Original Article

Adjuvant Treatment after Surgery for Endometrial Cancer: Survey of Practice among Thai Gynecologic Oncologists

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Objective: To evaluate the practice of Thai gynecologic oncologists regarding the adjuvant treatment after surgery for endometrial cancer.

Materials and Methods: A web-based survey by the Thai Gynecologic Cancer Society was conducted from August to October, 2019 to assess the pattern of gynecologic cancer management of the Thai gynecologic oncologists. The respondents had to have at least 1 year of practice in this field and were currently working in the country. Data of practice on postoperative adjuvant treatment for each stage of endometrial cancer were retrieved and analyzed.

Results: The mean age of all 167 gynecologic oncologists who responded to the questionnaire was 41.0±8.26 years. No adjuvant treatment was selected in 40% of stage IA and 3% of stage IB whereas all responded one or more types of adjuvant treatments for stage II and over. Pelvic radiation was most commonly used for stage I-II. Brachytherapy was the most common mode of radiation for stage IA (57.5%) and IB (88.1%) whereas external pelvic beam irradiation was more common in stage II (38.9% without and 36.5% with brachytherapy). Only 2 to 8% reported chemotherapy use for stage I-II and increased to 80 to 97% in stage III-IV. Chemotherapy was reported as the sole therapy in 20% of stage III and 70% of stage IV whereas the remaining had combined chemotherapy and radiation. Extended field radiation was used in 15 to 30% of stage IIIA to IIIC1 and 62% in stage IIIC2.

Conclusion: Thai gynecologic oncologists used adjuvant therapy mainly according to the stage of endometrial cancer. The main treatment for stage I-II was radiation therapy, with chemotherapy in some patients. Chemotherapy was the major adjuvant treatment (80 to 90%) of stage III and almost all stage IV.

Keywords: Survey, Practice, Gynecologic oncologist, Endometrial cancer, Adjuvant treatment

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After primary surgery for endometrial cancer (EMC), some patients may have some unfavorable features associated with the risk of failure after surgery. The adjuvant treatment is usually tailored upon various clinical and pathological risk factors. These factors are used to categorize the patients into low, intermediate, or high-risk groups. Several independent prognostic factors were recognized: age, histologic grade, lymphovascular space involvement (LVSI), depth of myometrial invasion, cervical invasion, and extrauterine involvement including lymph node status[1-3].

Although EMC is an estrogen-dependent disease that should respond to progestin therapy, the evidence from various studies and the meta-analytical study did not demonstrate the benefit of hormones being given as adjuvant therapy[4-8]. Moreover, higher numbers of inter-current deaths from cardiovascular and thromboembolic diseases among progestins users held against its use as adjuvant treatment in early-stage EMC[6,8]. Hence, the current adjuvant therapies for EMC which are commonly used are systemic chemotherapy and/or pelvic radiation therapy.

Postoperative adjuvant pelvic radiation therapy is used to reduce recurrence and hopefully to extend survival. Data from previous studies compared various modalities of radiation therapy: vaginal brachytherapy (or intracavitary radiation therapy; ICRT), external beam pelvic radiation therapy (EBPRT), or their combination. The main determinant in selecting the type of radiotherapy is a stage of EMC as well as other clinic-pathologic features i.e. age, type and grade of cancer, depth of myometrial invasion, and LVSI. Adjuvant therapy is rarely recommended for stage IA grade 1 or 2 diseases (low risk) whereas brachytherapy or observation is acceptable for stage IA grade 3[9]. For stage IB to II (intermediate- and high-risk), adjuvant EBRT is recommended

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to reduce loco-regional recurrences especially in high- or high-intermediate risk subgroups with these factors, i.e. grade 2 to 3, older age (>50 to 60 years), deep myometrial invasion, and LVSI[9-13]. With greater toxicities of EBRT, vaginal brachytherapy with less toxicity and shorter treatment time was tested in place of EBRT[14]. Lower vaginal relapse was demonstrated with the use of brachytherapy than the EBRT without the differences in pelvic/distant relapse and overall survival.

However, control of systemic failure and overall survival improvement could not be achieved with any modalities of radiation therapy[10,12,13,15-17]. Hence, chemotherapy (with or without radiation) has become another treatment modality after primary surgery in early-stage and especially in advanced stage III-IV when the diseases have extended outside the uterus and pelvic cavity wherein pelvic radiation is insufficient to eradicate the residual disease[18-23]. However, data were inconsistent regarding the survival benefit of adjuvant chemotherapy.

