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Prediction of Surgical Staging in Patients with Low-Risk Endometrial Cancer using Intraoperative Assessment of Myometrial Invasion and Preoperative Tumor Grading

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ABSTRACT

Objectives: To assess the benefit of intraoperative gross depth of myometrial invasion and preoperative grading as a predictor of final surgical staging in patients with low-risk endometrial cancer.

Materials and Methods: Retrospective chart review of all patients with endometrial cancer underwent surgery at Rajavithi Hospital from January 1st, 2002 to December 31st, 2006 for demographic and clinical data, preoperative tumor grading, intraoperative gross depth of invasion and final surgical staging.

Results: A total of 124 patients were eligible for analysis using data on intraoperative assessment of gross depth of myometrial invasion (no myometrial invasion or myometrial invasion less than 50%) and preoperative curettage/biopsy (grade 1 and 2). The intraoperative gross depth of myometrial invasion was upgraded 35.5% and discrepant 42.7% compared with pathologic myometrial invasion, whereas the preoperative tumor grading was upgraded 19.4% and discrepant 28.2% compared with final tumor grading. The predictive staging was clinically significantly upstaged 28 %, 30%, 33.3% and 21.4% of stage IAG1, IAG2, IBG1 and IBG2, respectively. Predictive staging resulted in suboptimal surgical treatment in 30.6% by relinquishment of lymphadenectomy.

Conclusions: The combination of preoperative tumor grading and intraoperative gross depth of myometrial invasion is the poor predictor for final staging.

Keywords: low-risk endometrial cancer, myometrial invasion, tumor grading, staging

Introduction

Endometrial cancer (EC) is the third most common gynecologic malignancy in Thailand[1-3]. The histologic grading (G) and depth of myometrial invasion (MI) appear to be the two most important factors to determine the risk for lymph node metastasis[4-5]. The incidence of pelvic lymph node metastasis in EC stage I is 3%, 9% and 18% for grade 1, 2 and 3, respectively[5]. Less than 5% of patients with no MI or with superficial (< 50%) MI lymph node metastasis, compared with

about 20% of patients with deep (> 50%) MI[5]. Women with EC grade 1 or 2 confined to the uterine body and no or minimal (less than 50%) MI were considered to be low-risk[5].

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) changed the staging of EC from a clinical to a surgical approach[6]. There is general agreement about the necessity of complete surgical staging for high-risk EC as the risk of nodal metastasis is high. Whereas the low-risk patients, who have positive nodes in less than 5% , had been question about the need for pelvic and paraaortic lymph node dissection with complete surgical staging[7-8]. The pendulum swings as some advocate only hysterectomy and bilateral salpingooophorectomy without node dissection for low-risk endometrial cancer[9] while others suggest comphrehensive surgical staging for all patients with low-risk disease[10].

The pre- and intra-operative identification of low-risk EC is essential for plan of management. Many modalities are used for prediction such as endometrial curettage/biopsy, MRI, and frozen section. The validity in risk assessment saves many patients from undergoing lymphadenectomy. The objective of this research is to assess the benefit of preoperative grading and intraoperative gross depth of MI as the predictors for final surgical staging in patients with low-risk EC.Both parameters are assessed as a routine steps for therapeutic management of EC.

Materials and methods

After obtaining Ethics Committed of Rajavithi Hospital approval, the authors retrospectively reviewed the medical records of all 708 patients with EC who had been treated at Rajavithi Hospital from January 1st, 2002 to December 31st, 2006. All patients had their initial diagnosis made by endometrial curettage/biopsy and had undergone a hysterectomy and appropriate surgical staging in Rajavithi Hospital. Attending pathologists reviewed all slides of endometrial biopsies and curettages that were read by outside pathologists.If the results are discordant, the researchers follows the interpretation of Rajavithi Hospital's pathologists. Attending gynecologic oncologists performed all surgeries.

