TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2017-3, Sayfa 19-24
Araştırma

The Tumor Grade Discrepancy in Endometrial Cancer Before and its Clınıcal Reflectıon

Endometriyum Kanserinde Cerrahi Öncesi ve Sonrası Tümör Grade Uyuşmazlığı ve Klinik Yansıması

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ABSTRACT

Aim: Histologic grading in endometrioid endometrial cancer is an important factor in surgical planning and prognosis. This study aimed to compare preoperative tumor grades to subsequent postoperative grades and explore the discrepancies for their possible effects on surgical management.

Material and methods: Medical records of patients with endometrial cancer diagnosis who underwent surgical staging at our institution between the years 2011 and 2016 were reviewed. Sixty seven out of 106 charts were found eligible and were evaluated for preoperative sampling method, preoperative grade, surgical procedure, postoperative grade and final pathology. Preoperative tumor grades were compared to final pathology grades of hysterectomy specimens.

Results: Out of 67 eligible cases, preoperative sampling method was endometrial biopsy (Pipelle) in 6 (9 %) and curettage for the rest 61 (91%). Preoperatively, 18 (26.8%) of them were regarded as grade 1 (G1), 44 (65.7%) of them as grade 2 (G2), and 5 (7.5%) of them as grade 3 (G3). Percentages for postoperative final grades were 20.9% for G1, 70.1% for G2, and 9% for G3. No significant difference was found between overall preoperative and postoperative grade results. However, 7 patients had a potentially clinical-significant grade discrepancy (10.3%): 4 downgrades (5.9%) (G3 to G2/ G1) and 3 (4.4%) upgrades (G1/G2 to G3). Depth of invasion (DOI) and preoperative-postoperative grade concordance rates were not found to be related either.

Conclusion: This study revealed that preoperative and postoperative histologic grade discrepancy rates may seem important although not reaching statistically significant levels. Clinical reflection of these rates seemed to be negligible due to other factors affecting management. The extent of the planned surgery must be customized to each patient's risk category while taking into account of other prognostic markers since the number of significant grade discrepancies alone may not necessarily reflect clinical significance.

Key Words: Endometrial cancer, Tumor, Grade discrepancy, Surgery

ÖZET

Endometriyum Kanserinde Cerrahi Öncesi ve Sonrası Tümör Grade Uyuşmazlığı ve Klinik Yansıması

Amaç: Endometrioid tip endometriyal kanserde histolojik grade, cerrahi planlamada ve prognoz için önemli bir faktördür. Bu çalışmada operasyon öncesi ve sonrası tümör grade'lerinin karşılaştırılması ve farklılıkların cerrahi yönetimdeki olası etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Kurumumuzda 2011 ve 2016 yılları arasında endometriyal kanser tanısı ile cerrahi evreleme yapılan hastaların tıbbi kayıtları gözden geçirildi. Bulunan 106 dosyadan 67'si çalışma kriterlerine uygun bulunarak operasyon öncesi örnekleme metodu, operasyon öncesi grade, cerrahi prosedür, postoperatif grade ve nihai patoloji açısından incelendiler. Operasyon öncesi tümör grade'leri, histerektomi örneklerindeki nihai patolojik evrelerle karşılaştırıldı.

Bulgular: Uygun bulunan 67 olgudan 6 tanesinde (%9) operasyon öncesi örnekleme metodu biyopsi (Pipelle), ve geri kalan 61 tanesinde (%91) ise küretajdı. Operasyon öncesi 18 olgu (%26.8) grade 1 (G1), 44 olgu grade 2 (G2) (%65.7) ve 5 olgu grade 3 (G3) (%7.5) olarak belirlenmişti. Operasyon sonrası nihai grade yüzdeleri ise G1 için %20.9, G2 için %70.1 ve G3 için ise %9'du. Operasyon öncesi ve sonrası grade yüzdelerinde anlamlı bir farklılık bulunmadı. Ancak, 7 hastada (%10.3) potansiyel olarak klinik-anlamlı grade farklılığı oldu: 4 olguda (%5.9) grade düşürme (G3'ten G2 veya G1'e) ve 3 olguda (%4.4) grade yükseltme (G1/G2'den G3'e). İnvazyon derinliği ile operasyon öncesi ve sonrası grade uyumluluğunun ilişkisi olmadığı izlendi.

