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# Contribution of PET/CT in Determining Lymph Node Metastasis Before Low Anterior Resection

## Aşağı Anterior Rezeksiyon Öncesi Lenf Nodu Metastazının Belirlenmesinde PET/BT'nin Katkısı

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## Abstract

The aim of this study was to evaluate the sensitivity of $^{18}$F-FDG (*fluorodeoxyglucose*) PET/CT (*positron emission tomography / computed tomography*) imaging performed for primary staging prior to surgery performed with the low anterior resection technique in detecting the presence of lymph node metastases detected in the mesorectal area. In our retrospective study, 44 patients who were operated for colorectal cancer in our Surgical Oncology Department between June 15, 2015 and June 15, 2020 and who underwent $^{18}$F-FDG PET/CT for preoperative staging were included. The demographic data of the patients were obtained from the records were taken during routine clinical interrogations before both surgery and PET/CT scan, and from the automation system records of our hospital. While 12 (27.3%) of the patients had vascular invasion, 32 (72.7%) did not. While 15 (34.1%) of the patients had perineural invasion, 29 (65.9%) did not. Histopathologically, the rates of lymph node metastasis were high in patients with vascular invasion and perineural invasion (p=0.005 and p=0.012, respectively). There was no significant relationship between the SUVmax value of the primary tumor in PET/CT and the presence/absence of lymph node metastasis histopathologically determined (p=0.405). The median tumor size of the primary mass lesion was 4 cm (15-150 mm). No significant correlation was found between tumor size and presence/absence of lymph node metastasis (p=0.587). Sensitivity of CT is 68.7%, specificity 44.4%, accuracy 55.8%, positive predictive value 52.3%, negative the predictive value was 61.5%; whereas the sensitivity of $^{18}$F-FDG PET/CT was found to be 78.9%, specificity 50%, accuracy 63.6%, positive predictive value 55.5%, negative predictive value 76.4%. In conclusion, despite advanced imaging techniques, it will not be possible to be sure of the presence/absence of metastatic lymph nodes without radical surgery. We think that PET/CT imaging has also an important place in determining distant lymph node metastases other than regional lymph node spread.

Keywords: Low Anterior Resection, Lymph Node Metastasis, PET/CT.

## Özet

Bu çalışmada amacımız, aşağı anterior rezeksiyon tekniği ile yapılan cerrahi operasyon öncesi primer evreleme amacıyla yapılan $^{18}$F-FDG (*florodeoksiglikoz*) PET/BT (*pozitron emisyon tomografi / bilgisayarlı*

*tomografi*) görüntülemesinin mezorektal alanda tespit edilen lenf nodu metastazlarının varlığını tespit etmedeki duyarlılığını değerlendirmektir. Retrospektif olan çalışmamıza 15 Haziran 2015 ve 15 Haziran 2020 tarihleri arasında Cerrahi Onkoloji Bilim Dalımızda kolorektal kanser nedeniyle opere edilen, cerrahi öncesi evreleme amacıyla $^{18}$F-FDG PET/BT yapılan 44 hasta dahil edildi. Hastalara ait demografik veriler hem cerrahi hem de PET/BT çekimi öncesi rutin klinik sorgulamalar sırasında yapılan kayıtlardan ve hastanemiz otomasyon sistemi kayıtlarından elde edildi. Hastalardan 12'sinde (%27.3) damar invazyonu varken, 32'sinde (%72.7) yoktu. Hastalardan 15'inde (%34.1) perinöral invazyon varken, 29'unda (%65.9) yoktu. Histopatolojik olarak damar invazyonu ve perinöral invazyonu olan hastalarda lenf nodu metastazı görülme oranları yüksekti (p=0.005 ve p=0.012, sırasıyla). PET/BT'de primer tümöre ait SUVmax değeri ile histopatolojik olarak tespit edilen lenf nodu metastazı varlığı/yokluğu arasında anlamlı ilişki bulunmadı (p=0.405). Primer kitle lezyonunun median tümör boyutu 4 cm (15-150 mm) idi. Tümör boyutu ile lenf nodu metastazı varlığı/yokluğu arasında da anlamlı ilişki bulunmadı (p=0.587). BT'nin sensitivitesi %68.7, spesifitesi %44.4, doğruluğu %55.8, pozitif prediktif değeri %52.3 ve negatif prediktif değeri %61.5 iken; $^{18}$F-FDG PET/BT'nin sensitivitesi %78.9, spesifitesi %50, doğruluğu %63.6, pozitif prediktif değeri %55.5 ve negatif prediktif değeri %76.4 olarak bulunmuştur. Sonuç olarak, gelişmiş görüntüleme tekniklerine rağmen radikal cerrahi yapılmadan metastatik lenf nodu varlığından/yokluğundan emin olunamayacaktır. PET/BT görüntülemenin bölgesel lenf nodu yayılımı dışında uzak lenf nodu metastazlarının belirlenmesinde de önemli bir yeri olduğunu düşünmekteyiz.

