 doi:10.20944/preprints202210.0005.v1

Article

Comparison of conventional imaging and 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the diagnostic accuracy of staging in patients with intrahepatic cholangiocarcinoma

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Abstract: 18F-fluorodeoxyglucose positron emission tomography and computed tomography (18F-FDG PET-CT) is increasingly used in the diagnosis, prognosis, staging, and treatment monitoring of many tumor types. However, only a small number of studies have reported the use of 18F-FDG PET-CT in intrahepatic cholangiocarcinoma (ICC). This study aimed to examine the accuracy of tumor staging in ICC by using 18F-FDG PET-CT. Between January 2009 and December 2020, patients with suspected ICC were retrospectively enrolled in the study and underwent imaging. The sensitivity and specificity of 18F-FDG PET-CT, CT, and magnetic resonance imaging (MRI) in detecting tumors, satellite focus, vascular invasion, and lymph node metastases were analyzed. The efficacy of 18F-FDG PET-CT for tumor staging was evaluated. Of the 110 patients who were enrolled in the study, 52 underwent surgical treatment and 45 were histologically diagnosed with ICC. When compared with CT or MRI, 18F-FDG PET-CT had similar sensitivity and specificity values for diagnosing satellite focus and vascular and bile duct invasion; however, PET-CT showed higher accuracy in diagnosing regional lymph node metastases. The accuracy of tumor staging by 18F-FDG PET-CT was higher than that by CT/MRI. Thus, 18FDG PET-CT may support tumor staging in ICC.

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Keywords: intrahepatic cholangiocarcinoma, 18F-fluorodeoxyglucose positron emission tomography, computer tomography, magnetic resonance imaging, tumor stage

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC). Epidemiological studies show that ICC is rare in most western countries. However, the incidence is exceptionally high in Asian countries like China, Korea, Japan, and Thailand. The northeastern region of Thailand has the highest incidence worldwide (85 per 100,000 population / year) [1]. ICC shares some common risk factors with HCC, such as hepatitis B or C viral infection, cirrhosis, diabetes, and alcohol abuse [2]. Early diagnosis of ICC is difficult, as the disease tends to be asymptomatic in the early stages. The TNM system of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) is widely used for ICC staging. However, until the 6th edition of this staging system, the staging of HCC and ICC was identical, but the distinction between these two different tumor types was introduced in the 7th edition of the staging system and updated in the current 8th edition. [3]. Computed tomography/magnetic resonance imaging (CT/MRI) are routinely used in the diagnosis and staging of ICC. However, the associated

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diagnostic accuracy, sensitivity, specificity, and TNM staging are considered suboptimal for ICC management [4,5].

Positron emission tomography (PET) using 18F-fluorodeoxyglucose (18F-FDG) is an imaging modality that measures the glucose metabolism rate in tumor cells. 18F-FDG PET-CT imaging provides biochemical information about tumors, which is not provided by other imaging modalities. An increased uptake of 18F-FDG represents enhanced glucose metabolism in cancer cells, which makes it a marker of tumor viability. 18F-FDG PET-CT is increasingly used in the diagnosis, prognosis, staging, and treatment monitoring of many tumor types [6-11]. However, only a small number of studies, presenting the advantages and disadvantages of this modality, have reported on the use of 18F-FDG PET-CT in ICC [12-17], which is not currently included in the routine clinical management of ICC [1,18]. Our preliminary findings have suggested that this modality may help identify lymph node and distant metastases in patients with ICC. Therefore, a cohort of patients with ICC was studied to compare the efficacy of 18F-FDG PET-CT with that of CT/MRI in tumor staging.