Sonuç: Bu çalışma endometrioid endometriyal kanserde operasyon öncesi ve sonrası histolojik grade uyumsuzluk oranı önemli miktarda gibi görünse de istatistikî anlama ulaşmadığını gösterdi. Bu oranların klinik yansıması da, hastalığın yönetimini etkileyen diğer faktörler yanında ihmal edilebilir düzeyde gibi görülmektedir. Grade uyuşmazlıkları, klinik olarak her zaman anlamlı olmadığından, uygulanacak cerrahi girişimin tarzı hastaların risk grubu ve diğer prognostik faktörleri de göz önünde bulundurarak planlanmalıdır.

Anahtar Kelimeler: Endometrial kanser, tümör, Grad uyuşmazlık, Cerrahi

Geliş Tarihi: 31/07/2018 Kabul Tarihi: 20/09/2018

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Table 1 • Demographic and clinic characteristics

	n (%)
Age (mean+/-SD)	57±8
Menopause	48 (71.6)
Smoker	2 (2.9)
Initial complaint	
Postmenopausal Bleeding	46 (68.7)
Abnormal Bleeding	12 (17.9)
Other	9 (13.4)
Diabetes	18 (26.8)
Hypertension	14 (20.9)
Gravida (median, 25th-75th percentile)	3 (2-5)
Parity (median, 25th-75th percentile)	2.5 (1.75-3)

Introductıon

Endometrial cancer is the second most common gynecologic cancer in developing countries. Type I cancers are endometrioid, estrogen dependent and typically have favorable prognosis (1). Majority of these patients are diagnosed in their early stages in consequence of alarming abnormal uterine bleeding symptom. In such instances, aspiration biopsy and endometrial curettage are valuable diagnostic sampling methods (2).

Histologic grading of endometrial cancer is important in planning the extension of lymph node sampling or dissection during surgery, although some authors recommend universal pelvic and paraaortic lymph node resection (3, 4). Intraoperative assessment of tumor grade and myometrial invasion on frozen specimens may not always be correlated with final pathology results (5). Likewise, there have been studies of preoperative and postoperative tumor grade comparisons with various concordance rates (6-10).

This study aimed to compare preoperative tumor grades to final grades on hysterectomy specimens in endometrial cancer patients who had had surgery at our institution to evaluate the clinical reflection of grade reassignments. The possible relation of tumor size and depth of invasion (DOI) to tumor grades were also investigated.

Materıal And Methods

This retrospective, medical record based study was conducted at Adnan Menderes University Hospital in Turkey. Institutional ethics committee approval was obtained prior to review of patient charts. Patients with endometrial cancer diagnoses who were operated in our clinic in the last 5 years were sorted out. Only endometrioid type endometrial cancer cases both from our institution and from referrals were accepted for the study. Pre-operative and postoperative tumor grade assignments were compared for each case. Also, place of sampling (our institution versus referral), sampling method (aspiration biopsy versus curettage), depth of invasion and p53 staining information were analyzed for the possible effect of grade assignment discrepancies.

A total of 106 patients were collected by chart review. Three patients were excluded for normal or endometrial hyperplasia in the final diagnosis; 29 referral cases were excluded for missing preoperative grade assignments. Additional seven patients were excluded for preoperative "complex atypical hyperplasia" report; four of them ended up G1 and three of them ended up G2 endometrioid adenocancer diagnoses. The remaining 67 cases were included in statistical analyses.

Sampling methods were either aspiration biopsy (Pipelle® Endometrial Suction Curettage, Cooper Surgical, Trumbull CT, USA) or endometrial curettage according to preoperative pathology reports. Postoperative grades were reported by the same pathologist at our institution based on previously published FIGO recommendations, in summary: G1: less than 5% nonsquamous or nonmorular solid growth pattern, G2: 6-50% of a nonsquamous or nonmorular solid growth pattern, and G3: more than 50% of a nonsquamous or nonmorular solid growth pattern (11). Also grades were upgraded to G3 if there was notable nuclear atypia. Depth of invasion (DOI) was classified in two groups as less than and more than half of whole myometrial thickness.

