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Treatments and Outcomes of Endometrial Cancers in Srinagarind Hospital

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ABSTRACT

Objectives: Endometrial cancer was the second most common gynecologic cancer. Despite many standard guidelines, variation of management could still occur. This study was done with the objectives to compare treatments in real-life practice to standard guidelines and oncologic outcomes to quality indicators.

Materials and Methods: This retrospective descriptive analytical study was conducted in 316 endometrial cancer patients registered at Srinagarind Hospital, Khon Kaen University, during 2016-2020. Forty-three patients were excluded and 273 were analyzed. Surgical and adjuvant treatments were compared to standard guidelines. Oncological outcomes were compared to quality indicators. Prognostic factors were also analyzed.

Results: Total hysterectomy with bilateral salpingo-oophorectomies was mostly done in all women (96.3%) and some of them were done via minimal invasive surgery (7.3%). Omentectomies were done in 75.1% and all were negative. Bilateral pelvic node dissection or sampling was done in 51.6%, while 84.9% that should be done in group of those were not. About two-thirds (64.5%) of patients received adjuvant therapies, which 91.5% of their waiting time was within 60 days after surgeries. external beam radiation therapy (EBRT) was done via three-dimensional technique 100%. Over- and under-treatment were found in 16.5% (95% confidence interval (CI) 10.9-22.0) and 19.9% (95%CI 13.9-25.8) of all adjuvant therapies. There was no death within 30 days after surgeries. Three-years overall survival (OS) and recurrence-free survival (RFS) rates were 93.4% and 94.9%, respectively. Significant prognostic factors for both kinds of survivals were stage and residual lesion.

Conclusion: Over- and under-treatment of adjuvant therapy were found in 16.5% and 19.9%, respectively. Oncologic outcomes were good and comparable with others' despite of low lymphadenectomy rate. However, according to the quality indicators, we had to increase our

minimal invasive surgery rate.

Keywords: treatments, outcomes, endometrial cancers, quality indicators.

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วิธีและผลการรักษาของโรคมะเร็งเยื่อบุโพรงมดลูกในโรงพยาบาลศรีนครินทร์

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บทคัดย่อ

วัตถุประสงค์*: โรคมะเร็งเยื่อบุโพรงมดลูก พบได้บ่อยเป็นอันดับสองของโรคมะเร็งทางนรีเวช แม้จะมีแนวทางการรักษามาตรฐานอยู่แล้วหลายฉบับ การรักษาที่แตกต่างออกไปจากแนวทางมาตรฐานก็ยังคงมีได้ การศึกษานี้จึงทำขึ้นโดยมีวัตถุประสงค์เพื่อเปรียบเทียบวิธีการรักษา ที่เกิดขึ้นในชีวิตจริงกับแนวทางการรักษามาตรฐาน และผลของการรักษามะเร็งชนิดนี้กับดัชนีชี้วัดคุณภาพ*

วัสดุและวิธีการ*: การศึกษาแบบเก็บข้อมูลย้อนหลังเชิงพรรณนาวิเคราะห์นี้ ได้ทำในผู้ป่วยโรคมะเร็งเยื่อบุโพรงมดลูก 316 รายที่ได้รับการวินิจฉัยและรักษาในโรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น ระหว่างปี ค.ศ. 2016-2020 คัดผู้ป่วยออก 43 ราย ตามเกณฑ์ แล้วเหลือเพียง 273 ในการวิเคราะห์ ผู้วิจัยได้เปรียบเทียบวิธีการรักษา ทั้งด้วยการผ่าตัดและการเสริมด้วยรังสีรักษาหรือเคมีบำบัด กับแนวทางมาตรฐาน และเปรียบเทียบผลการรักษา กับดัชนีชี้วัดคุณภาพ รวมไปถึงการวิเคราะห์หาปัจจัยการพยากรณ์โรคที่เกี่ยวข้อง*

ผลการศึกษา*: มีการผ่าตัดเอามดลูกและปีกมดลูกออกทั้งหมดในผู้ป่วยส่วนใหญ่ (ร้อยละ 96.3) โดยในบางรายได้ทำด้วยวิธีการผ่าตัดผ่านกล้อง (ร้อยละ 7.3) มีการตัดมันเปลวออกด้วยร้อยละ 75.1 ซึ่งมีผลการตรวจทางพยาธิวิทยาเป็นปกติทั้งหมด มีการสุ่ม/เลาะต่อมน้ำเหลืองในอุ้งเชิงกรานออกร้อยละ 51.6% ในขณะที่กลุ่มไม่ได้รับการสุ่ม/เลาะ ควรได้รับการสุ่ม/เลาะถึงร้อยละ 84.9 ประมาณสองในสาม (ร้อยละ 64.5) ของผู้ป่วยได้รับการรักษาเสริมโดยร้อยละ 91.5 มีระยะเวลาการรอคอยไม่เกิน 60 วันหลังผ่าตัด รังสีรักษานอกร่างกายใช้วิธีสามมิติร้อยละ 100 การรักษามากเกินไปและน้อยเกินไปพบได้ร้อยละ 16.5 (ช่วงเชื่อมั่นร้อยละ 95, 10.9-22.0) และร้อยละ 19.9 (ช่วงเชื่อมั่นร้อยละ 95, 13.9-25.8) ของการรักษาเสริมทั้งหมด ไม่พบว่ามีการเสียชีวิตภายใน 30 วันหลังผ่าตัด อัตราการอยู่รอดโดยรวมที่สามปีและอัตราการอยู่รอดปลอดโรคเท่ากับร้อยละ 93.4 และ 94.9 ตามลำดับ ปัจจัยการพยากรณ์โรคที่มีนัยสำคัญต่ออัตราการอยู่รอดทั้งสองชนิดคือ ระยะของโรคและการมีรอยโรคหลงเหลืออยู่หลังจากการผ่าตัด*

