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Comparison of the Endorectal Ultrasonography and Pathology in Preoperative Staging of Rectal Cancer

Rektum Kanserinde Preoperatif Evrelemede Endorektal Ultrasonografi ile Patolojik Bulguların Kıyaslanması

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Özet

Amaç: Kolorektal kanserler sindirim sisteminin en sık görülen kanserileridir. Rektum kanserini ameliyat öncesi evrelemek, günümüzde mevcut çok sayıdaki tedavi olanaklarından hastaya uygun birinin seçilmesinde karar verdirici olduğundan büyük önem taşımaktadır. Endorektal ultrason (ERUS), rektum kanserinin evrelemesini, tümörün rektum duvarı ile mezorektuma invazyonunu ve lenf bezi tutulumunu oldukça net bir şekilde gösterebilir. Bu çalışmada rektum kanseri evrelemesinde ERUS'un patoloji sonuçlarına göre etkinliğinin belirlenmesi hedeflenmiştir.

Yöntem: Bu çalışmada ameliyat edilen 40 rektum tümörlü hastada TNM sınıflamasına göre ERUS ile ameliyat öncesi evreleme sonuçları, patoloji sonuçları ile esas alınarak retrospektif olarak incelendi.

Gereç ve Yöntem: ERUS ile histopatolojik evrelendirme karşılaştırıldığında, 3 yıllık olan hasta takibimizde, 40 olgudan 27'sinde T evresi açısından doğru evreleme yapıldığı görüldü. ERUS'un tümörün T2, T3 ve T4 evreleri ayırıcı tanısında doğruluk oranı sırasıyla %79,5, %71,8 ve %87,2 olarak saptandı. ERUS'un lenf nodu metastazının tespit edilmesindeki duyarlılığı 71% ve özgüllüğü 50% olarak bulundu. ERUS'un lenf nodu metastazı ayırıcı tanısı için doğruluk oranı %61,5 idi. T evresinin tespitinde ERUS ile histapatolojik tanı arasındaki kappa değeri 0,38 idi.

Sonuç: Lokal ileri (T3 ve T4) rektal tümörlerinin belirlenmesinde, diğer evrelere göre daha yüksek duyarlılık ve doğruluk oranları ile ERUS daha yüksek tahmin gücüne sahiptir. Uygulanması kolay olmakla birlikte, yapan kişinin tecrübesi de önemlidir

Anahtar Kelimeler: Rektum kanseri; endorektal ultrason; evreleme.

Abstract

Introduction: Colorectal cancers are the most seen cancers in gastrointestinal track. Preoperative staging of rectum cancer is of great importance as it is decisive in choosing one of the many treatment options available today. Endorectal ultrasonography (ERUS) may demonstrate the stage of rectal cancer, invasion of the tumor through the rectal wall and mesorectum, and the lymph node involvement. This study aimed to determine the effectiveness of ERUS in rectal cancer staging according to pathology results.

Materials and Methods: In this study, the impact of preoperative staging with ERUS was investigated retrospectively in 40 patients with rectal tumors and compared with the final histopathological diagnosis based on the TNM staging.

Results: In our 3-year follow-up of patients, a comparison of ERUS outcomes with the final pathological diagnosis revealed that the correct stage was reached in 27 of 40 cases. The accuracy rates in differential diagnosis of T2, T3 and T4 stages of the tumor were found to be 79.5%, 71.8% and 87.2% via ERUS, respectively. The sensitivity of ERUS in detecting lymph node metastasis was 71% and its specificity was 50%. The accuracy rate of ERUS for differential diagnosis of lymph node metastasis was 61.5%. The kappa value between ERUS and histopathological diagnosis in determining the T stage was 0.381.

Conclusion: With higher sensitivity and accuracy rates compared to the other stages, ERUS has higher predictive power in determining locally advanced (T3 and T4) rectal tumors. ERUS is easy to implement, but experience of the person doing is also important.

Keywords: Rectal cancer; diagnostic imaging; tumor staging.