2. Materials and Methods

2.1 Patients

Patients who were diagnosed with ICC using CT/MRI at our department between January 2009 and December 2020 were retrospectively enrolled. These patients were then routinely investigated with conventional radiological imaging modalities, such as chest X-ray/CT, abdominal CT/MRI, to assess tumor stage. Simultaneously, 18F-FDG PET-CT was performed for these patients. All imaging examinations were performed within 4 weeks before treatment. Data on the patients' demographic and clinical characteristics were collected, and the TNM stage was assessed using the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system [3]. The study was conducted in accordance with the Declaration of Helsinki. Approval was granted by the local ethics committee (25-117). The requirement for informed consent was waived.

2.2 Conventional radiological imaging

Contrast-enhanced abdominal CT (Discovery CT 750HD, GE Medical Systems, Milwaukee, WI) and MRI at 3T scanner (Intera Acheiva 3T, Philips Healthcare, Best, Netherlands) or 1.5T scanner (1.5T Signa HDxt, GE Healthcare, Milwaukee, WI, USA) were used to evaluate the primary tumors and to detect any intraabdominal metastases. Chest X-ray and whole-body bone scintigraphy were used to identify distant metastases. After the injection of intravenous contrast (150 ml at 3 ml/s), CT and MRI scans of the abdomen were obtained with 5-mm collimation and a table speed of 5 mm/s. The images were reconstructed with 5-mm thickness. CT and MRI scans were interpreted by radiologists with over 10 years of experience. ICC was defined as an irregular mass with markedly low attenuation, peripheral rim enhancement followed by progressive and concentric filling with contrast, and focal dilatation of the intrahepatic ducts around the tumor. Enlarged lymph nodes identified on CT/MRI were measured along their short axes. "Lymph node metastasis" was defined as a short axis of ≥10 mm or when it increased by ≥20% on sequential CT/MRI scans within an interval of 4 weeks [20].

2.3 Positron emission tomography

^{18}F-FDG PET-CT images were obtained using a PET/CT scanner (Discovery PET/CT 710; GE Healthcare Life Sciences, Amersham Place, Little Chalfont, Buckinghamshire, England). The patients fasted for at least four hours before the intravenous administration of 3.0 MBq/kg of 18F- FDG (80.7–307.5 MBq). The blood sugar level was checked before administration, and none of the patients had a glucose level greater than 115 mg/dL. The patients underwent full-body scans. Imaging began approximately 60 min after an intravenous administration of 18F-FDG using the 3D time-of-flight mode (3D TOF), and helical CT data acquired with free breathing were used for attenuation correction. The CT scanning parameters were 120 kV, an automated tube current with a noise index of 23 for helical CT, 0.5 s/rotation, a pitch factor of 1.375, a detector configuration of 16 × 1.25 mm, a slice thickness of 3.75 mm, a slice interval of 3.27 mm, and a display field-of-view (DFOV) of 500 mm. All the PET images scanning were reconstructed using a block sequential regularized expectation maximization algorithm

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(BSREM). In this study, we adopted a β value of 800. The PET imaging properties were as follows: slice thickness and interval of 3.27 mm, matrix size of 192 × 192, and DFOV of 500 mm. Accurate positioning of the patient between transmission and emission scanning was performed using laser marking. Both attenuation-corrected and non-attenuation-corrected images were interpreted visually. The attenuation-corrected images were then analyzed semi-quantitatively using standard uptake values (SUV). Regions of interest were drawn over the area of maximum activity in a lesion. The SUV was calculated as follows: SUV = tissue concentration / (injected dose × body weight). A primary tumor was defined when a focal lesion with an increase in the uptake of 18F-FDG was detected, relative to the values observed in the surrounding normal tissue. A lymph node was defined as positive when SUVmax was ≥ 2.5 [20].

2.4 Statistical analysis

Continuous variables are presented as median (range). Categorical variables are presented as numbers or percentages, and were compared using the McNemar's test or Fisher's exact test. Analyses were performed using SPSS Statistics version 17.0 (SPSS; IBM, Tokyo, Japan). P-values of <0.05 were considered statistically significant.

