Preoperative Evaluation of Lymph Node Metastases in Patients with Gastric Cancer: An Analysis of Imaging Methods

Mide Kanseri olan Hastalarda Preoperatif Lenf Nodu Metastazının Değerlendirilmesi: Görüntüleme Yöntemlerin Analizi

Yusuf Günay[1], Emrah Çağlar[2], Esin Korkmaz[3], Rabiye Uslu Erdemir[4], İlhan Taşdöven[1], Ramazan Kozan[1]

[1]Department of General Surgery, Bulent Ecevit Üniversity, Zonguldak, Turkey
[2]Department of Radiology, Bulent Ecevit Üniversity, Zonguldak, Turkey
[3]Department of Pathology, Bulent Ecevit Üniversity, Zonguldak, Turkey
[4]Department of Nucleer Medicine, Bulent Ecevit Üniversity, Zonguldak, Turkey

Dergiye Ulaşma Tarihi: 26.06.2018 Dergiye Kabul Tarihi: 27.08.2018 Doi: 10.5505/aot.2018.92905

ÖZET

GİRİŞ ve AMAÇ: Mide kanseri olan hastalarda ameliyat öncesi evrelendirme cerrahi tedavi için gereklidir. Ancak ameliyat öncesi lenf nodu (LN) değerlendirilmesinde tek başına yeterli olabilecek bir test bulunmamaktadır. Bu çalışmanın amacı mide kanseri olan hastalarda, ameliyat öncesi LN tutulumunun değerlendirilmesinde pozitron emisyon tomografisi (PET/BT) ile bilgisayarlı tomografinin (BT) tanısal değerlerinin karşılaştırılmasıdır.
YÖNTEM ve GEREÇLER: Geriye dönük olarak gastrektomi ve D2 LN diseksiyonu ameliyatı olan seksen yedi hastanın değerlendirlmesidir. Görüntüleme yöntemleri ve patoloji raporları hasta dosyalarında toplandı.
BULGULAR: PET/BT ile BT arasında mide kanseri olan hastalarda LN tutulumun kestirim gücü arasında anlamlı bir fark bulunmadı (p>0.05). PET/BT'nin LN nodunu öngerme duyarlılığı, özgüllüğü, pozitif kestirim değeri (PKD) ve negatif kestirim değeri (NKD) ile doğruluk değeri %55.56, %54.55, %55.26, %75 ve %33.3 olarak hesaplanırken BT için % 57.69, %59.42, %70.27, and %46.88 olarak bulundu. Ancak, hem PET/BT ve BT birlikte kullanıldığında ameliyat öncesi mide kanseri olan hastalardaki LN metastazı belirlemede özgüllük PKD % 80 ve % 88.9 olarak bulundu. Sonuçlarımıza göre hastaya veya tümöre ait herhangi bir özelliğin PET/BT veya BT'nin LN metastazı öngörme gücü üzerinde etkisi görülmedi.
TARTIŞMA ve SONUÇ: PET/BT ve BT'nin birlikte kullanılması özgüllüğü ve PKD'ni arttırmaktadır. Bu artış, mide kanseri olan hastalarında ameliyat öncesi LN metastazı belirmede doğruluk değerini her iki testin ayrı ayrı kullanılmasında daha yüksektir.
Anahtar Kelmeler: Mide kanseri, lenf nodu, bilgisayarlı tomografi, pozitron emisyon tomografi

ABSTRACT

INTRODUCTION: Preoperative evaluation is necessary for the surgical treatment of gastric cancer (GC). Nonetheless, there is no single best diagnostic modality to predict lymph node metastases prior to surgery. The aim of this study was to analyze of the diagnostic utility of positron emission tomography-computed tomography (PET-CT) and CT for the preoperative evaluation of lymph node (LN) metastases in GC.
METHODS: Eighty seven patients with a history of GC, who underwent gastrectomy and D2 LN dissection were investigated. Imaging test results and pathology reports were collected from the patients' charts.
RESULTS: There was no statistical differences between PET/CT and CT scans in regard to predicting LN metastases in GC patients (p>0.05). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT scans in predicting LN metastases were 55.56%, 54.55%, 55.26%, 75%, and 33.3%, respectively, versus 60.47%, 57.69%, 59.42%, 70.27%, and 46.88% for CT scans, respectively. However, combined PET/CT and CT showed better outcomes and specificity with a PPV of 80% and 88.9%, respectively. No patients or tumor factors were found to increase the accuracy of LN metastasis prediction using either PET/CT or CT scans.
DISCUSSION AND CONCLUSION: The combination of CT and PET/CT scans increases the specificity and PPV. This increases the prediction accuracy of LN metastasis in GC patients compared to the use of each type of imaging modality alone.
Keywords: Gastric cancer, lymph node, computerized tomography, positron emmission tomography

Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com
Available at www.actaoncologicaturcica.com

INTRODUCTION

GC is still one of the main causes of death in the world (1). However, patient survival rates have been increasing in developed countries (2,3,4). It is well-known that lymph node (LN) metastases is a crucial prognostic factor in patients with GC (5,6). Thus, predicting LN status may help determine a patient's prognosis and develop a surgical plan. Surgery is still the only option for curing patients with non-metastatic GC. LN resection decreases recurrence and increases survival rates in patients with GC (7). Therefore, preoperative LN staging is essential for planning the optimal surgical treatment for GC, including LN dissection.

Although computerized tomography (CT) is one of the most common imaging tests used in patients with GC to predict LN metastases for preoperative evaluations, its accuracy is limited by the size of the LNs. Therefore, CT has some limitations for predicting LN metastases before surgery (8). On the other hand, 18-fluorodeoxyglucose (FDG) positron emission tomography integrated with CT (PET-CT) is used to investigate LN metastases of non-GCs because of its high specificity (9,10). The predictive value of PET/CT for LN evaluation is dependent on the ability of primary tumors to uptake 18-FDG, the number of LN metastases, the size of the LNs, and the presence of inflammation in areas of the body. Therefore, the usefulness of PET/CT in evaluating LN metastases needs to be interpreted according to each type of malignant tumor (11,12). Although, few studies have reported the preoperative value of PET/CT for LN in patient with GC (13,14), the predictive value of PET/CT versus CT in predicting LN metastases in GC patients has yet to be examined.

The aim of this study was to analyze the accuracy of preoperative PET/CT versus CT in evaluating preoperative LN metastases in patients with GC.

PATIENTS and METHODS

Between June 2012 and December 2017, 158 patients underwent surgical treatment for GC. Patients with non-adenocarcinomas, such as GISTs (Gastrointestinal stromal tumors), sarcomas, or distant metastases, were excluded. Of these patients, 97 had gastric adenocarcinoma with preoperative PET/CT and/or CT, but 10 patients' pathological reports were incomplete. Therefore, 87 patients were included. After obtaining approval from the hospital institutional review board, preoperative PET/CT and CT were reviewed retrospectively for evidence of primary GC and LN metastases. The imaging reports were compared to the pathological reports. The maximum standardized uptake values (SUV), tumor size, tumor location, tumor type, the number of LNs, and the tumor stage were retrieved from imaging reports. In addition to these data, each patient's age and gender were obtained from the charts.

Statistical analysis

Results were given as the means ± standard deviations. Results were compared using the Student's *t*-test and the Mann-Whitney U test. A multivariate analysis was then performed to identify independent risk factors for LN metastasis. The prediction of LN metastasis was calculated using receiver operating characteristic (ROC) curve analysis. The compliance of PET/CT and CT with the pathological LN metastasis was determined using McNemar, Kappa coefficient, and diagnostic screening tests, such as those for sensitivity and specificity. The confidence interval (CI) was set at 95%, and p-values were considered significant at a level of <0.05. Statistical analysis was performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (NCSS LLC, Kaysville, Utah, USA).

RESULTS

The data from 87 patients were analyzed. The mean age of the patients was 62.04±12.73 (range: 32–84) years. Sixty-five (67%) patients were male, and 32 (33%) were female. Of the 87 patients, 51 (58,6%) underwent total gastrectomy and D2 LN dissection, and 36 (41.4%) had a subtotal gastrectomy and D2 LN dissection.

Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com
Available at www.actaoncologicaturcica.com

Table 1: The results of histopathological data for 87 patients.