สรุป*: การรักษามากเกินไปและน้อยเกินไปพบได้ร้อยละ 16.5 และ 19.9 ตามลำดับ ผลการรักษามะเร็งได้ผลดีที่เปรียบ*

เทียบได้กับสถาบันอื่นๆ ทั้งที่มีอัตราการสุ่ม/เลาะต่อมน้ำเหลืองต่ำ อย่างไรก็ตาม หากพิจารณาเปรียบเทียบกับดัชนีชี้วัดคุณภาพ ผู้วิจัยยังจำเป็นต้องเพิ่มอัตราการผ่าตัดผ่านกล้อง

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Introduction

Cancers are the main cause of deaths worldwide and their prevalence tend to increase every year because of population shifting to elderly society[1]. World Health Organization (WHO) found that there were new 19 million cancer cases diagnosed and nearly 10 million cancer deaths in 2020[2]. In Thailand, breast cancer was the most common cancer in women (22.8%), and endometrial cancer was the second most common gynecologic cancers (4.6%, under cervical cancers) leading to 2.4% deaths[3].

Surgery is cornerstone of endometrial cancer for both staging and treatment to find out any indication for adjuvant therapy. Nowadays, 2009 International Federation of Gynecology and Obstetrics (FIGO) system is commonly used[4]. Surgical staging is consisted of total hysterectomy, bilateral salpingo-oophorectomy (TH/BSO) and lymph node assessment (pelvic and/or para-aortic lymphadenectomy). Omentectomy is considered in high-grade histology. Peritoneal cytology no longer affects FIGO 2009[5].

According to latest version of National Comprehensive Cancer Network (NCCN) 1.2022[6], adjuvant treatments have been mainly consisted of external beam radiation therapy (EBRT), vaginal brachytherapy (VBT) and systemic chemotherapy (CMT), being considered from FIGO stage, histologic grade, lymphovascular invasion (LVSI), age, depth of invasion, and peritoneal washing result of some high-grade histology. Authors considered this as standard guideline. Due to the easiness to follow without any need for molecular profiles data, which were still limited in many places, it was worldwide used, same as our institute. For oncological outcomes, there was also a Thai study[7] reported about survival, pathological and clinical presentation that about 80% of endometrial cancers coming with abnormal uterine bleeding (AUB) and their early stage leading to good prognosis with 5-year overall survival (OS) of 83.6%.

Despite many standard guidelines, variation of management could still occur in any real-life practices. There were substantial differences between those guidelines. Even within the same one, there also were many choices of treatments to choose. There was also a pattern of practice survey done in Australia and New Zealand[8] showing variability in adjuvant RT between VBT, EBRT, or both, particularly in stage II cases where there was lack of randomized data and discrepancies in consensus guidelines. For stage IIIA and IIIC1 cases, the majority suggested EBRT with or without VBT (79% and 77%) and of these, most were combined with CMT (61% and 88%).

The more advanced stage, the more invasive treatment procedures and modalities were recommended, but may lead to unnecessary complications without improving survival. As mentioned above, if there was indicated less aggressive treatment with equivalent outcomes, it would be better for patients. A recent review paper in 2021[9] mentioned that there was available evidence supporting VBT alone for stage I with high-intermediate risk (HIR) features or occult stage II. It provided non-different vaginal control with lower risk of toxicity compared to EBRT. VBT alone was a more non-toxic alternative to combined RT in medium risk. Superiority of VBT combined with 3 cycles of paclitaxel/carboplatin (PT), over standard EBRT in

early-stage endometrioid with HI- and hazard ratio (HR) features, was not demonstrated.

Decisions whether to perform lymphadenectomy and, if done, to what extent (bilateral pelvic node dissection or sampling (BPND/S) and/or para-aortic node dissection or sampling (PAND/S)) could be made based on preoperative and intraoperative findings[10,11]. However, this may be difficult to accurately determine final pathology results. In 2013, Belgian Cancer Registry used Rank method[12] (combination of consensus, review of the literature and panel of experts) to propose 36 quality indicators (QIs) for endometrial cancer management concerning all processes of care in different steps (treatment decision, surgery, adjuvant treatment and outcomes) and included 3 dimensions in quality of care (timeliness, effectiveness and safety). In 2017, a multicenter study has evaluated these QIs in 13 French University institutions and has identified 5 relevant QIs by their measurability (at least 80% of patients were affected by indicator) and improvability (difference between theoretical target and observed rate was below 5%)[13].