Every hysterectomies were performed transabdominally. Cytologic washings were taken from the peritoneal cavity. A thorough exploration of the abdomen and pelvis was then performed, including palpation of liver, gallbladder, stomach, bowel, omentum, spleen, diaphragm and lymph nodes. After hysterectomy, the uterus was removed from the operative field and opened. The endometrial cavity was inspected, and one or more incisions were made through the tumor, myometrium and serosa. The cut surfaces were examined, and depth of MI was estimated as no, less than 50%, or more than 50%. Pelvic and/or paraaortic lymphadenectomy were performed in these patients. Hysterectomy specimens were fixed and processed at Department of Pathalogy. The FIGO surgical staging recommendation (1988[6]) was determined according to the surgicopathologic findings and reviewed by the attending pathologists.

Patients were included in this study if they had preoperative tissue diagnosis of grade 1 or grade 2 endometrioid, endometrioid with squamous differentiation, mucinous or mixed mucinous-endometrioid adenocarcinoma, and an intraoperative gross depth of MI of less than 50%. Patients were excluded if (1) they had a preoperative diagnosis of grade 3 adenocarcinoma or histologic diagnosis other than above, such as papillary serous, clear cell or squamous cell carcinoma, (2) their intraoperative gross depth of MI was more than 50% or cervical/extrauterine extension was noted, and (3) they were found to have synchronous primary tumors on final pathologic evaluation.

Medical records were reviewed for the following data : age, parity, menopausal status, weight, underlying diseases, preoperative histologic type and grade, surgical procedures, intraoperative gross depth of MI, estimated blood loss, complications, postoperative histologic type, grade and stage. Tumor grading was based on the degree of glandular differentiation in accordance to FIGO guidelines[11]. The authors developed the predicted staging that combined

preoperative grade with intraoperative gross depth of MI (Table 1). These predictors were then compared with the final findings from surgico-pathological reports.

Three hundred eighty three out ot 708 patients had preoperative tissue diagnosis of grade 1 or grade 2 adenocarcinoma. Of all 383 patients, 125 were found to have intraoperative gross depth of MI less than 50%. One patient with synchronous endometrial and ovarian carcinoma was excluded.

Statistical evaluation was performed using SPSS version 11.5 software for Windows (Chicago, IL). Comparison between the categorical variables was performed by Chi-square test. The correlation was interpreted from strength of association, which was calculated by Spearman rank order correlation coefficient (r_s). A probability value (p-value) of < 0.05 was considered statistically significant.

Results

There were 124 patients with preoperative diagnosis of grade 1 or grade 2 adenocarcinoma and an intraoperative gross depth of MI less than 50%. These patients were assigned a predictive stage as described above. The demographic and clinical features of this group of patients are described in Table 2. The patients' mean age at presentation was 55 years. Surgical staging, denoting at least pelvic lymphadenectomy, was performed in 92.7% of cases, while the rate for complete surgical staging, denoting pelvic and paraaortic lymphadenectomy was 83.9%. Eleven patients were not underwent lymphadenectomy due to serious medical complications. Only one patient had obturator nerve injury.

The preoperative compared with final pathologic grade is summarized in Table 3. Since the Spearman rank order correlation coefficient (r_s) was 0.333 ($p < 0.001$), the preoperative tumor grade was moderately correlated with final grade. Twenty patients (20.2%) of preoperative grade 1 EC were upgraded, with 17.2% grade 2 and 3% grade 3. For the grade 2 lesions, 15 (60%) out of the 25 preoperative grade 2 lesions were changed on final pathology to grade 1 or grade 3. Four (16%) of the preoperative grade 2 lesions were upgraded to grade 3. In total, 35 (28.2%) of all the 124 cases had a discrepancy between preoperative and final histology, and 24 (19.4%) were upgraded to a higher grade. When considering all lesions thought to be grade 1 and 2, 7 (19%) of the 124 were altered to final grade 3.

The comparison between intraoperative with final depth of MI is shown in Table 4. The Spearman rank order correlation coefficient (r_s) was 0.321 ($p < 0.001$). Therefore, the intraoperative gross depth of MI was moderately correlated with final depth of MI. Twenty (58.8%) out of the 34 lesions thought to have disease limited to the endometrium on gross examination had pathologic MI. Forty seven percent of MI was less than half and 11.8% of them was more than half. Whereas 36.7% of lesions grossly defined as MI less than 50% were changed on final pathologic evaluation as no myometrial invasion or deep MI more than half, 10% no MI and 26.7% MI more than half. In conclusion, 42.7% of cases had discrepancy between intraoperative gross examination and final pathologic evaluation, while 35.5% had deeper MI than intraoperative assessment. When considering all lesions thought to be grossly invading less than 50%, 22.6% had deep MI more than half.

