ABSTRACT

Objective: The aim of this study was to determine treatment response, the recurrence rate, 3-year overall survival, 3-year recurrence-free survival, and associated prognostic factors for survival among advanced-stage endometrial carcinoma patients at Siriraj Hospital.

Methods: This study was conducted at the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University Bangkok, Thailand. A total of 415 patients that were diagnosed with advanced-stage endometrial carcinoma during January 1998 to December 2014 were enrolled. Data retrieved from medical records included baseline characteristics, surgico-pathological reports, treatment protocol, follow-up data, treatment response, and recurrence status. Three-year survival and recurrence-free survival were estimated by Kaplan-Meier method. Various factors were analyzed for significant association with survival.

Results: Four hundred of 415 cases were included in the final analysis. There were 282 (70.5%) and 118 (29.5%) patients that were diagnosed with stage III and IV disease, respectively. Two hundred and eighty-two patients had complete response after primary treatment, and 94 (33.3%) patients had disease recurrence. The median follow-up and survival times were 24.5 and 42.5 months, respectively. The 3-year survival rate was 50%, and the median recurrence-free interval was 12.25 months. Multivariate analysis revealed high-grade tumor histology, lymph node metastasis, Eastern Cooperative Oncology Group (ECOG) performance status, and menopausal status to be significant prognostic factors for overall survival.

Conclusion: Median survival among patients with advanced-stage endometrial carcinoma after primary treatment was 3 years. The significant prognostic factors were high grade tumor histology, lymph node metastasis, ECOG performance status, and menopausal status.

Keywords: Advanced stage; endometrial carcinoma; prognostic factor; recurrence; survival (Siriraj Med J 2020; 72: 117-124)
estrogen related, is more common than type II which is non-endometrioid or non-estrogen related. Type I usually occurs in younger age or perimenopausal women with a history of exposure to unopposed estrogen and it is associated with endometrial hyperplasia or endometrial intraepithelial neoplasia (EIN). Type II occurs in women without estrogen stimulation, and may arise in a background of atrophic endometrium. Type II endometrial carcinoma tends to occur in older, thin, postmenopausal women and it is associated with a poorer prognosis.1,3

The stage of cancer depended on surgicopathological staging according to International Federation of Gynecology and Obstetrics (FIGO) staging system. Approximately 75–80% of women with endometrial carcinoma were diagnosed at early stage and had excellent treatment outcomes.1 Conversely, advanced-stage patients (stage III–IV) who were diagnosed with extraterine diseases had poor prognosis and worse treatment outcomes.4

Surgery is the primary treatment for endometrial carcinoma patients. Many studies in Europe and America investigated the use of adjuvant chemotherapy and/or radiation therapy to improve the survival of patients with advanced-stage diseases. The overall survival time among advanced-stage patients is about 12–15 months.4–6 Alvaro, et al. reported histologic subtype, age, myometrial involvement, lympho-vascular space invasion, lymph node metastasis and residual tumor after surgery to be significantly associated with treatment outcomes in endometrial carcinoma.7

The objective of this study was to determine treatment response, the disease recurrence rate, 3-year overall survival, 3-year recurrence-free survival, and associated prognostic factors for survival among advanced-stage endometrial carcinoma patients at Siriraj Hospital – Thailand’s largest national tertiary referral center regardless of modality of adjuvant treatment which was generally required in advanced-stage cancer. This was the database of Division of Gynecologic Oncology, Siriraj Hospital and use to be the data for counselling patients in this group.

MATERIALS AND METHODS

This retrospective study was conducted at the Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, Faculty of Medicine Siriraj Hospital. The protocol for this study was approved by Siriraj Institutional Review Board (Si 439/2017).

Endometrial cancer patients who were treated during January 1998 to December 2014, and who had surgically and/or clinically confirmed FIGO stage III–IV endometrial cancer based on FIGO 2009 system7 were included. Patients who were treated before 2009 were restaged, and patients with previously diagnosed stage IIIA from positive cancer cells in peritoneal fluid alone were excluded from the study.

