Disease-specific Factors Influenced Lymph Node Metastasis of Diagnostic Accuracy of ^{18}F Fluorodeoxyglucose Positron Emission Tomography/computed Tomography in Colorectal Cancer : a Single-center Study

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Abstract

Background: The usefulness of preoperative lymph node metastasis diagnosis by 18F fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) in colorectal cancer management has been reported, but inadequate diagnostic accuracy precludes routine preoperative application. Therefore, the purpose of this study was to examine the factors influencing the diagnostic accuracy of lymph node metastasis by PET/CT in patients with colorectal cancer.

Methods: We retrospectively identified 864 patients who underwent preoperative PET/CT and colorectal cancer resection at Shizuoka General hospital from January 2017 to December 2019. We examined factors influencing the diagnostic accuracy of PET/CT to detect lymph node metastasis generally and lymph node metastasis for each TNM stage according to the UICC-TNM 8th edition.

Results: The overall sensitivity and specificity of PET/CT to detect lymph node metastasis in patients with colorectal cancer were 61.2% and 75.9%, respectively. Distant lymph node metastasis was diagnosed more accurately than regional lymph node metastasis. "T category" (T1/T2 vs. T3/T4) was an independent factor affecting the lymph node metastasis diagnostic capability among patients negative for lymph node metastasis [$p < 0.01$; odds ratio 2.20; 95% CI 1.28-3.84], while among patients positive for lymph node metastasis, "Tumor diameter" was significantly associated with the lymph node metastasis diagnostic capability on univariate analysis [$p = 0.02$]. The sensitivity and specificity of PET/CT for Stage I (T1/T2, N0) were 82.5% and 84.6%, respectively. For more advanced tumors, the diagnostic ability to detect lymph node metastasis decreased.

Conclusions: Disease-specific factors such as T category and tumor diameter significantly impacted on LN metastasis diagnosis by PET/CT in patients with colorectal cancer. We recommended the preoperative application of PET/CT only for the diagnosis of distant lymph node metastasis.

Background

Lymph node (LN) metastasis is one of the most important prognostic factors for patients with colorectal cancer (CRC) [1,2]. In Japan, when preoperative or intraoperative diagnosis confirms or is suspicious of LN metastasis, it is recommended to perform D3 [2]. D3 is similar to the concept of complete mesocolic excision with central vascular ligation, which is achieved en bloc removal of the diseased lesion with the increased amount of the colonic mesentery. [3-5]. Preoperative LN metastasis diagnosis is essential to achieve the concept of D3.

Preoperative LN metastasis diagnosis is mainly demonstrated by computed tomography (CT). Although examining morphological features and measurements using multiplanar reconstruction images of LN metastasis have been tried, both sensitivity and specificity are approximately 60%. Therefore, it is difficult to say that CT could accurately diagnose LN metastasis [6-8].

Recently, it has been shown that ^{18}F fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) can be useful for preoperative LN metastasis diagnosis of CRC by demonstrating metabolic information at the site of the lesion [9-12]. However, PET/CT is not the standard imaging modality for LN metastasis diagnosis. The reason was that it had not been examined which cases were useful for LN metastasis diagnosis by PET/CT. CRC causes inflammatory changes associated with tumors, such as obstructive colitis due to tumor stenosis or obstruction. Recognizing the extent to which PET/CT was affected by inflammatory changes specific to CRC might contribute to preoperative LN metastasis diagnosis accuracy. We thought that the ability to diagnose preoperative LN metastasis accurately would greatly help determine treatment strategies, such as whether or not to perform the preoperative treatment and the extent of LN dissection.

Therefore, the present study aimed to examine disease-specific factors that affect LN metastasis diagnosis of CRC by PET/CT and decide the eligible cases requiring PET/CT.