Although data demonstrate the role of adjuvant therapy in each stage of EMC with the recommendation from the international organizations[24-26], many other factors may influence the option of treatment, such as availability and access to the specific treatment, financial restrictions, compliance of the patients and family members, experience and preference of the gynecologic oncologist and radiation oncologist in each institution.

This survey study aimed to assess the pattern of adjuvant therapy for each stage of EMC and factors which might influence the type of treatment among the patients who were taken care of by the Thai gynecologic oncologists.

Materials and Methods

This cross-sectional survey study was conducted by the Thai Gynecologic Cancer Society (TGCS) in 2019. The society committee pondered on the current clinical practice on management of gynecologic cancer among Thai gynecologic oncologists, so the research group on this topic was set up. The questionnaire to collect data in several aspects of management for cancers of the cervix, uterus, and ovary was constructed, discussed, and revised until consensus. An approval from the Ethics Committees for Human Research of each collaborating institution was independently obtained (COAs: Faculty of Medicine Vajira Hospital, 097/2562; Rajavithi Hospital, 104/2562; Faculty of Medicine Chiang Mai University, OBG-2562-06506).

Inclusion criteria were Thai gynecologic oncologists who had been practicing in this field for at least one year and were currently practicing in the country at the time of this survey. The web-based questionnaire was opened for response from August to October, 2019 via https://forms.gle/e1WsBLcX5jVsXVgG8. The present study focused on adjuvant treatment after surgery for endometrial cancer patients. The options of adjuvant treatment e.g. a specific type of radiation therapy, chemotherapy, a combination of treatment, and other options were made for selection for each stage of endometrial cancer by the 2009 International Federation of Gynecology and Obstetrics (FIGO) i.e. stage IA, stage IB, and so on to stage IVB[27].

Data were analyzed using SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to analyze demographic data and were summarized as numbers with percentages, mean with standard deviation (SD). The types of adjuvant treatment were presented according to the FIGO stage of the disease.

Results

Among 170 gynecologic oncologists who responded to the questionnaire, 167 reported their practice regarding the type of adjuvant therapy for endometrial cancer after surgery. Various options of adjuvant therapy after surgery of each stage of cancer were reported (Table 1). Of note, no respondents reported the use of hormonal agents as adjuvant treatment for any stages of EMC.

For early-stage I-II, 40.1% of respondents reported no adjuvant treatment for stage IA and 3.0% for stage IB whereas all gave one or more modes of adjuvant treatment for stage II. Among those who considered the adjuvant treatment for these early-stage diseases, radiation therapy was most commonly used. Vaginal brachytherapy was the most common mode of treatment for stage IA (57.5%) and IB (88.1%), either alone (56.3% for stage IA and 70.7% for stage IB) or combined with EBPRT (1.2% and 17.4% for stage IA and IB, respectively). Surprisingly, chemotherapy was also considered as an option for stage IA and stage IB (1.8% of each, either as a combination with radiation or as chemotherapy alone). For stage II, almost all received radiation therapy, most as EBPRT either alone or with brachytherapy and few with EFRT. Chemotherapy was selected as an option, either with radiation (7.2%) or chemotherapy alone (1.8%).

For stage III, only pelvic radiation therapy use (EBPRT with or without brachytherapy) ranged from 16 to 18% in stage IIIA to IIIB when the diseases were still in the pelvis and dropped to approximately 1 to 2% in stage IIIC when the disease may have spreaded beyond the pelvis. Instead, chemotherapy with pelvic radiation was more common in this stage III. Nearly equal of 47 to 48% of the respondents selected this treatment option for stage IIIA, IIB, and IIIC1 and 18% in stage IIIC2 in which EFRT was commonly added. On the other hand, EFRT was additionally used with pelvic radiation, chemotherapy, or both in increasing frequency from stage IIIA to stage IIIC: 15.6% for stage IIIA, 19.2% for stage IIIB, 29.4% for stage IIIC1, and 62.3% for stage IIIC2. Chemotherapy alone as reported in approximate frequency in nearly 20% for each sub-stage of stage III. For stage IV, chemotherapy alone was the most common adjuvant treatment reported by the respondents (70.1%).

