# ความชุกในการแพร่กระจายของมะเร็งเยื่อบุโพรงมดลูกไปยังต่อมน้ำเหลืองในอุ้ง เชิงกราน ในโรงพยาบาลศรีนครินทร์

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# Prevalence of Pelvic Lymph node Metastases in Endometrial Cancer Patients at Srinagarind Hospital

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**หลักการและเหตุผล:** ในโรงพยาบาลศรีนครินทร์ ผู้ป่วย โรคมะเร็งเยื่อบุโพรงมดลูก ได้รับการรักษาด้วยการผ่าตัด เพื่อ กำหนดระยะของโรคมาตั้งแต่ปี พ.ศ. 2539 ตามคำแนะนำของ International Federation of Gynecology and Obstetrics (FIGO) ในปี ค.ศ.1988 อย่างไรก็ตาม กลุ่มวิจัยยังไม่มีข้อมูลเกี่ยวกับ ความชุกในการแพร่กระจายของมะเร็งเยื่อบุโพรงมดลูกไปยัง ต่อมน้ำเหลืองในอุ้งเชิงกรานและปัจจัยเสี่ยงต่างๆ ที่มีผลต่อ การแพร่กระจายของมะเร็งเยื่อบุโพรงมดลูกไปยังต่อมน้ำเหลือง ในอุ้งเชิงกราน ในโรงพยาบาลศรีนครินทร์ ซึ่งอาจมีผลต่อ แนวทางการรักษาได้

**วัตถุประสงค์:** เพื่อทราบถึงความชุกในการแพร่กระจายของ มะเร็งเยื่อบุโพรงมดลูกไปยังต่อมน้ำเหลืองในอุ้งเชิงกรานและ ปัจจัยเสี่ยงต่างๆ ที่มีผลต่อการแพร่กระจายของมะเร็งเยื่อบุ โพรงมดลูกไปยังต่อมน้ำเหลืองในอุ้งเชิงกราน

**วัสดุและวิธีการ:** ผู้วิจัยได้เก็บข้อมูลผู้ป่วยมะเร็งเยื่อบุโพรง มดลูก ที่ได้รับการรักษาด้วยการผ่าตัดเพื่อกำหนดระยะของ โรคที่โรงพยาบาลศรีนครินทร์ ระหว่างเดือนมกราคม 2539 ถึงเดือนกรกฎาคม 2548 จากเวชระเบียนผู้ป่วยนอกและ เวชระเบียนผู้ป่วยใน

**รูปแบบการศึกษา:** การศึกษาเชิงพรรณนา แบบเก็บข้อมูล ย้อนหลัง

**สถานที่ศึกษา:** โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

**ผลการศึกษา:** มีผู้ป่วย 199 คน ที่ได้รับการผ่าตัดเพื่อจัดระยะ ของโรคในช่วงเวลาดังกล่าว พบว่าความชุกในการแพร่กระจาย

**Background:** Since 1996, endometrial cancer patients at Srinagarind Hospital (SNH) have been surgically staged according to recommendation of International Federation of Gynecology and Obstetrics (FIGO) 1988. However, there was no data about the prevalence and predicting factors of pelvic lymph node metastases in the patients with endometrial cancer in SNH before. These data could lead to either supporting or objection of our practice.

**Objectives:** To determine the prevalence and predicting factors of pelvic lymph node metastases in endometrial cancer patients at Srinagarind Hospital

**Materials and methods:** Medical records of endometrial cancer patients, whose were primarily surgically treated at Srinagarind Hospital during January, 1996 to July, 2005, were collected and analyzed by retrospective chart reviews.

**Design:** Retrospective descriptive study

**Setting:** Srinagarind Hospital, Faculty of Medicine, Khon Kaen University

**Results:** 199 endometrial cancer patients were treated with surgical staging procedures. Prevalence of pelvic lymph nodes metastases was 11.6% (23/199). Only lymphovascular space invasion was found to be the significant predicting factor for pelvic lymph node metastases.