Methods

Patients

In this retrospective study, we enrolled patients diagnosed with CRC at Shizuoka General hospital from January 2017 to December 2019. Preoperative staging was performed by colonoscopy, CT and PET/CT, and magnetic resonance imaging (MRI) in case of rectal cancer located below the peritoneal reflection. Surgical strategy, including LN dissection, was determined according to preoperative staging. The patients with suspicion of LN metastasis underwent D3 and the other patients D2 or D3, according to T category [2]. D3 was performed for Stage IV with resectable distant metastases. LN dissection was not performed for palliation.

Inclusion and Exclusion Criteria

We analyzed the medical records of patients who underwent preoperative PET/CT, followed by curative resection. We excluded patients who underwent emergency surgery and those with an interval of > 1 month between PET/CT and surgery.

Study Groups

Intra-abdominal LNs were divided into two groups (RG and DG) according to the anatomical location. RG consisted of patients with LNs along the vascular arcades of marginal vessels, which were proximal to the primary tumor, referred to as regional LNs group. DG consisted of patients with LNs along the superior mesenteric artery or inferior mesenteric artery, referred to as distant LNs group. D2 is defined as the dissection of RG, and D3 is defined as the dissection of RG and DG.

We compared the ability of PET/CT to diagnose LN metastasis between RG and DG, and examined whether the ability to diagnose LN metastasis was affected by distance from the tumor. Subsequently,

disease-specific factors that could influence LN metastasis diagnosis were examined for RG and DG. According to the preoperative PET/CT, the patients were divided into two groups, positive and negative for LN metastasis. Furthermore, the positive group was divided into two groups, true positive group and false positive group. Likewise, the group diagnosed as negative for preoperative LN metastasis was divided into two groups, true negative group and false negative group.

Variable and Measures

A cross-sectional analysis was performed to compare the surgical and pathological findings with the PET/CT results, across both groups. LN metastasis was diagnosed by using an optimized standardized uptake value max (SUV max) cut off value of 2.5 [12].

Disease-specific factors examined, that could influence LN metastasis diagnosis, were tumor SUV max, tumor diameter, macroscopic type, histological type, T category, circumferential ratio of the tumor, malignant colorectal stenosis, sidedness and location. Patient factors were age, sex, and body mass index.

Based on the UICC-TNM 8th edition, LN metastasis diagnostic ability of PET/CT for each TNM stage was also examined [13].

Statistical analysis

Statistical comparisons were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). Student's t-test was used to compare normally distributed continuous variables. The difference between discrete variables expressed as frequencies (percentages) was analyzed using chi-square test. Multivariate analysis was performed on factors that were statistically significant in univariate analysis. Multivariable logistic regression models were used to examine the factors that may have affected LN metastasis diagnosis of CRC. A P-value of <0.05 was regarded as statistically significant.

Results

A total of 1131 patients, diagnosed with CRC at Shizuoka General Hospital from January 2017 to December 2019, were included. Cases were excluded if no PET/CT was performed, underwent palliative surgery, missing essential data, and interval of > 1 month between PET/CT and surgery. As a result, 864 patients were included in the analyses for this study (Table 1).

The diagnostic capability of PET/CT between lymph node locations

The overall sensitivity, specificity and accuracy of PET/CT in the detection of LN metastasis for CRC were 61.2%, 75.9% and 70.9%, respectively. In RG, sensitivity, specificity and accuracy were 59.1%, 74% and 67.7%, and in DG, 72.3%, 99.6% and 98.8%, respectively. The diagnostic capability of PET/CT was significantly higher for DG than the entire group ($p < 0.001$), in contrast to a non-significant difference between RG and the entire group (Table 2).

The diagnostic values based on disease-specific factors

Due to the high diagnostic value of PET/CT in the detection of DG in CRC, only RG was examined. The eligible 864 patients were divided into positive and negative preoperative LN metastasis. The 501 patients diagnosed as positive for LN metastasis by preoperative PET/CT were divided into two groups, true-positive group (380 cases) and false-positive group (121 cases). The 363 patients diagnosed as negative for preoperative LN metastasis were divided into two groups, true-negative group (216 cases) and false-negative group (147 cases) (Figure 1).