3. Results

From January 2009 to December 2020, 182 patients were clinically diagnosed with ICC. Among them, 110 patients agreed to participate in this study, including 52 patients who underwent surgical treatment. Among the 52 patients who had a pathological diagnosis, 45 had ICC and were included in this study (Table 1).

Table 1. Demographic and clinical characteristics of patients undergoing laparotomy (n=45)

Parameter	case or median (range)
Age (year)	68 (50-77)
Sex(male/female)	26/19
Hepatitis (B/C)	4/8
CA199 (> 39 / ≤ 39 U/ml)	30/15
CEA (> 10 / ≤ 10 ug/L)	11/34
AFP (> 20 / ≤20 ug/L)	6/39
Tumor location (left lobe/right lobe)	22/23
SUVmax of tumor	8.9(3.4-17.2)
SUVmax of lymph node (> 2.5 / ≤2.5)	20/25
Tumor size (> 5 / ≤5cm)	27/18
Tumor number(single/multiple)	28/17
Macroscopic vascular invasion (yes/no)	4/41
Cancer embolus in bile duct (yes/no)	5/40
Lymph node metastases (yes/no)	20/25
Nerve invasion (yes/no)	4/41
Peripheral tissue invasion (yes/no)	2/43

CA19-9: carbohydrate antigen 19-9; CEA: carcino-embryonic antigen; AFP: alpha feto-protein; SUVmax: maximum of standardized uptake value.

Seven were diagnosed histopathologically with HCC. Among 45 patients with ICC, 40 underwent hepatectomy plus lymphadenectomy, and 5 underwent exploratory laparotomy

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only because of intraoperative detection of abdominal metastases. Moreover, 58 cases were considered unresectable preoperatively due to multiple tumors in the future remnant liver (n = 4), peritoneal dissemination (n = 4), distant lymph node metastasis (n = 18), and distant organ metastases (n = 32). Among 45 patients that underwent surgery, 17 patients had multiple tumors, 4 had vascular invasion, 5 had bile duct invasion, and 20 had regional lymph node metastases (Table 2).

Table 2. Diagnosis of multiple tumors, macrovascular invasion, bile duct invasion, regional lymph node metastases and distant metastases by imaging modality

	CT	MRI	PET-CT	CT vs. MRI vs. PET-CT)	CT vs. PET-CT)	MRI vs. PET-CT)
Diagnosis of multiple tumors						
Sensitivity	8/17(47%)	9/17(53%)	5/17(29%)	N.S.	N.S.	N.S.
Specificity	28/28(100%)	27/28(96%)	28/28(100%)	N.S.	N.S.	N.S.
PPV	8/8(100%)	9/10(90%)	5/5(100/100%)	N.S.	N.S.	N.S.
NPV	28/37(76%)	27/35(77%)	28/40(70%)	N.S.	N.S.	N.S.
Accuracy	36/45(80%)	36/45(80%)	33/45(73%)	N.S.	N.S.	N.S.
Diagnosis of macrovascular invasion						
Sensitivity	3/4(75%)	3/4(75%)	2/4(50%)	N.S.	N.S.	N.S.
Specificity	38/41(93%)	39/41 (95%)	40/41 (98%)	N.S.	N.S.	N.S.
PPV	3/12(25%)	3/8(38%)	2/4(50%)	N.S.	N.S.	N.S.
NPV	38/39(97%)	39/40(98%)	40/41(98%)	N.S.	N.S.	N.S.
Accuracy	41/45(91%)	42/45(93%)	42/45(93%)	N.S.	N.S.	N.S.
Diagnosis of bile duct invasion						
Sensitivity	1/5(20%)	3/5(60%)	1/5(20%)	N.S.	N.S.	N.S.
Specificity	38/40(95%)	38/40 (95%)	40/40(100%)	N.S.	N.S.	N.S.
PPV	1/5(20%)	3/6(50.0%)	1/1(100%)	N.S.	N.S.	N.S.
NPV	38/39(97%)	38/39 (97%)	40/41(98%)	N.S.	N.S.	N.S.
Accuracy	39/45(87%)	41/45(91%)	41/45(91%)	N.S.	N.S.	N.S.
Diagnosis of regional lymph node metastases						
Sensitivity	8/20(40%)	10/20(50%)	16/20(80%)	0.04	0.01	0.04
Specificity	20/25(80%)	21/25 (84%)	22/25(88%)	N.S.	N.S.	N.S.
PPV	8/13(62%)	10/15(67%)	16/18(89%)	0.04	0.02	N.S.
NPV	20/35(57%)	21/33(64%)	22/25(88%)	<0.01	<0.01	0.02
Accuracy	28/45(62%)	31/45(69%)	38/45(84%)	<0.01	<0.01	0.02