At our center, the standard operation included peritoneal washing for cytology and total hysterectomy with bilateral salpingo-oophorectomy. Among patients considered at-risk for extraterine disease, such as high-grade tumor, large tumor volume, deep myometrial invasion or non-endometrioid subtype, pelvic and/or paraaortic lymphadenectomy or sampling was required. All of the preceding operative procedures were performed by gynecologic oncologists.

Response criteria was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Complete Response (CR) means disappearance of all known lesion(s). Partial Response (PR) means at least 30% decrease in the sum of diameters of known lesions, Progressive Disease (PD) means at least 20% increase in the sum of diameters of known lesions and/or the appearance of new lesion(s). Stable Disease (SD) means neither shrinkage nor increase to qualify for PR nor PD.9 Patients that were previously evaluated for treatment response by World Health Organization (WHO) criteria or RECIST guideline version 1.0 were reevaluated using the current RECIST guideline version 1.1.

Follow-up data that was collected after complete treatment included careful history taking, and pelvic and physical examinations by gynecologic oncologist every 3 to 4 months for the first 2 years after treatment, every 6 months for the next 3 years and every year thereafter. Imaging study was performed when indicated. Recurrence of disease was defined as evidence of measurable disease and/or pathology/cytology confirmation.9 The sites of recurrence were classified as local (intra-pelvic region), distant (extra-pelvic region) or both.

Sample size calculation

The sample size for this study was calculated based on the previously reported estimated 12 percent rate of advanced-stage among patients with endometrial carcinoma.9 At least 451 patients were required to achieve 95% confidence level with a type I error at 0.05. Overall survival (OS) was defined as the time between the first date of primary treatment and the date of death from any cause or the last follow-up. Recurrence-free survival (RFS) was defined by the last date of primary treatment to the date of confirmed disease recurrence. This study did not separately analyzed the data of patients who had initially stable or progressive diseases, or the data of patients that received other alternative or second-
line treatments. These should, therefore, be considered possible confounding factors.

**Statistical analysis**

Descriptive statistics were used to assess and summarize patient baseline characteristics, surgical data, histopathology, treatment details, response status and recurrence status. Categorical data are shown as number and percentage, and continuous data are presented as mean plus/minus standard deviation. Duration of follow-up was defined as the date of last treatment to the date of death or last follow-up. OS and RFS were each estimated using the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard models were used to identify any statistically significant prognostic factors. Associations are reported as hazard ratios (HRs) and 95% confidence interval (CIs). P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics version 16 (SPSS, Inc., Chicago, IL, USA).

**RESULTS**

During January 1998 to December 2014, the incidence of endometrial cancer at our center was 1,456 cases, and 415 (28.5%) of those were diagnosed with advanced-stage (stage III/IV) endometrial carcinoma. Fifteen of 415 patients that had incomplete data and/or incorrect staging were excluded. The remaining 400 patients were included in our final analysis.

The mean age and body mass index (BMI) of patients in this study was 58.5 years and 25.4 kg/m², respectively. Three-quarters of cases were menopause at the time of diagnosis. Most patients presented with abnormal vaginal bleeding and had good performance status. Eighty-seven percent of cases (348/400) underwent primary surgery. Most (334/348) of those operations were performed via laparotomic approach. During surgery, 268 and 155 of 334 cases received pelvic and paraaortic nodal evaluation, respectively. Complete removal of disease was achieved in 270 of 348 cases that underwent primary surgery. The most common histologic subtype was endometrioid carcinoma (246/400, 61.5%). Fifty-four percent of cases had high-grade (grade 3) tumor histology. There were 282 (70.5%) and 118 (29.5%) cases that were diagnosed with stage III and IV disease at first diagnosis, respectively. Demographic, clinical, surgical and pathological characteristics of patients are shown in Table 1.

After complete primary treatment, complete response, partial response, stable disease and progression of disease was observed in 282 (70.5%), 7 (1.8%), 25 (6.2%) and 86 (21.5%) cases, respectively. Details relating to second-line or alternative treatment were not included in this study.

