

RESEARCH COMMUNICATION

Comparison between Clinical and Surgical Staging for Endometrial Cancer in Thailand

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Abstract

Objectives: To compare preoperative clinico-pathological findings and clinical staging of endometrial cancers (EMC) with postoperative surgico-pathological findings and final surgical staging. **Materials and Methods:** All EMC patients who underwent surgical staging between January 1993 and December 2008 were identified from the tumor registry of the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, of our institution. Clinico-pathological data were extracted from the patients' charts and pathological reports, including clinical stage assignments before the operation, and compared to the surgico-pathological findings. **Results:** Two hundred and thirty five EMC patients were included in this study. Mean age was 55.8±9.9 years. All except one had clinical stage I and II disease. The most common preoperative histopathology of endometrial tissue was endometrioid adenocarcinoma, with or without squamous differentiation (164 cases or 69.8%), while grade II tumors accounted for 107 cases (46.7%). Cervical involvement was evidenced from endocervical curettage in 58/235 cases (24.7%). From the final surgico-pathologic findings, the surgical stages were the same as clinical stage in 145 patients (61.7%), sixty patients (25.5%) being upstaged and 30 patients (12.8%) downstaged. Histopathology of endometrial cancer from hysterectomy was the same as for the preoperative tissues in 175 cases (74.5%), without change in preoperative grading in 155 (67.6%), upgrading in 57 (25%) and downgrading in 17 (7.4%). **Conclusion:** Clinical staging was comparable to surgical staging in approximately 61.7% and final surgical staging change was evident in 38.3%, with postoperative histopathological change in 25.5%. Preoperative endocervical curettage had false positive and false negative rates of 60.3% and 14.1% respectively. Thus clinicians should be aware of these possibilities in preoperative counseling for patients and planning surgical procedures.

Key Words: Endometrial cancer - clinical staging - surgical staging

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Introduction

In the United States, endometrial cancer (EMC) is the most common malignancy of the female genital tract (Shaeffer et al., 2005; Berek et al., 2007; Jemal et al., 2007), accounting for almost one half of all gynecologic cancers and was estimated to be the cause of female cancer deaths in 3%. In Thailand, EMC is the third most common malignancy of the female genital tract, ranking behind cervical and ovarian cancers, with an incidence rate of 2.8:100,000 women (Khuhaprema et al., 2007).

The evaluation and definite management of EMC has been standardized throughout since 1971 when the International Federation of Gynecology and Obstetrics (FIGO) introduced "clinical staging" to evaluate the status of cancer before a definite treatment. Data required for the FIGO 1971 clinical staging were: uterine size, cervical involvement by cancer, and any extrauterine clinical evidences of metastasis from the imaging studies. Because of its convenience and being practical for any gynecologic practitioners, this clinical staging had been practiced for

several years. In 1988, the FIGO then replaced the 1971 clinical staging by the surgical staging (FIGO, 1971; Creasman et al., 1987) which has been practiced as a standard staging and treatment for EMC up to present. This revision based on the obvious imprecision and inconsistency of clinical staging which did not correlate well with the surgical findings (Graham et al., 1971; Morrow et al., 1991). The FIGO surgical staging (Creasman et al., 1987; FIGO, 1989; Berek, 2007) includes complete exploration of the abdominal cavity, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and sampling evaluation of retroperitoneal lymph nodes (LN). From a surgical treatment, more volume of cancer tissue could be subjected for a thorough pathological assessment resulting in a change of tumor grading or even the tumor histopathology. Furthermore, the real extent of diseases could be evaluated. For examples, cervical tissue involvement, depth of cancer invasion into myometrium, or extrauterine including LN metastases could be accurately evaluated from the surgical specimens (Graham et al., 1971; Morrow et al., 1991).