Kolmogorov-Smirnov test was used for testing of quantitative variables' distribution. Since quantitative variables were not distributed normally, Mann-Whitney U test was used to compare two groups and descriptive statics were reported as median (25th-75th percentile). Normally distributing quantitative variables' descriptive statistics were given as mean ± standard deviation (SD). Marginal Homogeneity test was used for preoperative and postoperative grade comparisons. Qualitative variables were compared by Chi-square analysis and descriptive statistics were given as numbers and percentages. $p<0.05$ was regarded as statistically significant.

Materıal And Results

Among 67 cases that were included in statistical analyses, preoperative samplings were accomplished at our institution in 42 cases (62.6%) and 25 cases (37.4%) were referred from outer clinics. The mean age was 57±8 with a range of 33-80 years. Demographic characteristics were presented in Table 1. Preoperative

Tablo 2 • Comparison of preoperative and postoperative grade assignments.

		Preoperative Grade			P
		G1	G2	G3	
Postoperative Grade	G1	5 (35.7%)	8 (57.1%)	1 (7.1%)	
	G2	12 (25.5%)	33 (70.2%)	2 (4.3%)	0.384
	G3	1 (16.7%)	3 (50%)	2 (33.3%)	

G1: Grade 1, G2: Grade 2, G3: Grade 3

grades were evaluated on specimens obtained by Pipelle biopsy in 6 (9%) and on curettage specimens in 61 cases (91 %). Of the 67 cases, 18 (26.8%) of them were assigned as G1, 44 (65.7%) as G2, and 5 (7.5%) as G3, preoperatively (Table 2).

All 67 cases underwent surgery. Thirty-nine of them had total abdominal extrafascial hysterectomy (TAH)/ Bilateral salpingoopherectomy (BSO)/ Pelvic-paraaortic lymph node dissection (PPLND) and omentectomy – omental biopsy (58.2%); 16 of them had TAH/BSO/ Omentectomy – omental biopsy (23.9 %), 12 of them had TAH/BSO (17.9%). During surgery and by frozen pathology, 41 patients were regarded as stage 1A (65.6 %), 13 patients were stage 1B (19.4 %), 5 patients were stage 2A (7.4%), 3 patients were stage 3A (4.4 %) and 2 patients were stage 3C (2.9%). Postoperatively, 14 cases were assigned as G1 (20.8 %), 47 were G2 (70.1%), and 6 were G3 (8.9 %) (Table 2).

No statistically significant difference was found between overall preoperative and postoperative grade assignments (p= 0,384). The overall concordance rate was 59.7 %. The concordance rates per grades were 27.7 % for G1, 75% for G2 and 40% for G3. In total, 7 patients had a potentially clinical-significant discrepancy (G3 to G1/2 or G1/2 to G3): 4 patients were downgraded (5.9%) and 3 patients were upgraded (4.4%). When we focus on differences with a potential to change the scope of surgery, only in two patients tumor grades were changed by two grades postoperatively: one patient was downgraded from G3 to G1, and other was upgraded from G1 to G3. There were also 3 patients who were initially graded as G3, but then downgraded to G2 and 2 patients were G2 and were upgraded to G3. Interestingly, in all of these last 5 patients, tumors had invaded more than half and required more extensive surgery.

There was no significant difference in grade reassignments when results from our institution and outer clinics compared (p= 0,716). Number of patients with Pipelle sampling was not enough to analyze the possible effect of sampling method on grade comparisons (Pipelle biopsy vs. curettage).

In terms of DOI, tumors had been found to be invaded more than half of the myometrium in 21 (31.3%) and less than half in the remaining 46 cases (68.7%). DOI seemed to have no effect on final grades: p= 0,827 for less than half and p= 0,083 for more than half invasion. Although there were inadequate numbers of G3 cases to look into a possible effect, no significant differences were found between preoperative and postoperative tumor grades regarding parameters of gravidity, parity and tumor size (p= 0,139, p= 0,122 p= 0.12, respectively).

In this study group, p53 information was available in 36 cases. Twenty-six (%72.2) of them had abnormal p53 immunostaining pattern and 10 of them (27.8%) had normal pattern. There were no significant differences on grade comparison when p53 expressions were regarded (p= 0,346 for abnormal pattern and p= 0,157 for normal pattern).