Pathology results	Data	n (%)
Regional LN	N0	29 (33,4)
	N1	11 (12,6)
	N2	14 (16,1)
	N3	1 (1,2)
	N3a	19 (21,8)
	N3b	10 (11,5)
	Nx	3 (3,4)
Primary tumor	T1a	4 (4,6)
	T1b	7 (8,0)
	T2	7 (8,0)
	T3	39 (44,8)
	T4	1 (1,2)
	T4a	25 (28,8)
	T4b	4 (4,6)
TNM stage	1a	8 (9,2)
	1b	10 (11,5)
	2	13 (14,9)
	3a	9 (10,3)
	3b	8 (9,2)
	4	39 (44,8)

A total of 40 (41.2%) patients had a preoperative PET/CT, but only 22 (55%) displayed FDG uptake in LNs. The mean number of PET/CT-positive LNs was 4.45±2.65 (range: 1–10). Of these 22 LNs, 16 (72.2%) were in a perigastric location, while six (27.3%) were at distant locations. The mean of the SUV max for the primary tumor was 9.93±7.83 (range: 2.2–36), whereas it was 6.14±3.52 (range: 2.2–14.5) for the LN. Of the 78 (80.4%) patients with preoperative CT, 43 (55.1%) had a positive LN. The mean short axis length for the LNs was 17.05±12.84 (range: 2–60) mm. The locations of positive LNs based upon the CT were 27 (62.8%) in perigastric locations and 16 (37.2%) were distant LNs. CT identified the primary tumor in 63 (80.8%) patients. Of these GCs, 30 (47.6%) were on the antrum, 21 (33.3%) on the corpus, five (7.9%) on the fundus, four (6.4%) on the cardia, and three (4.8%) were diffuse gastric tumors. The average size of the primary tumors identified by CT was 23.51±24.16 (range: 1–160) mm. Of the 87 adenocarcinoma types identified, 45 (51.7%) were poorly differentiated, 36 (41.3%) were moderately differentiated, and six (6.9%) were well-differentiated (Table 1). Of the 87 patients, 56 (64.4%) had pathological LN metastasis. The mean number of LNs was 21.47±13.88 (range: 1–71) for each patient, while the metastatic LN number was 5.95±7.88 (range: 1–35).

A statistical analysis showed that there was an association between the PET/CT results and pathological LN, and this was noted as 8.5% (Kappa coefficient: 0.085). However, the correlation was not statistically significant (p=0.725, Table 2). Of the 40 patients who underwent a preoperative PET/CT, 21 (52.5%) displayed FDG uptake, which were considered as positive LNs, whereas in 18 (45%) patients, the LNs did not take up FDG and were considered as negative LNs. However, 14 of 21 patients (66.7%) had experienced a pathological LN metastasis. Based on these results, the sensitivity, specificity, and accuracy of preoperative PET/CT for identifying LN metastases in gastric adenocarcinoma were 55.56%, 54.55%, and 55.26%, respectively. Moreover, the positive and negative predictive values of preoperative PET/CT scans to predict LN metastases in gastric adenocarcinoma patients were 75% and 33.3%, respectively.

There was a statistical relation among the preoperative LN prediction of CT and pathological LN metastasis, and the level of compliance was found to be 17.4% (Kappa coefficient: 0.174). However, the correlation was not statistically significant (p=0.216, Table 3). Of the 78 patients who underwent preoperative CT, 43 (55.1%) had positive LNs identified by this method. However, histopathological examination identified metastatic LNs in 26 out of 43 (60.4%) patients. Based on these results, it showed that the sensitivity, specificity, and accuracy of preoperative CTs in identifying LN metastases in gastric adenocarcinoma were 60.47%, 57.69%, and 59.42%, respectively. Moreover, the positive predictive value (PPV) and negative predictive value (NPV) of preoperative CT scans in predicting LN metastases in GC were 70.27 % and 46.88%, respectively. Of the 87 patients, 23 (26.4%) underwent both preoperative PET/CT and CT scans. In 23 patients, eight (34.8%) had inconsistent results for the prediction of LN metastases between PET/CT and CT.

Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com
Available at www.actaoncologicaturcica.com

Table 2: A comparison of PET/CT-based prediction of LN metastases and histopathological findings.

	Pathological LN (-)	Pathological LN (+)	Total	*p*
PET/CT LN (-)	**6 (15,8)**	12 (31,6)	18 (47,4)	***0,725***
PET/CT LN (+)	5 (13,2)	**15 (39,5)**	20 (52,6)	
Total	11 (28,9)	27 (71,1)	38 (100)	
Sensitivity	55,56 %			
Specificity	54,55 %			
Positive predictive value	75,00 %			
Negativepredictive value	33,33 %			
Accuracy	55,26 %			

McNemar Test

Table 3: A comparison of CT prediction of LN metastases and histopathological findings.