Introduction

Colorectal cancers are the most common tumors of the gastrointestinal tract. It is among the leading causes of cancer-related mortality and morbidity. In terms of incidence, the colorectal cancers come in second place for both sexes (1). Preoperative staging of rectal cancer is essential since the most critical decision-making factor is the correct staging of the tumor to determine the most suitable treatment for patients. In the preoperative staging period, besides a clinical examination, the imaging methods are also used to evaluate local and distant metastasis (2-5). To date, many classifications have been used to evaluate the stage of rectal cancer. The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) have developed a universal staging for all anatomic layers (2, 6, 7). TNM stage highlights the depth of invasion, the number and location of metastatic lymph nodes, and the presence or absence of distant metastases. Due to the importance of

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staging, new tests have been used for staging of rectal tumors. Endorectal ultrasound (ERUS) demonstrates the stage of rectal cancer, invasion of the tumor into the rectal wall and the mesorectum, and lymph node involvement (5). Since all rectal layers can be observed by ultrasonographic staging of the rectal tumor, ERUS is useful in detecting tumor depth and lymph nodes, two critical prognostic factors in TNM staging. It plays a role in determining the choice of surgery and treatment modality to be applied. It can also be used for early detection of local recurrence during the postoperative follow-up of patients (5, 8, 9). There have been several imaging techniques for a complete, correct preoperative staging, including magnetic resonance imaging, multidetector computed tomography, and 18 F-fluorodeoxyglucose-positron emission tomography/computed tomography (10-13). These techniques have been used to predict the gold standard of postoperative verification of histopathological analysis for rectal tumors (11). However, these studies have yielded controversial outcomes. In this study, patients with a histopathological diagnosis of rectal cancer were analyzed to compare the preoperative staging via ERUS.

Materials and Methods

All consecutive patients diagnosed with rectal cancer who were staged preoperatively by ERUS were retrospectively analyzed. Al Zahra Hospıtal Ethical approval of the institutional review of the board was obtained (The approval number: 2020.141301). The data was collected from the database of Şişli Etfal Research and Training Hospital, Istanbul, Turkey between 2001-2004. The interval between ERUS and surgery was approximately ten days, and the tumors were localized between 1 and 10 cm from the anal verge. Rectal cancer was staged using the AJCC-TNM classification.

T-Primary tumor

Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues T4 Tumor directly invades other organs or structures and/or perforates visceral peritoneum

N-Regional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in one to three regional lymph nodes
N2 Metastasis in four or more regional lymph nodes

M-Distant metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

The patients with preoperative neoadjuvant radiotherapy were also included. But, patients with occlusive tumors were omitted.

ERUS technique: For the ERUS examination, 5, 7, 10 MHz frequencies were used in the ultrasound device (B-K Medical Falcon 2101 Ultrasound machine w/8658T & 8658S transuder & printer, 2000) with a probe. An experienced endoscopist did the examinations with balloon-covered probes vented and filled with fluid, having 360 degrees of view. All studies were done with the same tool and by one person. Enema was applied to the patients before the procedure, and examinations were made in the Sims position. ERUS image and schematic view of the ERUS device, probes, and rectal layers used are given in Figure 1. Five layers of the rectal wall was observed in ERUS. Lymph nodes with a diameter of at least 5 mm were regarded as metastatic if they were well marginated and hypoechogenic. The findings of ERUS were staged according to the TNM criteria and compared with histopathological diagnoses.

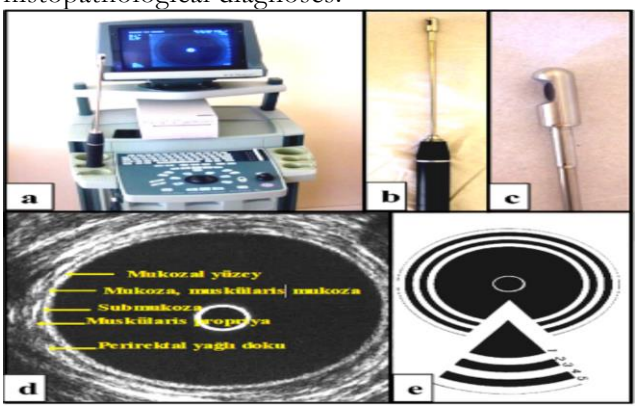

Figure 1. a) Endorectal ultrasonography (ERUS) device, b & c) ERUS probes, d) ERUS image of the rectal layers, e) Schematic view of rectal layers.