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These prognostic factors would certainly direct to an appropriate adjuvant treatment postoperatively (Orr et al.,1998; Tang et al.,1998)

Despite the clear benefit of surgical over clinical staging, the latter is still useful in certain conditions. First example of these is the patients who are not suitable for major surgery may be offered an alternative radiation treatment prior to surgery or as a sole treatment in a clinically localized disease (Ngyen et al.,1998; Nag et al., 2000) Another example is the patients who have grade 1 adenocarcinoma without other risk factors of myometrial invasion or extrauterine metastasis would be classified as low-risk and may not require an extensive surgical staging evaluation, LN resection in particular. These patients, especially those who are remote from the gynecologic oncology service, could probably be taken care by any non-oncologic surgeon (Creasman et al.,1987; Stiner et al.,2003; Ayha et al.,1994). Another instance is among the young EMC patients who still require their fertility function that a conservative treatment might be an option providing that the EMC is in early stage by a clinical evaluation (Ramirez et al.,2004; Chiva et al.,2008). However, one must be aware of the limitations of extrapolating the accurate final pathologic results by the preoperative and intraoperative findings. This issue certainly raises the controversial criteria to decide for an exemption of a "complete surgical staging" (Creasman et al.,1987; Stiner et al.,2003; Ayha et al.,1994).

This study aimed to compare the clinical stage to the surgical stage. Data obtained preoperatively were also studied in comparison to the information revealed from the final surgical specimens from a surgical staging procedure.

Materials and Methods

The study obtained an approval from the Ethics Committee for Research involving Human Subjects of Bangkok Metropolitan Administration. We searched the tumor registry of the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, BMA Medical College and Vajira Hospital to identify patients with EMC treated at the institution between January 1993 and December 2008. Inclusion criteria were: patients with EMC who had a complete preoperative clinical evaluation in our institution, had a primary or preoperative endometrial pathological diagnosis in the Department of Anatomical Pathology of the institution, and underwent surgical staging in our institution with complete surgico-pathological reports. In the patients whose EMC were diagnosed from outside pathological laboratories, the pathological reports must have been presented upon referral and preferably with the slides for the review by our pathologist.

Preoperative clinical evaluation generally include complete blood count, blood chemistry, pelvic ultrasonography, and chest x-ray. Other diagnostic tests, such as, body fluid for cytology; computerized tomography; gastro- or colono-scopes are performed as indicated by the clinical findings. The surgical staging in our Gynecologic Oncology Unit followed the FIGO

surgical staging and generally include total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, and pelvic (PN) with or without para-aortic lymph node (PAN) resection. Exclusion criteria were patients whose medical records including the pathological reports were not available or did not have preoperative endometrial pathological evaluation, and patients who had preoperative chemotherapy or radiation therapy.

Data collected were: age of the patients, preoperative pathological findings and, endometrial histopathology and grade of tumors from endometrial sampling or fractional curettage, presence of cervical involvement from the endocervical curettage, clinical staging, surgico-histopathologic findings from the surgical staging including depth of myometrial invasion, gross intraperitoneal/ adnexal metastases, peritoneal cytology, final histopathology, tumor grades and the status of pelvic and paraaortic lymph nodes. The clinical stage of endometrial cancer was assigned according to the FIGO staging 1971 based on the preoperative clinical findings while the FIGO 1988 surgical stage was obtained from the surgico-pathological reports. Histopathologic change was defined when the endometrial histopathologic subtype from the hysterectomy specimen was different, had mixed component other than that obtained preoperatively, or when no specific subtype in the preoperative curettage was clarified or revised to specific histopathologic subtype.

Data were analyzed using SPSS statistical software, version 11.5 (SPSS, Chicago, IL). Descriptive statistics were used for demographic data and were summarized as number with percentage, mean with standard deviation, or median with range. Preoperative clinico-histopathological data and clinical staging were compared to the final histopathological and surgical staging.

Results

During the study period, 246 EMC patients were identified. Eleven patients whose ages ranged from 34-65 years underwent surgery for preoperative diagnoses of leiomyoma or adenomyosis or ovarian masses without endometrial sampling because they had no signs or symptoms suggesting endometrial lesions. Although surgical staging was also performed in these patients based on intraoperative findings, they were excluded from the study. Two hundred and thirty five patients met all inclusion criteria and were included in the study. Mean age of the patients was 55.8 + 9.9 years (range, 30-84 years). More than 2/3 of the patients (163 patients or 69.4%) were older than 50 years.

