnosis of CCA, characterisation of the tumour, accurate staging, particularly in selecting patients for curative surgery, and detection of recurrence. Magnetic resonance imaging (MRI) (MRI, magnetic resonance cholangiopancreatography, contrast-enhanced and diffusion-weighted imaging) and contrast-enhanced computed tomography (CT) are two main non-invasive staging modalities that are routinely used. Although ^{18}Fluorine-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT), which combines anatomical and functional imaging, has made an important contribution to the assessment of nodal and distant metastatic disease status and the detection of recurrence, its routine clinical use remains controversial (8,11,12). While some studies have identified prognostic factors: LN involvement, distant metastasis, tumour diameter, tumour grade, vascular invasion, R0 resection, it is important to note that these factors primarily relate to postoperative outcomes (6,13). Determining the group of patients with poor prognosis or high risk of recurrence prior to treatment is another important factor that may be effective in selecting the correct staging and curative surgical option. in addition to its role in diagnosis and staging, the contributions of ^{18}F-FDG PET/CT in predicting the prognosis of the disease have been reported (14,15). In our study, we

aimed to evaluate the diagnostic efficacy of ^{18}F-FDG PET/CT parameters, and their relationship with prognostic data in patients with CCA. In addition investigated the prognostic value of the spleen/liver ^{18}F-FDG uptake ratio in patients with CCA, which has been reported in a few studies in the literature (16).

Materials and Methods

Patient Group

We studied 39 patients, who met the inclusion criteria, diagnosed with CCA by imaging or pathology, from a group of 161 patients who underwent staging ^{18}F-FDG PET/CT imaging between 2013 and 2023. Descriptive characteristics (sex, age at diagnosis, date of diagnosis, dates of treatment initiation and last follow-up), ^{18}F-FDG PET/CT staging findings, MRI, contrast-enhanced CT images, and survival characteristics were retrospectively recorded and analysed. Patients who had undergone local or systemic treatment and surgery prior to ^{18}F-FDG PET/CT imaging, patients whose archives did not contain sufficient information on the parameters to be used in the study, and patients with a metastatic second malignancy other than CCA were not included in the study. The definition of recurrence was the detection of local recurrence or distant metastatic lesions on MRI/CT and ^{18}F-FDG PET/CT imaging for restaging/therapy response if performed. Local recurrence was defined in the presence of the following findings: a) soft tissue with a tendency to enlarge in the primary tumour lesion on conventional imaging; causing disruption of the normal anatomical structure and/or obstruction/dilatation of the biliary tract, b) soft tissue with increased ^{18}F-FDG uptake on PET/CT that can be distinguished from an inflammatory lesion (especially in stented cases). Regional LN involvement was considered positive if it showed increased ^{18}F-FDG uptake or if its short axis was greater than 10 mm in the absence of increased metabolism. Again, metastatic involvement was defined as focal areas of ^{18}F-FDG uptake, even if normometabolic, not supported by physiological/inflammatory processes or accompanied by a suspicious morphological abnormality. Regional LN involvement was limited to the periduodenal, hilar, and peripancreatic regions, except for those defined as distant metastases. This retrospective study was conducted with the approval of the Ege University Medical Research Ethics Committee (decision no: 24-6T/48, date: 06.06.2024).

^{18}Fluorine-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Imaging and Interpretation of Images

^{18}F-FDG PET/CT imaging was performed with a Siemens Biograph Truepoint-16 device. Images were interpreted as PET, CT, and fusion PET/CT across different slices (coronal, transverse, sagittal), utilizing visual and semiquantitative parameters. The standardised uptake value was calculated as follows: SUV= [tissue radioactivity concentration (Bq per mL)]/[injected radiopharmaceutical activity (Bq)/the body mass (g)]. Attenuation-corrected images were evaluated in two stages by two nuclear medicine specialists using the patients' archive data. The area of interest was drawn from the primary tumor site in cases detected by PET/CT, and from the area defined by conventional imaging and/or pathological sampling in cases not detected by PET/CT but diagnosed by other methods (CT or MRI). In addition to SUV_{max} (g/mL) and SUV_{mean} (g/mL) values, metabolic tumour volume (MTV) and tumour lesion glycolysis (TLG) values were determined by automated contouring, at 40% threshold. A 3 cm diameter area of interest was drawn from the right lobe of the liver and the spleen, and SUV_{max} values of the disease-free liver parenchyma/spleen parenchyma were measured. In addition, a 1 cm spherical region of interest was drawn through the descending aorta to measure blood pool SUV_{max}. The parameters tumour/liver SUV_{max} ratio [tumor-to-liver ratio (TLR)], tumour/blood pool SUV_{max} ratio [tumor-to-background ratio (TBR)], and tumour/spleen SUV_{max} ratio [tumor-stroma ratio (TSR)] were determined by comparing the SUV_{max} values of the primary tumour with the SUV_{max} values of the liver parenchyma, blood pool, and spleen. Date of diagnosis, date of last follow-up, and date of death for deceased patients were recorded. Progression-free survival (PFS) was defined as the time from first local-systemic treatment/curative surgery to relapse or death from any cause, while overall survival (OS) was defined as the time from diagnosis to death from any cause.