Statistical analysis: Results of the histopathological analysis were regarded as the standard reference point for ERUS. Descriptive statistics were given as mean ± standard deviation for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. Normality of the numerical variables was checked by the

Kolmogorov-Smirnov test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ERUS were calculated for T and N staging considering the histopathological results. The correlation of the ERUS with the histopathology considering T stage of the tumors was compared by a kappa agreement coefficient (κ). The kappa value was presented with its standard error and 95% confidence interval values. The degree of the aggrement was determined based on κ values as follows: slight (0-0.2), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.0).

Table 1: Demographics of the patients (n = 40)

Variable	
Age (year)	61.68 ± 13.19
Gender	
Male	27 (67.5)
Female	13 (32.5)
Stage with ERUS	
uT1	1 (2.5)
uT2	3 (7.5)
uT3	29 (72.5)
uT4	7 (17.5)
Diameter (cm)	5.64 ± 2.48
Diagnosis	
Adenocarcinoma	36 (90)
Mucinous adenocarcinoma	1 (2.5)
Malignant melanoma	2 (5)
Signet ring cell carcinoma	1 (2.5)
Stages after pathological examination ‡	
pT1	0 (0)
pT2	10 (25)
pT3	24 (60)
pT4	6 (15)

Mean ± Standard deviation, : n (%), ERUS: Endorectal ultrasonography.

Table 2: Accuracy rates of endorectal ultrasonography in tumor (uT1-uT4) and lymph node staging (uN0, uN1) compared with pathological findings (pT1-pT4) and (pN0, pN1).

	T staging				**N staging**		
	pT1	pT2	pT3	pT4		pN0	pN1
uT1	0	1	0	0	uN0	15	9
uT2	0	2	1	0	uN1	6	9
uT3	0	6	21	2			
uT4	0	1	2	4			
Total	0	10	24	6		21	18

Table 3: Predictive statistical values of ERUS.

		Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
T staging						
	T2	22.2	96.7	80.6	66.7	79.5
	T3	87.5	46.7	72.4	70.0	71.8
	T4	66.7	90.9	57.1	93.8	87.2
N staging		71	50	63	60	61.5

The level of statistical significance with 0.95 confidence limits was set at p = 0.05. Statistical analysis was performed using a statistical package (IBM, SPSS software, 21.0, Chicago, IL, USA).

Results

There were 40 patients with a mean age of 61.68 ± 13.19 years. The majority of the patients were male (67.5%). Adenocarcinoma was the most common pathological diagnosis detected in 36 patients (90%) (Table 1). According to ERUS, uT3 stage was the most common stage seen in 29 patients (72.5%). The mean diameter of the tumors was 5.64 ± 2.48 cm. Pathological analysis revealed that pT3 was the most common stage seen in 24 patients (60%). Comparing the findings of ERUS with pathological T staging at the end of a 3-year follow-up, 27 of 40 cases were correctly staged (Table 2). After the exclusion of a patient with T2 tumor who was misdiagnosed as T1 via ERUS, the highest sensitivity of ERUS was detected for T3 tumors as 87.5%. For T4 tumors, ERUS had the accuracy rate of 87.2% that was higher than the other T stages (Table 3). Over-staging for ERUS was detected in nine patients (22.5%), whereas under-staging was seen in four patients (10%) (Figure 2). Thirty-nine patients were examined for the lymph node metastasis. There was one patient whose tumor could not be resected due to the local involvement of perirectal organs. Of 39 patients, uN0 and uN1 were reported in 15 (38.5%) and six patients (15.4%), respectively. There were nine patients (23.1%) with pN1 stage (Table 2). The total accuracy rate of ERUS in the differential diagnosis of lymph node metastasis was found to be 61.5. Besides, the sensitivity of ERUS was 71%, and the specificity was 50% (Table 3). The kappa agreement coefficient analysis showed that the correlation between ERUS and the histopathological analysis considering T staging was fair ($\varkappa$=0.381, standard error=0.134, 95% CI: 0.118-0.644, p=0.001).