All 235 patients underwent endometrial tissue sampling: six were obtained by endometrial biopsy and 229 by fractional curettage. From these pre-operative endometrial specimens, the most common histologic subtype was endometrioid adenocarcinoma with or without squamous differentiation (164 cases or 69.8%). One of which also had clear cell carcinoma component. Eight cases (3.4%) were diagnosed as clear cell, papillary serous, mucinous carcinomas, and malignant mixed

Table 1. Comparison of Histopathology of Preoperative Uterine Tissue and Hysterectomy Specimens

	ES	S	CC	Undiff	AC	MM	VG	Total
ES	162	0	1	0	0	0	1	164
Serous	2	1	0	0	0	0	0	3
Mucinous	0	0	1	0	0	0	0	1
Clear cell	0	0	1	0	0	0	0	1
AdenoCA	46	0	1	0	15	0	1	63
MM	0	0	0	1	0	2	0	3
Total	210	1	4	1	15	2	2	235

ES, Endometrioid +/-squamous differentiation; Undiff, Undifferentiated; AC, NOS; MM, malignant mixed Mullerian tumor; VG, villoglandular

Mullerian tumors. The remaining 63 cases (26.8%) were diagnosed as adenocarcinoma without specified subtype. From the hysterectomy specimens, the endometrial histopathologic subtypes of cancer were the same as preoperative tissue in 175 cases (74.5%) while 60 cases (25.5 %) had revision of histopathology, had additional mixed component, or had more specified subtype. The majority of the endometrium from hysterectomy was also endometrioid adenocarcinoma but in a higher proportion (216 cases, 91.9%); 18 of which with squamous differentiation while six cases had other component of papillary serous, clear cell, villoglandular or undifferentiated carcinomas. Most tumors with the preoperative diagnosis of adenocarcinoma without specified subtype were finally diagnosed as endometrioid adenocarcinoma with or without squamous differentiation, clear cell, or villoglandular subtypes leaving 15 cases remained the diagnosis of non-specific adenocarcinoma while three cases with preoperative diagnosed MMMT, only one case was poorly differentiated carcinoma in final hysterectomy specimen. Detailed comparison of histopathology of preoperative uterine tissue and hysterectomy specimen is shown in Table 1.

Regarding the grade of tumors from the preoperative uterine tissues, six cases were simply diagnosed as endometrioid or no specific type adenocarcinoma without any pathologic grading. The curettage procedure in these patients was performed elsewhere outside the institution when the pathological slides were reviewed to confirm cancer diagnosis without detailed grading. From the remaining 229 cases, grade II was most commonly found (107 cases or 46.7%) while grade I and grade III tumors comprised 33.2% and 20.1% (76 and 46 cases respectively). From 235 hysterectomy specimens, grade II tumors constituted the majority of the tumors, but in a higher proportion (117/235 cases or 49.8%). Among the 229 cases with data of grading in both settings, the grade remained the same in 155 cases (67.7%) while 57 (24.9%) and 17 cases (7.4%) were up- and down- graded, respectively. Tumors grade I were upgraded to grade II or grade III tumors in 36/76 cases (47.4%) while grade II tumors were upgraded to grade III in 21/107 cases (19.6%). Only nine grade II (8.4%) and eight grade III tumors were down-graded (17.4%). Detailed comparison of grading from the uterine sampling and hysterectomy among the 229 patients who had tumor grading in both specimens is shown in Table 2.