Statistical Analysis

The data in the study were analysed using SPSS version 25 (SPSS Inc., Chicago, IL). Normality was analysed using Shapiro-Wilk tests. The χ^2 and Fisher's exact tests (for categories with expected values <5) were used to analyze categorical variables, and independent two-sample t-test and Mann-Whitney U test were used to analyze the relationship between the dependent variable and numerical data. Numerical data are expressed as mean ± standard

deviation and median with 1st and 3rd quartiles (interquartile range), depending on whether they have a normal or skewed distribution. Categorical data are expressed as number and percentage. The Spearman correlation test was used to determine correlations between PET/CT parameters and serum carbohydrate antigen 19-9 (Ca19-9), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) levels. Receiver operating characteristic curves and Youden's index were used to calculate cut-off values of ^{18}F-FDG PET/CT-derived parameters for recurrence, and to categorise them. The Kaplan-Meier method was used for OS and PFS, and the log-rank test and Cox regression analysis were used to compare the incidence of events between patient groups.

The confidence interval for the tests was 95% and the statistical significance level (p) was 0.05.

Results

A total of 39 patients (19 women and 20 men) were included in the study. The diagnosis of CCA was confirmed pathologically in 28 patients, while 11 patients were diagnosed with CCA during follow-up with imaging studies. The clinical and imaging data of the patients are shown in the table (Table 1). The primary tumour was intrahepatic in 34 (87.2%) patients and extrahepatic in 5 (12.8%) cases. The primary lesion was detected by staging PET/CT in 37 patients (94.9%). Similarly, the primary lesion could not be detected by conventional imaging modalities in 2 cases only. Regional LN involvement or distant metastasis was detected by PET/CT in 35 (89.7%) patients, and in 14 (40%) of these, the metastatic focus could not be detected by conventional methods. The only metastatic site not detected by PET/CT but identified by MR/CT was the liver. In 14 (35.9%) patients, local recurrence and new/progressing metastases were detected during follow-up. Only 3 of these patients were still alive at the end of follow-up. No significant differences in PET/CT parameters (SUV_{max}, SUV_{mean}, MTV, TLG, spleen/liver ratio, TLR, TBR, TSR) were observed between patients with iCCA and eCCA (Table 2). No significant difference was observed between iCCA and eCCA cases with regard to the location of the metastatic focus (p=0.3) and regional LN involvement (p=0.424). No significant correlation was found between PET/CT parameters and Ca19-9 and CEA levels (p>0.05). Again, no significant difference in PET/CT parameters was observed between patients with AFP levels above and below the cut-off of 2.72 (p>0.05). Regional LN involvement, location of the metastatic focus, PET/CT parameters, serum CA19-9, CEA, and AFP levels did not have a significant effect on PFS and OS (Table 3). The cut-off values of PET/CT parameters associated with the development of relapse were determined. For each parameter, they were as follows: SUV_{max} 20.92 g/mL, SUV_{mean} 11.23 g/mL, MTV 24.54 mL, TLG 288.03 g, SLR 0.94, TLR 4.28, TBR 8.69, TSR 7.05. When comparing the groups, PFS was significantly shorter in patients with SLR values below 0.94 compared to the others (Table 4). Similarly, PFS was significantly shorter

