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Grade and Maximum Tumor Dimension as Determinants of Lymphadenectomy in Patients with Endometrioid Endometrial Cancer (EEC)

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Abstract**—**Introduction: Endometrial Cancer is a common gynecologic malignancy primarily treated with complete surgical staging, which may include complete pelvic and para-aortic lymphadenectomy. The role of lymphadenectomy is controversial, especially the intraoperative indications for the procedure. Three factors are important in decision to proceed with lymphadenectomy: Myometrial invasion, maximum tumor dimension, and histology. Many institutions incorporate these criteria in varying degrees in the decision to proceed with lymphadenectomy. This investigation assesses the use of intraoperatively measured MTD with and without pre-operative histologic grade. Methods: This study compared retrospectively EEC patients with intraoperatively measured MTD ≤2 cm to those with MTD >2 cm from January 1, 2002 to August 31, 2017. This assessment compared those with MTD ≤ 2cm with endometrial biopsy (EB) grade 1-2 to patients with MTD > 2cm with EB grade 3. Lymph node metastasis (LNM), recurrence, and survival were compared in these groups. Results: This study reviewed 222 patient cases. In tumors > 2 cm, LNM occurred in 20% cases while in tumors ≤ 2 cm, LNM was found in 6% cases (p=0.04). Recurrence and mean survival based on last follow up visit in these two groups were not statistically different (p=0.78 and 0.36 respectively). Data demonstrated a trend that when combined with preoperative EB International Federation of Gynecology and Obstetrics (FIGO) grade, a higher proportion of patients with EB FIGO Grade 3 and MTD > 2 cm had LNM compared to those with EB FIGO Grade 1-2 and MTD ≤ 2 cm (43% vs, 11%, p=0.06). LNM was found in 15% of cases in which lymphadenectomy was performed based on current practices, whereas if the criteria of EB FIGO 3 and MTD > 2 cm were used the incidence of LNM would have been 44% cases. However, using this criterion, two patients would not have had their nodal metastases detected. Compared to the current practice, the sensitivity and specificity of the proposed criteria would be 60% and 81%, respectively. The PPV and NPV would be 43% and 90%, respectively. Conclusion: The results indicate that MTD combined with EB FIGO grade can detect LNM in a higher proportion of cases when compared to current practice. MTD combined with EB FIGO grade may eliminate the need of frozen section sampling in a substantial number of cases.

Keywords**—**Endometrial cancer, FIGO grade, lymphadenectomy, tumor size.

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I. Introduction

ENDOMETRIAL cancer is widely studied in the literature for its increasing incidence and continues to be the most common gynecologic cancer in the United States [1]. The lifetime incidence is 2-3%, with a median age at diagnosis of 63 years and median age at death of 73 years [1]. Efforts to reduce disease recurrence or improve the prognosis of individuals have focused on intraoperative management [2]. Current surgical pathology reports for endometrial carcinoma typically include the grade, depth of myometrial invasion, cervical involvement, lymphovascular space involvement, and histologic type [3]. However, staging guidelines do not include an in-depth evaluation of tumor size as a parameter. Tumor size has not been consistently included as a parameter in risk determination and, thus, not included as a prognostic indicator in terms of clinical/surgical management [4]. This may be due to a lack of consensus as to an accepted universal measurement of the tumor size.

According to data published from experts at the Mayo Clinic, patients are considered as low risk (LR) for nodal metastasis if three specific criteria on final pathology reports were met: 1) less than 50% invasion, 2) tumor size less than 2 cm and 3) well or moderately differentiated (grade 1 or grade 2) endometroid histology [3]. Furthermore, a study done at Northwestern University found that "only 4% of patients with tumor size less than or equal to 2 cm had LNM; this increased to 15% for tumors more than 2 cm and further increased to 35% when the entire uterine cavity was involved (multivariate p = 0.01)" [5]. 98% of patients with a tumor size less than or equal to 2 cm were alive at five years [5]. In those with tumor size greater than 2 cm and individuals with tumors involving the whole uterine cavity, 84% and 64% were alive in five years, respectively [5].