The median follow-up time was 24.5 months (interquartile range [IQR]: 3.3-53.1), and one-third (94/282) of complete response patients had disease recurrence. The median recurrence-free interval was 12.25 months (range: 0.99-80.49). The patterns of recurrence were intra-pelvis, extra-pelvis and both in 31.9% (30/94), 48.9% (46/94) and 19.2% (18/94) of patients, respectively. The 3-year recurrence-free survival (RFS) rate was 67%, the 3-year overall survival (OS) rate was 50%, and the median survival time was 42.5 months (range: 10.1-75.0). Fig 1 shows Kaplan-Meier survival analysis compared between stage III disease with stage IV disease.

Univariate analysis for factors significantly associated with OS and RFS is shown in Table 2. The factors significantly associated with OS included age, postmenopause status, performance status, residual tumor after primary surgery, non-endometrioid histologic subtype, tumor grading, FIGO staging, deep myometrial invasion, lymphovascular space invasion, positive peritoneal cytology, lymph node metastasis, extra-pelvic metastasis, receiving adjuvant treatment and initial treatment response. The factors significantly associated with RFS were age, postmenopause, non-endometrioid histologic subtype, tumor grading, FIGO stage IVB, deep myometrial invasion and extra-pelvic metastasis.

Multivariate analysis showed grade 3 tumor, lymph node metastasis, ECOG performance status and postmenopausal status to be significant prognostic factors for OS with adjusted hazard ratios (HRs ) of 17.0 (95% confidence interval [CI]: 3.1-92.1), 8.5 (95% CI: 2.1-34.4), 7.8 (95% CI: 1.5-40.2), and 6.9 (95% CI: 2.3-20.2), respectively. Extra-pelvic metastasis, grade 3 tumor and age were significant factors for RFS with adjusted HRs of 10.4 (95% CI: 4.5-26.9), 9.5 (95% CI: 2.0-44.7), and 1.1 (95% CI: 1.0-1.1), respectively (Table 3).