Table 1. Clinical characteristics and descriptive findings of the patient group

Characteristics		**n**
Age		37-83 (mean:63)
Gender	Male	n=20 (51.3%)
	Female	n=19 (48.7%)
Tumor location	Intrahepatic	34 (87.2%)
	Extrahepatic	5 (12.8%)
PET/CT	Primary lesion +	37 (94.9%)
	Regional LN +	21 (53.8%)
	Distant metastasis +	35 (89.7%)
MRI/Contrast-enhanced CT	Primary lesion +	37 (94.9%)
	Regional LN-distant metastasis +	22 (56.4%)
Distant metastasis	LN	20 (51.3%)
	Liver	10 (25.6%)
	Peritoneal spread	6 (16.7%)
	Pulmonary	5 (12.8%)
	Bone	3 (7.7%)

LN: Lymph node, MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography/computed tomography

Table 2. Analysis between clinical features, PET/CT parameters and tumor location			
	iCCA (n=34)	**eCCA (n=47)**	**p-value**
SUV_{max}	15.31±6.27	14.75±7.29	0.855
SUV_{mean}	8.48±3.89	8.54±4.89	0.976
MTV	55.12 (23.05-86.98)	8.9 (4.85-366.63)	0.120
TLG	436.86 (212.88-665.05)	75.87 (45.94-2987.01)	0.106
Splen/liver SUV_{max}	0.75±0.15	0.85±0.24	0.207
TLR	2.67 (1.92-3.93)	3.44 (1.95-3.65)	0.894
TBR	4.24 (3.09-6.13)	5.58 (3.29-6.56)	0.790
TSR	4.06 (2.48-5.44)	3.31 (2.55-4.65)	0.657

PET/CT-related parameters are shown as means ± SD or median (IQR). The units of the following parameters were as follows: SUV_{max} and SUV_{mean} are g/mL, MTV is mL, TLG is g.
PET/CT: Positron emission tomography/computed tomography, SD: Standard deviation, MTV: Metabolic tumour volume, TLG: Tumour lesion glycolysis, TLR: Tumor-to-liver ratio, TBR: Tumor-to-background ratio, TSR: Tumor-stroma ratio, iCCA: Intrahepatic cholangiocarcinoma , eCCA: Extrahepatic cholangiocarcinoma

Table 3. Univariate analysis of clinical features and PET/CT parameters regarding PFS and OS		
	PFS	**OS**
SUV_{max}	0.318	0.723
SUV_{mean}	0.283	0.594
MTV	0.932	0.249
TLG	0.633	0.238
Splen/liver SUV_{max}	0.798	0.297
TLR	0.170	0.711
TBR	0.161	0.705
TSR	0.176	0.584
Regional lymph node involvement	0.742	0.428
Distant metastatis (Liver-LN-peritonel spread/ visceral organ-bone)	0.371	0.095

PET/CT-related parameters are shown as means ± SD or median (IQR). The units of the following parameters were as follows; SUV_{max}'s and SUV_{mean}'s are g/mL, MTV's is mL, TLG's is gr.
LN: Lymph node, PET/CT: Positron emission tomography/computed tomography, SD: Standard deviation, MTV: Metabolic tumour volume, TLG: Tumour lesion glycolysis, TLR: Tumor-to-liver ratio, TBR: Tumor-to-background ratio, TSR: Tumor-stroma ratio, PFS: Progression-free survival, OS: Overall survival

Table 4. Univariate analysis of PET/CT parameters regarding PFS	
	PFS
SUV_{max} (<20.92 / ≥20.92)	0.155
SUV_{mean} (<11.23 / ≥11.23)	0.127
MTV (<24.54 / ≥24.54)	0.819
TLG (<288.03 / ≥288.03)	0.429
Splen/liver SUV_{max} (<0.94 / ≥0.94)	**0.040**
TLR (<4.28 / ≥4.28)	0.127
TBR (<8.69 / ≥8.69)	0.127
TSR (<7.05 / ≥7.05)	0.127
Regional lymph node involvement	0.742
Distant metastatis (Liver-LN-peritonel spread/visceral organ-bone)	0.371

PET/CT-related parameters are shown as means ± SD or median (IQR). The units of the following parameters were as follows; SUV_{max}'s and SUV_{mean}'s are g/mL, MTV's is mL, TLG's is gr.
LN: Lymph node, PET/CT: Positron emission tomography/computed tomography, SD: Standard deviation, MTV: Metabolic tumour volume, TLG: Tumour lesion glycolysis, TLR: Tumor-to-liver ratio, TBR: Tumor-to-background ratio, TSR: Tumor-stroma ratio, PFS: Progression-free survival

in patients with a spleen/liver SUV_{max} ratio below 0.94 compared to the other group (p=0.04) (Figure 1).

