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Potential Factors Associated with Pelvic Lymph Node Metastasis in Endometrioid Endometrial Carcinoma

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ABSTRACT

Objectives: To explore factors that associated with pelvic lymph node metastasis in endometrioid endometrial carcinoma

Materials and Methods: Two hundred and ninety-three patients with endometrioid endometrial carcinoma, who received surgical staging in Siriraj Hospital during 2008-2016, were studied. The relationship between pelvic lymph node metastasis and these data: demographic factors, biochemical markers, preoperative and intraoperative tumor characteristics were analysed by using a logistic regression model.

Results: From multivariate analysis, associated factors were grade of tumor, platelet count, deep myometrial invasion (deep MI: more than half of myometrial invasion) and size of tumor. Platelet count and size of tumor were re-calculated. Thrombocytosis (platelet count more than or equal to 380,000/mm^3) and large tumor (tumor size more than or equal to 6 centimeters) were statistically significant for cut-off point.

Conclusion: Grade of tumor, platelet count, more than half of depth of myometrial invasion and size of tumor, were associated with pelvic lymph node metastasis in endometrioid endometrial carcinoma.

Keywords: endometrial carcinoma, risk factors, pelvic lymph node metastasis.

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ปัจจัยที่สัมพันธ์กับการแพร่กระจายไปต่อมน้ำเหลืองในอุ้งเชิงกรานในมะเร็งเยื่อบุมดลูกชนิด endometrioid

ประกาศิษฐ์ คะระวานิช, อรรถพล ใจชื่น

บทคัดย่อ

วัตถุประสงค์: *เพื่อค้นหาปัจจัยที่สัมพันธ์กับการแพร่กระจายไปต่อมน้ำเหลืองในอุ้งเชิงกรานในมะเร็งเยื่อบุมดลูกชนิด endometrioid*

วัสดุและวิธีการ: *การศึกษาย้อนหลังโดยนำข้อมูลจากผู้ป่วยมะเร็งเยื่อบุมดลูกชนิด endometrioid 293 ราย ที่ได้รับการผ่าตัดประเมินระยะของโรคในโรงพยาบาลศิริราช ระหว่างปี พ.ศ.2551-2560 มาศึกษาความสัมพันธ์ระหว่างการกระจายของมะเร็งไปยังต่อมน้ำเหลืองอุ้งเชิงกรานและปัจจัยต่างๆ ได้แก่ ข้อมูลพื้นฐานของผู้ป่วย ค่าผลเลือด การประเมินคุณลักษณะของเนื้องอกก่อนผ่าตัดและระหว่างผ่าตัด โดยนำไปวิเคราะห์ข้อมูลผ่านการวิเคราะห์ถดถอยโลจิสติกส์ จากนั้นนำตัวแปรที่มีนัยสำคัญมาให้คะแนนถ่วงน้ำหนักเป็นจำนวนเต็ม โดยอ้างอิงจากค่า odds ratio ที่ใกล้เคียงที่สุดของแต่ละตัวแปร ในที่สุดจะนำผลรวมมาคำนวณเพื่อทำนายโอกาสที่จะเกิดการกระจายไปยังต่อมน้ำเหลืองอุ้งเชิงกราน*

ผลการศึกษา: *จากการวิเคราะห์พหุตัวแปร ปัจจัยที่มีนัยสำคัญ ได้แก่ ระดับทางพยาธิวิทยาของเนื้องอก การเพิ่มขึ้นของจำนวนเกล็ดเลือด การลุกลามเข้ากล้ามเนื้อมดลูกชั้นลึก (กำหนดให้เกินครึ่งหนึ่งของชั้นกล้ามเนื้อทั้งหมด) และเนื้องอกขนาดใหญ่ สำหรับจำนวนเกล็ดเลือด และขนาดเนื้องอกได้รับการคำนวณอีกครั้งเพื่อหาจุดตัดที่เหมาะสม ผลลัพธ์คือการเพิ่มขึ้นของจำนวนเกล็ดเลือดตัดที่มากกว่า เท่ากับ 380,000 เซลล์ต่อลูกบาศก์มิลลิเมตร ส่วนขนาดเนื้องอก 6 เซนติเมตร ขึ้นจัดเป็นเนื้องอกขนาดใหญ่*

สรุป: *ระดับทางพยาธิวิทยาของเนื้องอก, การเพิ่มขึ้นของจำนวนเกล็ดเลือด, การลุกลามเข้ากล้ามเนื้อมดลูกชั้นลึก และเนื้องอกขนาดใหญ่ เป็นปัจจัยที่สัมพันธ์กับการแพร่กระจายไปต่อมน้ำเหลืองในอุ้งเชิงกรานในมะเร็งเยื่อบุมดลูกชนิด endometrioid*

คำสำคัญ: *มะเร็งเยื่อบุมดลูก, ปัจจัยเสี่ยง, การแพร่กระจายของต่อมน้ำเหลืองในอุ้งเชิงกราน*

Introduction

Endometrial carcinoma is the most common gynaecologic malignancy in developed countries. The incidence is increasing in developing countries including Thailand. From national cancer institute, endometrial carcinoma is currently the third most common gynaecologic cancer in Thailand[1]. Approximately eighty percent of cases are endometrioid type which usually presents in early stage and suitable for surgical staging: total hysterectomy, bilateral salpingo-oophorectomy and lymph node evaluation. Adjuvant managements will be tailored according to the uterine lesion and lymph node status[2, 3].