These 5 QIs were; QI 1: Proportion of patients who are alive at 3 years after their diagnosis, QI 2: Proportion of patients receiving adjuvant treatment, within a maximum waiting time of 60 days, QI 3: Proportion of patients who received adjuvant EBRT with intensity modulated radiotherapy (IMRT) or three-dimensional conformal radiotherapy (3DCRT) techniques, QI 4: Proportion of patients with clinical stage I cancer who underwent minimally invasive surgery (MIS) laparoscopy or robot-assisted, QI 5: Proportion of patients operated who died within the 30 days after surgery. Two QIs covered dimension in quality of care about adjuvant treatment (QI 2, 3), one about surgical management (QI 4), and two covered outcomes (QI 1, 5). Recently, a study was done in 2019 to evaluate French quality of care using these published relevant indicators[14].

However, it has not been yet explored about treatments and outcomes of practice in Srinagarind Hospital comparing with standard guideline and other country or institution. Despite there was the study already done in Thailand[7], only aspects of outcomes were evaluated, not any about the treatment comparison. Furthermore, the study was done a long time ago. Many things would be changed more or less, especially in demographic data and recommended management. In Thailand, even in different institutions of the same region, they could have their own unique ways of practice which were individualized. Therefore, the merit of conducting this study should be at least the awareness of authors' treatment outcomes and vulnerability for further improvement.

Materials and Methods

Srinagarind Hospital, Khon Kaen University, had been using Heath Object (HO) Program to collect patients' data in electronics' pool, which was paperless based, since January 2014. However, the system was not completely functioning until 2016. Therefore, this study was conducted in endometrial cancers patients diagnosed in Srinagarind Hospital from January 2016 to December 2020 retrieving data from the HO. A total of 316 women were diagnosed as endometrial cancers during that period (Inclusion criteria). Exclusion criteria were as follows: 1) surgeries were done elsewhere, 2) surgeries were not done, 3) final diagnoses were uterine sarcomas, 4) surgeries were done after 2020, and 5) incomplete data collection. This study was approved by the Office of the Khon Kaen University Ethics Committee in Human Research on 14 June 2021 (HE641320). In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed. After then, this retrospective study was conducted.

The following data were collected: age, parity, marital status, health insurance, Body Mass Index (BMI), other medical illnesses, previous abdominal surgeries, symptoms, mean time to surgeries, stages, histology, myometrial invasion ≥ 50%, isthmus, cervical and serosal involvement, LVSI, precision of endometrial biopsies, co-existing diseases, surgical treatments related procedures, adjuvant treatments and survival according to clinical and pathological features. Categories of BMI were classified into underweight (< 18.5 kg/m^2), normal (18.5 – < 23 kg/m^2), overweight

(23 – < 25 kg/m^2) and obese (≥ 25 kg/m^2). Other medical illnesses were underlying diseases in nervous, cardiovascular, pulmonary, gastrointestinal, renal, endocrine and/or musculoskeletal systems excluding cancers or gynecological diseases.

For adjuvant radiation therapy, the indicated patients were homogeneously scheduled following NCCN guideline[6]. External-beam doses for microscopic disease were 45 – 50 Gy or up to 60 – 70 Gy in macroscopic disease dividing into 25 – 28 fractions. Regimens were 6 – 7 Gy x 3 – 5 fractions for VBT alone and 4 – 6 Gy x 2 – 3 fractions for EBRT boost.

Recurrence-free survival (RFS) and overall survival (OS) were determined. RFS was defined as interval from end of treatment to recurrence time, disease progression or dead. For patients who were lost to follow-up, RFS data was right censored at time of the last evaluation or contact when they were known to be free from recurrence. OS were defined as time from date of diagnosis to deaths from any causes. For ones alive at time of study, survival data were right censored at date of last follow-up visit.

Sample size was calculated using 5-year OS rate of endometrial cancers from the study that was previously done in Thailand[7]. in which was 83.6%. Authors inferred that this study would get the same rate, if appropriate treatment was managed. The sample size was estimated to be about 250. Because no harm would be received from a retrospective study design, authors chose to use all patients' data within the above-mentioned period analyzed for more precision. With those numbers, it could be sufficient to show precise 95% confidence interval (CI) of proportion and rates with alpha error of 5% and test power of 80%.

Descriptive statistics (mean, number, standard deviation and percentage) were used to describe demographic data. Student t-test and Chi-square or Fisher's exact test were used to compare characteristics between groups. OS and RFS were analyzed by Kaplan-Meier method and were compared between groups with log rank test and cox proportional hazard regression model. We considered a p value of < 0.05 as statistically significant. All data analyses were performed using IBM SPSS statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp).

Results

Not all data from 316 patients were analyzed, due to 43 of them were excluded by the criteria mentioned above. Details were described in Fig. 1. Finally, there were 273 fully retrieved datasets for analyses. Baseline characteristics were demonstrated in Table 1. Mean age was 58.6 years. Sixty-one (22.3%) were nulliparity. Most of them were married (85%) and had civil servant medical benefit scheme (CSMBC) and universal coverage (UC) as their health insurances (52.8% and 40.3%, respectively). Mean BMI was 26.3 kg/m2. Over a half of women was overweight or more (54.9%), had at least 1 underlying medical illness (63.7%) and previous abdominal surgery (60.5%).