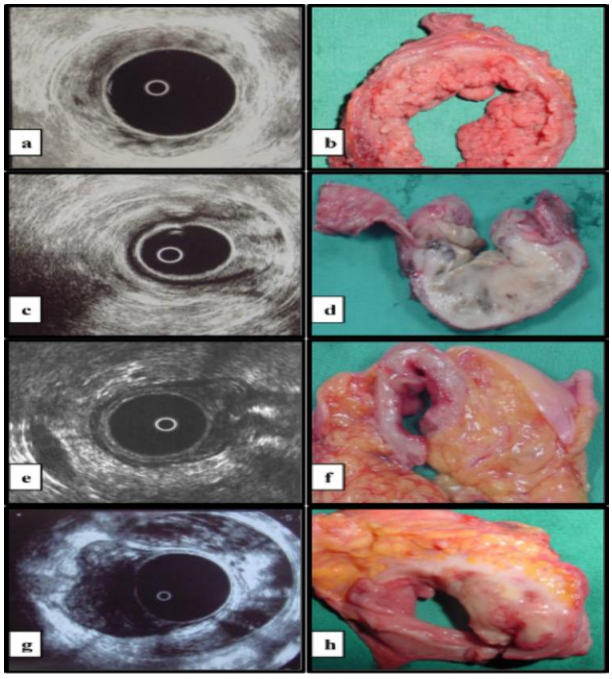

Figure 2. (a, b) uT1 / pT2: A patient with an adenocarcinoma developed based on villous adenoma. By using endorectal ultrasonography (ERUS), the patient was diagnosed as uT1. Pathologically, the tumor was found to be invasive into the muscular layer and was diagnosed as pT2. (c, d) uT3 / pT4: The tumor filled the mesorectum and invaded into the mesorectal fascia. The tumor diagnosed as T3 stage with ERUS was reported at pT4 stage. (e, f) uT4 / pT2: Since the mesorectum fascia margin could not be discriminated against in this patient, the tumor was imaged in ERUS as exceeding the mesorectum and evaluated at the uT4 stage. However, as observed macroscopically, the tumor was not invasive to the mesorectum and was reported at pT2. (g, h) uT3 / pT2: The tumor appeared to be invasive to the mesorectum due to a peritumoral inflammation was evaluated at uT3 stage by ERUS but was found at pT2 by the pathological examination of the specimen.

Discussion

In many studies, rectum tumor invasion's diagnostic accuracy has been reported as 81-94% by using ERUS (5, 9, 14, 15). Over staging was reported as approximately 10%, and under staging was around 5%. In a study by Garcia-Aguilar et al. (16) the preoperative diagnostic accuracy of rectal wall invasion by ERUS was found as 69%, over staging as 18%, and under staging as 13%. The sensitivity of ERUS to differentiate T3 tumors was 87.5% and the correct staging was achieved in 27 of 40 cases in this study. The accuracy rate for T4 tumors was determined to be 87.2%. Apart from subjective factors, difficulty in differentiating an adenoma from an early-stage carcinoma, inflammatory cell accumulation, desmoplastic changes, hypervascularity, and close relation to the anal canal may be due to clinical conditions affecting the accuracy of ERUS in detecting rectal lesions (5, 9, 16, 17). It has been suggested how much the tumor is invasive to the mesorectum affects the local recurrence and survival (18). In ERUS, the margins of the mesorectal fascia cannot be tracked precisely. The tumor is considered T4 if it is less than 1 mm closer to the mesorectal fascia. In the light of this information, high-resolution pelvic phase MRI can show us how much invasive T3 tumor is into the mesorectum. Significant accuracy rates have been obtained when compared to pathology specimens (5, 17). Several studies have compared the outcomes of rectal touch, ERUS, CT, and MRI