Endometrioid carcinoma patients are usually old age, obese and related with medical condition such as diabetes mellitus or hypertension[2]. Two randomized trials concluded that no survival benefit from lymph node removal in endometrial carcinoma patients[4, 5]. However, SEPAL study showed therapeutic benefit of pelvic and para-aortic lymph node dissection in endometrial carcinoma patients[6]. This procedure increased blood loss, operative time and sometime complicated by lymphocele and lymphedema. Most of the guidelines suggested selective pelvic and para-aortic lymph node dissection in the high risk cases such as high grade, large tumor, deep myometrial invasion or extrauterine disease[2, 7, 8]. Advanced imaging did not have good sensitivity to detect lymph node metastasis in endometrial carcinoma. Aleediman, et al recently showed the preoperative serum inflammatory response associate with lymph node metastasis in endometrial carcinoma including lower haemoglobin level, higher neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte multiplication (MNM) and platelets count[9].

In Thailand, there were no studies that indicate significant factors associated with pelvic lymph node metastasis. The objective of this study was to explore factors that associated with pelvic lymph nodes metastasis in endometrioid endometrial carcinoma patients. This may help to define which cases may be able to omit lymph node dissection or which cases should have lymph node dissection to avoid those side effects.

Materials and Methods

We conducted the case-control study for this objective. After approved by Siriraj Institutional Review Board, data from Medical Statistic Unit was retrospectively reviewed. Patients with endometrioid endometrial carcinoma underwent surgical staging, including pelvic lymph node dissection at Siriraj Hospital during 2008-2016 were included. Incomplete pathologic and laboratory data were excluded. Case was defined as endometrioid endometrial carcinoma that had positive pelvic lymph node metastasis. Control was endometrioid endometrial carcinoma that had no pelvic lymph node metastasis. From pilot study of 30 cases, the ratio of case and control was 1:3. Sample size was calculated using variables that associated with pelvic lymph node metastasis such as age, grade of tumor, size of tumor and more than half of depth of myometrial invasion. Age yielded the highest number of 72 cases and 216 controls. Totally 293 patients were enrolled. Cases were all pelvic lymph node metastasis patients during that period. Three controls were randomly selected from negative pelvic lymph node patients at the same 3 months' time period of each case.

Preoperative data included age, body mass index (BMI) at the date of surgery, grade of tumor from endometrial biopsy data and complete blood count (CBC) within 3 months before surgery. CBC data including, hemoglobin (Hb), hematocrit (Hct), absolute neutrophil count (ANC), platelet count, NLR and PLR were collected. Intraoperative data included tumor size, depth of myometrial invasion, cervical stromal involvement and ovarian involvement were collected. Pathological examination pelvic lymph nodes were divided patients into case and control group.

The data was analysed by the application of SPSS statistics 21. T-test was used for continuous data while Pearson chi-square test and Mann-

Whitney test were used to analyse the association between each categorical variables and pelvic lymph node metastasis. Logistic regression analysis was performed to determine independent associated factors for pelvic lymph node metastasis adjusting for potential confounders.

Results

The total of 293 patients were recruited, 72 cases and 221 controls. Mean age was similar in case and control group, 57.46 and 57.78 years respectively. In univariate analysis; mean BMI, hemoglobin, hematocrit, platelet count, NLR and PLR, high grade of tumor, tumor size, more than half of myometrial invasion and cervical stromal involvement increased risk for pelvic lymph node metastasis (Table 1). The median number of lymph node obtained was 13 (13.5 in case and 13 in control group). The ratio of positive LN in patient obtained less than 13 lymph nodes and more than or equal to 13 lymph nodes were 25% (33/132) and 24.22% (39/161).

Table 1. Unadjusted variables comparing between pelvic LN metastasis and no pelvic LN metastasis.