Among 17 patients with multiple tumors, 10, 11, and 6 were diagnosed by CT, MRI, and PET-CT, respectively. The corresponding accuracy rates for diagnosing multiple tumors were 80%, 80%, and 73%, respectively. Among 4 patients with vascular invasion, two, three, and two patients were diagnosed by CT, MRI, and PET-CT, respectively. The accuracy rates for diagnosing vascular invasion were 91%, 93%, and 93%, respectively. Among 5 patients with bile duct invasion, one patient, three patients, and one patient were diagnosed by CT, MRI, and PET-CT, respectively. The corresponding accuracy rates for diagnosing bile duct invasion were 87%, 91%, and 91% respectively. Moreover, 20 patients had histologically confirmed metastases in the regional lymph nodes. Regional lymph node metastases were detected by CT in 8 patients (sensitivity = 40.0%), by MRI in 10 patients (sensitivity = 50%), and by PET-CT in 16 patients (sensitivity = 80%). The corresponding specificity rates were 80%, 84%, and 88%, respectively. PET-CT showed higher accuracy (84%) than CT (62%) and MRI (69%) at diagnosing lymph node metastasis in patients with ICC ($P < 0.01$). Among 31 patients with lymph nodes of >1 cm, 19 (61%) patients had lymph node metastases. Among 14 patients with lymph nodes of ≤1 cm, 1 (7.1%) were positive for metastases. There was a positive association between lymph node metastases status and lymph node size ($P < 0.01$).

The TNM staging of each patient was assessed using PET-CT or conventional radiological imaging including abdominal CT or MRI, chest X-ray, and whole-body bone scintigraphy

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(CT/MRI) evaluations. PET/CT scan results changed the TNM staging as determined by CT/MRI in 45 patients. Among them, 16/15/9 patients were down-staged and 5/4/1 were up-staged by CT/MRI/PET-CT when compared with pathological examination. The accuracy of tumor staging by PET-CT was higher than that by CT/MRI (PET-CT vs. CT vs. MRI: 35/45 vs.24/45 vs. 26/45, $P < 0.05$) (Tables 3 and 4).

Table 3. Tumor stage assessed by CT, MRI, and PET-CT

Stage	CT	MRI	PET-CT	Pathological examination
I	22	22	14	18
II	7	5	1	6
III A	0	1	0	1
III B	8	10	16	20
IV	0	0	0	0

Table 4. Changed tumor staging assessed by CT, MRI, and PET-CT, respectively.

	Up stage	Down stage	Unchanged	The accuracy
CT	5	16	24	24/45(53%)*
MRI	4	15	26	26/45(58%)**
PET-CT	1	9	35	35/45(78%)***

*P(CT vs. PET-CT) = 0.01, **P(MRI vs. PET-CT) = 0.07, *** P(CT vs. MRI vs. PET-CT) = 0.03

4. Discussion

Surgical resection remains the only curative treatment for patients with ICC. However, recurrence is common, and prognosis is poor even after surgery [1]. Lymph node metastasis is associated with a poor prognosis in ICC [20, 21]. Although surgical treatment with extended lymphadenectomy may have more favorable surgical outcomes, recent guidelines suggest that patients with lymph node metastases should not undergo surgery [1]. Thus, accurate preoperative assessment of lymph node and distant metastases is important to help prevent overtreatment with surgery. Conventional CT and MRI scans often fail to detect lymph node and distant metastases in patients with cholangiocarcinoma [12,13].