evaluations in preoperative staging (3, 5, 6, 16-18). The MRI and CT are advantageous in showing the invasion to the surrounding tissues, the involvement of distant lymph nodes such as distant metastases, lateral pelvic nodes, and obturator lymph nodes. However, there is currently a lack of accurate indication of the depth of wall invasion by both imaging systems, which is crucial for the surgeon. Although transrectal MR, which is performed by combining an endorectal coil to the conventional MR technique, especially in T staging of rectum cancer, has the similar accuracy rates with ERUS, the cost of procedures is the most important reason why not widely used (9). In such suspicious cases, some authors recommend lymph node biopsy accompanied by ultrasound (7, 16, 17). It should also be noted that microscopic invasion can occur even in normal-sized lymph nodes. It is recommended to use high frequency (10 MHz) probes to demonstrate micrometastases in lymph nodes with ERUS. Our study evaluated the lymph nodes of larger than 5 mm in size with ERUS at 10 MHz frequency. In 15 of 39 patients, we detected these lymph nodes, which is considered malignant by ERUS. Malignant lymphadenopathy was observed in 9 (60%) of these patients. In 24 of 39 patients, a malignant lymph node could not be observed with ERUS, but 37.5% of these patients had pathologically malignant lymphadenopathy. Today, the surgical treatment of rectal cancer varies according to stages. The treatment modalities of patients show differences after staging with ERUS. For instance, the small, polypoid, well-differentiated T1 tumors located at 8-10 cm from the anal verge, which are well staged with ERUS, are treated with transanal (local) excision. On the other hand, the Miles operation is performed if the tumor margins hold the sphincter (19). And since its possibility of lymph node metastasis is very low, no additional surgical treatment is required. In patients with distal localization staged at T2 with ERUS, an RT or chemoradiotherapy and subsequent surgery can be applied to prevent local recurrence and increase survival, since the mesorectum's thickness in the distal rectum is significantly reduced (19). If the tumor is localized in the upper 1/3 of the rectum, the radical surgical interventions and postoperative chemotherapy are applied in tumors at T2 and T3 stages diagnosed with ERUS. If the tumor is localized in the middle 1/3 of the rectum, radical surgery is performed in uT2 tumors. According to the recent publications, the distance of tumors at the uT3 stage, diagnosed by ERUS, to the mesorectal fascia is investigated pelvic phase MRI. If it is more than 5 mm, a surgical treatment and subsequent chemotherapy are applied (19, 20). uT3 tumors closer than 5 mm to the mesorectal fascia need preoperative RT or chemoradiotherapy to reduce local recurrence and prolong survival. If uT2 and uT3 tumors are in the lower 1/3 of the rectum, they need RT or chemoradiotherapy before surgery. uT4 tumors exactly need a preoperative RT or chemoradiotherapy regardless of the localization. Two other advantages of RT and chemotherapy before surgery are reducing adjuvant treatment toxicity and an increased possibility of sphincter preservation (19, 20). The limitations of ERUS are the inability to image the obstructive tumor's proximal regions, showing not very high diagnostic accuracy rate for the lymph nodes leading to a sub-staging. Since the tumor inflammation causes high staging, especially in T2 tumors because of its hypoechoic symptoms, ERUS may result in sub-staging. In this study, we aimed to evaluate the impact of preoperative ERUS compared with postoperative final pathological diagnosis in patients operated by one of the authors of the study. Operator dependency was another critical limitation in these studies. If possible, the examination performance by different physicians may help overcome intra- and inter-observer dependency problems.

Conclusion

For preoperative staging of rectal tumors, ERUS can be used as an adjunctive technique for this purpose. Due to its variable accuracy and operator dependency, prospective studies with other staging techniques are needed to clarify controversial issues.

Ethical Approval: The study was approved by the institutional review of the board (The approval number: 2020.141301) and was conducted in accordance with the principles of the Declaration of Helsinki.

Authorship Contributions: Concept: M.Ö, Design: M.Ö, Data Collection or Processing: M.Ö, Analysis or Interpretation: M.Ö, N.A.H, Literature Search: N.A.H, Writing: M.Ö, N.A.H.

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References

1. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al.