Among patients negative for LN metastasis by preoperative PET/CT, a significant difference was noted between true and false-negative cases for "Macroscopic Type", "T category" and "Circumferential ratio of the tumor". No significant difference was observed in other factors. "Macroscopic Type", "T category" and "Circumferential ratio of the tumor" were examined by multivariate analysis, and "T category" was found to be an independent factor for LN metastasis diagnosis of CRC (Table 3).

Among patients positive for LN metastasis by preoperative PET/CT, only "Tumor diameter" was significantly associated with LN metastasis diagnosis of CRC on univariate analysis [true-positive group: 47.3mm, false-positive group: 53.5mm, $p=0.02$]. No significant difference was observed in other factors (Table 4).

Comparison of diagnostic value of PET/CT between TNM stages

The LN metastasis diagnostic capability of PET/CT for stage I was significantly higher than the other stages. The LN metastasis diagnostic capability of Stage II and Stage III was about 60%, and the diagnostic capability decreased as the tumor stage increased (Table 5).

Discussion

This study examined the disease-specific factors that affected LN metastasis diagnosis of patients with CRC by PET/CT in the retrospective, single-center study. We reported that the diagnostic capability of PET/CT was better for distant LN metastasis than for regional LN metastasis. Regional LN metastasis diagnosis was affected by disease-specific CRC factors. The results demonstrated that "T category" was an independent factor for false-negative LN metastasis diagnosis, while "Tumor diameter" was significantly associated with false-positive LN metastasis diagnosis.

Preoperative diagnosis of CRC is performed using various modality such as colonoscopy, CT, MRI, and PET/CT [14]. As for LN diagnosis, MRI has a high diagnostic capability [15,16]. However, it cannot be applied generally to preoperative CRC cases because the imaging range of MRI is limited. PET/CT was recognized as a useful imaging modality for LN metastasis diagnosis in addition to distant metastasis [9-12]. For advancing the diagnostic performance of LN metastasis, some studies focused on selecting SUV max optical cut-off values for LN metastasis and the relationship between SUV max and LN size

[9,10,17]. However, it was not examined how CRC-specific characteristics impacted preoperative LN metastasis diagnosis by PET/CT.

Based on this study, “T category” was an independent factor for false-negative LN metastasis diagnosis. In general, deep penetration correlates with the frequency of LN metastasis [18]. And LNs are near the tumor and merge with the FDG accumulation of the primary tumor, making it difficult to distinguish LN metastasis from the primary tumor [19,20].

“Tumor diameter” was strongly linked with false-positive LN metastasis diagnosis in patients with CRC. Large tumor size is expected to provide a more intense antigenic immune challenge to the draining LN, resulting in nodal hyperplasia. Then large tumor size could cause reactive enlargement of regional LNs [18,21]. The cause of false-positive LN metastasis was considered the accumulation of FDG in response to reactive enlargement of LNs.

However, these disease-specific effects of CRC had little effect in DG. In a past study, it had been reported that the LN metastasis diagnosis at a distance from the tumor by PET/CT was high [17]. The high diagnostic capability of LN metastasis distant from the tumor makes it possible to recognize the extent to which LN metastasis extends horizontally or vertically from the tumor. As a result, it will contribute to the determination of the extent and endpoint of LN dissection.

As for the LN diagnostic capability for each stage by PET/CT, it was useful in Stage I. As the tumor stage increases, the increased “T category” and “Tumor diameter” appeared to decrease the LN metastasis diagnostic capability. In the treatment strategy for CRC, surgery is the basis of the treatment in Stage I. In the case of Stage II and Stage III, multidisciplinary treatment, including preoperative treatment, is required [22,23]. Therefore, the diagnostic capability for Stage II and Stage III is essential in preoperative diagnosis. In this study, the LN metastasis diagnostic capability of Stage II and Stage III by PET/CT was not high, so LN metastasis diagnosis by PET/CT might not contribute to treatment selection for patients with CRC.