Table 2. Comparison of Grading from the Uterine Sampling and from Hysterectomy Specimens (N=229)

Hysterectomy	Preoperative			Total
	Grade I (%)	Grade II (%)	Grade III (%)	
Grade I	40 (52.6)	33 (43.5)	3 (3.9)	76
Grade II	9 (8.4)	77 (72.0)	21 (19.6)	107
Grade III	3 (6.5)	5 (10.9)	38 (82.6)	46
Total	52	115	62	229

Note : The curettage procedure in 6 patients performed elsewhere outside the institution when the pathological slides were reviewed to confirm cancer diagnosis without detailed grading

Table 3. Endocervical Pathology from Preoperative Curettage and Hystectomy

Hysterectomy	Curettage		Total
	Involvement (%)	No involvement (%)	
Involvement	23 (40.0)	35 (60.0)	58 (24.7)
No involvement	25 (14.1)	152 (85.9)	177 (75.3)
Total	48 (20.4)	187 (79.6)	235 (100)

Involvement, cervical involvement

Table 4. Comparison of Preoperative Clinical Stage and Surgical Stage

	Clinical				Total
	I	II	III	IV	
Surgical I	131	15	31	0	177
II	30	13	14	0	57
IV	0	0	0	1	1
Total	161	28	45	1	235

Endocervical curettage was also performed preoperatively in all 235 patients as an additional procedure to endometrial biopsy (six patients) or as a part of fractional curettage (229 patients). Positive cancer tissue was evidenced in 58 cases (57 clinical stage II and one clinical stage IV) and were negative in 177 cases. Comparing to the hysterectomy specimens, the preoperative endocervical diagnoses were correct in 175 cases (74.5%). Only 23/58 cases (39.7%) of the positive preoperative endocervical curettage truly had cervical involvement leaving 35 cases (60.3%) having false positive diagnosis. On the other hand, 25/177 patients (14.1%) whose endocervices were actually involved by cancer in the hysterectomy were not detected from the curettage (false negative). The results of endocervical pathology from preoperative curettage and hysterectomy are shown in Table 3.

Comparison of clinical and surgical stages are shown in Table 4. From 235 patients, 177 patients (75.3%) had clinical stage I while 57/58 patients with endocervical involvement were diagnosed as clinical stage II. Another patient who also had positive endocervical curettage had stage IV disease from the pulmonary metastasis evidenced from chest x-ray. After surgical staging, 145/235 (61.7%) had the same surgical as clinical stages. Sixty patients (25.5%) had diseases upstaged surgically while 30 patients (12.8%) had down-stage diseases. Among 177 patients who were evaluated as clinical stage I, 131 patients (74.0%) also had surgical stage I while 46 patients (26.0%) were surgically upstaged. From the 57 patients with

Table 5. Comparison of Clinical/Surgical Staging with Sites of Extrauterine Invasion/Metastasis (N=235)

	Invasion/Metastasis				Total
	None	Extrauterine	Lymph node	Cervix	
Stage I	131 (74.0)	7 (4.0)	24 (13.6)	15 (8.4)	177
II	30 (52.6)	4 (7.0)	10 (17.5)	13 (22.8)	57
IV			1 (100)		1
Total	161 (68.5)	12 (5.1)	34 (14.5)	28 (11.9)	235

Note: Clinical stage IV had extrauterine invasion include lymph node metastasis and cervical involvement; % data in parentheses

clinical stage II, only 13 patients had a confirmed diagnosis of surgical stage II with endocervical invasion by cancer while 14 patients (24.6%) were upstaged to stage III disease. All the down-stage cases were the 30 stage II patients (52.6%) who had had positive endocervical curettage but did not have endocervical involvement from the hysterectomy specimen and who were finally surgical stage I.

Extrauterine cancer spread evidenced from the operative findings in 46/235 patients (19.6%), including 45 clinical stages I-II and one stage IV diseases. The sites of extrauterine involvement were: positive peritoneal cytology only (two patients), adnexa +/- uterine serosa involvement +/- intra-abdominal tumor spread (11 patients), or retroperitoneal LN metastasis (35 patients: 5/35 also had adnexa or vaginal cancer invasion). Thirty-one (17.5%) of 177 patients with clinical stage I, and 14 (24.5%) of 57 patients with clinical stage II had extrauterine spread of cancer.