Anahtar Kelimeler: Aşağı anterior rezeksiyon, Lenf nodu metastazı, PET/BT.

## Introduction

According to Globocan 2018 data, colorectal cancers (CRC) constitute 10.2% of all cancers, and cancers developing from the rectum and rectosigmoid region constitute approximately thirty percent of all colorectal cancers [1]. Quality oncological surgical treatment is essential for optimal treatment responses in these cancers, and the type of surgical treatment varies depending on the location of the tumor. The rectum is roughly divided into three parts as the upper, middle and lower rectum. While the lower rectum is extraperitoneal, only the anterior face is covered by the peritoneum in the middle rectum. In the upper rectum, the anterior and lateral faces are covered with the peritoneum.

Low anterior resection (LAR) is one of the standard surgical techniques used in the surgical treatment of cancers located in the middle rectum and 1/3 of the upper rectum. The LAR technique is a surgical technique that defines the transabdominal removal of tumor tissue after resection of the rectum in which the anastomosis level remains below the peritoneal reflection. With this technique, the sigmoid colon and its meso are dissected so that it is 2 cm below the tumor. Rectum and entire mesorectum are resected. The splenic flexure and left half of the transverse column are freed by dissections to reduce the tension that may occur in the anastomosis. When the colorectal anastomosis is performed with the help of a circular stapler, the rings removed from the stapler tip are controlled. It is very important for the safety of the anastomosis that these rings are completely circular and contain all layers in the intestinal wall. In case of tension in the anastomosis, when it is not sure that the ends of the anastomosis are vascularized, and in cases such as anastomosis in the distal area very close to the anal canal, the patient can be opened a loop ileostomy or colostomy as anastomosis protection [2,3].

Nowadays, there is a significant decrease in the local recurrence rates of these cancers thanks to multidisciplinary approaches and the algorithms of adjuvant and neoadjuvant treatments besides oncological surgery. Despite this, high local recurrence rates are still reported due to incomplete resection [4]. Unlike many other types of cancer, surgical treatment plays an important role in colorectal cancers, especially in the invasive group, even in advanced stages, due to the risks of obstruction, hemorrhage and perforation. It is important to evaluate the presence/absence of extramesorectal lymph node metastases in rectal cancers both before and after surgery and neoadjuvant therapy. In fact, the actual staging of colorectal cancers is usually done according to the pathological examination of the specimens removed after surgery.

Our aim in this study is to evaluate the sensitivity of $^{18}$F-FDG (*fluorodeoxyglucose*) PET/CT (*positron emission tomography / computed tomography*) imaging performed for primary staging prior to surgery performed with the low anterior resection technique in detecting the presence of lymph node metastases detected in the mesorectal area.

## Material and Method

*Patient population*

In our retrospective study, 44 patients who were operated for colorectal cancer in our Surgical Oncology Department between June 15, 2015 and June 15, 2020 and who underwent $^{18}$F-FDG PET/CT for preoperative staging were included. Patients receiving neoadjuvant chemotherapy or chemoradiotherapy were not included in the study. Lower rectal tumors undergoing abdominoperineal resection were not included in the study due to the difference in surgical technique. The demographic data of the patients were obtained from the records made during routine clinical interrogations before both surgery and PET/CT scan, and from the automation system records of our hospital. This study was conducted in accordance with the World Medical Association Helsinki Declaration.

*$^{18}$F-FDG PET/CT imaging procedure and acquisitions analysis*

A combined PET/CT device was used for PET imaging )Discovery600 PET/CT GE Medical System, USA). It was recommended that patients fast for at least 6 hours and whose blood glucose level was <180 mg/dL before the injection. Attenuation correction of PET images with the CT data was performed. After the CT scan, standard PET imaging was performed from the cranium to the mid-thigh with an acquisition time of 3 min/bed in 3-dimensional mode. All PET studies were acquired in 3-D mode. CT images were acquired with 70mA, 120 kV, axial slice thickness of 2.5 mm. After PET and Ct imaging were completed, axial, sagittal and horizontal sections were obtained. The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to processing Workstation (AW Volume Share5 GE Medical Systems S.C.S. France). Interpretations were performed with both visual and semiquantitative analyses.