It was extremely difficult to diagnose LN metastasis of CRC by PET/CT. This was the same result by CT from a recent big data study [24]. However, PET/CT was useful for LN metastasis diagnosis of DG and Stage I because of less impact on disease-specific factors in CRC. By limiting the cases, we thought PET/CT could be a useful preoperative diagnostic modality.

The limitations of this study were that it was a single-center study and used a fixed SUV max cut-off value. It has been reported that SUV max cut off value for LN metastasis changed depending on LN size [9]. In this study, a SUV max cut-off value for LN was set to 2.5 with reference to past meta-analysis [12], so small lymph node metastasis cases were possibly overlooked.

Conclusion

Disease-specific factors had a significant impact on the LN metastasis diagnosis of PET/CT for patients with CRC. The high diagnostic capability of PET/CT for LN metastasis distant from the tumor suggested that it might contribute to the determination of LN dissection range.

List Of Abbreviations

PET/CT: 18F fluorodeoxyglucose positron emission tomography/computed tomography

LN: lymph node

CRC: colorectal cancer

CT: computed tomography

MRI: magnetic resonance imaging

SUV max: standardized uptake value max

Declarations

Ethics approval and consent to participate:

This study was approved by the independent ethics committee of our hospital in November 2019 (IRB number: SGHIRB#2019080). The requirement of patient consent was waived because of the retrospective nature of the study.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

Kyota Tatsuta wrote the manuscript. Mayu Sakata and Kiyotaka Kurachi conceived and designed the analysis. Takafumi Kawamura and Hiroyuki Hazama collected the data. Yoshifumi Morita, Hiroto Kikuchi, Yoshihiro Hiramatsu, Ko Ohata and Noriyuki Oba contributed data and performed the analysis. Hiroya Takeuchi approved the finally version to be published.

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Tables

Table 1.

Patient characteristics

	n=864
Age (years), median (range)	70 (29-93)
Male sex, cases (%)	497 (58)
Body mass index (kg/m ²), median (range)	22.5 (13.7-35.2)
CEA (ng/ml), median (range)	4.5 (0.4-1616)
CA19-9 (U/ml), median (range)	14 (1-833)
Location, cases (%)	
colon	569 (66)
rectum	295 (34)
Histological type, cases	
tubular adenocarcinoma	805
papillary adenocarcinoma	5
poorly differentiated adenocarcinoma	19
mucinous adenocarcinoma	8
carcinoid tumor	6
others	21
Pathological Stage*, cases	
Stage I	276
Stage II	217
Stage III	317
Stage IV	54

* According to the UICC-TNM, 8th edition

Table 2.

Comparison of the diagnostic capability of PET/CT between lymph node locations

	All lymph nodes	Regional lymph nodes group**	Distant lymph nodes group***	Univariate analysis All vs. RG P-value	Univariate analysis All vs. DG P-value
Sensitivity, %	61.2	59.1	72.3	0.95*	<0.01*
Specificity, %	75.9	74.0	99.6	0.94*	<0.01*
Accuracy, %	70.9	67.7	98.8	0.83*	<0.01*

Lymph node metastases were diagnosed using an optimized SUVmax cutoff value of 2.5.

*** Chi-square test,

*** Regional lymph nodes were defined as those located along the peripheral vessels and proximal to the primary tumor.

*** Distant lymph nodes were defined as nodes along the superior mesenteric artery or inferior mesenteric artery.

Table 3.