Characteristic	Pelvic LN metastasis (n = 72)	No pelvic LN metastasis (n = 221)	p value
Mean age (years)	57.46	57.78	0.82
Mean BMI (kg/m^2)	25.57	27.97	< 0.001
Hemoglobin (g/dL)	12	12.6	0.001
Hematocrit (%)	36.36	38.63	< 0.001
NLR	3.66	2.22	< 0.001
ANC (/mm^3)	4800	4340	0.05
PLR	159.21	123.37	< 0.001
Platelet (/mm^3)	304,500	270,000	0.002
Grade of tissue sampling			
- Grade 1	16 (22.2%)	119 (53.9%)	
- Grade 2	30 (41.7%)	75 (33.9%)	
- Grade 3	26 (36.1%)	27 (12.2%)	
Median size of lesion (cm) (range)	8 (1-10)	3 (0-8)	< 0.001
> 50% depth of myometrial invasion	50 (69.4%)	58 (26.2%)	< 0.001
Cervical stromal involvement	16 (22.2%)	11 (5.0%)	< 0.001
Ovarian involvement	7 (9.7%)	8 (3.6%)	0.06
Median number of LN (range)	13.5 (1-36)	13 (1-48)	0.509

LN = lymph node
BMI = body mass index
NLR = neutrophil-lymphocyte ratio
ANC = absolute neutrophil count
PLR = platelet-lymphocyte ratio

Logistics regression model had been used for multivariate analysis. Factors associated with pelvic lymph node metastasis were higher grade of tumor, more than half of myometrial invasion, platelet count

and tumor size (Table 2). We explored the cut-off points for both platelet count and size of lesion by using receiver operating characteristics (ROC) curve. The proper cut-off point for platelet count was greater than or equaled to 380,000/mm^3 with the area under ROC curve of 0.624 (Fig. 1a). The proper cut-off point of tumor size was larger than or equaled to 6 centimeters with the area under ROC curve of 0.711 (Fig. 1b). Logistic regression was recalculated using platelet count greater than or equaled to 380,000/mm^3 and tumor size larger than or equaled to 6 centimeters as two new categorical variables. Factors associated with pelvic lymph node metastasis were higher grade of tumor, more than half of myometrial invasion, platelet count greater than 380,000/mm^3 and tumor size larger than 6 centimeters (Table 3).

Table 2. Odds ratios from logistic regression model with dependent variables and pelvic LN metastasis.

	Adjusted ORs	p value
BMI (kg/m^2)	0.948	0.072
Grade	5.974	< 0.001
Hemoglobin (g/dL)	0.863	0.703
Hematocrit (%)	1.028	0.834
NLR	1.047	0.523
PLR	1.002	0.653
Platelet (/mm^3)	1.000	0.005
Size of tumor (cm)	1.142	0.006
> 50% depth of myometrial invasion	5.156	< 0.001
Cervical stromal involvement	1.063	0.906
Ovarian involvement	1.35	0.699

LN: lymph node
ORs: odds ratio
BMI: body mass index
NLR: neutrophil-lymphocyte ratio
PLR: platelet-lymphocyte ratio

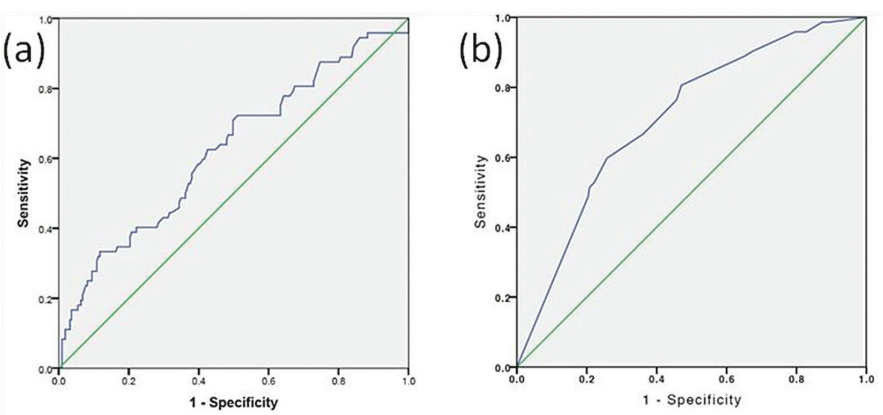

Fig. 1. Receiver operating characteristic curves of factors prediction of pelvic lymph node metastasis (a) platelet count (b) size of tumor.

Table 3. Odds ratios from logistic regression model with dependent variables and pelvic LN metastasis after new cut-off point of platelets and size of tumor.