The predictive staging is demonstrated in Table 5. The Spearman rank order correlation coefficient (r_s) was 0.192 ($p = 0.032$). So, the predicted staging was poorly correlated with final surgical staging. Of the 115 cases that underwent lymphadenectomy, 6 (5.2%) was found to have nodal metastasis. The authors also determined clinically significant upstaging of the predictive stage. Which cases were considered clinically significantly upstaged if the patients would have undergone complete staging, had the surgeon known intraoperatively what the final pathologic results would present. Therefore, these cases were understaged if the surgeon relied entirely on preoperative grade and intraoperative gross depth of MI. Seven cases (28%) with predictive IAG1 were clinically significantly upstaged, as were two cases (22.2%) with predicted IAG2, 26 cases (34.2%) with predictive IBG1 and three cases (21.4%) with predictive IBG2. In total, 38 (30.6%)

of all the 124 cases were clinically significant upstaged and resulted in suboptimal surgical treatment.

Univariate analysis of the predictive variables of final surgical staging (Table 6) showed no significant association between clinical variables, preoperative tumor grade, intraoperative gross depth of MI and predicted staging with final surgical staging for low-risk EC.

Table 1. Construction of predictive staging

Predictive staging	Preoperative tumor grading	Intraoperative gross depth of myometrial invasion
IAG1	Grade 1	No invasion
IAG2	Grade 2	No invasion
IBG1	Grade 1	Less than 50%
IBG2	Grade 2	Less than 50%

Table 2. Patients' demographics and clinical features

Patients' demographics and clinical features	n = 124
Age (yr), mean (SD)	55 (8.57)
Menopausal status (%)	
Premenopausal	51 (41)
Postmenopausal	73 (59)
Weight (kg), mean (SD)	69.5 (14.98)
Underlying diseases (%)	
No	64 (51.6)
Diabetes	13 (10.5)
Hypertension	22 (17.7)
Diabetes and Hypertension	17 (13.7)
Other	8 (6.5)
Preoperative tumor histology (%)	
Endometrioid	110 (88.7)
Endometrioid with squamous differentiation	10 (8.1)
Mucinous	1 (0.8)
Mixed endometrioid and mucinous	3 (2.4)
Surgical procedure performed (%)	
Staging procedure	115 (92.7)
Complete staging procedure	104 (83.9)
Estimated blood loss (mL), median (range)	400 (100-3000)
Complications (%)	
Obturator nerve injury	1 (0.8)

Abbreviation: SD = standard deviation

Table 3. Preoperative compared with final tumor grading

Preoperative tumor grading	Final tumor grading, n (%)			
	G1	G2	G3	Total
G1	79 (79.8)	17 (17.2)	3 (3.0)	99
G2	11 (44.0)	10 (40.0)	4 (16.0)	25

Abbreviation: G = grade

*Spearman rank correlation coefficient (r_s) = 0.333, $p < 0.001$

Table 4. Intraoperative gross depth of myometrial invasion compared with final pathologic evaluation

Intraoperative gross depth of MI	Final pathologic evaluation, n (%)			
	No MI	MI < 50%	MI > 50%	Total
No MI	14 (41.2)	16 (47.0)	4 (11.8)	34
MI < 50%	9 (10.0)	57 (63.3)	24 (26.7)	90