Lymphadenectomy is associated with the possibility of intraoperative morbidity, lengthened surgical time, and the possibility of post-operative morbidities such as neuropathy or lymphedema [6]. Accurate measurements of tumor size, with and without preoperative histologic grade, could help determine

which patients are candidates for more aggressive surgical management based on their prognosis, specifically lymph node dissection. This would reduce surgery time, healthcare costs, hospital stays, post-operative complications and most importantly, morbidities/mortality [7].

This research focused on whether tumor size, with and without preoperative histologic grade, is a significant parameter for prognosis (predictor of LNM) and clinical decision making (whether to proceed with lymph node dissection) in patients with endometrial cancer undergoing surgical management. This study focused on determining whether tumor size, with and without preoperative histologic grade, is a predictor of candidates for lymph node dissection.

II. Materials and Methods

A. Study Design

This is a retrospective cohort study of patients diagnosed with endometrial cancer from January 1, 2002-August 31, 2017 at St. John Hospital and Medical Center who are 50 years of age or older and are undergoing surgical treatment.

Patient demographics, medical comorbidities (body mass index, hypertension, and diabetes mellitus), final FIGO grade, biopsy FIGO grade, presence of myometrial invasion, date/ type of surgery, tumor dimensions, histological type, presence of lymph node invasion (defined as the histological presence of disease in the pelvic, aortic or any other regional lymph nodes), number/date/site of recurrence, previous surgeries, and survival (measured by days since last known visit or follow-up) information was collected.

Patients with a diagnosis other than adenocarcinoma (i.e. uterine sarcoma, leiyomyosarcoma, endometrial stromal sarcomas, undifferentiated endometrial sarcoma) were excluded from the study. Those who were lost to follow-up, deceased prior to follow-up or passed away from unrelated conditions were excluded from our study.

Patients who did not undergo surgical intervention, had a positive genetic influence on their diagnosis, or had other organ cancers were also excluded. From this patient group, the prognosis, specifically cancer recurrence, based on tumor size and extent of surgery was collected. The study was approved by the St. John Hospital and Medical Center's Institutional Review Board.

B. Power Analysis

Based on a literature review, it estimated that approximately 4% of patients with a small tumor size (<2 cm) had nodal metastasis [5]. For patients with larger tumors, this percentage increased to 15-30% [5]. To show an effect size of 4% to 15%, this study included 111 patients per group in the assessment, for 80% power and alpha = 0.05. To obtain a sample size of 222 patients, approximately 750 charts were reviewed.

C. Statistical Analysis

Descriptive statistics were calculated. Associations between categorical variables were made with Chi-square. Differences between groups on continuous variables were analyzed with t-tests. Predictors of LNM, if any, were identified with logistic regression. P values <0.05 were considered significant. SPSS version 22 was used.

III. Results

A. Participants and Demographics

The analysis included a total of 222 patients with 111 patients in the tumor size ≤2 cm group and 111 patients in the tumor size >2 cm group. The mean age of the participants was 64.3 years of age (SD=8.7). Average body mass index (BMI) was 36.5 kg/m^2 (SD=10.9). Approximately 61% (n=86) of the participants had a diagnosis of hypertension and 25% (n=35) were diabetic (as shown in Table I).

TABLE I
DEMOGRAPHICS OF THE PATIENTS

n=222; Mean +/- SD or n (%)	
Age (yrs)	64.3 +/- 8.7
BMI	36.5 +/-10.9
Hypertension	86 (61)
Diabetes Mellitus	35 (25)

SD: standard deviation. BMI: kg/m^2, hypertension in mm/Hg

B. Clinical Course

Of the 86 patients who underwent an EB, 66% (n=64) of the participants had grade 1 disease while 20% (n=19) had grade 2 disease. Approximately 14% (n=3) had biopsy FIGO grade 3. Final FIGO grade was also assessed. There were 64% (n=142) of the participants with final FIGO grade of 1, 23% (n=51) grade 2, and 13% (n=29) with grade 3. In this analysis, 19% (n=42) of the participants did not have myometrial invasion, 59% (n=130) had ≤50% myometrial invasion and 22% (n=49) had >50% myometrial invasion. LNM was detected in 15% (n=18) and recurrence occurred in 6% (n=13) of the participants in the study (Table II).