Of note, when chemotherapy was used in combination with radiation, the majority used them in a sequential pattern more frequently than a sandwich pattern: 127 (74.7%) compared to 43 (25.3%) respectively. The

Table 1. The pattern of adjuvant therapy after surgery by stage of endometrial cancer (n = 167)

Stage	Adjuvant therapy							
	None	Radiation alone			Radiation plus chemotherapy			CMT alone
		ICRT	EBPRT	EBPRT+ICRT	RT*+EFRT	RT*+CMT	RT*+EFRT+CMT	CMT+EFRT	
I									
IA	67 (40.1)	94 (56.3)	1 (0.6)	2 (1.2)	-	1 (0.6)	-	-	2 (1.2)
IB	5 (3.0)	118 (70.7)	12 (7.2)	29 (17.4)	-	2 (1.2)	-		1 (0.6)
II	-	21 (12.6)	65 (38.9)	61 (36.5)	5 (3.0)	11 (6.6)	1 (0.6)	-	3 (1.8)
III									
IIIA	-	-	21 (12.6)	10 (6.0)	7 (4.2)	80 (47.9)	4 (2.4)	15 (9.0)	30 (17.9)
IIIB	-	-	20 (12.0)	7 (4.2)	7 (4.2)	78 (46.7)	7 (4.2)	18 (10.8)	30 (17.9)
IIIC1	-	-	3 (1.8)	1 (0.6)	11 (6.6)	81 (48.5)	15 (9.0)	23 (13.8)	33 (19.7)
IIIC2	-	-	1 (0.6)	-	11 (6.6)	30 (17.9)	44 (26.4)	49 (29.3)	32 (19.2)
IV	-	-	-	-	4 (2.4)	25 (15.0)	10 (6.0)	10 (6.0)	118 (70.6)

CMT = chemotherapy, EBPRT = external-beam pelvic radiation therapy, EFRT = extended field radiation therapy, ICRT = intracavitary radiation therapy (vaginal brachytherapy)
* RT referred to external-beam pelvic radiation therapy with or without intracavitary radiation therapy

chemotherapy regimen used in an adjuvant, as well as neoadjuvant or salvage settings, were presented in detail in another report[28].

Discussion

Although there had been many studies evaluating the efficacy of specific adjuvant therapy in certain groups of EMC, few studies reported the type of treatment for each stage of EMC. One previous study by the authors, which evaluated the type and pattern of adjuvant therapy in EMC, found various treatments for each stage of endometrial cancer[29]. However, data were derived from a single institution. Another recent international multicenter study that focused on adjuvant therapy for stage III EMC reported survival outcomes by each substage (IIIA, IIIB, and IIIC) and by different types of adjuvant treatment (radiation, chemotherapy or chemoradiation)[30]. This national survey study evaluated the practice of Thai gynecologic oncologists in almost all major institutions for cancer care regarding the adjuvant treatment for EMC patients.

No respondents in this study reported hormonal agents as adjuvant treatment for any stages of EMC. This was most likely due to available evidence-based data showing no benefit of its use in this setting[4-8]. Various types of adjuvant therapy for each stage of EMC were demonstrated. For stage IA as defined by FIGO 2009, the results were quite surprising that more than half provided adjuvant therapy. A few possible reasons for this frequent adjuvant treatment in stage IA were discussed in our group. First, most evidence-based data from the trials were based on previous FIGO staging when stage IA included only those without myometrial invasion and when stage IB or stage IC encompassed cancer which invaded less than or more than half of myometrial invasion respectively. When the new FIGO staging had included previous stages IA and IB together, some may still consider brachytherapy for some patients with the current stage IA particularly those with myometrial invasion. Second, being a survey study comprising of general questions without a specific scenario including details of disease i.e. histopathology, grade, and age of the patients, some respondents might be cautious for the other risk factors aside from the stage itself.

Comparing to stage IA, both brachytherapy and EBPRT were used more frequently in stage IB and especially in stage II. This finding was most likely based on data from previous studies which showed adjuvant EBPRT could reduce locoregional recurrences from approximately 6 to 14% to 2 to 5% compared to observation or brachytherapy (odds ratio 0.27)[9-13,17]. Although one large trial had demonstrated that brachytherapy was not less effective than EBPRT in terms of pelvic relapse and survival[14], data were still limited and seemed to have no obvious impact on the real clinical practice of the Thai gynecologic oncologists. The respondents were probably still worried and tended to consider 'more' than 'less' treatment, so EBPRT with or without brachytherapy was reported in 25% for stage IB and 75% for stage II.