Abbreviation: MI = myometrial invasion

* Spearman rank correlation coefficient (r_s) = 0.321, $p < 0.001$

Table 5. Predictive staging compared with final staging

Predicted staging	Final staging, n (%)										
	IAG1	IAG2	IBG1	IBG2	IBG3	IC	IIA	IIB	IIIA	IIIC	Total
IAG1	9		9			2		2	1	2	25
	(36.0)		(36.0)			(8.0)		(8.0)	(4.0)	(8.0)	
IAG2	2		4	1	1	1				1	10
	(20.0)		(40.0)	(10.0)	(10.0)	(10.0)				(10)	
IBG1	4		37	9	1	17	1	2	3	1	75
	(5.3)		(49.3)	(12)	(1.3)	(22.7)	(1.3)	(2.7)	(4.0)	(1.3)	
IBG2		1	5	5		1				2	14
		(7.1)	(35.7)	(35.7)		(7.1)				(14.3)	

* Spearman rank correlation coefficient (r_s) = 0.192, $p = 0.032$

Table 6. Univariate analysis of predictors of final surgical staging

Variables, n(%)	Final surgical staging		p
	IAG1, IAG2, IBG1, IBG2 (n = 86)	Non- IAG1, IAG2, IBG1, IBG2 (n = 38)	
Age			
≤ 55 years	47 (54.7)	17 (44.7)	0.31
> 55 years	39 (45.3)	21 (55.3)	
Body weight			
≤ 70 kg	43 (50)	23 (60.5)	0.27
> 70 kg	43 (50)	15 (39.5)	
Underlying disease			
No DM and/or HT	49 (57)	23 (60.5)	0.71
DM and/or HT	37 (43)	15 (39.5)	
Preoperative tumor grading			
G1	68 (79.1)	31 (81.6)	0.75
G2	18 (20.9)	7 (18.4)	
Intraoperative gross depth of MI			
No MI	25 (29.1)	9 (23.7)	0.54
MI < 50%	61(70.9)	29 (76.3)	
Predicted staging			
IAG1-IAG2	25 (29.1)	10 (26.3)	0.75
IBG1-IBG2	61(70.9)	28 (73.7)	

Abbreviation: DM = diabetes mellitus, HT = hypertension, G = grade, MI = myometrial invasion

Discussion

The results of this study were similar to previous findings that the predictive staging does not accurate predict the final staging. Michael et al[12] compared preoperative histology and intraopertive gross depth of invasion with final pathologic evaluation on hysterectomy specimens and concluded that these predictors had poor correlated with the final staging of the EC. Similarly, the authors also found a substantial number of patients had understaged disease when the surgeon had relied on predictive staging. Ben-Shachar et al[13] reported the significantly impacted on postoperative treatment decision in 29% of patients presenting with grade 1 EC who undergone surgical staging.

The surgical staging includes extensive surgery with complete exploration of the abdominal cavity, peritoneal cytology and evaluation of the lymph nodes. Pelvic lymph node metastases are present in less than 5% of grade 1 and 2 tumors with superficial myometrial invasion, in about 15% of grade 1 and 2 tumors with deep myometrial invasion or grade 3 tumor with superficial invasion, and in more than 40% of grade 3 tumors with deep myometrial invasion[5]. The extent of the surgical staging among women with low-risk EC has been the subject of debate[14]. Selective node sampling is of dubious value as a routine; complete lymphadenectomy being reserved for cases with high-risk features. But the lymphadenectomy is not therapeutic benefit in low-risk EC[7,15,16]. Therefore, the women with low-risk disease can generally be safely operated on by a general gynecologist. However, many individuals with EC are obese or elderly, with other medical problems.Therefore, clinical judgment is required to determine whether additional surgery is necessary.

Although many publications including this one

have found the poor correlation between preoperative and final grade as well as intraoperative gross and final depth of myometrial invasion in EC specimens, many surgeons use combined predictors as an intraoperative decision-making tool in deciding whether or not to undertaken complete lymphatic staging in these patients.

The depth of myometrial invasion has poorer correlation with final staging than preoperative tumor grading. The most accurate method of assessing depth of myometrial invasion is magnetic resonance imaging (MRI), specificity 80-90%[17]. Recently, many centers use frozen sections obtained intraoperatively to assess tumor grade and depth of myometrial invasion. Sanjuan et al[18] reported using of the combination of preoperative biopsy and intraoperative frozen section as the best way to decide whether a lymphadenectomy is necessary. This resulted in low rate of understaging patients. Review of five studies, specificity of intraoperative gross assessment of myometrial invasion (85-91%)[19-21] was slightly less than frozen section (87-95%)[21-23]. Currently, there are no proven methods to predict which patients are at low risk of lymph node metastasis[24].