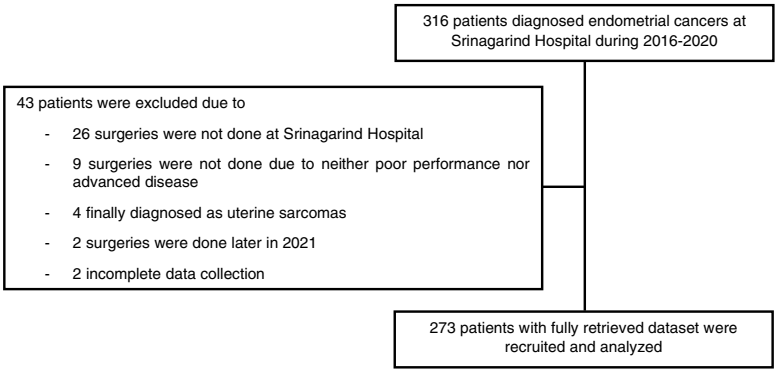

Fig. 1. Participants flow diagram.

Table 1. Baseline characteristics/ demographic data of endometrial cancers (n = 273).

Baseline characteristics/ demographic data	n (%)
Age (years) (mean ± SD)	58.6 ± 9.2
Parity	
0	61 (22.3)
1	31 (11.4)
≥ 2	181 (66.3)
last (years) (mean ± SD)	31.2 ± 9.7
Status	
Single	40 (14.6)
Married	232 (85.0)
Divorced	1 (0.4)
Health insurance	
Civil servant medical benefit scheme (CSMBC)	144 (52.8)
Universal coverage (UC)	110 (40.3)
Social security scheme (SSS)	8 (2.9)
Self-pay	11 (4.0)
BMI categories	
Underweight	13 (4.8)
Normal	110 (40.3)
Overweight	94 (34.4)
Obese	56 (20.5)
BMI (kg/m^2) (mean ± SD)	26.3 ± 5.3
Other medical illnesses	
1	61 (22.3)
≥ 2	113 (41.4)
Previous cancers	19 (7.0)
Previous abdominal surgeries	
1	132 (48.4)
≥ 2	33 (12.1)

SD: standard deviations, BMI: body mass index

Clinical and pathological features were shown in Table 2. Patients came with only one symptom and were found more than multiple complaints (57.1% and 42.9%, respectively). Most of them had abnormal uterine bleeding (AUB) (93.8%) and were in early stages (72.9%). About half were found ≥ 50% myometrial invasion (51.6%), isthmus involvement (50.2%) and positive for LVSI (45.8%). Twenty-four women did not undergo endometrial biopsies (EBs) or did but no malignancy was found (8.8%). Mean time from symptoms to surgeries was 6.4 months and from diagnoses to surgeries was 2.4 months. Endometrioid was the majority of pathology (78%). Half of women who underwent EBs had same results as final ones (53.5%), with quarter of underdiagnosis (28.5%). Common co-existing diseases were myoma uteri (45%) and adenomyosis (39.5%). There were 2.9% of second primary ovarian cancers.

Table 2. Clinical and pathological features of endometrial cancers (n = 273).

Clinical and pathological features	n (%)
Symptoms	
1	156 (57.1)
≥ 2	117 (42.9)
Abnormal uterine bleeding (AUB)	256 (93.8)
Pelvic mass	52 (19)
Abnormal Pap smear[a]	41 (15)
Intrauterine content from imaging	39 (14.3)
Mean time (months) ± SD	
Symptoms to surgeries	6.4 ± 6.7
Diagnoses to surgeries	2.4 ± 2.6
Stages	
I	166 (60.8)
II	33 (12.1)
III	55 (20.1)
IV	19 (7)
Histology	
Endometrioid grade 1 (G1)	103 (37.7)
Endometrioid grade 2 (G2)	65 (23.8)
Endometrioid grade 3 (G3)	45 (16.5)
Serous	14 (5.1)
Clear cell	11 (4)
Mixed carcinoma[b]	20 (7.4)
Carcinosarcoma[c]	15 (5.5)
Myometrial invasion ≥ 50%	141 (51.6)
Isthmus involvement	137 (50.2)
Cervical involvement	78 (28.6)
Serosal involvement	17 (6.2)
Lymphovascular invasion (LVSI)	125 (45.8)
Precision of endometrial biopsies (EB)	256 (93.8)
Correct	137 (53.5)
Incorrect	21 (8.2)
Underdiagnosed	73 (28.5)
Overdiagnosed	25 (9.8)
Co-existing diseases	
Endometrial hyperplasia	61 (22.3)
Endometritis or cervicitis	16 (5.9)
Endometrial or endocervical polyp	27 (9.9)
Myoma uteri	123 (45)
Adenomyosis	108 (39.6)
Tubal lesions (hydro-, haemato- or pyosalpinx)	54 (19.8)
Benign ovarian tumors[d]	23 (8.4)
Other ovarian cancers	8 (2.9)

[a] 17 atypical glandular cell, 11 adenocarcinoma, 7 atypical glandular cell, favor neoplasia, 4 atypical squamous cell of undetermined significance of and 1 each of low grade squamous intraepithelial lesion and high grade squamous intraepithelial lesion.

[b] 5 each of G2 and G3+clear cell, 3 G1+mucinous, 2 each of G3 and clear cell+serous and 1 each of G1+clear cell, G2+serous and G3+mucinous.

[c] 6 G3+leiomyosarcoma, 5 G2+leiomyosarcoma, 2 G1+leiomyosarcoma and 1 each of G2+serous+leiomyosarcoma and serous+leiomyosarcoma.

[d] tubo-ovarian abscess, polycystic ovary, serous or sero-mucinous cystadenoma or borderline ovarian tumors, dermoid, endometrioma, fibro-thecoma and Brenner's tumor

SD: standard deviations.