Regarding the role of adjuvant chemotherapy in early-stage EMC, this survey demonstrated that

chemotherapy (alone or with radiation) was selected as an adjuvant treatment in less than 10% for stage I-II. Although the questionnaire in the survey did not query the rationale of adjuvant treatment selected, the authors discussed the few possible reasons for the trend among the Thai gynecologic oncologists that chemotherapy was rarely considered despite the limited benefit of radiation to control systemic failure or to improve survival[10,12,13,15]. First, data from several trials which compared adjuvant chemotherapy to radiation in EMC after surgery, most included patients with various stages of diseases (from stage I to stage III)[18-20,22,23], so conclusion statement could not be made for certain stage I or stage II. Second, inconsistent findings from these trials were reported[18-20,22,23]. The inconsistent findings were also found among the few trials which compared radiation and chemotherapy to radiation alone[31,32]. One trial found significant survival benefit of concurrent chemoradiation followed by chemotherapy over radiation alone in stage I-III EMC patients[31]. However, another trial focusing on high-risk stage I-II could not demonstrate the survival benefit of adjuvant chemotherapy after radiation over radiation therapy alone[32]. The Thai gynecologic oncologists, who probably concerned about the inconsistent results from previous studies regarding the benefit of chemotherapy in early-stage EMC patients, might be reluctant to use CMT (which required a longer period of treatment and higher toxicity) especially in most EMC patients who were frequently old and with co-medical illnesses.

For stage III EMC, our survey found increasing use of chemotherapy. Although several trials had shown inconsistent data regarding a superior survival advantage of chemotherapy with or without radiation over radiation alone as adjuvant treatment[18-20,22,23], findings from the systematic review and meta-analysis showed significant benefit of chemotherapy in terms of reduction of systemic failure, higher rates of progression-free and overall survivals[33]. Hence, chemotherapy had become a common adjuvant therapy for EMC at present. This was evidenced in this study that chemotherapy was selected as an adjuvant therapy either alone or in combination with radiation treatment in most patients.

With heterogeneous features of cancer involvement in stage III disease, EFRT might have a role as an additional treatment as it had been used in a few trials[20,22,23]. The present study also found that EFRT was additionally used with pelvic radiation, chemotherapy, or both, with a consecutive increase in frequency from stage IIIA to stage IIIC1 as a prophylactic treatment and to stage IIIC2 to eradicate any gross or microscopic diseases which might extend outside the pelvis to upper abdomen or para-aortic node in particular. The inconsistent use of EFRT might partly lie on an awareness of its gastrointestinal side effects especially in EMC patients who are generally overweight or obese.

Regarding the pattern of chemotherapy given, previous studies gave chemotherapy in different patterns. Aside from given as the only treatment[20-22], chemotherapy was also given in combination with radiation therapy in different patterns: as a combined treatment in a sequential manner with radiation[18,19,23] or concurrent chemoradiation followed by additional cycles of chemotherapy[31,34]. This survey found that the majority of the Thai gynecologic oncologists gave both treatments in a sequential pattern (75%) (more than a sandwich pattern).

In summary, the results from this survey study represented the concepts of the Thai gynecologic oncologists regarding their clinical practice of giving adjuvant therapy after surgery in EMC. The decision on the choice of treatment of most gynecologic oncologists was possibly based mainly on evidence-based data from several large trials[10,12-15,18-20,22,23], systematic review with meta-analysis[17,33], and recommendations from the European and USA organizations[24-26,35]. Nevertheless, the details of treatment demonstrated in this survey reflected that the type of adjuvant treatment was refined according to each sub-stage of disease, and also probably other features of the patients and their diseases. An availability or access to the modes of treatment especially radiation therapy in each institution may be explored in a future study to assess the lackings and the needs in each region of the country.

What is already known on this topic?

Few international organizations have recommended various modes of adjuvant treatment for endometrial cancer after surgery. The treatment mainly depends on the International Federation of Gynecology and Obstetrics stage of the disease. In real clinical practice, however, the type and pattern of adjuvant treatment may not follow all recommendations but modified upon the context of the service settings.

What this study adds?