Discussion

CCA is the second most common primary hepatobiliary tumour and has a non-specific clinical presentation, an aggressive course, and a poor prognosis, particularly in advanced stages. The only curative treatment is surgery. Given the recurrence and advanced disease observed in 2/3 of cases, it is important to identify surgical candidates and possible prognostic criteria associated with recurrence. The contribution of ^{18}F-FDG PET/CT, the use of which is controversial for diagnosis/staging purposes other than MR-CT, is one of the issues still under evaluation. It can provide data related to recurrence/survival prior to treatment/surgery compared to prognostic factors defined by postoperative features (tumour diameter, tumour grade, vascular invasion, R0 resection, etc.). Our main aim was to evaluate the diagnostic efficacy, contribution to disease management, and prognostic efficacy of ^{18}F-FDG PET/CT staging parameters. We also investigated the prognostic value of the spleen/liver FDG uptake ratio in patients with CCA.

Table 5. Studies with multivariate analysis of clinical characteristics and PET/CT parameters		
	Prognostic	**Non-prognostic**
Yachi et al. (21)	SUV_{max}	-/NM
Pevner and Tanvetyanon (26)	SUV_{max}, Ca19-9	-/NM
Lin et al. (23)	SUV_{max}, TNR	-/NM
Sabaté-Llobera et al. (17)	CEA, TLR	SUV_{max}, Ca19-9
Lee et al. (18)	-	SUV_{max}, SUV_{mean}, MTV, TLG, SUV_{peak}
Lee et al. (24)	TLG	MTV, SUV_{max}
Harimoto et al. (25)	SUV_{max}, TLG	MTV, CEA, Ca19-9

NM: Non-mentioned, PET/CT: Positron emission tomography/computed tomography, MTV: Metabolic tumour volume, TLG: Tumour lesion glycolysis, TLR: Tumor-to-liver ratio, Ca19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen

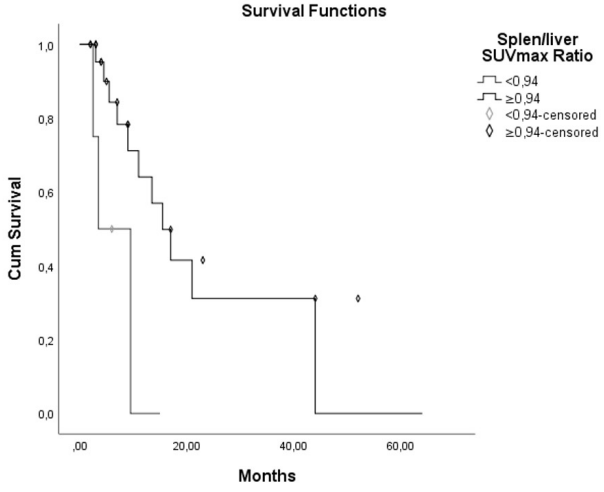

Figure 1. Survival table delineated by the splen/liver SUV_{max} ratio (p=0.04)