18F-FDG PET is a radiological technique that combines anatomic and functional imaging. It is increasingly used in the management of many tumors [22-25]. Most studies find it valuable in diagnosing and staging tumors when compared with traditional imaging techniques such as CT and MRI. It has also been reported as useful in malignant biliary cancer, including ICC, as it outperformed CT and MRI at detecting lymph node metastases [13, 14, 20]. Herein, the sensitivity, specificity, and accuracy values of 18F-FDG PET for detecting lymph node metastases were significantly higher than those of CT/MRI imaging. Compared with CT/MRI, 18F-FDG PET imaging involves the uptake of 18F-FDG, reducing the risk of misdiagnosis, which is associated with CT/MRI and evaluations by relatively inexperienced radiologists. 18F-FDG PET has limitations at detecting small lesions with low tumor metabolism. Herein, 18F-FDG PET was not superior at diagnosing satellite lesions (Figure 1) and vascular and bile duct invasion (Figure 2).

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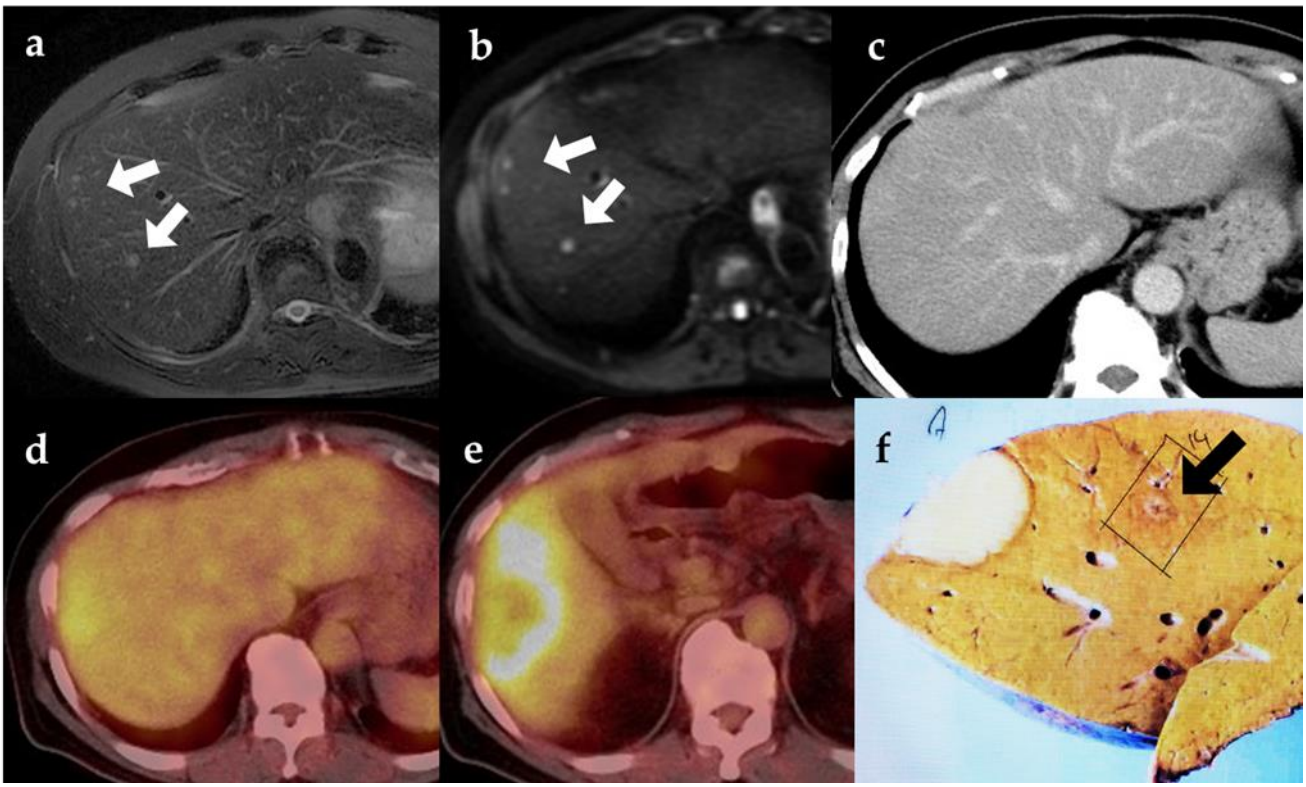