**Conclusion:** As prevalence of pelvic lymph nodes metastases was 11.6% and postoperative lymphovascular space invasion was the only a significant predicting factor

ของมะเร็งเยื่อบุโพรงมดลูกไปยังต่อมน้ำเหลืองในอุ้งเชิงกราน เป็นร้อยละ 11.6 และปัจจัยเสี่ยงที่มีความสัมพันธ์กับการแพร่ กระจายของมะเร็งเยื่อบุโพรงมดลูกไปยังต่อมน้ำเหลืองใน อุ้งเชิงกราน มีเพียงปัจจัยเดียว คือ การลุกลามเข้าหลอดเลือด และน้ำเหลือง

<u>สรุป:</u> ความชุกในการแพร่กระจายของมะเร็งเยื่อบุโพรงมดลูก ไปยังต่อมน้ำเหลืองในอุ้งเชิงกรานพบร้อยละ 11.6 และถึงแม้ การลุกลามเข้าหลอดเลือดและน้ำเหลือง จะเป็นปัจจัยเสี่ยงที่ บ่งชี้ถึงการแพร่กระจายของมะเร็งเยื่อบุโพรงมดลูกไปยังต่อม น้ำเหลืองก็ตาม แต่การตรวจหาปัจจัยดังกล่าวต้องอาศัยผล การตรวจทางพยาธิวิทยา ซึ่งเป็นขั้นตอนหลังจากการผ่าตัด แล้ว ดังนั้นการผ่าตัดเพื่อกำหนดระยะของโรค จึงยังคงมีความ จำเป็น

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for pelvic lymph node metastases. Routine surgical staging procedures in our endometrial cancer patients were supported.

**Key words:** Prevalence, pelvic lymph nodes, endometrial cancer

## Introduction

Before retroperitoneal lymph node assessment was introduced to the 1988 FIGO staging of endometrial cancer, which was revised in 2000[1], the history of the staging had been developed for almost half of the century. Since The International staging system, which was used to referred as the "League of Nations" staging system in 1951-1961[2], the staging was simple dividing patients into two groups as diseases confined to the uterus and beyond. Until the former of the clinical staging system established in 1961, which was revised as the 1971 FIGO staging[3], it was used as a standard staging system during that time frame. In 1984, the study of clinico-pathologic findings to assess the retroperitoneal lymph node was held by Boronow et al[4] and led to GOG33 study by Creasman et al.[5] Both studies showed 10% incidence of nodal metastases in clinical stage I. The risk factors were high histologic grading, aggressive cell types, depth of myometrial invasion, cervical and extra-uterine diseases. A year later, the new 1988 FIGO staging was set up following those studies.

Since 1996, endometrial cancer patients at Srinagarind Hospital (SNH) have been surgically staged, except cases with severe medical illness, gross cervical lesion, advanced pelvic diseases and distant metastases, which had to be treated with either preoperative radiation or radiation alone. However, there was no data about the prevalence and predicting factors of pelvic lymph node metastases in the patients with endometrial cancer at SNH before. These data could lead to either supporting or objection of our practice. Therefore, this study was conducted to determine the prevalence and predicting factors of pelvic lymph node metastases in patients with endometrial cancer at Srinagarind Hospital.

## Materials and Methods

Reviewing from January 1996 to July 2005, we found that the total number of endometrial cancer patients treated at Srinagarind Hospital was 445 patients. The data were collected from retrospective reviews of medical records of the patients who were treated primarily by surgical procedures at Srinagarind Hospital. Patients with endometrial cancer were included in this study if they underwent extrafascial hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection with or without para-aortic lymph node sampling and procurement of peritoneal cytology. Age, menopausal status, body mass index (BMI), histologic subtypes, histologic grades, depth of myometrial invasion, isthmic part involvement, cervical and adnexal metastases were collected. Pelvic lymph node metastatic status was noted. All advanced cases, which

were treated with preoperative radiation, radiation alone or inoperable and palliation were excluded from the study.

We had enrolled 199 cases, which suited for the inclusion criteria. All of 199 cases were surgically staged by the procedures as followings; extrafascial hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection with or without para-aortic lymph node sampling and procurement of peritoneal cytology. Only surgically staged cases were analyzed based on pelvic nodal status. In univariate analysis, the binary crude Odds was used to determine the significance of each factor. The logistic model was used to determine the independent factors in multivariate analysis.

## Statistic analysis

We calculated the sample size of about 246 patients and tried to collect data from in-patient and out-patient medical records of the patients who were admitted from January 1996 to July 2005. Finally, 199 patients were suited for the inclusion criteria. If we recalculate the sample size by increasing error of P (d) to ten percent, the new sample size would be only 62 patients. Therefore, we decided to use the whole data from 199 patients.

After we completed the data record by using the statistic software, our statistician found that 193 patients were matched for analyze. First, we analyzed by the univariate analysis to find out the crude Odds ratio. Then we used the significant factors from the univariate analysis in the multiple logistic regression analysis to prove the most significant factor for predicting pelvic lymph node metastases further.