*Statistical analysis*

The data obtained were evaluated with the SPSS 23.0 program (Statistical Package for the Social Sciences, SPSS Inc., Chicago). The normality of the data was examined with the Kolmogorov-Smirnov test. If the data provided the parametric conditions, they were analyzed with the independent sample t test for two independent groups and the F test (ANOVA) for more than two groups. If any or all of the assumptions were not met, Mann Whitney U test was used for two independent groups and Kruskal Wallis test was used for more than two independent groups. Chi-square test was used to evaluate the data obtained by counting. The level of error was taken as 0.05.

## Results

The study group comprised 26 (59.1%) men and 18 (40.9%) women. The median age at the time of cancer diagnosis was 66 years (range, 33–83 years). The tumor type in all patients in our study was adenocarcinoma. When evaluated according to the TNM (tumor, node and metastasis) classification; one (2.3%) of our patients was reported as carcinoma in situ (Stage 0), five (11.4%) of our other patients were Stage I, 17 (38.6%) were Stage II, 15 (34.1%) were Stage III and six (13.6%) were Stage IV. According to the localization of the tumor; 21 (47.7%) were in the upper rectum, four (9.1%) were in the middle rectum, 11 (25%) were in the sigmoid and eight (18.2%) were in the rectosigmoid location. Patients and tumor characteristics are given in Table 1. The number of median lymph nodes removed in our study was 15. There was no significant relationship between the age of our patients and the presence of lymph node metastasis (p=0.377).

While 12 (27.3%) of the patients had vascular invasion, 32 (72.7%) did not. While 15 (34.1%) of the patients had perineural invasion, 29 (65.9%) did not. Histopathologically, the rates of lymph node metastasis were high in patients with vascular invasion and perineural invasion (p=0.005 and p=0.012, respectively). There was

no significant relationship between the SUVmax value of the primary tumor in PET/CT and the presence/absence of lymph node metastasis histopathologically determined (p=0.405). The median tumor size of the primary mass lesion was 4 cm (15-150 mm). No significant correlation was found between tumor size and presence/absence of lymph node metastasis (p=0.587). The comparison of lymph node data in the histopathological evaluation of our patients and lymph node data defined in CT and $^{18}$F-FDG PET/CT reports are given in Table 2, and the sensitivity of CT is 68.7%, specificity 44.4%, accuracy 55.8%, positive predictive value (PPV) 52.3% and negative predictive value (NPV) was 61.5%; whereas the sensitivity of $^{18}$F-FDG PET/CT was found to be 78.9%, specificity 50%, accuracy 63.6%, PPV 55.5% and NPV 76.4%.

**Table 1.** Demographic and clinico-histopathologic characteristics.

| Characteristics | | n | % |
|---|---|---|---|
| Age (years) | Median age at diagnosis 66 (range 33–83 years) | | |
| Sex | Female | 18 | 40.9 |
| | Male | 26 | 59.1 |
| Stage | Stage 0 | 1 | 2.3 |
| | Stage I | 5 | 11.4 |
| | Stage II | 17 | 38.6 |
| | Stage III | 15 | 34.1 |
| | Stage IV | 6 | 13.6 |
| Localization | Sigmoid | 11 | 25 |
| | Upper Rectum | 21 | 47.7 |
| | Middle Rectum | 4 | 9.1 |
| | Rectosigmoid | 8 | 18.2 |

**Table 2.** Comparison of the presence/absence of lymph node metastasis according to $^{18}$F-FDG PET/CT and diagnostic CT reports for staging and the lymph node metastasis data.

| Characteristics | CT (%) *n=34* | $^{18}$F-FDG PET/CT (%) *n=44* |
|---|---|---|
| Sensitivity | 68.7 | 78.9 |
| Specificity | 44.4 | 50.0 |
| Accuracy | 55.8 | 63.6 |
| Positive Predictive Value | 52.3 | 55.5 |
| Negative Predictive Value | 61.5 | 76.4 |

FDG; fluorodeoxyglucose. PET/CT; positron emission tomography / computed tomography.