	Pathological LN (-)	Pathological LN (+)	Total	*p*
CT LN (-)	**15 (21,7)**	17 (24,6)	32 (46,4)	***0,216***
CT LN (+)	11 (15,9)	**26 (37,7)**	37 (53,6)	
Total	26 (37,7)	43 (62,3)	69 (100)	
Sensitivity	60,47 %			
Specificity	57,69 %			
Positive predictive value	70,27 %			
Negativepredictive value	46,88 %			
Accuracy	59,42 %			

McNemar Test

Table 4: ROC results. The value of PET/CT and CT for predicting preoperative LN metastases.

Area Under the Curve

				Asymptotic 95% Confidence Interval	
Test Result Variable(s)	**Area**	**Std. Error[a]**	**Asymptotic Sig.**	**Lower Bound**	**Upper Bound**
PET/CT LN	0,698	0,122	***0,161***	0,458	0,938
CT LN	0,646	0,134	***0,302***	0,382	0,909

Table 5: Logistic regression analysis of histopathological tumor types on pathological LN metastases.

Histopathological type of tumor (differentiation)		p	ODDS	95% C.I.for ODDS Lower	Upper
Step 1[a]	**Well**	0,068			
	Moderately	0,219	3,143	0,507	19,492
	Poorly	0,038*	7,111	1,116	45,292

**p<0,05*

Table 6: Logistic regression analysis of tumor stage on pathological LN metastasis.

T stage		p	ODDS	95% C.I.for ODDS Lower	Upper
Step 1[a]	**T1**	0,002**			
	T2	0,525	0,444	0,037	5,406
	T3	0,019*	6,000	1,351	26,649
	T4	0,002**	13,333	2,592	68,589

**p<0,05* ***p<0,01*

Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com
Available at www.actaoncologicaturcica.com

However, 18 (78.3%) patients had consistent results between PET/CT and CT. Thus, the sensitivity, specificity, PPV, NPV, and accuracy in patients between PET/CT and CT were 61.5%, 80%, 88.9%, 44.4%, and 66.7%, respectively.

The ROC analysis revealed that the area under the curve for PET/CT was 69.8%, and the standard deviation was 10.5%. Meanwhile, the area under the curve and standard deviation were 64.6% and 12.3%, respectively, for the CT scan (Figure 1) with regard to predicting preoperative LN metastases in GC. When these results were compared, there were no statistically significant differences in the preoperative prediction of LN metastasis between PET/CT and CT in any TNM stage (p=0.602, Figure 1).

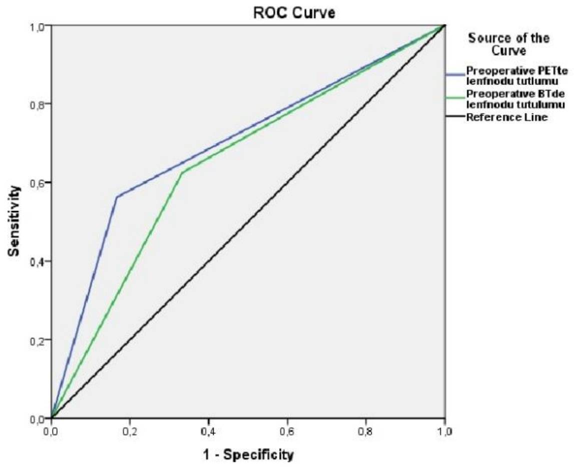

Figure 1. The area under curve for PET/CT in the analysis of ROC.

A multivariant logistic regression analysis was performed to determine the potential factors in assessing pathological LN metastases. The histological type of adenocarcinoma was found to be an independent risk factor for LN metastasis (p<0.05). Poorly differentiated adenocarcinoma was a potential risk compared with well-differentiated tumors, and the risk was statistically significant (OR: 7.111, 95% CI: 1.116–45.292, p<0.05). The risk for moderately differentiated adenocarcinoma compared to well-differentiated adenocarcinoma was higher, but not statistically significant (p=0.219, Table 5). The logistic regression analysis of tumor size in predicting preoperative LN metastases revealed that tumor size is an independent risk factor (p<0.05, Table 6). By comparing T3 versus T1, the risk was found to be statistically significant (OR: 6.000, (95% CI: 1.351–26.649, p=0.019). Meanwhile, the risk of T4 compared with T1 was statistically significant (OR: 13.3, 95% CI: 2.59, p<0.01).