## Results

The distribution of all factors in 199 patients was shown in Table 1. The mean age at diagnosis was 53.9 years (range 31-72, SD 8.6 years). 83 patients (41.7%) were in range of 51-60 years. 124 patients (62.3%) were postmenopause. 105 patients (52.8%) had BMI more than 25 kg/m², whereas 34 patients (17.1%) were diagnosed as obesity (BMI more than 30 kg/m²). From the postoperative surgical specimen histology, almost cases (177/199 or 88.9%) had endometrioid adenocarcinoma subtype. 34 patients (18.2%) had grade 3 lesions and 60 patients (30.2%) had deep myometrial invasion. 26 patients (13.1%) were found to have disease in the

isthmus of the uterus. Cervical metastases were found in 51 patients (25.6%). 12 patients (6.0%) had metastases to one or both of the adnexae. Lymphovascular space invasion was present in 52 patients (26.1%). 23 patients (11.6%) had pelvic node metastases.

The stage distribution is shown in Table 2. 129 patients (64.9%) were in stage I, 32 patients (16.1%) were in stage II, 34 patients (17.1%) were in stage III, and only 4 patients (2.0%) were in stage IV. The association of grade of tumor with depth of invasion was evaluated. In general, the depth of invasion increased as the grade became less differentiated. 79% of grade 1 lesions had endometrial or inner half of myometrial invasion only. More than half (52.9%) of grade 3 tumors had deep myometrial invasion. However, about one-fifth (21.0%) of grade 1 tumors had deep myometrial invasion.

In univariate analysis, all studied factors were shown in Table 3. 23 patients (11.6%) had metastases to pelvic nodes. From preoperative fractional curettage histology, we found that three factors (histologic subtypes of endometrium and endocervix, histologic grade of endocervix) were not significantly correlated with pelvic node metastases. From postoperative surgical specimen histology, we found that two factors (isthmic involvement and endocervical glandular involvement) were not significantly correlated with pelvic node metastases. But all of these factors; histologic grade 2, 3 of tumor (from preoperative fractional curettage), tumor size, outer myometrial invasion, stromal invasion of endocervix, uterine serosa invasion, adnexal metastases, and lymphovascular space invasion, had correlation to pelvic node metastases.

We further used the multiple logistic regression analysis to determine the independent factors of pelvic lymph node metastases. All of eight significant factors in univariate analysis were analyzed by the multiple logistic regression analysis. The result was found that only lymphovascular space invasion, which increased risk of pelvic node metastases about 11.6 times (95% CI, 4.2-31.9) (Table 4), was the independent factor of pelvic lymph node metastases in our study.

## Discussion

Pelvic and para-aortic nodal statuses are the powerful prognostic factors in endometrial cancer[6] and were included in the FIGO surgical pathological staging in

**Table 1** The distribution of factors of all surgically staged patients

| Factors | | Total | |
|---|---|---|---|
| | | N | % |
| 1. Age | < 50 years | 68 | 34.2 |
| | > 60 years | 131 | 65.8 |
| 2. Menstruational status | premenopause | 75 | 37.7 |
| | postmenopause | 124 | 62.3 |
| 3. BMI | < 25 Kg/m$^2$ | 94 | 47.2 |
| | 25-30 Kg/m$^2$ | 71 | 35.7 |
| | > 30 Kg/m$^2$ | 34 | 17.1 |
| 4. Surgical procedure | TAH, BSO, Omentectomy, BPND | 117 | 58.8 |
| | TAH, BSO, Omentectomy, BPND, PAS | 48 | 24.1 |
| | RHND, BSO | 5 | 2.5 |
| | others | 29 | 14.6 |
| 5. Histologic subtypes* | no residual tumor | 12 | 6.0 |
| | endometrioid adenocarcinoma | 177 | 88.9 |
| | clear cell adenocarcinoma | 2 | 1.0 |
| | mucinous adenocarcinoma | 4 | 2.0 |
| | squamous carcinoma | 1 | 0.5 |
| | mixed carcinoma | 3 | 1.5 |
| 6. Histology* | grade1 | 109 | 58.3 |
| | grade2 | 44 | 23.5 |
| | grade3 | 34 | 18.2 |
| 7. Tumor size | ≤ 2 cm. | 106 | 53.3 |
| | >2 cm. | 93 | 46.7 |
| 8. Tumor location | body | 173 | 86.9 |
| | isthmus | 3 | 1.5 |
| | both | 23 | 11.6 |
| 9. Myometrial invasion | no | 30 | 15.1 |
| | inner | 109 | 54.8 |
| | outer | 60 | 30.2 |
| 10. Cervical metastases | no | 148 | 74.4 |
| | gland | 18 | 9.0 |
| | stromal | 24 | 12.1 |
| | both | 9 | 4.5 |
| 11. Uterine serosal invasion | no specimen | 1 | 0.5 |
| | negative | 190 | 95.5 |
| | positive | 8 | 4.0 |
| 12. Adnexal metastases | no metastases | 187 | 94.0 |
| | left | 5 | 2.5 |
| | right | 3 | 1.5 |
| | bilateral | 4 | 2.0 |
| 13. Vaginal metastases | no specimen | 168 | 84.4 |
| | negative | 27 | 13.6 |
| | positive | 4 | 2.0 |