## Discussion

Colon cancer is one of the most common types of cancer worldwide and is a leading cause of cancer-related death. TNM stage of the disease affects prognosis and stage I colon cancer has shown good prognosis. In colorectal cancers, the most common metastasis occurs to lymph nodes, and it is known that the presence of lymph node metastasis reduces survival [5]. Although surgical treatment is the main treatment in colorectal cancer, adjuvant chemotherapy applications decrease the incidence of recurrence in high-risk patients. In studies conducted, the presence of lymphovascular invasion in the tumor is one of the most important factors in the development of lymph node metastasis [6]. Perineural invasion is a histopathological finding associated with more aggressive tumor types and poor prognosis [7]. The American Joint Committee on Cancer (AJCC) staging manual also identifies perineural invasion as an explicit prognostic factor and risk factor for recurrence. According to the study of Cao et al.

[7], there is a significant correlation between perineural invasion and lymph node involvement. According to our results, there was a significant relationship between perineural invasion and lymph node metastasis rates (p=0012). Interestingly in the study made by Zhang et al. [5], the rate of lymph node metastasis is higher in young patients compared to the elderly. In our study, no significant relationship was found between the presence of lymph node metastasis and age. However, this may be related to the limited number of our patients. As shown in many other previous studies, there is no relationship between primary tumor size and the presence of lymph node metastasis (LNM) [8,9]. In our study, in accordance with the literature, no relationship was found between LNM and the size of the primary tumor.

Tumor management primarily requires correct staging. $^{18}$F-FDG PET/CT imaging is one of the important imaging extermination methods for preoperative staging of CRC. In colorectal cancers, in addition to resection of the primary tumor, lymphoareolar tissue with lymphatic drainage should be resected. For this reason, determining the extent of lymphadenectomy is also a guide in determining the most appropriate surgical technique. Unlike other malignancies in colorectal cancers, TNM classification includes more details than others, and the number of metastatic lymph nodes is important for N stage. For this reason, for correct staging in patients who will undergo CRC resection and who have not received neoadjuvant therapy, many organizations, notably AJCC guidelines, "National Cancer Institute" (NCI) and "American Society of Clinical Oncology" (ASCO), stated that at least 12 lymph nodes should be dissected [10,11]. In colorectal cancers, regional lymph nodes are located along the large vessels feeding the colon and rectum, around the vascular networks formed by the marginal arteries and along the mesocolic border. Lymph node involvement other than pericolic and mesenteric lymph nodes are considered metastatic disease (M1 disease). Endoscopic ultrasonography is recommended primarily for first staging in rectal cancers. Magnetic resonance imaging (MRI) is also recommended to evaluate the mesorectal nodal status in medium and high-risk patient groups. However, imaging techniques and primary nodal staging are very difficult in rectal cancers. Because the size of the lymph node around the tumor is small enough to be a few millimeters. The strength of CT is its high accuracy in detecting anatomical abnormalities. When determining the malignancy character of the lymph node in MRI and CT imaging, the short axis being over 9 mm, irregular border, heterogeneous texture, and a round shape are considered as malignancy criteria [12]. Despite these definitions, there is no precise cutoff value in terms of size to be called malignant lymph node. Deciding whether lymph nodes are pathological or not according to anatomical image criteria is the main limitation of CT. Because a lymph node under 9 mm may contain metastatic cells, reactive or inflammatory lymph nodes may be above 1 cm. In addition, the density used during lymph node evaluation in CT can be misleading. While high-density lymph nodes are expected to be of malignant character, lymph node density may be low, such as metastases of mucinous tumors.

The basis of $^{18}$F-FDG PET/CT imaging is to evaluate metabolic activity as well as size and characterization. Although small in PET images, the presence of tumor content can be demonstrated metabolically or enlarged reactive lymph nodes can be distinguished. The problem with PET imaging is the difficulty in calculating the correct SUV value due to the partial volume effect encountered when the lymph node size is small. Thanks to advanced PET/CT imaging performed with multi-slice CT attenuation in today's conditions, the partial volume effect is significantly reduced and the detection of lesions over 5 mm can be successfully performed [13]. However, in colorectal cancers, regional lymph nodes are usually small and are often located in the immediate vicinity of the primary tumor, so FDG affinity of lymph nodes is often difficult to understand due to the intensity of FDG activity of the primary tumor. In addition, inflammation may cause false positive FDG affinity in lymph nodes, while significant FDG affinity may not be observed in cystic and mucinous nodal metastases.