DISCUSSION

In spite of recent advances in diagnostic methods, the rate of inconsistency in preoperative and postoperative staging of GC still is high, and it is reported in one-third of patients (15,16). The reasons for the inconsistency in staging in GC patients before surgery are either incomplete preoperative assessments or insufficient preoperative imaging methods. Inaccurate preoperative assessments may lead to ineffective treatments or unnecessary overtreatment (17). Thus, we analyzed the results of the two most common modalities used in evaluating preoperative GC staging. In this study, our data showed that neither PET/CT nor CT are the best imaging tests for predicting LN metastasis in GC patients as standard tests. In contrast, these techniques may help predict LN staging if used in combination.

One of the most common imaging tests used for preoperative LN assessments in GC patients is the CT scan. However, as previously reported in the literature (17), CT has many limitations, such as evaluating LN only based on size. Thus, evaluating preoperative LNs using CT does not allow a clinician to differentiate malignancy from reactive or infected LNs (17). Moreover, micro metastases of LNs are well-known, and it is very difficult to predict these using CT (18). Even though there was an association between preoperative CT and pathological findings in this study, the sensitivity, specificity, PPV, and NPV were not great enough to predict preoperative LN metastases in GC patients, and these results were consistent with a previous study (8). Also consistent with literature, this study did not reveal LN size or location to be independent factors that increase the sensitivity or specificity of CT in predicting LN metastases (17). Meanwhile, in contrast to previous reports, we did not find

Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com
Available at www.actaoncologicaturcica.com

potential effects of LN staging, in predicting LN metastases using CT (19). Overall, our results showed that CT may not be the best imaging test to use when trying to predict pre-operative LN metastases in GC patients as a standard test.

In contrast to CT, PET/CT identifies LN metastases based on metabolic activity, not on LN size. One of the advantages of PET/CT over CT is the ability to identify micrometastases in LNs. However, PET/CT has some disadvantages, such as the inability to discriminate metastases from infections or reactivity, which has been reported in the literature and confirmed in this study. We found that the greatest FDG uptake occurred in the perigastric area, which was most likely due to increased inflammation near the primary tumor. This is consistent with previous findings in the literature (20). In a multivariant and ROC analysis, it was revealed that the sensitivity of PET/CT was too low to predict LN metastases in GC patients, and this result is consistent with those in the literature (14). Moreover, this study did not reveal any effect of SUVmax or the number of LNs examined using PET/CT with regard to predicting LN metastases.

Although, the differences were not significant between PET/CT and CT in predicting LN metastases, our analysis showed that PET/CT has higher specificity and PPV, whereas CT has greater sensitivity. This is consistent with previous reports (21,22,23,24). In this study, we also analyzed the results of patients having CT and PET/CT. Combined CT and PET/CT increases the specificity, PPV, and accuracy of predicting LN metastases in GC patients. Therefore, combining the use of CT and PET might be helpful in predicting LN metastases in GC patients compared to each technique alone.

Even though our results revealed that tumor type and size are two independent risk factors for LN metastases in GC patients, neither one was a factor that increases the sensitivity or specificity of predicting LN metastases using CT or PET/CT. Overall, this study did not identify any tumor or patient-specific factors that affected the capacity of PET/CT or CT to predict LN metastases, such as tumor location, subtotal versus total gastrectomy, patient's age, gender, or number of LNs. Since this study was related to the preoperative assessment of LN metastases, we did not evaluate postoperative outcomes or perform a patient survival analysis.

As limitation of this study, it is a retrospective study with limited inheritance. Second, this study had a small number of patients undergoing CT and PET/CT, and this may have resulted in a lower sensitivity compared to other studies in the literature (25,26). Third, the number of CT and PET/CT scans were not the same between the experimental groups.

CONCLUSION

The sensitivity, specificity, PPV, and NPV of both CT and PET/CT were not high enough to predict LN metastases in GC patients when the techniques were used alone. However, the combination of CT and PET/CT scans yielded higher specificity and PPV, possibly increasing the ability to predict LN metastases in GC patients compared to the use of each imaging technique alone.

Acknowledgment

We would like to thank Emine Bor for her great assistance in statistics.

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Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com

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Adress for correspondence: Yusuf Günay, Bülent Ecevit University, Department of General Surgery, Kozlu, 67100, Zonguldak, Turkey
e-mail: drygunay@yahoo.com
Available at www.actaoncologicaturcica.com