* Hysterectomy specimen

**Table 1** The distribution of factors of all surgically staged patients (continue)

| Factors | | Total | |
|---|---|---|---|
| | | N | % |
| 14. Lymphovascular space invasion | negative | 147 | 73.9 |
| | positive | 52 | 26.1 |
| 15. Pelvic lymph nodes metastases | negative | 176 | 88.4 |
| | right | 10 | 5.0 |
| | left | 8 | 4.0 |
| | bilateral | 5 | 2.6 |

TAH = trans abdominal hysterectomy

BSO = bilateral salpingo-oophorectomy

BPND = bilateral pelvic nodes dissection

PAS = para-aortic node sampling

RHND = radical hysterectomy with pelvic nodes dissection

**Table 2** Stages of endometrial cancer patients

| Stages | n | % |
|---|---|---|
| IA | 24 | 12.1 |
| IB | 83 | 41.7 |
| IC | 22 | 11.1 |
| IIA | 12 | 6.0 |
| IIB | 20 | 10.1 |
| IIIA | 9 | 4.5 |
| IIIB | 3 | 1.5 |
| IIIC | 22 | 11.1 |
| IVA | 0 | 0 |
| IVB | 4 | 2.0 |
| Total | 199 | 100 |

1988. Identification of lymph node metastases is an integral part of surgical staging procedures in patients with endometrial cancer since then. In our study, the prevalence of pelvic node metastases was 11.6%, which was similar to reports of Boronow et al.[4] and Creasman et al[5] but less than reports of Lapinska-Szumczyk et al.[7] and Lo et al.[8]

Various studies have shown that the predicting factors of pelvic lymph node metastases were high grade of tumor, depth of myometrial invasion and intraperitoneal metastases,[5] lymphovascular space invasion, cervical invasion.[9] Our study found that it was only lymphovascular space invasion by using the multiple logistic regression analysis. This factor was also significantly proven in many reports.[4,5,8-12] However, this factor could not be determined definitely during the operation, even by using frozen section in our institute.

To predict about pelvic lymph nodes status, preoperative factors including serum CA-125 level and ultrasound examination were not useful.[8] However, intraoperative factors or pathological factors including palpable enlarged lymph nodes, myometrial invasion, histologic types, histologic grades, cervical invasion, and lymphovascular space invasion were significantly associated with nodal metastases, but we could not evaluate them before the operation. Watanabe et al also pointed out that the ability of pathologic risk factors to predict nodal metasteses was even worse in low risk patients.[8]

Larson et al.[13] reported that pelvic and para-aortic lymphadenectomy could be added to hysterectomy and bilateral salpingo-oophorectomy in patients with endometrial cancer without clinically significant increasing in morbidity or mortality. Furthermore, Kilgore et al.[14] showed that there was significant survival advantage for patients having multiple-site node samplings (mean number of nodes[11]), overall and in high-risk and low-risk groups. This was strong suggesting of a therapeutic benefit.