All 235 patients underwent PN resection while 189 (80.4 %) also had additional paraaortic lymph nodes sampling. Median number of LN obtained was 30 nodes (range, 1-60 nodes). Out of 35 patients with lymph nodes metastases, 24 had clinical stage I, 10 had stage II, and the only patient who had stage IV disease from pulmonary metastasis detected preoperatively. Eleven (31.4%) patients had both pelvic and paraaortic lymph nodes involvement while 20 (57.2%) had only pelvic lymph nodes metastasis. Isolated paraaortic lymph nodes metastases were evidenced in four patients (11.4%). Focusing to the 177 patients who had clinical stage I, 24 (13.6%) had positive lymph nodes; 20 of them had only positive lymph nodes without evidence of other uterine metastasis and five of whom had only grade I tumor from preoperative uterine curettage (2/5 also had confirmed grade I from hysterectomy). Only 10/57 clinical stage II patients had positive lymph nodes; one of them had grade I tumor from curettage tissue (but later was revealed as grade II tumor from final pathology). The sites of extrauterine invasion/ metastasis in all 235 patients are shown in Table 5.

Discussion

Our study showed that clinical evaluation of EMC is not as accurate as the findings from the surgical staging in terms of histology, tumor grading, endocervical involvement and extent of diseases leading to a considerable difference between clinical and surgical staging.

Regarding the tumor histology, we found that 25.5% had histopathologic changes. This figure was less than the other studies which reported the revision of histopathology in 27–50% (14 Cowles, 29 Campbell). This change may be due to tissue limitation which represented only a small focus of endometrium obtained by curettage. The clinical significance of the difference is when the more aggressive histology, which requires extensive or complete surgical staging, is revealed. Of note, among our 26 cases with additional mixed component of histopathology, more aggressive histology (clear cell, papillary serous, undifferentiated tumor) were revealed in six cases.

Overall tumor grades changes were found in 32.4% of our patients, 25% of them were the up grading. Our findings were in the range as those reported from the other studies, 30 %-40% (Cowles et al.,1985; Campbell et al.,1998; Daniel et al.,1998; Lason et al.,1995; Eltabbakh et al.,2005), especially the upgrading of tumors which were found in 18%-29%. However, our study found lower percentages of down grading tumor than the others, 7.4% compared to 14.5-17.8% respectively (Cowles et al.,1985; Lason et al.,1995; Campbell et al.,1998; Daniel et al.,1998).

The important clinical concern of grade change is probably more of the upgrading because this may lead to a different surgical approach. Although the surgical FIGO staging required lymph nodes sampling as a part of the surgical procedures, many authors found that grade I tumor which appeared limit to the endometrium had negligible risk of lymph nodes involvement and the procedure of lymph nodes sampling may be exempted to avoid the morbidity and mortality form lymphdenectomy (Creasman et al., 1987; Takeshima et al.,1996; Mariani et al.,2000; Zuurendonk et al.,2006). If this approach relied on the preoperative pathological grade finding, the 5/68 (7.4%) patients with clinical stage I and tumor grade I, who may be omitted from lymph nodes resection, virtually had lymph nodes metastasis and would be understaged.

Finding of endocervical involvement by EMC preoperatively is a risk factor of extrauterine involvement and is an indication for a complete surgical staging of lymph nodes resection (Bijen et al.,2009). Furthermore, positive endocervical involvement by cancer may provide an alternative option of surgical procedures. Simple hysterectomy followed by adjuvant radiation therapy could still be performed in the clinical stage II disease. However, some surgeons preferred the radical hysterectomy followed by adjuvant radiation therapy if indicated based on data from previous reports that this approach significantly improved 5-year disease-free survival rate compared to the simple hysterectomy with adjuvant radiation therapy: 73– 94 % VS 68- 82.8% (Conelison et al.,1999; Mariani et al.,2000; Cohn et al.,2007).

However, the true incidence of cervical involvement could not be accurately predicted by curettage. Our study found 14.1 % false negative rates of endocervical involvement. This finding might mislead to the understaging procedure. On the other hand, we found 60.3% false positive rate which was in the range of 13-62% reported by several authors (Cowles et al.,1985;

Ayhan et al.,1994, Leminen et al.,1995). This incidence might have led to unnecessary extensive surgical procedure of radical hysterectomy or lymph nodes resection. Only one study reported a very high false positive rate of 92% (Campbell et al.,1998). One obvious reason for the false positive findings of malignant cells in endocervical tissue is contamination during the curettage procedure or the pathological specimen submission.