**DISCUSSION**

The incidence rate of advanced stage (stage III, IV) endometrial carcinoma in this study was 28.5%, which is higher than the rates reported from previous studies. The incidence rate of advanced-stage endometrial carcinoma was 12% in a Taiwanese study, and 8.7% in a study by Alvaro, et al. This difference in rates between our study and the aforementioned two studies can be explained by the fact that three-quarters of the patients in our study were menopause with a high proportion of high-grade tumor histology and non-endometrioid (non-estrogen-related) subtype, which has an aggressive
### TABLE 1. Demographic and clinical characteristics of enrolled patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean±SD</strong></td>
<td>58.5±9.9</td>
</tr>
<tr>
<td><strong>Presenting symptom, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal vaginal bleeding</td>
<td>344 (86.0%)</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>17 (4.2%)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>13 (3.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (6.5%)</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
</tr>
<tr>
<td>Premenopause</td>
<td>101 (25.2%)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>299 (74.8%)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>240 (60.0%)</td>
</tr>
<tr>
<td>1</td>
<td>122 (30.5%)</td>
</tr>
<tr>
<td>2</td>
<td>24 (6.0%)</td>
</tr>
<tr>
<td>3</td>
<td>14 (3.5%)</td>
</tr>
<tr>
<td><strong>Primary surgery, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52 (13.0%)</td>
</tr>
<tr>
<td>Yes</td>
<td>348 (87.0%)</td>
</tr>
<tr>
<td><strong>Residual tumor, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>270 (67.5%)</td>
</tr>
<tr>
<td>≤1 cm</td>
<td>24 (6.0%)</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>54 (13.5%)</td>
</tr>
<tr>
<td><strong>FIGO stage (2009), n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>94 (23.5%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>34 (8.5%)</td>
</tr>
<tr>
<td>IIIC1</td>
<td>103 (25.8%)</td>
</tr>
<tr>
<td>IIIC2</td>
<td>51 (12.8%)</td>
</tr>
<tr>
<td>IVA</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>IVB</td>
<td>113 (28.2%)</td>
</tr>
<tr>
<td><strong>Histology, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>246 (61.5%)</td>
</tr>
<tr>
<td>Non-endometrioid</td>
<td>154 (38.5%)</td>
</tr>
<tr>
<td><strong>Tumor grade, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>65 (16.2%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>119 (29.8%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>216 (54.0%)</td>
</tr>
<tr>
<td><strong>Peritoneal cytology, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Negative for malignancy</td>
<td>214 (53.5%)</td>
</tr>
<tr>
<td>Positive for malignancy</td>
<td>73 (18.2%)</td>
</tr>
<tr>
<td><strong>Lymph node metastasis, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Negativity</td>
<td>94 (23.5%)</td>
</tr>
<tr>
<td>Only pelvic LN metastasis</td>
<td>116 (29.0%)</td>
</tr>
<tr>
<td>Only PAN metastasis</td>
<td>18 (4.5%)</td>
</tr>
<tr>
<td>Both pelvic LN and PAN metastases</td>
<td>45 (11.2%)</td>
</tr>
<tr>
<td><strong>Adjuvant therapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>49 (12.2%)</td>
</tr>
<tr>
<td>CT alone</td>
<td>188 (47.0%)</td>
</tr>
<tr>
<td>RT alone</td>
<td>79 (19.8%)</td>
</tr>
<tr>
<td>Combined RT and CT</td>
<td>84 (21.0%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; pelvic LN = bilateral pelvic lymph node; PAN = paraaortic lymph node; CT = chemotherapy; RT = radiation therapy
### TABLE 2. Univariate analysis for prognostic factors of overall survival and recurrence-free survival.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Overall survival</th>
<th></th>
<th></th>
<th>Recurrence-free survival</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>&lt;P-value&gt;</td>
<td></td>
<td>HR (95% CI)</td>
<td>&lt;P-value&gt;</td>
</tr>
<tr>
<td>Age</td>
<td>1.039 (1.022-1.057)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>1.041 (1.019-1.063)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>2.595 (1.000-3.962)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>2.160 (1.290-3.618)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>ECOG status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 0</td>
<td>1</td>
<td></td>
<td></td>
<td>1.316 (0.846-2.048)</td>
<td>0.223</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>1.677 (1.169-2.404)</td>
<td><strong>0.005</strong></td>
<td></td>
<td>1.287 (0.403-4.111)</td>
<td>0.670</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>5.312 (3.166-8.913)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ECOG 3</td>
<td>9.948 (5.387-18.370)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Residual tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 cm</td>
<td>3.565 (2.076-6.121)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>2.371 (1.141-4.927)</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>3.819 (2.531-5.763)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>0.793 (0.344-1.824)</td>
<td>0.585</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1</td>
<td></td>
<td></td>
<td>3.622 (2.191-5.886)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Serous</td>
<td>3.542 (2.409-5.206)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>1.535 (0.477-4.942)</td>
<td>0.472</td>
</tr>
<tr>
<td>Clear cell</td>
<td>2.629 (1.261-5.481)</td>
<td><strong>0.010</strong></td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Serous</td>
<td>9.356 (1.279-68.438)</td>
<td><strong>0.028</strong></td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Poorly-differentiated cell</td>
<td>6.902 (3.952-12.053)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>6.214 (2.427-15.908)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Mixed</td>
<td>2.127 (1.261-3.587)</td>
<td><strong>0.005</strong></td>
<td></td>
<td>2.964 (1.623-5.413)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>3.565 (2.076-6.121)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>2.371 (1.141-4.927)</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>9.948 (5.387-18.370)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>19.279 (4.561-81.498)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Tumor grading</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2.038 (1.006-4.127)</td>
<td><strong>0.048</strong></td>
<td></td>
<td>2.636 (0.994-6.992)</td>
<td>0.051</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6.112 (3.189-11.714)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>8.371 (3.365-20.824)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>FIGO staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>1</td>
<td></td>
<td></td>
<td>3.622 (2.191-5.886)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>2.821 (1.377-5.777)</td>
<td><strong>0.005</strong></td>
<td></td>
<td>0.357 (0.084-1.513)</td>
<td>0.162</td>
</tr>
<tr>
<td>Stage IIIC1</td>
<td>1.803 (1.024-3.173)</td>
<td><strong>0.041</strong></td>
<td></td>
<td>1.156 (0.656-2.038)</td>
<td>0.616</td>
</tr>
<tr>
<td>Stage IIIC2</td>
<td>2.621 (1.427-4.816)</td>
<td><strong>0.002</strong></td>
<td></td>
<td>1.642 (0.872-3.094)</td>
<td>0.125</td>
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<tr>
<td>Stage IVA</td>
<td>16.762 (4.914-57.174)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Stage IVB</td>
<td>6.527 (3.945-10.800)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>2.606 (1.500-4.525)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1/2</td>
<td>2.261 (1.502-3.405)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>1.712 (1.009-2.904)</td>
<td><strong>0.046</strong></td>
</tr>
<tr>
<td>&gt;1/2</td>
<td>2.621 (1.391-3.555)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>1.228 (0.755-1.997)</td>
<td>0.408</td>
</tr>
<tr>
<td>Peritoneal cytology positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for malignancy</td>
<td>1.806 (1.104-2.953)</td>
<td><strong>0.018</strong></td>
<td></td>
<td>1.504 (0.883-2.564)</td>
<td>0.133</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic LN positive alone</td>
<td>0.799 (0.421-1.518)</td>
<td>0.494</td>
<td>0.510 (0.232-1.120)</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>Pelvic LN positive alone</td>
<td>5.011 (1.678-14.963)</td>
<td><strong>0.004</strong></td>
<td></td>
<td>1.041 (0.294-3.693)</td>
<td>0.950</td>
</tr>
<tr>
<td>Both Pelvic and PAN</td>
<td>3.498 (1.964-6.227)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>1.955 (1.007-3.796)</td>
<td><strong>0.048</strong></td>
</tr>
<tr>
<td>Extrapelvic metastasis</td>
<td>3.863 (2.787-5.355)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td>2.365 (1.516-3.688)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td></td>
<td></td>
<td>1.034 (0.419-2.549)</td>
<td>0.942</td>
</tr>
<tr>
<td>Partial response</td>
<td>3.476 (1.263-9.564)</td>
<td><strong>0.016</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>9.410 (5.287-16.749)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12.326 (8.443-17.994)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A p-value<0.05 indicates statistical significance