**Table 3** Crude Odds analysis of pelvic node metastases among studied factors

| Factors | Pelvic lymph node status | | | | Crude Odds Ratio | 95% CI |
|---|---|---|---|---|---|---|
| | negative | | positive | | | |
| | No | % | No | % | | |
| **Endometrial histology** | | | | | | |
| (from preoperative curettage) | | | | | | |
| No | 1 | 100.0 | | | | |
| Endometrioid | 162 | 90.0 | 18 | 10.0 | | |
| Serous | 1 | 100.0 | | | | |
| Clear cell | 3 | 75.0 | 1 | 25.0 | | |
| Mucinous | 2 | 66.7 | 1 | 33.3 | | |
| Squamous | 2 | 100.0 | | | | |
| Mixed | 2 | 100.0 | | | | |
| **Endometrial grade** | | | | | | |
| (from preoperative curettage) | | | | | | |
| Grade1 | 124 | 96.1 | 5 | 3.9 | 1.0 | |
| Grade2 | 22 | 73.3 | 8 | 26.7 | 8.9 | 2.7-29 |
| Grade3 | 25 | 73.5 | 9 | 26.5 | 8.9 | 2.7-28 |
| **Endocervical histology** | | | | | | |
| (from preoperative curettage) | | | | | | |
| Endometreoid | 29 | 82.9 | 6 | 17.1 | 0.9 | 0.3-2.8 |
| Mucinous | 1 | 100.0 | | | 0.0 | 0.0 |
| No | 50 | 82.0 | 11 | 18.0 | 1.0 | |
| **Endocervical grade** | | | | | | |
| (from preoperative curettage) | | | | | | |
| grade1 | 22 | 91.7 | 2 | 8.3 | 0.4 | 0.1-2.0 |
| grade2 | 4 | 57.1 | 3 | 42.9 | 3.4 | 0.7-17.5 |
| grade3 | 4 | 80.0 | 1 | 20.0 | 1.1 | 0.1-11.2 |
| **Tumor size** | | | | | | |
| > 2 cm. | 77 | 82.8 | 16 | 17.2 | 2.9 | 1.2-7.5 |
| ≤ 2 cm. | 99 | 93.4 | 7 | 6.6 | 1.0 | |
| **Tumor location** | | | | | | |
| isthmus | 3 | 100.0 | | | 0.0 | 0.0 |
| body | 155 | 89.6 | 18 | 10.4 | 1.0 | |
| both | 18 | 78.3 | 5 | 21.4 | 2.4 | 0.8-7.2 |
| **Myometrial invasion** | | | | | | |
| no | 29 | 96.7 | 1 | 3.3 | 1.0 | |
| inner | 103 | 94.5 | 6 | 5.5 | 1.7 | 0.2-14.6 |
| outer | 44 | 73.3 | 16 | 26.7 | 10.5 | 1.3-83.9 |
| **Endocervical invasion** | | | | | | |
| no | 136 | 91.9 | 12 | 8.1 | 1.0 | |
| gland | 17 | 94.4 | 1 | 5.6 | 0.7 | 0.1-5.5 |
| stromal | 23 | 69.7 | 10 | 30.3 | 4.9 | 1.9-12.7 |

**Table 3** Crude Odds analysis of pelvic node metastases among studied factors (continue)

| Factors | Pelvic lymph node status | | | | Crude Odds Ratio | 95% CI | p-value* |
|---|---|---|---|---|---|---|---|
| | negative | | positive | | | | |
| | No | % | No | % | | | |
| **Uterine serosa invasion** | | | | | | | |
| positive | 4 | 50.0 | 4 | 50.0 | 9.0 | 2.1-39.2 | 0.007* |
| negative | 171 | 90.0 | 19 | 10.0 | 1.0 | | |
| **Adnexal metastases** | | | | | | | |
| positive | 8 | 66.7 | 4 | 33.3 | 4.4 | 1.2-16.1 | 0.024* |
| negative | 171 | 90.0 | 19 | 10.0 | 1.0 | | |
| **Lympho-vascular space invasion** | | | | | | | |
| positive | 35 | 67.3 | 17 | 32.7 | 11.4 | 4.2-31.1 | 0.001* |
| negative | 141 | 95.9 | 6 | 4.1 | 1.0 | | |

* Analyzed by the Univariate logistic regression

**Table 4** Multiple logistic model

| | B | S.E. | Wald | df | Sig. | Exp(B) | 95.0% CI for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| LVSI(1) | 2.4496 | 0.5 | 22.42 | 1.0 | 0.000 | 11.6 | 4.2 | 31.9 |
| Constant | -3.1427 | 0.4 | 56.81 | 1.0 | 0.000 | 0.0 | | |

We concluded that the prevalence of pelvic lymph nodes metastases was 11.6% in our endometrial cancer patients. Only lymphovascular space invasion was found as the significant predicting factor for pelvic lymph node metastases. This factor could not be determined definitely during the operation in our institute, our current practice in routine surgical staging for endometrial cancer patients was supported.

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