	Adjusted ORs	p value
BMI (kg/m^2)	0.951	0.092
Grade	5.654	< 0.001
Hemoglobin (g/dL)	0.878	0.738
Hematocrit (%)	1.016	0.902
NLR	1.068	0.553
PLR	1.001	0.809
Platelet > 380,000/mm^3	3.306	0.004
Size of tumor > 6 cm	2.213	0.020
> 50% depth of myometrial invasion	5.435	< 0.001
Cervical stromal involvement	1.083	0.879
Ovarian involvement	1.411	0.657

LN: lymph node
ORs: odds ratio
BMI: body mass index
NLR: neutrophil-lymphocyte ratio
PLR: platelet-lymphocyte ratio

Discussion

Pelvic lymph node dissection is one of the important steps of surgical staging for endometrioid endometrial carcinoma and affects further treatments. However, this procedure can lead to numerous complications. The survival benefit is still inconclusive. Selective pelvic lymph node dissection is widely practiced but there are no definite data to support surgeons' judgments. The median number of lymph node was 13, similar to our previous data[10]. We did not exclude the patient with lymph node obtained less than 13 because the ratio of pelvic lymph node metastasis was comparable with the group of lymph node more than or equal to 13, 25% and 24.22%, respectively.

This study found that there were four factors associated with pelvic lymph node metastasis: higher grade of tumor, depth of myometrial invasion, larger tumor size and higher platelet count. There are no doubt in higher tumor grade and deep myometrial invasion to be indications for pelvic and para-aortic lymph node dissection as suggest in most of the guideline[2, 7, 8]. According to previous data, there were some different details for tumor size and platelet count. Previous data suggested that lesions larger than 2 centimeters were associated with pelvic lymph node metastasis[11, 12]. Our study found that the tumor size of 6 centimeters was the most proper cut-point in multivariate analysis.

Shah, et al studied the relationship of tumor size and lymph node metastasis. The result showed that only tumor size greater than or equal to 8 centimeters conferred a significant risk of lymph node metastasis[13]. However, in multivariate logistic regression, tumor size did not show the statistically significance with the odds ratio of 1.3 (95% CI, 1.0-1.6). This result may be affected by including of the non-endometrioid tumor which has high metastatic nature even with the small tumor. The only 3 variables that remained significant independent predictors were clear cell or papillary serous, grade 3 histology and lymphovascular space invasion. Our study did not include non-endometrioid histology which had the higher risk of lymph node metastasis and already recommended by Society of Gynecologic Oncology to undergo lymphadenectomy in every

patient[14]. The lymphovascular space invasion data were mostly obtained from hysterectomy specimen, barely mentioned in endometrial sampling specimen. We did not include this postoperative factor in our predictors. The grade 3 histology obviously showed the same result as ours.

Teixeira, et al found that grade of tumor, tumor extension (International Federation of Gynecology and Obstetrics stage) and lower uterine segment involvement were significant factors for lymph node metastasis on multivariate analysis[15]. These data were supported our data on grade 3 histology and deep myometrial invasion. However, size of tumor was not a significant factor. The size of tumor was obtained from pathology report which may alter the real size of tumor. Our study reported the median size of tumor at 3 and 8 centimeters in no pelvic lymph node metastasis group and pelvic lymph node metastasis group, respectively. While Teixeira, et al found median size of tumor at 3.5 and 5 centimeters. Another possible reason, multicenter sites may have different method in tumor size collection. Zhang, et al., also reported the clinicopathological factors associated with pelvic lymph node metastasis. Only deep myometrial invasion and lymphovascular space invasion were independent risk factors, based on multivariate analysis[16]. Unfortunately, most of interested factors were obtained from postoperative data. This may not help to decide who should undergo lymph node dissection.

For platelet count, Luomaranta indicated thrombocytosis from average Finnish female population as > 360,000/mm^3[17], Aleediman used ≥ 297,500/mm^3 as cut-point by computing from ROC curve[9]; while our study found that 380,000/mm^3 was the most proper cut-point for thrombocytosis, also calculated from ROC curve. Moreover, although other biomarkers were announced as significant data responsible for host immune response: leukocytosis in Luomaranta's study and lower Hb level, higher NLR, PLR in Aleediman's study[9, 17]; our study found no significant associations between those biomarkers and pelvic lymph node metastasis except thrombocytosis.

Compared with previous studies, especially in Thailand, this research had covered more aspects including demographic data, preoperative histopathological examination, preoperative immune-response biomarkers, intraoperative gross tumor size, and extrauterine evaluation. Moreover, these data were collected from a reliable system which the data can be traced back for more than a decade. Using routine data such as preoperative endometrial biopsy result and complete blood count did not increase any cost. However, there were some limitations from retrospective data collection. We excluded patients who did not undergo pelvic lymph node dissection. These patients could also be in very early stage or very advanced stage of disease. We plan to use the data from logistic regression model for calculation the risk scoring formula, then prove the formula and absolutely comparing with pre-existing formula in a further prospective study.

Conclusion

Factors associated with pelvic lymph node metastasis in endometrioid endometrial carcinoma were high grade tumor, thrombocytosis (more than 380,000/mm^3), tumor size larger than 6 centimeters and deep myometrial invasion.

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Potential conflicts of interest

The authors declare no conflict of interest.

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