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ENDOMETRİYAL KANSERİN PROGNOSTİK FAKTÖRLERİ ÜZERİNDE TÜMÖRSÜZ MESAFENİN ETKİSİ

THE EFFECT OF TUMOR FREE DISTANCE ON THE PROGNOSTIC FACTORS OF ENDOMETRIAL CANCER

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ÖZET

AMAÇ: Endometrial kanserin (EK) prognostik faktörlerinde tümörsüz mesafenin (TFD) önemini değerlendirmeyi ve ileri evre EK'ni öngörmek için en iyi TFD cut-off değerini belirlemeyi amaçladık.

GEREÇ VE YÖNTEM: Bu çalışmaya EK tanısı alan 153 olgu dahil edildi. Myometriyal invazyonun derinliği (DOI) ve TFD ölçüldü ve EK için prognostik faktörler ile DOI ve TFD arasındaki ilişkiler değerlendirildi.

BULGULAR: TFD ve DOI'nin ortalama ± standart sapma değerleri sırasıyla 12 ± 6 ve 7 ± 6 mm olarak hesaplandı. TFD ve DOI, lenf nodu (LN) metastazı, lenfovasküler alan invazyonu (LVSI) ve servikal tutulum ile anlamlı şekilde ilişkiliydi. Daha kısa TFD, daha yüksek tümör grade, pozitif sitoloji ve LVSI ile anlamlı şekilde ilişkiliydi. Daha kısa DOI, LN metastazı ve servikal tutulum ile anlamlı şekilde ilişkiliydi. ROC eğrisi analizinde, LN metastazı için optimal TFD cut-off değerinin %48 olduğunu gösterildi ve %47'lik DOI, LN metastazı için en iyi sensitivite ve spesifiteye sahipti.

SONUÇ: TFD, DOI ile karşılaştırıldığında LVSI'yi öngörmede daha üstün iken DOI, LN metastazını öngörmede iyi bir tanısal performans gösterdi. Endometriyal kanserin prognostik faktörleri üzerinde TFD ve DOI'nin etkisini öngörmede daha fazla çalışmalara ihtiyaç vardır.

ANAHTAR KELİMELER: Endometrial kanser,Lenfatik metastaz, Miyometrium, Prognoz.

ABSTRACT

OBJECTIVE: We aimed to evaluate the importance of tumor-free distance (TFD) in prognostic factors of endometrial cancer (EC) and determine the best TFD cut-off value for predicting advanced EC.

MATERIAL AND METHODS: This study included 153 patients diagnosed with EC. The depth of myometrial invasion (DOI) and TFD were measured, and the associations between prognostic factors for EC and DOI and TFD were evaluated.

RESULTS: The mean ± standard deviation values of TFD and DOI were 12 ± 6 and 7 ± 6 mm, respectively. TFD and DOI were significantly related to lymph node (LN) metastasis, lymphovascular space invasion (LVSI) and cervical involvement. A shorter TFD was significantly associated with a higher tumor grade, positive cytology and LVSI. Shorter DOI was significantly associated with LN metastasis and cervical involvement. A receiver operating characteristics curve analysis demonstrated that the optimal TFD cut-off value was 48% for LN metastasis. A DOI of 47% had the best sensitivity and specificity for LN metastasis.

CONCLUSIONS: TFD was superior for predicting LVSI as compared to DOI, whereas DOI showed good diagnostic performance for predicting LN metastasis. Further studies are needed to predict the effect of TFD and DOI on the prognostic factors of endometrial cancer.

KEYWORDS: Endometrial cancer, Lymphatic metastasis, Myometrium, Prognosis.

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INTRODUCTION

Endometrial cancer (EC) is one of the most common gynaecological cancers in the world (1), and 417,000 new cases were diagnosed and 97,000 deaths were reported worldwide in 2020 (2). The main mechanism for the development of EC is unclear. Some of the risk factors for EC are obesity, hypertension, premature menarche and delayed menopause (3, 4). Surgical stage, histology and the presence of extra-uterine disease are major prognostic factors for EC (5, 6). Other risk factors are age, myometrial invasion, lymphovascular invasion (LVSI), cervical involvement, tumor-positive peritoneal cytology and tumor size (7). Total abdominal hysterectomy and bilateral salpingo-oophorectomy are the first treatment options for EC (8). Surgery plays an important role in EC treatment and staging according to the International Federation of Gynaecology and Obstetrics (FIGO) classification system (9). Routine lymphadenectomy has been associated with increased blood loss and operating time (10). Use of the "Mayo Clinic algorithm" has been proposed to predict lymph node (LN) involvement in patients with EC to avoid unnecessary LN dissection, and depth of myometrial invasion (DOI) is the most important criterion, as LN metastatic risk is 3–5% for superficial tumors based on this criterion. However, identifying the endometrial-myometrial junction and predicting myometrial invasion is challenging in some cases (11, 12). Tumor free distance (TFD), which is the distance from the uterine serosa to the deepest part of the tumor, has been suggested as an objective alternative for DOI. In this study, we evaluated the importance of TFD in prognostic factors of EC and determined the best TFD cut-off value for predicting advanced EC.