Another possibility which may affect the false positive rate is the pathological interpretation based on the type of endocervical involvement. Some pathologists may strictly define the endocervical involvement when the cancer is really evidenced in the cervical stroma while the others would report this incidence when the malignant tissue is only present in the endocervical portion of the specimens submitted. Thus, the surgeon should be cautious about these pitfalls to prevent an inappropriate surgical treatment. Pathological slide review with a detailed discussion with the pathologist of the institution including intraoperative evaluation of the lesion should be emphasized.

In a subset of patients with clinical stage I, 26% had extrauterine metastasis which was higher than the other studies which reported this incidence ranging from 19-22% (Chen et al.,1985; Creasman et al.,1987). The differences among studies may lie on the prevalences of other prognostic risk factors, such as, tumor grade or depth of tumor invasion which in turn were related to extrauterine disease (Creasman et al.,1987). Focusing on the incidence of only lymph nodes metastasis in clinical stage I disease, our figure of 13.6% was in the range of 4.6-18.7% reported from the others studies (Morrow et al.,1991; Lampe et al.,1994; Kamura et al.,1999; Zuurendonk et al., 2006; Chi et al., 2008). The 5.6 % incidence of isolated paraaortic nodes metastasis in clinical stage I patients in our study was also similar to those reported from the others, 5-8.5% (Creasman et al.,1987; Hirahatake et al.,1997).

In another subset of patients with clinical stage II, 26.3% had extrauterine metastasis which was comparable to the findings from other studies, 20-40% (Chen et al.,1985; Leminen et al.,1995; Orr et al., 1998). However, the incidence of pelvic or paraaortic LN metastases in our study was lower than others, 17.5 % compared to 31.0-35.0% (Morrow et al.,1991; Kamura, et al.,1999) and 7.0% compared to 15.7% (Hirahatake et al.,1997), respectively. Aside from the variation in the presence of other prognostic risk factors which affected the incidence of LN metastasis in early clinical stage, the difference in these studies might also lie on the techniques in each institution to perform LN resection, such as, the extent or concern about the number of LN obtained.

The accuracy of clinical stage comparing to the final surgical stage in our study was nearly 2/3 of the cases. Overall stage change of approximately 38% in our study was close to 20-51% as having been reported by the others (Cowles et al.,1985; Ayhan et al.,1994; Leminen et al.,1995). We found that approximately 25% of the patients who were in apparent clinical stage I and II turned out to be in stage III from various findings of extrauterine or lymph nodes metastasis. To emphasize on the incidence

of lymph nodes metastasis, 13.6% of clinical stage I and 17.5% of stage II were upstaged to surgical stage IIIc from isolated lymph nodes metastasis without any other extrauterine risk factors. Aside from total abdominal hysterectomy and bilateral salpingo-oophorectomy, several authors emphasized on the meticulous exploration of abdominal cavity including biopsy of any suspicious areas and sampling evaluation of retroperitoneal lymph nodes (both pelvic and paraaortic nodes) in patients with clinical stage I and II EMC (Morrow et al.,1991; Hirahatake et al.,1997).

The physician should be aware of the limitation of clinical staging for endometrial cancer when the complete surgical staging is to be avoided. Through counseling with the patients for these possibilities must be conducted before any conservative treatment is attempted or when the endometrial cancer patients are under the care of the general gynecologist.

In conclusion, clinical staging was comparable to surgical staging in approximately 61.7% of cases and final surgical staging change was 38.3% while postoperative histopathological change was 25.5%. The tumor grading was 25% upgraded and 7.4% downgraded. Preoperative endocervical curettage had false positive and false negative 60.3% and 14.1% respectively. Thus clinicians should be aware of these possibilities for a preoperative counseling with the patients and the plan of a surgical procedure.

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