According to Bamba and Itabashi [14], $^{18}$F-FDG PET/CT has high sensitivity and positive

predictive value. According to them, the diagnosis of proximal lymph node metastases is more difficult due to its proximity to the primary lesion, however, its diagnostic value is high in the evaluation of lateral pelvic lymph nodes. Güney et al. [15] found high sensitivity and negative predictive value of $^{18}$F-FDG PET/CT in the detection of regional lymph node metastases (88.5% and 84.2%, respectively). In our study, we found that the sensitivity and negative predictive value of $^{18}$F-FDG PET/CT was superior to CT in determining metastatic lymph nodes.

The present study had some limitations. The first is that our study is retrospective. Secondly, lymphovascular invasion which are identified high risk factors for LNM, were not assessed.

## Conclusion

Despite advanced imaging techniques, it will not be possible to be sure of the presence / absence of metastatic lymph nodes without radical surgery. We think that PET/CT imaging has an important place in determining distant LNM other than regional lymph node spread.

**Conflict of interest:** The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support to this study.

## References

**1.** Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424. [Crossref] [PubMed]

**2.** Keçer M. Colon Cancers. In: Kalaycı G (ed), General Surgery 2 (2nd edition). 2002, Istanbul, Nobel Medical Bookstore. pp:1343-59.

**3.** Topuz E, Aykan FN, Digestive System Cancers. 1998, Istanbul University Institute of Oncology Publications. pp:373-475.

**4.** Boot J, Gomez-Munoz F, Beets-Tan RGH. Imaging of rectal cancer. Radiologe 2019; 59(Suppl 1):46-50. [Crossref] [PubMed]

**5.** Zhang QW, Sun LC, Tang CT, Liang Q, Zhou YY, Chen HM, et al. Inverse Association of Age with Risk of Lymph Node Metastasis in Superficial Colorectal Cancer: A Large Population-Based Study. Oncologist 2020; 25(6): e920-e927. [Crossref] [PubMed]

**6.** Yamamoto S, Watanabe M, Hasegawa H, Baba H, Yoshinare K, Shiraishi J, et al. The risk of lymph node metastasis in T1 colorectal carcinoma. Hepatogastroenterology 2004; 51(58): 998-1000. [PubMed]

**7.** Cao Y, Deng S, Yan L, Gu J, Li J, Wu K, et al. Perineural invasion is associated with poor prognosis of colorectal cancer: a retrospective cohort study. Int J Colorectal Dis 2020; 35(6): 1067-75. [Crossref] [PubMed]

**8.** Wada H, Shiozawa M, Katayama K, Okamoto N, Miyagi Y, Rino Y, et al. Systematic review and meta-analysis of histopathological predictive factors for lymph node metastasis in T1 colorectal cancer. J Gastroenterol 2015; 50(7): 727-34. [Crossref] [PubMed]

**9.** Oh JR, Park B, Lee S, Han KS, Youk EG, Lee DH, et al. Nomogram Development and External Validation for Predicting the Risk of Lymph Node Metastasis in T1 Colorectal Cancer. Cancer Res Treat 2019; 51(4): 1275-84. [Crossref] [PubMed]

**10.** Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000; 124(7): 979-94. [Crossref] [PubMed]

**11.** Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al.; National Cancer Institute Expert Panel. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93(8): 583-96. [Crossref] [PubMed]

**12.** Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2018; 28(4): 1465-75. [Crossref] [PubMed]

**13.** Cherry SR, Sorenson JA, Phelps ME. Positron Emission Tomography (Chapter 18). Cherry SR, Sorenson JA, Phelps ME (eds), Physics in Nuclear Medicine (4th edition). 2012, Elsevier, Philadelphia. pp:307-343. [Crossref]

**14.** Bamba Y, Itabashi M. Positron Emission Tomography/Computed Tomography in Colorectal Cancer (Chapter 5). Fujii H, Nakamura H, Yasuda S (eds), Applications of FDG PET in Oncology. 2021, Singapore, Springer Nature Pte Ltd. pp:71-75.

**15.** Guney IB, Teke Z, Kucuker KA, Yalav O. A prospective comparative study of contrast-enhanced CT, contrast-enhanced MRI and 18F-FDG PET/CT in the preoperative staging of colorectal cancer patients. Ann Ital Chir 2020; 91: 658-667. [PubMed]