Colorectal cancer. Nat Rev Dis Primers 2015; 1:15065.
2. Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ. MRI of Rectal Cancer: Tumor Staging, Imaging Techniques, and Management. Radiographics 2019;39(2):367-387.
3. Iqbal A, George TJ. Randomized Clinical Trials in Colon and Rectal Cancer. Surg Oncol Clin N Am 2017;26(4):689-704.
4. Özkan E, Yıldız MK, Odabaşı HM, Eriş C, Abuoğlu HH, Günay E et al. The Association of Lymph Node Number with Prognosis/Prognostic Factors in Colorectal Cancer. Turk J Colorectal Dis 2013; 23:178-185.
5. Altıntoprak F, Balık E, Hacıahmetoğlu T, Eren T, Yamaner S, Bulut T et al. The comparison of endorectal magnetic resonance imaging and endorectal ultrasound for the staging of rectal cancer. Turk J Colorectal Dis 2009; 19:24-30.
6. Beets-Tan RG, Beets GL. Local staging of rectal cancer: a review of imaging. J Magn Reson Imaging 2011;33(5):1012-1019.
7. Skandarajah AR, Tjandra JJ. Preoperative loco-regional imaging in rectal cancer. ANZ J Surg 2006;76(6):497-504.
8. Horvat N, Petkovska I, Gollub MJ. MR Imaging of Rectal Cancer. Radiol Clin North Am 2018;56(5):751-774.
9. Hasak S, Kushnir V. Rectal Endoscopic Ultrasound in Clinical Practice. Curr Gastroenterol Rep 2019;21(4):18.
10. Cipe G, Ergul N, Hasbahceci M, Firat D, Bozkurt S, Memmi N, et al. Routine use of positron-emission tomography/computed tomography for staging of primary colorectal cancer: does it affect clinical management? World J Surg Oncol 2013;11:49.
11. Bøgsted M, Holt G, Eld M, Ljungmann K, Falkmer UG. Is the accuracy of preoperative MRI stage in rectal adenocarcinoma influenced by tumour height? Acta Oncol 2018;57(6):728-734.
12. Crimì F, Lacognata C, Cecchin D, Zucchetta P, Pomerri F. Rectal cancer staging: An up-to-date pictorial review. J Med Imaging Radiat Oncol 2018 Jul 5.
13. Moreno CC, Sullivan PS, Mittal PK. Rectal MRI for Cancer Staging and Surveillance. Gastroenterol Clin North Am 2018;47(3):537-552.
14. Wang X, Gao Y, Li J, Wu J, Wang B, Ma X et al. Diagnostic accuracy of endoscopic ultrasound, computed tomography, magnetic resonance imaging, and endorectal ultrasonography for detecting lymph node involvement in patients with rectal cancer: A protocol for an overview of systematic reviews. Medicine (Baltimore) 2018; 97(43):e12899.
15. Burdan F, Sudol-Szopinska I, Staroslawska E, Kolodziejczak M, Klepacz R, Mocarska A et al. Magnetic resonance imaging and endorectal ultrasound for diagnosis of rectal lesions. Eur J Med Res 2015;20(1):4.
16. Garcia-Aguilar J, Pollack J, Lee SH, Hernandez de Anda E, Mellgren A, Wong WD et al. Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. Dis Colon Rectum 2002:45(1):10-15.
17. Memon S, Lynch AC, Bressel M, Wise AG, Heriot AG. Systematic review and meta-analysis of the accuracy of MRI and endorectal ultrasound in the restaging and response assessment of rectal cancer following neoadjuvant therapy. Colorectal Dis 2015;17(9):748-761.
18. Boot J, Gomez-Munoz F, Beets-Tan RGH. Imaging of rectal cancer. Bildgebung des Rektumkarzinoms. Radiologe 2019;59(1):46-50.
19. Lawson EH, Melvin JC, Geltzeiler CB, Heise CP, Foley EF, King RS et al. Advances in the management of rectal cancer. Curr Probl Surg 2019; 56(11):100648.
20. Zolfaghari S, Williams LJ, Moloo H, Boushey RP. Rectal cancer: current surgical management. Minerva Chir 2010;65(2):197-211.