Table 3 shows surgical treatment procedures. Minimal invasive surgery (MIS) was done in 7.3%. TH/BSO was mostly done in all patients except 4 bilateral salpingectomies (1 bilateral oophorectomy was done later), 3 unilateral SOs, 2 subtotal hysterectomies, and 1 radical hysterectomy (RH). Omentectomies were done in 75.1% and all were negative. Peritoneal washings were done in 15.0% with 7.3% positive. Half of all women (51.6%) underwent BPND/S with mean number of collected nodes was 9.3 (no data in one case) and their sizes ranged from 0.6-1.4 cm (no data in 18 cases and unilateral PND/S in 7 cases). In the group of whom BPND/S was done, nearly half were collected with adequate number of nodes (42.6%). In 9 patients BPND/S could be omitted, authors still did BPND/S (the reasons would be pre-operative EBs were serous and/or intra-operative tumor sizes were almost 2 cm and/or LNs were palpable). In the group of whom BPND/S was not done, there were 84.9% that should be done. Only 8.4% underwent PAND/S with mean number of collected nodes was 3.2 (failed to get tissue in one case) and their sizes ranged from 0.8-1.3 cm. Three patients underwent PAND/S without BPND/S (all positive). Residual tumors were left in 13.6% and post-operative complications occurred in 15% which common ones were bowel events (36.6%) and wound dehiscence (29.3%). Pre-operative neoadjuvant therapies and enoxaparin were given in 4.4% and 2.6%, respectively.

Table 3. Surgical treatments related procedures of endometrial cancers (n = 273).

Surgical treatments related procedures	n (%)
Minimal invasive surgery (MIS)	20 (7.3)
Total hysterectomy (TH) and bilateral salpingo-oophorectomy (BSO)	263 (96.3)
Omentectomy	205 (75.1)
Peritoneal washing	41 (15.0)
- Positive	3 (7.3)
Bilateral pelvic node dissection or sampling (BPND/S)	141 (51.6)
- Total number (mean ± SD)	9.3 ± 5.9
- Size range (Centimeters) (min-max mean ± SD)	min 0.6 ± 0.5 max 1.4 ± 0.9
BPND/S were done in	141 (51.6)
- Could be omitted	9 (6.4)
- Adequate number (≥ 10 collected nodes)	60 (42.6)
BPND/S were not done in	132 (48.4)
- Should be done	112 (84.8)
Para-aortic node dissection or sampling (PAND/S)	23 (8.4)
- Total number (mean ± SD)	3.2 ± 2.4
- Size range (Centimeters) (min-max mean ± SD)	min 0.8 ± 0.8 max1.3 ± 0.8
Other procedures (adhesiolysis, appendectomy, biopsy, etc.)	59 (21.6)
Residual tumors	37 (13.6)
Post-operative complications	41 (15.0)
- Bowel events (evisceration, hernia, tear, etc.)	29 (36.6)
- Wound dehiscence	12 (29.3)
Pre-operative treatments	19 (7.0)
- Neoadjuvant therapy	12 (4.4)
- Enoxaparin	7 (2.6)

SD: standard deviations

Adjuvant treatments were classified in Table 4 depending on stages and histology following NCCN Guidelines Version 1.2022 in Uterine Neoplasms which was the latest update[6]. A total of 176 patients received adjuvant therapies (64.5%). After excluding 3 cases who received only neoadjuvant courses (without further treatment), there were 161 women receiving adjuvant CMTs and/or RTs (91.5%) within 60 days after surgeries (mean waiting time ± SD: 39.8 ± 22.5 days). About 40% of patients who received adjuvant therapies were given EBRT/VBT+CMT which was the most common treatment.

Over- and under-treatments were found in 16.5% (95%CI 10.9-22.0) and 19.9% (95%CI 13.9-25.8), respectively, comparing with NCCN guideline as a standard[6]. In stage IAG1, there was 1 overtreatment receiving VBT alone without neither LVSI nor age ≥ 60 years. CMT was given as neoadjuvant therapy using 4 cycles of PT due to concurrent ovarian cancer (no further adjuvant course). In stage IAG2, there were also 3 patients getting adjuvant CMT PT 6 cycles from their other primary ovarian cancers. Due to no role of EBRT in this group, there was 1 overtreatment. In stage IAG3, because no role of CMT, there were 10 overtreatments in this group (1 received EBRT without neither LVSI nor age ≥ 70 years). There was also 1 case that refused any adjuvant therapy, which was designated as an under-treatment (at least VBT was preferred in this group). In stage IA with high grade histology, there was 1 overtreatment due to no role of EBRT in clear cell without invasion and 4 under-treatments, including 3 no adjuvant therapy and 1 only a cycle of CMT (at least 4 cycles of CMT were preferred in this group). For stage IA, overtreatment group had no recurrence with 1 each of radiation burn and proctitis except 1 case that we found no data after 13 months. In undertreatment group also had no recurrence without any complication.