Fig. 1. MRI (a, b) showed a satellite nodule (white arrow) separated from the main tumor, which was confirmed by histopathology (f; black arrow) but was not detected on CT (c) or PET-CT (d, e).
(a) T2-weighted MR image, (b) diffusion-weighted MR image (b factor=800), (c) contrast-enhanced CT, (d) PET-CT, (e) PET-CT showed main tumor, (f) gross specimen

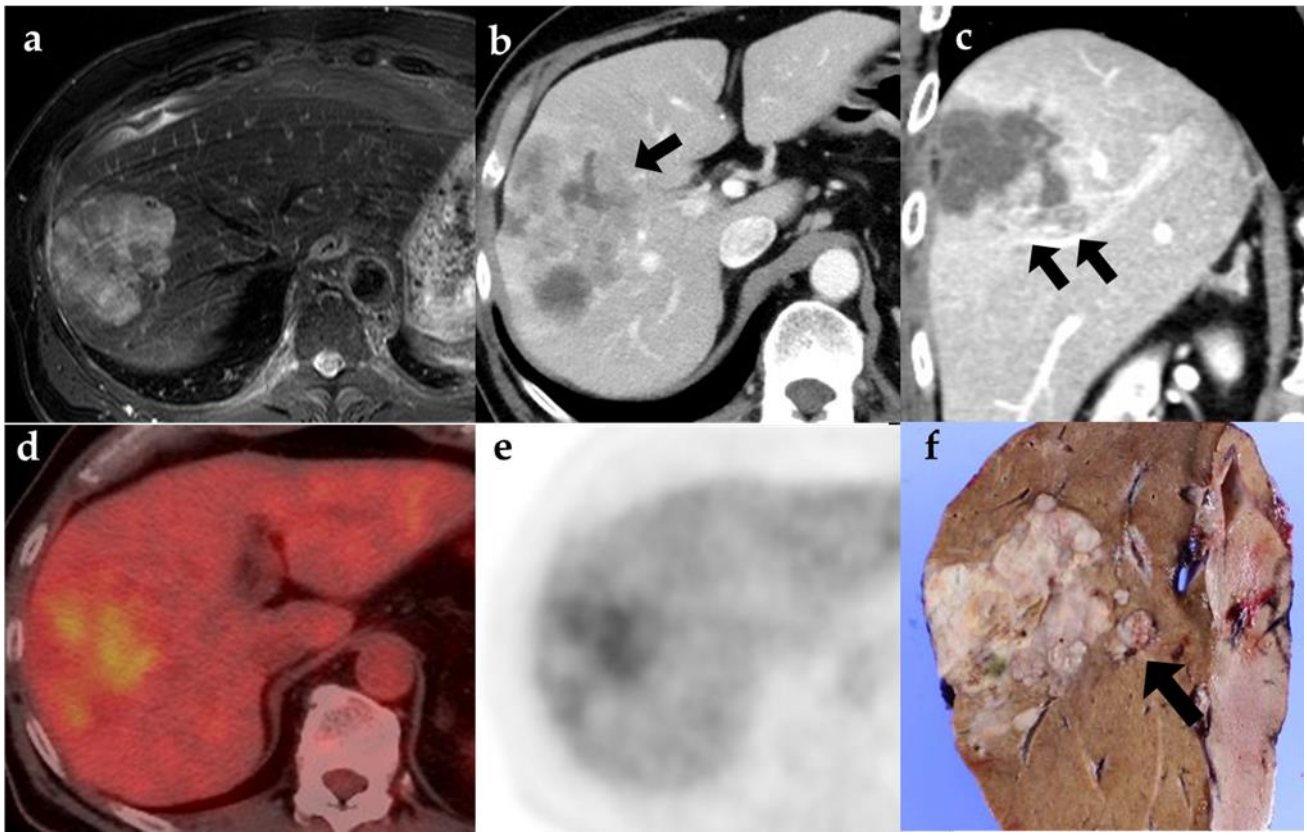

Fig. 2. Contrast-enhanced CT showed bile duct (b; arrow) and vascular emboli (c; arrow), which were not detected on MRI (a) or PET-CT (d, e)
(a) T2-weighted MR image, (b) axial section of contrast-enhanced CT, (c) coronal section of contrast-enhanced CT (d, e) PET-CT, (f) gross specimen (vascular emboli; arrow)

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Conventional imaging techniques, such as CT and MRI, help diagnose lymph node metastases when the lymph node size is ≥ 1 cm. In this study, the relationship between lymph node size and lymph node metastasis was positive. However, among patients with lymph nodes of > 1 cm, 38 cases (61.3%)

were positive for metastases. Among patients with lymph nodes of ≤1 cm, 2 (7.1%) cases were diagnosed with metastasis. Thus, lymph node size of > 1 cm is not an accurate indicator of metastasis risk. Using a high SUV, 18F-FDG PET showed high sensitivity, specificity, and accuracy at detecting lymph node metastasis. Most previous studies on 18F-FDG PET for malignant tumors highlighted the modality's capacity to detect distant metastatic lesions and tumor recurrence. These findings were validated in this study.

As a whole-body imaging technique, 18F-FDG PET is more powerful than conventional imaging techniques like abdominal CT/MRI. PET-CT imaging had a higher accuracy in tumor staging than CT/MRI in patients who received treatment different from what was originally planned. This study showed that 18F-FDG PET may help assess lymph node metastases. Moreover, this modality may be used as a complementary examination in patients with ICC alongside CT/MRI.