**Abbreviations:** HR = hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; pelvic LN = bilateral pelvic lymph node; PAN = paraaortic lymph node
TABLE 3. Multivariate analysis for prognostic factors of overall survival and recurrence-free survival.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Overall survival</th>
<th>Recurrence-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.962 (0.908-1.020)</td>
<td>0.195</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>6.874 (2.343-20.168)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>ECOG status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ECOG 1</td>
<td>0.405 (0.165-0.998)</td>
<td>0.050</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>7.845 (1.533-40.129)</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>ECOG 3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Residual tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≤1 cm</td>
<td>4.054 (0.786-20.909)</td>
<td>0.094</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>2.573 (0.823-8.049)</td>
<td>0.104</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>0.711 (0.277-1.829)</td>
<td>0.480</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1.883 (0.436-8.134)</td>
<td>0.396</td>
</tr>
<tr>
<td>Mucinous</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Poorly-differentiated</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mixed</td>
<td>2.154 (0.685-6.773)</td>
<td>0.189</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>2.904 (0.316-26.662)</td>
<td>0.346</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>0.051 (0.005-0.556)</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>Tumor grading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>2.765 (0.495-15.453)</td>
<td>0.247</td>
</tr>
<tr>
<td>Grade 3</td>
<td>17.018 (3.143-92.135)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>FIGO staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>4.866 (0.001-7.439)</td>
<td>0.884</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1/2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;1/2</td>
<td>0.950 (0.372-2.429)</td>
<td>0.915</td>
</tr>
<tr>
<td>LVSI</td>
<td>1.467 (0.658-3.272)</td>
<td>0.349</td>
</tr>
<tr>
<td>Peritoneal cytology positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for malignancy</td>
<td>0.957 (0.375-2.443)</td>
<td>0.927</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>8.496 (2.100-34.363)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>PAN positive alone</td>
<td>4.561 (1.665-12.499)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Both pelvic and PAN</td>
<td>4.337 (1.838-10.233)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Extrapelvic metastasis</td>
<td>0.001 (0.000-3.942)</td>
<td>0.912</td>
</tr>
</tbody>
</table>