The Thai gynecologic oncologists generally used pelvic radiation therapy as an adjuvant treatment for endometrial cancer patients after surgery. Chemotherapy which was rarely used in stage I-II was more common in stage III-IV especially in combination with radiation. Extended field radiation therapy was increasingly common from stage IIIA-IIIC1 to stage IIIC2.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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การรักษาเสริมหลังการผ่าตัดของมะเร็งเยื่อโพรงมดลูก: การสำรวจแนวปฏิบัติของแพทย์มะเร็งนรีเวชไทย

จักรพันธ์ ขุนณรงค์, ศรัญญา ชาญพานิชกิจโชติ, สุมนมาลย์ มนัสศิริวิทยา, วรพจน์ เชาวะวณิช, จตุพล ศรีสมบูรณ์, ศิริวรรณ ตั้งจิตกมล, สมาคมมะเร็งนรีเวชไทย

วัตถุประสงค์: เพื่อประเมินแนวปฏิบัติในการรักษาเสริมหลังการผ่าตัดมะเร็งเยื่อบุโพรงมดลูกของแพทย์มะเร็งนรีเวชไทย

วัสดุและวิธีการ: การศึกษานี้เป็นส่วนหนึ่งของการศึกษาสำรวจโดยสมาคมมะเร็งนรีเวชไทยเกี่ยวกับแนวปฏิบัติของการรักษามะเร็งนรีเวชตั้งแต่เดือนสิงหาคมถึงเดือนตุลาคม พ.ศ. 2562 โดยเชิญแพทย์มะเร็งนรีเวชไทยที่ปฏิบัติงานมาแล้วอย่างน้อย 1 ปี และปัจจุบันยังทำงานในประเทศให้ตอบแบบสอบถามทางเว็บ เพื่อรวบรวมและวิเคราะห์ข้อมูลเกี่ยวกับการรักษาเสริมในแต่ระยะของโรคของมะเร็งเยื่อบุโพรงมดลูก

ผลการศึกษา: จากผู้ตอบแบบสอบถามจำนวน 167 ราย อายุเฉลี่ยคือ 41.0±8.26 ปี ประมาณร้อยละ 40 และร้อยละ 3 ของผู้ตอบแบบสอบถาม ไม่ได้ให้การรักษาเสริมใด ๆ ในผู้ป่วยระยะ IA และระยะ IB ตามลำดับ ในขณะที่ผู้ป่วยระยะ II ขึ้นไปทุกรายจะได้รับการรักษาอย่างน้อย 1 วิธี การให้รังสีรักษาบริเวณอุ้งเชิงกรานเพียงอย่างเดียวเป็นการรักษาเสริมที่ใช้มากที่สุดสำหรับผู้ป่วยในระยะต้น (ระยะ I และ II) โดยการใส่แร่ในช่องคลอดเป็นการรักษาเสริมที่ใช้บ่อยที่สุดในผู้ป่วยระยะ IA (ร้อยละ 57.5) และระยะ IB (ร้อยละ 88.1) ขณะที่การฉายแสงภายนอกบริเวณอุ้งเชิงกรานเป็นการรักษาที่ให้บ่อยในผู้ป่วยระยะที่ II โดยร้อยละ 38.9 เป็นการฉายแสงภายนอกเพียงอย่างเดียวและร้อยละ 36.5 เป็นการรักษาร่วมกับการใส่แร่ พบว่ามีการใช้ยาเคมีบำบัดเป็นการรักษาเสริมเพียงร้อยละ 2 ถึง 8 ในระยะ I และ II และเพิ่มเป็นร้อยละ 80 ถึง 97 ในระยะ II และ IV โดยเป็นการให้เคมีบำบัดเพียงอย่างเดียวประมาณร้อยละ 20 ในผู้ป่วยระยะ 3 และร้อยละ 70 ในผู้ป่วยระยะ IV และเป็นการให้เคมีบำบัดร่วมกับรังสีรักษาในผู้ป่วยกลุ่มที่เหลือนอกจากนี้ยังมีการใช้การฉายแสงรักษาเสริมแบบขยายขอบเขตไปช่องท้องด้านบนประมาณร้อยละ 15 ถึง 30 ในผู้ป่วยระยะ IIIA ถึงระยะ IIIC1 และร้อยละ 62 ในระยะ IIIC2

สรุป: แพทย์มะเร็งนรีเวชไทยให้การรักษาเสริมในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกตามระยะของโรค การรักษาหลักในผู้ป่วยมะเร็งระยะ I และ II คือการรักษาด้วยรังสีรักษาและอาจมีการให้เคมีบำบัดร่วมด้วยในบางรายมีการใช้ยาเคมีบำบัดเป็นหลัก ในผู้ป่วยระยะ III ประมาณร้อยละ 80 ถึง 90 และเกือบทั้งหมดของผู้ป่วยระยะ IV