In stage IBG1, there were 8 overtreatments due to no role of EBRT in this group. One was given CMT from co-existing ovarian cancer. Eight patients did not receive RT, but there were only 6 undertreatments (2 neither LVSI nor age ≥ 60 years could be observed). In stage IBG2, there were 8 overtreatments, because there was no role of combined EBRT/VBT in this group. There were 2 undertreatments from no adjuvant therapy (at least VBT was preferred in this group). In stage IBG3, there were 5 undertreatments because they did not receive adjuvant RT which was at least preferred in this group. In stage IB with high grade histology, there were 3 undertreatments, including 1 without adjuvant therapy, 1 with only 3 cycles of CMT and 1 CS (carcinosarcoma) with only RT (at least CMT was preferred in this histology). For stage IB, there was no recurrence in overtreatment group but 2 cases of radiation proctitis, while 1 case was found no data after 3 months. Two cases without data after 3 and 9 months and a death from disease recurrence were found in undertreatment group.

In stage II endometrioid, there were 3 undertreatments, including 2 no adjuvant therapy and 1 only VBT and CMT (at least EBRT if grade 3 and ≥ 50% myometrial invasion). In stage II with high grade histology, there was 1 undertreatment due to only a cycle of CMT. For stage II, there was no recurrence in the undertreatment group. In stage III, there were 8 undertreatments, including 7 no adjuvant therapy and 1 only RT (at least CMT was preferred). For stage III, in the undertreatment group we found 2 deaths from disease recurrence and 3 cases with no data after 4, 9 and 16 months. In stage IV, there were 2 undertreatments, including 1 VBT alone and 1 no adjuvant therapy (at least CMT was preferred). Both of them were dead from advanced disease.

For treatment outcomes, there were 37 recurrences (13.6%) with mean time ± SD from surgeries to recurrences was 15.8 ± 11.2 months. Recurrent types were locoregional, distant and combined in 10.8%, 37.8%, and 51.4%, respectively. Fifteen patients did not receive any further treatment (40.5%). In those whom received, nearly half of them got CMT (48.6%), some were followed by RT

or given after surgeries, and some received EBRT alone. Survival rates, including 30-day, 1-, 3- and 5-year of OS and RFS were 100%, 93.4%, 81%, 76.2% and 99.6%, 94.9%, 86.2%, 83.6%, respectively. Graphs of survival time were demonstrated in Fig. 2 and 3.

Table 4. Adjuvant treatments of endometrial cancers (n = 176).

Stages	EBRT	VBT	EBRT/VBT	CMT	EBRT/ VBT+CMT	Over-treated	Under-treated
IA (31/105)							
- G1 (2/58)	-	1 (7.7)	-	1 (2.1)	-	1 (3.4)	-
- G2 (6/20)	-	2 (15.4)	1 (2.4)	3 (6.2)	-	1 (3.4)	-
- G3 (12/13)	-	-	3 (7.3)	2 (4.2)	7 (9.9)	10 (34.5)	1 (2.9)
- High grade (11/14)	-	-	-	5 (10.4)	6 (8.5)	1 (3.4)	4 (11.4)
IB (48/61)							
- G1 (13/20)	1 (33.3)	4 (30.8)	7 (17.1)	1 (2.1)	-	8 (27.6)	6 (17.1)
- G2 (14/16)	2 (66.7)	4 (30.8)	8 (19.5)	-	-	8 (27.6)	2 (5.7)
- G3 (11/14)	-	-	4 (9.8)	2 (4.2)	5 (7.0)	-	5 (14.3)
- High grade (10/11)	-	-	2 (4.9)	1 (2.1)	7 (9.9)	-	3 (8.6)
II (31/33)							
- Endometrioid (24/26)	-	1 (7.7)	15 (36.6)	2 (4.2)	6 (8.5)	-	3 (8.6)
- High grade (7/7)	-	-	-	1 (2.1)	6 (8.5)	-	1 (2.9)
III (48/55)	-	-	1 (2.4)	18 (37.5)	29 (40.8)	-	8 (22.9)
IV (18/19)	-	1 (7.7)	-	12 (25)	5 (7.0)	-	2 (5.7)
Total (176/273) n (%)	3 (1.7)	13 (7.4)	41 (23.3)	48 (27.3)	71 (40.3)	29 (16.5)	35 (19.9)

EBRT: external beam radiation therapy, VBT: vaginal brachytherapy, CMT: chemotherapy

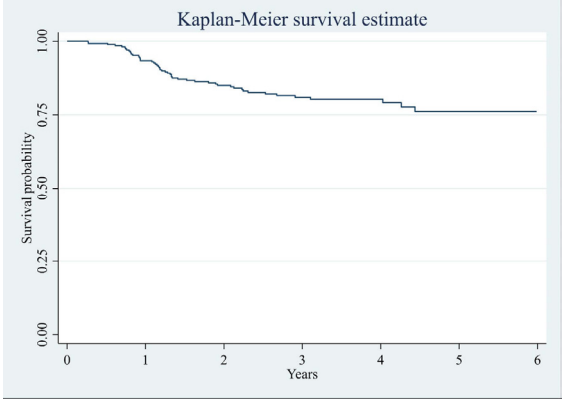

Fig. 2. Overall survival (OS).

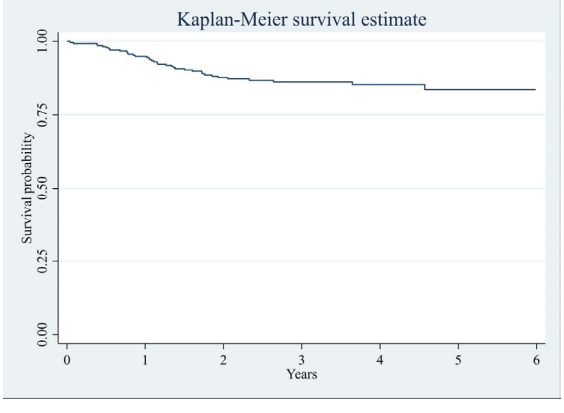

Fig. 3. Recurrence free survival (RFS).