A p-value<0.05 indicates statistical significance

**Abbreviations:** HR = hazard ratio; CI = confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; pelvic LN = bilateral pelvic lymph node; PAN, paraaortic lymph node
nature. The combination of these factors increased the number of patients with advanced-stage disease.

The age group that had the most advanced-stage endometrial cancer from Surveillance, Epidemiology and End Results (SEER) data was 55–64 years, and this is similar to the mean age at first diagnosis of 58.5 years in our study. Abnormal vaginal bleeding was the most common presentation. Although they were diagnosed with advanced stage, most of the patients in our study had good performance status (ECOG 0-1) at diagnosis, so we could not predict the severity of disease by patient performance or clinical symptoms. The most common histologic subtype was endometrioid subtype, but the proportions of non-endometrioid subtype and high-grade tumor differentiation were both higher when compared to the proportions previously reported for all stages of endometrial carcinoma.

These differences in findings may be attributable to difference among races, as suggested by Koshiyama, et al. That group found different histologic subtypes of epithelial ovarian cancer among different nationalities.

The 3-year OS of advanced-stage endometrial cancer in this study was 50%. This is similar to the 48.8% rate reported by Alvaro, et al., but it is lower than the rate reported from a Taiwanese study that included only endometrioid subtype. Our result showed that patient survival decreased rapidly when they did not achieve complete response after primary treatment. Approximately seventy percent of had evidence of extra-pelvic recurrence, which is consistent with hematogenous spreading in advanced-stage cancer. Systemic adjuvant therapy should, therefore, be considered in advanced-stage endometrial carcinoma even though the survival benefit of adjuvant treatment is inconclusive and still being debated.

Univariate analysis showed multiple factors affected OS and RFS in advanced-stage endometrial carcinoma. Subsequent multivariate analysis revealed the most significant prognostic factors for OS to be grade 3 tumor (similar to previous studies), lymph node metastasis, ECOG performance status and postmenopausal status. Extra-pelvic metastasis, tumor grading and age were significant prognostic factors for RFS.

Limitations

This study has some mentionable limitations. First, the total number of enrolled cases in this study was smaller than the calculated sample size, which means that our study may have lacked the statistical power needed to identify all significant associations and differences. However, the incidence rate of advanced-stage endometrial cancer in this study was higher than the rates reported from previous studies. Moreover, our sample size was larger than the sample size from any other single-center study reported from Thailand. However, this can be improved the accuracy and reliability of the results by multicenter study. Secondly, this study did not separately analyzed data from patients who had initially stable or progressive diseases, or from patients received other alternative or second-line treatment, and both of these factors could affect patient survival. Lastly, the retrospective, non-randomized nature of data collection resulted in some incomplete information.

In conclusion, the results of this study revealed a rate of advanced-stage endometrial cancer at first diagnosis of 28.5%. Seventy percent of patients had complete response after primary treatment. The 3-year recurrence free survival (RFS) rate was 67%, and about half of patients succumbed to their disease within 3 years after primary treatment.
treatment. The significant prognostic factors for overall survival were grade 3 tumor, lymph node metastasis, ECOG performance status and postmenopausal status.

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REFERENCES