TABLE II
CLINICAL COURSE OF THE PATIENTS

n=222; Mean +/- SD or n (%)	
Tumor Size	
< or = 2 cm	111 (50)
> 2 cm	111 (50)
Biopsy FIGO grade	
1	64 (66)
2	19 (20)
3	3 (14)
Final FIGO grade	
1	142 (64)
2	51 (23)
3	29 (13)
Myometrial invasion	
None	42 (19)
< or = 50%	130 (59)
> 50%	49 (22)
LNM	18 (15)
Recurrence	13 (6)

n: number of patients

C. Measured Parameters among Patients

By looking at tumor size alone, 6% (n=3) of the patients with tumor size ≤2 cm had LNM compared to 20% (n=15) of the patients with >2 cm tumor size (p=0.040). Recurrence was also assessed based on tumor size. 5% (n=6) of the patients with

tumor size ≤2 cm had disease recurrence whereas 6% (n=7) of patients with tumor size > 2 cm had disease recurrence (p=0.780). The mean survival was 1549 (SD=1176) days for the participants in the tumor size ≤2 cm group vs 1406 (SD=1174) days for the tumor size >2 cm group (p=0.360) (Table III).

TABLE III
PRESENCE OF LNM, RECURRENCE, AND SURVIVAL (DAYS TO LAST KNOWN VISIT) BASED ON TUMOR SIZE

	Tumor ≤2cm n = 111 Mean +/- SD or n (%)	Tumor >2cm n = 111 Mean +/- SD or n (%)	p-value
LNM	3 (6)	15 (20)	0.040
Recurrence	6 (5)	7 (6)	0.780
Days to last known visit	1549.9 +/- 1176.2	1406.4 +/- 1173.9	0.36

SD: standard deviation. n: number of patients

When tumor size and EB FIGO grade were analyzed in combination, in those patient with EB FIGO Grade 1-2 and tumor size ≤2 cm, 11% (n=2) had LNM compared to 43% (n=3) of the patients with EB FIGO grade 3 and tumor size >2 cm experienced LNM (p=0.06) The EB FIGO grade 1-2 and tumor size ≤2 cm patients had 5% (n=2) recurrence while EB FIGO grade 3 and tumor size >2 cm group had had 0 patients with recurrence (p=0.550). The mean survival for the EB FIGO grade 1-2 and tumor size <2 cm group and EB FIGO grade 3 and tumor size >2 cm group was 1605 (SD=1192) and 1164 (SD=1487) days, respectively (p=0.388) (Table IV).

TABLE IV
PRESENCE OF LNM, RECURRENCE, AND SURVIVAL (DAYS TO LAST KNOWN VISIT) BASED ON TUMOR SIZE AND BIOPSY FIGO GRADE

	Bx FIGO Grade 1-2 & Tumor ≤2cm n = 40 Mean +/- SD or n (%)	Bx FIGO Grade 3 and Tumor >2cm n = 7 Mean +/- SD or n (%)	p-value
LNM	2 (11)	3 (43)	0.060
Recurrence	2 (5)	0 (0)	0.550
Days to last known visit	1605 +/- 1191.6	1163 +/-1486.6	0.388

SD: standard deviation. n: number of patients

Lastly, in those with a final FIGO grade 1-2 and myometrial invasion ≤50%, 8% (n=5) had LNM while in those with a final FIGO grade 3 and myometrial invasion >50%, 39% (n=7) had LNM (p=0.001). Mean survival for the final FIGO grade 1-2 and myometrial invasion ≤50% was 1630 (SD=1198) days and 1456 (SD=1352) days for the final FIGO grade 3 and myometrial invasion >50% (p=0.560) (Table V). Fig. 1 provides a summary comparing the presence of LNM based on tumor size, biopsy FIGO grade, final FIGO grade, and myometrial invasion (Fig. 1).