Table 5 lists potential clinical and pathological features as prognostic factors for survival. Univariate cox proportional hazards models were fit for each covariate with both survivals. Factors that had a p value of less than 0.2 were considered feasible for multivariate analysis. Variables were subject to backwards elimination using an alpha of 0.05 for removal. Finally, there were 4 and 3 statistically significant prognostic factors for OS and RFS, consecutively which consisted of advanced stages, residual lesion (for both OS and RFS), non-endometrioid histology, LVSI (for OS only), and underlying diseases ≥ 2 (for RFS only).

Table 5. Survival of patients according to clinical and pathological features (n = 273).

Clinical and pathological features	Overall Survival Time		Recurrence-Free Survival Time	
	HR (95%CI), p	aHR (95%CI, p)	HR (95%CI), p	aHR (95%CI, p)
Age ≥ 60 years	1.094 (0.605, 1.976), 0.767	-	1.013 (0.525, 1.953), 0.969	-
Advanced stage (III – IV)	10.875 (5.383, 21.972), < 0.001	4.190 (1.898, 9.247), < 0.001	8.084 (3.986, 16.396), < 0.001	3.982 (1.742, 9.105), 0.001
Non-endometrioid histology	3.850 (2.137, 6.937), < 0.001	2.544 (1.398, 4.629), 0.002	2.317 (1.177, 4.562), 0.015	-
High grade histology (endometrioid grade 3 and non-endometrioid histology)	3.518 (1.907, 6.487), < 0.001	-	1.793 (0.940, 3.420), 0.077	-
Myometrial invasion ≥ 50%	8.080 (3.188, 20.480), < 0.001	-	4.479 (1.966, 10.203), < 0.001	-
Isthmus involvement	2.904 (1.498, 5.628), 0.002	-	2.222 (1.116, 4.423), 0.023	-
Cervical involvement	4.994 (2.711, 9.198), < 0.001	-	4.294 (2.226, 8.285), < 0.001	-
Serosal involvement	5.745 (2.732, 12.082), < 0.001	-	5.030 (2.198, 11.511), < 0.001	-
Lympho-vascular invasion	8.658 (3.665, 20.453), < 0.001	3.854 (1.551, 9.574), 0.004	3.686 (1.783, 4.618), < 0.001	-
Lymph node dissection	0.707 (0.393, 1.272), 0.247	-	0.901 (0.473, 1.718), 0.752	-
Underlying diseases ≥ 2	0.671 (0.361, 1.249), 0.209	-	0.434 (0.205, 0.919), 0.029	0.393 (0.185, 0.837), 0.015
Previous abdominal surgeries ≥ 2	0.540 (0.167, 1.746), 0.304	-	0.404 (0.097, 1.682), 0.213	-
Residual lesion	7.541 (4.186, 13.586), < 0.001	2.462 (1.286, 4.713), 0.007	10.739 (5.590, 20.628), < 0.001	5.547 (2.582, 11.916), < 0.001

* HR: hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval, p: p value

Discussion

Srinagarind Hospital is one of the largest tertiary-care hospitals in Thailand. Authors found that there were 273 patients coming to treat endometrial cancer during 2016-2020 compared to those 261 patients during 1992-2008 in Vajira Hospital[7], which is at the same level of healthcare. Equal cases occurred in shorter period of time might indicate increasing incidence year by year. Patients' baseline characteristics/ demographic data were quite similar, including age, parity, underlying diseases, previous cancers, stages, histology and symptoms in which most common one was AUB. Three less common ones were pelvic mass, abnormal Pap smear and intrauterine content from imaging.

Over- and under-treatment of adjuvant therapy were found in 16.5% (95%CI 10.9-22.0) and 19.9% (95%CI 13.9-25.8), respectively. For over-treatment, the modality that was given more than suggestions had no survival benefit but risk for unnecessary complications, similar to a report from the study in Korea[15]. A total of 44 patients with mostly stage IIIC (IIIC1 36.4% and IIIC2 59.1%) received complete staging procedures including lymphadenectomy (pelvic, para-aortic and/or supraclavicular) and adjuvant CMT (75%) or chemoradiation (25%). Survival rates were not different (DFS, 81.8% vs 82.1%, p = 0.743; OS, 90.9% vs 95.8%, p = 0.537) between the 2 groups. Incidence rates of grade 2/3 gastrointestinal complications (36.4% vs 0.0%, p < 0.001) and grade 2 lymphedema (36.4% vs 9.1%, p = 0.032) were higher in chemoradiation comparing with CMT[15].