Factors associated with false negative lymph node metastasis diagnosis of colorectal cancer by FDG-PET/CT

	True-negative group (n=380)	False-negative group (n=121)	Univariate analysis P-value	Multivariate analysis*** P-value Odds Ratio (95% CI)
Age (years), median (range)	69 (31-93)	72 (34-92)	0.15*	
Male sex, n (%)	222 (58)	70 (66)	0.94**	
BMI (kg/m ²), median (range)	22.7 (13.7-32.3)	22.9 (14.6-35.2)	0.74*	
Tumor SUV max, median (range)	7.9 (0-42.1)	8.7 (0-169)	0.20*	
Tumor diameter (mm), median (range)	25 (3-88)	30 (2-75)	0.20*	
Macroscopic Type			<0.01**	0.17 1.53 (0.83-2.84)
Type 0, cases (%)	150 (39)	22 (17)		
others, cases (%)	230 (61)	99 (83)		
Histological type, cases (%)			0.19**	
adenocarcinoma, cases (%)	365 (96)	112 (93)		
others, cases (%)	15 (4)	9 (7)		
T category, cases (%)			<0.01**	<0.01 2.20 (1.28-3.84)
T1 / T2	243	44		
T3 / T4	137	77		
Circumferential ratio of the tumor, cases (%)			<0.01**	0.36 1.29 (0.74-2.24)
Circumference tumor	55 (14)	34 (28)		
others	325 (86)	87 (72)		
Malignant colorectal stenosis, cases (%)	15 (4)	11 (9)	0.05*	

Sidedness, cases (%)			0.87**
right	134 (35)	41 (34)	
left	246 (65)	80 (66)	
Location			0.65**
colon	308 (81)	101 (83)	
rectum	72 (19)	20 (17)	

*Student t-test, **Chi-square test,

**** Multivariable logistic regression models were used to examine each factor influencing the diagnostic accuracy of lymph node metastasis of colorectal cancer by FDG-PET/CT

BMI, Body mass index

Table 4.

Factors associated with false positive lymph node metastasis diagnosis of colorectal cancer by FDG-PET/CT

	True-positive group (n=216)	False-positive group (n=147)	Univariate analysis P-value
Age (years), median (range)	69 (29-88)	70 (41-91)	0.37*
Male sex, n (%)	125 (58)	73 (53)	0.46**
BMI (kg/m ²), median (range)	22.1 (13.9-33.9)	22.3 (15-34.8)	0.88*
Tumor SUV max, mean (range)	11.5 (3.4-34.9)	12.4 (0-50)	0.11*
Tumor diameter (mm), median (range)	47.3 (10-110)	53.5 (9-160)	0.02*
Classification of gross appearance			0.40**
Type 0, cases (%)	6 (3)	7 (5)	
others, cases (%)	210 (97)	130 (95)	
Histological type, cases (%)			0.30**
well / moderate, cases (%)	204 (94)	143 (97)	
others, cases (%)	12 (6)	4 (3)	
T stage, cases (%)			0.96**
T1 / T2	25 (12)	16 (11)	
T3 / T4	186 (88)	131 (89)	
The bowel circumference of tumor, cases (%)			0.81**
Circumference tumor	119 (55)	79 (58)	
others	97 (45)	68 (42)	
Tumor stenosis, cases (%)	22 (10)	17 (12)	0.81**
Sidedness, cases (%)			0.43**
right	61 (28)	48 (35)	
left	155 (72)	99 (65)	
Location			0.52**
colon	163 (75)	116 (79)	
rectum	53 (25)	301(21)	

*Student t-test, **Chi-square test,

BMI, Body mass index

Table 5.

Comparison of the diagnostic value of PET/CT between TNM stages **

	Stage I T1, T2 N-	Stage II T3, T4 N-	Stage III T1~T4 N+ M-	Stage IV M+	All Stages	Univariate analysis*** P-value
Sensitivity, %	82.5	63.5	76.3	54.5	61.2	0.17*
Specificity, %	84.6	66.2	52.1	13.2	75.9	<0.01*
Accuracy, %	84.4	64	68	17.1	70.9	0.04*

*** Chi-square test,

*** According to the UICC-TNM, 8th edition

*** Statistical comparison between Stage I and all stages

Figures

Figure 1

Patient flow chart *Patients with a medical history affecting examination outcome, such as diabetes, did not undergo PET/CT.

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