Differences and Relationships Between Clinical Findings and PET/CT Parameters

It is known that the incidence of eCCA is higher than that of iCCA in routine clinical practice. However, the different clinical presentation of both subtypes, including late-onset biliary obstruction and advanced stage of disease at diagnosis in iCCA-compared to hilar tumours- and tumour growth pattern, together with the retrospective nature of our study, may explain the predominance of iCCA in our cohort of patients referred with suspected metastases. Although the efficacy of PET/CT and conventional methods in detecting the primary lesion is similar, we believe that it would be more appropriate to test these data in prospective studies with this as the primary focus and a large patient population. In addition, we found that PET/CT was more effective than conventional methods in detecting regional nodal involvement and distant metastases and, consequently, in changing the modality/stage of the disease. Our findings in this regard were largely similar to those reported in the literature (11,14,17,18,19,20). In our study, we examined the SUV_{max} parameter, which is used in current practice, as well as the SUV_{mean} parameter and the MTV and TLG values based on volumetric assessment. In addition, the TLR value was used to minimise differences in the basal FDG uptake of the liver and bias in this area. TBR and TSR were additional parameters evaluated for similar purposes in our study. A further analysis was performed on the SLR parameter, which is known to be particularly effective for staging in the diagnosis of lymphoma, and has been evaluated in a small number of studies for patients with CCA (16). In the literature, it has been reported that both SUV_{max} and TLR were higher in patients with iCCA than in patients with eCCA (17,21). In our study, no significant difference was found in the PET/CT parameters we examined according to tumour location. It has been reported that possible factors such as patient selection (resectability, inclusion of non-CCA cancers such as gallbladder cancer in studies), tumour cell origin, and tumour growth pattern may be responsible for these differences observed between studies. Again, regional nodal involvement did not differ according to tumour location in our study, and this finding is consistent with the literature (17). Although not specific for the disease, serum tumour markers such as CA19-9, CEA, and AFP are used in the diagnosis and follow-up of patients with CCA and especially in the follow-up of recurrence. Sabaté-Llobera et al. (17) reported that SUV_{max} and TLR were significantly but weakly correlated with serum CA19-9 and CEA levels. In our data, no significant difference or correlation was found between these serum markers and PET/CT parameters.

Prognosis

As previously described in the literature for various types of cancer, prognostic parameters in CCA are predominantly associated with post-operative processes. However, it is important to identify poor prognostic markers in cases where curative surgery is not an option, and especially

in the early stages of the disease, before treatment or surgery. Accordingly, the prognostic efficacy of various clinical/imaging factors in patients with CCA has been described (Table 5) (11,14,17,18,21,22,23,24,25,26). In univariate analysis, regional LN involvement, metastatic location, PET/CT parameters, serum CA19-9, CEA, and AFP levels did not significantly affect PFS and OS. However, when the Youden index was used to determine cut-off values for SUV_{max}, SUV_{mean}, MTV, TLG, TLR, TSR, and SLR values, PFS was significantly shorter in patients with SLR values below 0.94 compared with the others. Although it provides a different perspective, we would like to point out that in our patient population, the survival analysis applied by setting cut-offs has limited power. This limitation is due to significant heterogeneity in the number of patients in the groups. Our study has several key findings. One was the evaluation of clinical and prognostic differences, as well as the effects on patients across a wide range of parameters. A contributing factor was the relatively high homogeneity of the patient group in our study in terms of tumour location (87.2% iCCA) and stage (94.9% stage IV), despite considering differences in prognosis between patients at different stages and at diagnosis of iCCA-eCCA patients.

Study Limitations

We emphasise that our study should be evaluated in light of several limitations. Most importantly, our study carries a foreseeable risk of selection bias due to its retrospective nature. Another disadvantage is the relatively small number of patients with eCCA in our cohort, which limits the evaluation of clinical and prognostic factors according to tumour location, although this was not the main aim of our study.

Conclusion

In conclusion, we consider that ^{18}F-FDG PET/CT is a useful imaging modality in cases of CCA, as it allows functional imaging in addition to anatomical imaging and allows whole-body imaging, especially when compared to MRI. In this regard, we would like to reiterate the necessity of PET/CT in cases of CCA, especially considering its greater effectiveness than conventional imaging in disease management and detection of regional/distant metastases. We note that the SLR parameter, which has been evaluated in a few studies, especially in the hepatobiliary cancer group, may be an effective factor in the development of recurrence in cases with CCA. We speculate that the conflicting findings in prognostic factors observed in our study and in the literature may be secondary to the composition of the patient group (iCCA-eCCA, additional diagnoses such as gallbladder cancer that cause heterogeneity) and other disease-related factors (differences in patient stage). In this context, we would like to emphasise again the need for prospective studies evaluating large series of patients.

Ethics

Ethics Committee Approval: This retrospective study was conducted with the approval of the Ege University Medical Research Ethics Committee (decision no: 24-6T/48, date: 06.06.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.T., Concept: F.T., Design: F.T., Data Collection or Processing: F.T., K.M., Analysis or Interpretation: F.T., K.M., Literature Search: F.T., Writing: F.T.,Ü.Y.

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