MATERIALS AND METHODS

Patients with EC who underwent for primary surgical therapy at the Gynecologic Oncology Department of a tertiary referral hospital from 2012 to 2014 were included in this retrospective study. Hysterectomy, bilateral salpingo-oophorectomy, omentectomy and retroperitoneal LN dissection were performed in all patients. Patients were excluded if they were managed in other centres, had incomplete medical records, or underwent histological evaluation at another centre. All pathological specimens were evaluated by the same pathologists, and DOI was defined as the distance from the deepest tumor level to the endometrial-myometrial junction. TFD was defined as the deepest tumor level to the uterine serosa. In the present study, histologic grade (1, 2, and 3), tumor diameter (<2 cm, and > 2 cm), LVSI, cervical involvement, positive peritoneal cytology, omental metastasis, adnexial metastasis, lymph node metastasis (pelvic, and para-aortic), DOI, TFD, and myometrial thickness were evaluated (9). In the univariant analysis of the cases in terms of DOI and TFD, grade (1 and 2 vs. 3), tumor diameter (<2 cm, and > 2 cm), LVSI, cervical involvement, positive peritoneal cytology, adnexial involvement and omental metastasis were evaluated, and significant factors were analyzed multivariant.

Ethical Committee

Approval for this study was obtained from Selcuk University, Faculty of Medicine, Ethics Committee with decision 2013/18 in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The data were analyzed using SPSS for Windows software (ver. 15.0; SPSS Inc., Chicago, IL, USA). The associations between TFD and DOI and endometrial prognostic factors were determined using univariate and multivariate logistic regression analyses. A receiver-operating characteristic (ROC) curve analysis was performed to determine the best TFD and DOI cut-off values for predicting each prognostic factor. We computed percentages by dividing each variable by the total myometrial thickness.

RESULTS

A total of 153 patients with EC managed with primary surgery were included in this study. The mean age of the patients was 58.8 ± 10.3 years. The tumor histological types were endometrioid in 146 (95.5%), mixed adenocarcinoma in three (2%), undifferentiated adenocarcinoma in two (1.3%), mucinous adenocarcinoma in one (0.7%) and transitional adenocarcinoma in one (0.7%). Tumor grades were grade 1 in 95 (62.1%), grade 2 in 34 (22.2%) and grade 3 in 24 (15.7%) patients.

The mean ± standard deviation values for myometrial thickness, TFD, DOI and anteroposterior diameter of the uterus were 18 ± 5, 12 ± 6, 7 ± 6 and 41 ± 15 mm, respectively. Twenty-five patients (16.3%) had LVSI, 22 (14.4%) had LN metastasis, 14 (9.2%) had adnexial involvement, 33 (21.6%) had lower uterine segment involvement, 17 (11.1%) had positive cytology and nine (5.9%) had omental metastasis. **Tabel 1** shows the baseline characteristics and FIGO stages of the patients.

Table 1: Clinical and pathologic characteristics of patients

Variable		n (%)
Grade		
	1	95 (62,1%)
	2	34 (22,2%)
	3	24 (15,7%)
Tumour diameter		
	<2 cm	36 (23,5%)
	>2cm	117 (76,5%)
LVSI		25 (16,3%)
Cervical involvement		33 (21,5%)
Positive peritoneal cytology		17 (11%)
Omental metastasis		7 (4,5%)
Adnexial metastasis		14 (9,1%)
Lymph node metastasis		22 (14,3%)
	Pelvic	22 (14,3%)
	Para-aortic	12 (7,8%)
DOI±SD (mm)		7±6
TFD±SD (mm)		12±6
Myometrial thickness ±SD (mm)		18±5

A univariate analysis was performed to compare the associations between TFD and DOI with different surgical-pathological prognostic factors. TFD and DOI were significantly related to LN metastasis, LVSI and cervical involvement. Neither TFD nor DOI were associated with adnexal or omental metastasis. Interestingly, shorter TFD had more predictive value than DOI for high-grade tumors and positive cytology (p = 0.002 and 0.005, respectively) **Table 2**.