Compared to current practice, the sensitivity (SN) and specificity (SP) of the proposed criteria was 60% and 81%, respectively (Fig. 2). The positive predictive value (PPV) and negative predictive value (NPV) was 43% and 90%, respectively (Fig. 2). Additional univariate analysis was conducted to compare EB FIGO grade category and LNM. Specifically, in those with EB FIGO grade 1-2, 6.7% (n=3) of the patients had LNM compared to 23.1% (n=3) of patients with EB FIGO grade 3 (p=0.119). Multivariate analysis, binary logistic regression, was performed to determine significant predictors of LNM. The odds of predicting LNM by a patient's EB FIGO grade score was 0.231 (CI=0.040-1.335) (p=0.102) (Table VI). With regards to tumor size, the odds of predicting LNM was 0.583 (CI=0.093-3.650) (p=0.564) (as shown in Table VI).

TABLE V
PRESENCE OF LNM, RECURRENCE, AND SURVIVAL (DAYS TO LAST KNOWN VISIT) BASED ON MYOMETRIAL INVASION AND FINAL FIGO GRADE

	Final FIGO Grade 1-2 and Invasion ≤50% n = 122 Mean + SD or n (%)	Final FIGO Grade 3 and Invasion >50% n = 20 Mean + SD or n (%)	p-value
LNM	5 (8)	7 (39)	0.001
Days to last known visit	1630.0 +/-1198.3	1455.7 +/- 1352.3	0.560

SD: standard deviation. n: number of patients

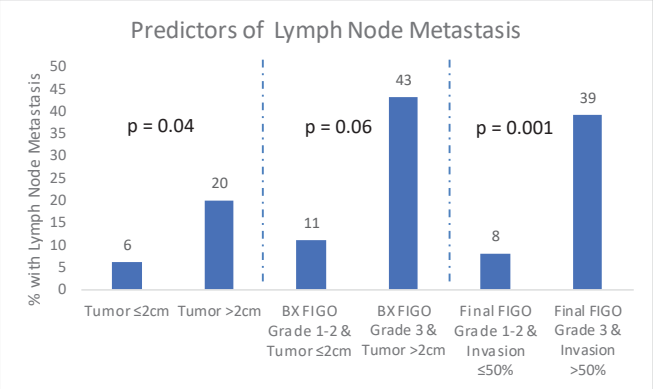

Fig. 1 The presence of LNM based on tumor size, biopsy FIGO grade, final FIGO grade, and myometrial invasion. Tumor size and final FIGO grade + myometrial invasion were significant predictors of LNM. Biopsy FIGO grade + tumor size approached significance

TABLE VI
LOGISTIC REGRESSION: PREDICTORS OF LNM

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	p-value
BX FIGO Grade	0.231	0.040	1.335	0.102
Tumor Size	0.583	0.093	3.650	0.564

CI: confidence interval. Bx: biopsy

IV. DISCUSSION

This study evaluated the use of measured MTD with and without preoperative histologic grade to help determine which patients are candidates for more aggressive operations, specifically lymphadenectomy, based on their prognosis (presence of LNM). Based on these results, patients with tumor size ≤2cm were significantly less likely to have LNM compared to those with a tumor size >2cm. When combined with preoperative EB FIGO grade, a higher proportion of patients with EB FIGO Grade 3 and MTD >2cm had LNM compared to those with EB FIGO Grade 1-2 and MTD ≤2cm. This result approached significance. Furthermore, compared to current

practice, this study's NPV and PPV values were comparable. Current practice has centered on three main factors: depth of myometrial invasion >50%, MTD >2cm and high-grade histology, and require two out of the three criteria to be satisfied before deciding on proceeding with lymphadenectomy [3]. Rather, this assessment's results indicate that EB FIGO grade with intraoperative measured tumor size may be just as good of a predictor of LNM, and thus satisfy the criteria to proceed with lymphadenectomy, when compared to the current practice.