The limitation of this study is only some patients underwent lymphadenectomy and patients with stage IIIC disease were missing. Thus, these predictors may be poorer than these estimates.

Conclusion

Combination of preoperative tumor grading and intraoperative gross depth of myometrial invasion is a poor predictor for final staging in patients with low-risk EC. Thirty percent of patients will not undergo complete staging according to these indicators. Without lymphadenectomy, patients with low-risk EC may br received incomplete postoperative management.

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การทำนายระยะโรคในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกความเสี่ยงต่ำโดยประเมินการลุกลามกล้ามเนื้อมดลูกขณะผ่าตัดและเกรดมะเร็งก่อนผ่าตัด

มรุต ญาณารณพ, สุเพ็ชร ทุ้ยแป

วัตถุประสงค์ *: เพื่อประเมินการใช้ความลึกของการลุกลามเข้ากล้ามเนื้อมดลูกที่ประเมินขณะผ่าตัดและเกรดของมะเร็งเยื่อบุโพรงมดลูกที่ได้รับการวินิจฉัยก่อนผ่าตัดมาใช้เป็นตัวทำนายระยะโรคมะเร็งเยื่อบุโพรงมดลูก ความเสี่ยงต่ำ*

วิธีดำเนินการทำวิจัย *: ทบทวนเวชระเบียนผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกที่เข้ารับการผ่าตัดในโรงพยาบาลราชวิถี ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2545 ถึง 31 ธันวาคม พ.ศ. 2549 โดยเก็บข้อมูลลักษณะทางประชากรและคลินิก, เกรดของมะเร็งก่อนผ่าตัด, ความลึกของการลุกลามเข้ากล้ามเนื้อมดลูกประเมินขณะผ่าตัดด้วยตาเปล่า และระยะโรคกำหนดหลังผ่าตัด*

ผลการวิจัย *: ผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกความเสี่ยงต่ำที่ทำนายไว้ 124 ราย ซึ่งประเมินจากความลึกของการลุกลามเข้ากล้ามเนื้อมดลูกที่ประเมินขณะผ่าตัด (ไม่พบการลุกลามหรือลุกลามเข้ากล้ามเนื้อมดลูกน้อยกว่าร้อยละ 50) และเกรดของมะเร็งที่ได้รับการวินิจฉัยก่อนผ่าตัด (เกรด 1 และ 2) พบว่าความลึกของการลุกลามเข้ากล้ามเนื้อมดลูกที่ประเมินขณะผ่าตัดมีการลุกลามมากกว่าเดิมร้อยละ 35.5 และไม่ตรงกับความลึกของการลุกลามที่ประเมินหลังผ่าตัดร้อยละ 42.7 เกรดมะเร็งที่ได้รับการวินิจฉัยก่อนผ่าตัดมีเกรดที่รุนแรงมากกว่าเดิมร้อยละ 19.4 และไม่ตรงกับเกรดมะเร็งหลังผ่าตัดร้อยละ 28.2 ระยะโรคที่ทำนายระยะ IAG1, IAG2, IBG1 และ IBG2 มีการเปลี่ยนแปลงเป็นระยะโรคที่รุนแรงกว่าระยะเดิมทั้งสี่ระยะ ร้อยละ 28, 30, 33.3 และ 21.4 ตามลำดับ โดยรวมแล้วผู้ป่วยที่ได้รับการทำนายเป็นมะเร็งเยื่อบุโพรงมดลูกความเสี่ยงต่ำจะได้รับการผ่าตัดที่ไม่เหมาะสมถึงร้อยละ 30.6*

สรุป *: การใช้ความลึกของการลุกลามเข้ากล้ามเนื้อมดลูกที่ประเมินขณะผ่าตัดด้วยตาเปล่าและเกรดของมะเร็งเยื่อบุโพรงมดลูกที่ได้รับการวินิจฉัยก่อนผ่าตัดเพียงสองอย่างอาจจะไม่น่าเชื่อถือในการทำนายระยะโรค*