The major limitations of this study were: first, only patients with mass-forming type of ICC were included. Second, 58 patients with abdominal metastases did not receive surgery and lacked histological staging findings, and were thus not eligible for tumor staging. Third, this study was not a randomized controlled study and may be affected by selection bias. Thus, a well-designed randomized controlled trial is required to validate these findings.

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5. Conclusions

When compared with CT or MRI, 18F-FDG PET-CT had similar sensitivity and specificity values for diagnosing satellite focus and vascular and bile duct invasion; however, PET-CT showed higher ac-curacy in diagnosing regional lymph node metastases. The accuracy of tumor staging by 18F-FDG PET-CT was higher than that by CT/MRI. Thus, 18FDG PET-CT may support tumor staging in ICC.

Author Contributions: Conceptualization: M.T.; methodology: M.T.; formal analysis: E.N..; image analysis: E.N. and M.T.; data curation: E.N., M.T., R.K., S.I., and A.K.; writing—original draft preparation: E.N.; writing—review and editing: E.N., M.T..; supervision: T.M., K.I. All authors have read and agreed to the published version of the manuscript.

Funding: No specific funding was received for this research.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Kindai University Faculty of Medicine (Registration number: 25-117).

Informed Consent Statement: The requirement for informed consent was waived because of the retrospective nature of the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available owing to privacy.

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

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