In women who underwent BPND/S (51.6%), 13.5% were upstaged, and in who underwent PAND/S (8.4%), 26.1% were upstaged. The 10 lymph nodes cutoff was chosen based on the Gynecologic Oncology Group (GOG) criteria for adequate lymphadenectomy[16], which authors also found in 42.6%. Comparing with Surveillance, Epidemiology, and End Results (SEER) data from the study including > 80,000 patients in USA during 2000-2011, lymphadenectomy was done in 57.1% which were adequate in 61.5%[17]. Previously, a full standard lymphadenectomy was recommended for all patients in author's institute. However, more selective and tailored approach is now suggested to avoid systematic overtreatment[18]. Systematic lymph node dissection (LND) was recommended in HR but its role in HI- and IR was inconclusive, therefore, there was a study reported in 2019 of more than 5,000 German patients about this topic[19]. LND was performed in 20.2%, 53% and 63.7% within low-, I-/HI- and HR groups (there was 58.5%, 30.1% and 11.4% in each group, respectively). Lymph node involvement was diagnosed in 1.7%, 9.6% and 19.3%, respectively. There was no significant difference in time to local-, lymph node recurrence or distant metastases, between ones with and without LND. After adjusting for age and comorbidity-status, also, no significant difference in OS was found. By the way, from 132 women who did not undergo BPND/S (47.7%), only 15.1% were reasonable for omitting LND[10]. This meant that there were 84.9% of them missing chances to be upstaged and to get their tumor out. More than 4 out of 5 missing the chances in this group was quite a large room for authors' improvement.

In spite of standard guidelines to follow, variation of management would still occur, even in a tertiary-care institute. The low rates of both peritoneal washing and lymphadenectomy of ours could be due to individual multifactorial causes. Although positive cytology did not impact on upstaging[5], it was a personal preference to do peritoneal washing as a standard of surgical staging or not. In the authors' institute, there was multidisciplinary consultation between gynecologic oncologist and radiologist to choose any appropriate adjuvants for each patient. VBT alone was not a common way of ours but boost after EBRT, which would mainly affect rates of overtreatment in stage IB low grade (G1 – 2). These were found over a half as shown in Table 4. From this reason, some surgeons may infer that EBRT and VBT would be anyway given in whom having grossly intraoperative stage IB. Finally, they came up with assumption that omitting lymphadenectomy could

cause less complication. By the way, it was not yet to neither summarize nor suggest skipping nodal dissection with adding EBRT, without more data and details about oncological outcomes and adverse events from this comparison.

Comparing with the study in France[14], authors' results for 4 out of 5 QIs were better except only MIS rate that we had to improve; QI1: Proportion of patients who are alive 3 years after their diagnosis (81% vs 77%), QI 2: Proportion of patients receiving adjuvant treatment, within a maximum waiting time of 60 days (93% vs 47.8%), QI 3: Proportion of patients who received adjuvant EBRT with IMRT or 3DCRT (100% vs 83.3%), QI 4: Proportion of patients with clinical stage I cancer who underwent MIS (7.3% vs 17.3%), and QI 5: Proportion of patients operated who died within the 30 days after surgery (0% vs 0.5%). However, in Thailand, MIS are not available for all patients. They had to pay 10,000-20,000 THB more to get this kind of operation in author's institute.

For treatment outcomes, 5-year OS and RFS (76.2 % and 83.6%) were slightly lower than the study previously done in Thailand (83.6% and 86.5%)[7]. These could be due to shorter follow-up times (5 vs 16 years). Rates of BPND/S and PAND/S, which were much less in our study (51.6% vs 93.1% and 8.4% vs 70.5%), did not seriously affect survivals, and were not the significant prognostic factors, as seen in Table 5. Anyway, for univariate analysis, clinical and pathological features as prognostic factors for survivals were quite similar (as they were not statistically significant different). After multivariate analysis, there were 4 and 3 statistically significant prognostic factors for OS and RFS, consecutively which consisted of advanced stages, residual lesion (for both OS and RFS), non-endometrioid histology, LVSI (for OS only), and underlying diseases ≥ 2 (for RFS only).

Endometrial cancer is histologically classified into type I and type II in relation to estrogen. Clinicopathological analysis revealed that type II (non-endometrioid) is generally more aggressive than type I (endometrioid) and is associated with poorer prognosis even when diagnosed at early stage[20]. Data from study done in Japan found there were 2 times more recurrences of type II than type I (34% VS 17%) in patients without residual tumor[21]. Women with type I were associated with obesity and more likely to die of cardiovascular disease than cancer[22]. A study done in China showed that metabolic syndrome was closely related to OS (HR 2.14, p = 0.032) and RFS (HR 1.80, p = 0.045) by univariate but not multivariate analysis[23]. More specifically, patients with 3 or more components had worse outcome than those with lesser ones. According to what authors mentioned above, the reason why women with underlying diseases ≥ 2 had better RFS than those with one or none, should be that type I patients were included more in this group. Unfortunately, authors found no statistically significant correlation to those 4 significant prognostic factors (advanced stages, residual lesion, non-endometrioid and LVSI, by post-hoc analyses). This might have occurred by chance.

Conclusion

Over- and under-treatment of adjuvant therapy were found in 16.5% (95%CI 10.9-22.0) and 19.9% (95%CI 13.9-25.8), respectively. The oncologic outcomes were good and comparable with others' despite of low lymphadenectomy rate. However, according to quality indicators, authors had to increase minimal invasive surgery rate. The strengths were that this was the second study done in Thailand evaluating outcomes of endometrial cancers and the first study comparing about treatment methods and oncological outcomes to standard guideline and quality indicators. Retrospective design was the limitation of this study, it could be more reliable with prospective design and data about targeted therapy and molecular profiles.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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