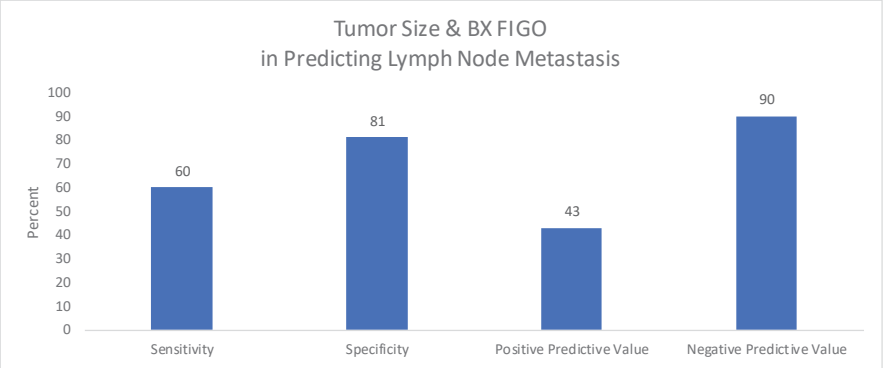

Fig. 2: Compared to current practice, the sensitivity and specificity of this study's proposed criteria was 60% and 81%, respectively. The PPV and NPV was 43% and 90%, respectively.

Protocols for assessment of lymph node involvement have been studied in the past [8]. The most widely used is The Mayo Clinic algorithm for surgical management of endometrial cancer published in 2004 [9]. Per their assessment, lymphadenectomy is no longer necessary for a subset of endometrial cancer patients with low-risk features [10]. The low-risk features have been defined as; "endometrioid type EC, FIGO grade 1 or 2 histology, myometrial invasion (MMI) ≤50%, and primary tumor diameter (PTD) ≤2 cm." [10]. The remainder of the patients would be classified as high-risk and be candidates for systematic lymphadenectomy [11]. A study by Karalok et al. reported that the rate of lymph node involvement in EEC is approximately 15% [12]. Their reported rate is similar to the rate of LNM in this study. Considering this rate, 75% of the women with endometrial cancer would require systematic (LND) when using the Mayo Criteria [12]. Using this assessment's proposed criteria of EB FIGO 3 and MTD >2cm, 43% of patients would require systematic LND and this approached significance. The major difference between this study and the Mayo criteria is that this assessment proposes bypassing intraoperative histologic assessment. Furthermore, the proposed criteria does not require assessing the depth of myometrial invasion intraoperatively, which is associated with risks and difficulties.

This study has several limitations. First, the retrospective nature of the study is a limitation [13]. Although the proposed criteria approached but did not reach statistical significance, this could be due to the small difference in the number of participants with LNM (three vs two individuals) between the biopsy FIGO grade 3 and tumor size >2 cm group vs biopsy FIGO grade 1-2 and tumor size ≤2 cm group. However, a bigger sample size would detect a larger difference between the two groups and the results would likely be statistically significant. Using the proposed criteria, two patients would not have had their nodal metastases detected. Another limitation involves adequately measuring intraoperative MTD. Currently, there is no uniform tool that is used to accurately measure this specimen and minute differences in measurements can be impactful in the patient's management. Over the years, there were multiple and different pathologists providing their histological interpretation of the specimen [14]. Creating a uniform interpretation by a single gynecologic pathologist can help overcome this limitation. Creating an accurate measuring tool and uniform interpretation can help overcome another limitation of this study which involves the two patients whose nodal metastases would not have been detected by using the proposed criteria. This study did not assess post-operative management of the patients, such as chemoradiation therapy, re-operation and close follow-up visits. Future studies can be conducted to determine the extent to which post-operative management protocols impact the presence of LNM [15]. The small sample size of patients with EB (n=58) reports available in this data was also a limitation. Evaluating a larger sample size of patients with known EB diagnosis would likely reveal that EB FIGO grade is a predictor of LNM.

In conclusion, tumor size combined with EB FIGO grade can eliminate the need of frozen section sampling in a substantial number of cases. By assessing a larger sample size with known EB FIGO grade and addressing the limitations, this study could yield statistically significant results. This would demonstrate that it is, in fact, preoperative EB and MTD, regardless of myometrial invasion, that determine whether to proceed with lymphadenectomy. Counterarguments may support universal sentinel node biopsy in all patients. This study is not aimed at replacing certain practices; rather it serves as an additional resource when deciding which patients to proceed with more aggressive surgical management. This becomes important when dealing with patients who have multiple medical comorbidities and the risks of a longer surgical procedure outweigh the benefits. In sum, this assessment's proposed criteria could potentially reduce overall patient morbidities and mortality; which include surgery time, healthcare costs, hospital

stays, and post-operative complications (such as post-operative drainage following lymph node dissections).

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