Tablo 3 • Depth of tumor invasion and postoperative grade

		Postoperative Grade			
		G1	G2	G3	P
Tumor Invasion	<1/2*	12 (66%)	32 (72.7%)	2 (40%)	0,827
	Invasion	6 (33.3%)	12 (27.3%)	3 (60%)	0,083

*<1/2: less than half myometrial invasion, **>1/2: more than half myometrial invasion

Discussion

Endometrial cancer continues to be a significant healthcare problem. Many factors influence on survival rates such stage, tumor grade, lymphovascular space invasion and molecular markers (12-14). Planning on the type and extent of the surgical procedure is an important step in management. Preoperative tumor grade of samples obtained via curettage and aspiration biopsies give valuable clues about prognosis and helps in planning surgical intervention. This study showed that preoperative and postoperative tumor grade discrepancies may be encountered to a certain rate in endometrial cancer. However, it is essential to know if these discrepancies are clinically meaningful and to what extent we are doing unnecessary or inadequate surgeries.

Even though Pipelle aspiration biopsy and curettage comparisons have been shown to give similar diagnostic yields, some have argued that preoperative and postoperative tumor grade results may be discordant no matter what the specimen obtaining methods were (8, 15). In theory, such discrepancy could cause inadequate staging surgery or overtreatment by performing unnecessary lymph node dissections and increased morbidity. It is well known that endometrial cancer may be heterogeneous, various grades of tumor can present in the same specimen at the same time (16). That is why one should not expect to find perfect concordance rates between endometrial biopsy grades and final hysterectomy grades at all times. There is also growing evidence that specimens obtained via endometrial curettage are reflecting actual FIGO grades more accurately than office endometrial samplings (8). This study had inadequate number of samplings to analyze the difference between Pipelle and curettage.

Despite nearly 60% concordance rate overall, the result of this study implied that the preoperative grade assessments by different pathologists were in accordance with final grades on hysterectomy specimens in terms of potential management changing situations. There were only two cases with significant grade change by two. One was downgraded from G3 to G1. The tumor was reported as superficially invasive at the microscopic level and G1 in final pathology. Other case was an 80-year-old lady with postmenopausal bleeding complaint whose grade was upgraded from G1 to G3. However, in this case, LND would still not be opted due to her comorbidities even it was invaded more than half in frozen.

Therefore, none of our patients with potentially significant grade change had inadequate surgery or overtreatment because of preoperative grade assignments except the one incompletely staged patient with significant comorbidities as mentioned above.

In a study from Göksedef et al., overall accuracy of preoperative grading was reported as 64.1%; while 3.6% of the cases were upgraded (G1 to G3), and 6.7 % of the cases were downgraded after surgery with 10.3% total rate of significant grade change (10). However, in another study with 653 patients who were preoperatively diagnosed G1 cancers without deep invasion, it was calculated that only 1% would result in missing nodal involvement (9). Their reported rates of significant downgrading and upgrading by two grades (1% and 2%, respectively) were also similar to our numbers.

Tumor size and DOI are two other risk factors for nodal involvement for the cancer of endometrium. Intraoperative inspection of tumor invasion has high specifity but low sensitivity rates (92% vs. 75%) (17). Frozen section may not be helpful in increasing this sensitivity, especially in low grade tissues (18, 19). Our study also implies that DOI and p53 data may not be useful to increase this concordance rate either.

In conclusion, this study demonstrated 4.4% upgrade and 5.9% downgrade rates of grade reassignments with potential to change surgical management in endometrioid type of endometrial cancer. Even though agreement to preoperative grades was not perfect, expected rate of significant grade change that could affect the surgical management seemed to be minimal, since the true high grade lesions are tend to be more invasive as this study implied. Accordingly, we did not have any patients who would have been treated differently if we had known the final grades beforehand. However endometrial cancer patients and their tumors are heterogeneous and we need even better concordance rates. Future development of molecular markers and/or clinical algorithms may improve the accuracy of preoperative grade assignments and minimize the number of both inadequate and unnecessary surgical interventions.

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