TFD and DOI were entered into a multivariate logistic regression analysis with LN metastasis, cervical involvement, high-grade tumor, positive cytology and LVSI. DOI had predictive value for LN metastasis (p = 0.036) and cervical involvement (p = 0.017), whereas TFD had predictive value for LVSI (p = 0.014) Table 2.

Table 2: Univariable and multivariable regression analysis of DOI and TFD as predictors of outcomes for endometrial cancer prognostic factors

Outcome	Predictor	Univariable		Multivariable	
		Estimated OR (95%CI)	P value	Estimated OR (95%CI)	P value
Lymph node metastasis	DOI	2,464 (1,294-4,692)	**0,006***	2,771 (1,072-7,168)	**0,036***
	TFD	0,177 (0,70-0,453)	**0,000***	0,380 (0,130-1,107)	0,076
LVSI	DOI	2,644 (1,389-5,035)	**0,003***	2,358 (0,900-6,174)	0,081
	TFD	0,125 (0,048- 0,328)	**0,000***	0,243 (0,078-0,755)	**0,014***
Tumour grade (1-2 vs 3)	DOI	1,612 (0,953-2,725)	0,075	1,265 (0,509-3,146)	0,403
	TFD	0,470 (0,154-1,433)	**0,002***	0,321 (0,114-0,903)	**0,031***
Cervical involvement	DOI	1,999 (1,140-3,506)	**0,016***	2,643 (1,187-5,884)	**0,017***
	TFD	0,392 (0,203-0,756)	**0,005***	0,702 (0,326-1,510)	0,365
Positive cytology	DOI	1,563 (0,904-2,700)	0,110	1,232 (0,093-1,053)	0,689
	TFD	0,267 (0,104- 0,685)	**0,006***	0,314 (0,443-3,426)	0,063
Adnexal involvement	DOI	1,386 (0,773-2,483)	0,273		
	TFD	0,694 (0,298- 1,614)	0,396		
Omental metastasis	DOI	1,656 (0,895-3,065)	0,108		
	TFD	0,470 (0,154-1,433)	0,185		

The ROC curve demonstrated that the optimal TFD cut-off value was 48% (area under the curve [AUC], 0.754; 95% confidence interval [CI], 0.620–0.888) for LN metastasis and a DOI of 47% had the best sensitivity and specificity (AUC, 0.749; 95% CI, 0.616–0.882) for LN metastasis. TFD and DOI had the same sensitivity (72%) and specificity (78%) for these cut-off values to predict LN metastasis. A TFD of 68% had the best sensitivity (92%) and specificity (58%) for predicting LVSI (AUC, 0.812; 95% CI, 0.723–0.900), and a DOI of 68% had the best sensitivity (92%) and specificity (57%) (AUC, 0.805; 95% CI, 0.716–0.894). When the quantitative values for each measurement were compared, the optimal cut-off value for DOI was 6.5 mm with 72% sensitivity and 65% specificity (AUC, 0.745; 95% CI, 0.617–0.872), and the optimal cut-off value for TFD was 9.5 mm, with 73% sensitivity and 72% specificity (AUC. 0.762; 95% CI, 0.643–0.881) **(Figure 1)**.

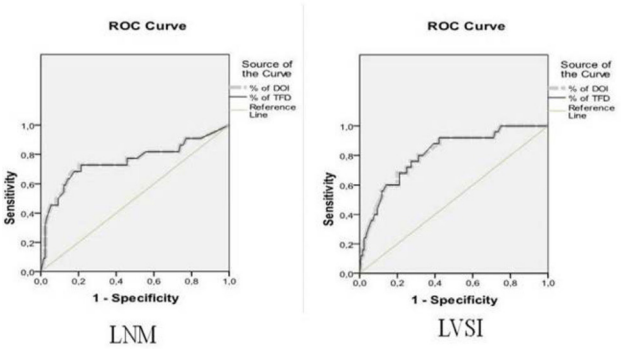

Figure 1: Receiver operator characteristics (ROC) curve for TFD and DOI in predicting lymph node metastasis and lymphovascular side invasion. LNM: Lymph node metastasis, LVSI: lymphovascular side invasion.

DISCUSSION

Myometrial invasion and lymph node metastasis are two of the most prognostic factors in endometrial cancer. While surgical resection of the uterus and ovaries is the first-choice treatment for EC, the lymphadenectomy procedure is still in debate (13). Surgical staging of EC is associated with higher mortality and morbidity rates, and predicting advanced disease is critical (14). Many studies have predicted the advance stages of EC to avoid unnecessary LN dissection. It has been demonstrated that deeper myometrial invasion is associated with higher LN metastasis, recurrence and death rates (15-18). Our prediction of LN metastasis was similar to that in previous studies, and a relationship between DOI and LN metastasis was demonstrated in the univariate and multivariate models. Determining DOI can be difficult in patients with myometrial pathologies, such as adenomyosis and leiomyoma, or those with large intrauterine lesions (19). Measuring TFD is simpler than measuring DOI, and we determined and compared the diagnostic accuracies of TFD and DOI. Ali et al. demonstrated that 12% of pathological results involve chance according to the invasion categories after re-evaluation (20). The most common reasons for miscalculating DOI are adenomyosis and exophytic tumors. We did not experience difficulties determining the endometrial-myometrial junction, or DOI. None of the pathological results changed after measuring TFD, and we did not demonstrate the superiority of TFD to DOI.

Lindauer et al. reported that TFD is a simple measurement that can be used to predict advanced disease. According to Lindauer et al., TFD has a higher predictive value than DOI for positive cytology, LVSI, tumor grade, cervical involvement, and death (21). Similarly, Chattopadhyay et al. showed that TFD was an independent predictor of death from disease, recurrence and lymph node metastasis. TFD was determined to be a better predictor than DOI and myometrial invasion (22). In this study, a negative correlation was found between TFD and LN metastasis, LVSI, cervical involvement and positive peritoneal cytology. The relationships between TFD and these variables were demonstrated in the univariate model. However, only LVSI was a significant predictor in the multivariate model, suggesting that TFD is not an independent risk factor for advanced EC.

Geels et al. reported optimal DOI and TFD cut-off values of 3.75 and 7.25 mm, respectively for disease recurrence (23). In our study, the median DOI and TFD values were 4 and 7 mm, respectively. Another study suggested that a TFD cut-off value of 11 mm has the highest sensitivity and specificity for predicting LVSI (24). Different TFD and DOI cut-off values have been reported in several studies (25 - 27). In our series, the optimal DOI cut-off value was 6.5 mm, with 72% sensitivity and 65% specificity, and the optimal TFD cut-off value was 9.5 mm, with 73% sensitivity and 72% specificity. These data suggest that DOI and TFD vary among institutions and that it will be difficult to determine a universal cut-off value. Thus, the percentages of these variables are more valuable than actual quantitative measurements. Van der Putten et al.'s study showed that degree of myometrial invasion can be evaluated in more patients according to DOI and TFD and is a practical method in daily procedures (12). In the present study, the best TFD cut-off values as percentages of TFD and DOI for the LN metastasis were 48% and 47%, respectively. These cut-off values were all near 50%, which is the commonly accepted value to predict advanced-stage EC. Thus, these results are similar to previous studies and suggest that a 50% cut-off value is reasonable for both DOI and TFD.

Clinical outcomes have been compared in several studies by dividing the population according to DOI, TFD or myometrial invasion. Some studies have suggested that TFD has an unfavourable effect on recurrence and death rates (23, 26). Geels et al. reported that the number of patients who require adjuvant therapy increases when using TFD (23). Schwab et al. concluded that DOI has more predictive value than TFD (28). Besides, Doghri et al. showed that DOI and TFD were not statistically significant between clinicopathologic data and survival rates. But DOI was superior at predicting recurrence than TFD (27). Oge et al. reported that TFD, DOI and %myometrial invasion were not statistically significant in terms of prognosis and recurrence in early stage endometrium cancer (29).

Vasilios et al.'s meta-analysis showed that TFD was associated to with survival rates in studies, but not the presence of lymphovascular involvement and lymphatic methastasis. However, It may be a prognostic factor to predict survival (30). In this study, we compared the number of patients requiring adjuvant therapy by considering TFD, DOI and the conventional 50% rate of myometrial invasion. All of these methods determined the same number of patients for adjuvant therapy. We could not demonstrate the clinical consequences of TFD or DOI. The optimal DOI and TFD cut-off values for quantitative measurements were not reliable because of institutional differences. Therefore, the current concept, based on a percentage of myometrial invasion, is the most valuable method for determining advanced stage EC (12).

Our study had some limitations. We did not perform a survival analysis because of the short study duration, and this was a single-centre study. However, LN dissection was performed in all patients, which allowed us to discuss absolute LN metastatic rates. As a result, TFD was superior for predicting LVSI as compared to DOI, whereas DOI showed good diagnostic performance for predicting LN metastasis. Further studies are needed to predict the effect of TFD and DOI on the prognostic factors of endometrial cancer.

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