Original Article

Pre-operative Assessment and Neoadjuvant Therapy Prior to Surgery for Advanced Endometrial Cancer: Survey of Practice among Thai Gynecologic Oncologists

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Objective: To determine the methods that Thai gynecologic oncologists used to assess the operability and neoadjuvant treatment in apparently advanced endometrial cancer.

Materials and Methods: This study was a part of the national survey project by the Thai Gynecologic Cancer Society on the management of gynecologic cancer in Thailand. All Thai gynecologic oncologists who had been in practice for at least 1 year were invited to respond about their practice to the online questionnaire open from August to October, 2019. Data on the methods to assess the operability of advanced endometrial cancer and the type of neoadjuvant treatment before surgery were abstracted from the database and analyzed.

Results: Among 170 respondents, 48.8% performed physical examination along with imaging study to assess the operability whereas 25.9% relied only on an imaging study. The most common imaging study was a computed tomography scan (84.1%). The respondents who worked in training hospitals used special imaging studies (aside from ultrasonography) significantly more frequently than those in service-only hospitals, 95.3% vs. 84.5% (p = 0.022). Regarding the neoadjuvant therapy before surgery, chemotherapy (58.7%), chemotherapy combined with radiation (41.9%), and radiation therapy alone (33.5%) were selected as modes of treatment. Radiation therapy was selected as an option more frequently among the respondents working in government and in training hospitals compared to private and service-only hospitals: 36.2% vs. 5.6% (p = 0.009) and 40.7% vs. 25.0% (p = 0.022), respectively. Combined radiation and chemotherapy were more frequently selected among the respondents who had been in practice ≥5 years (48.5%) vs. <5 years (31.0%), p = 0.022.

Conclusion: An assessment of operability and neoadjuvant therapy before surgery in advanced endometrial cancer among the Thai gynecologic oncologists varied. These were influenced by the hospital's features and experience of the respondents.

Keywords: Survey, Practice, Endometrial cancer, Operability, Neoadjuvant therapy

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Surgical staging of endometrial cancer (EMC) is the operative procedure to remove the uterus, both adnexa, and lymph node sampling. These surgico-pathological findings designate the stage of EMC according to the International Federation of Gynecology and Obstetrics (FIGO) criteria[1]. This primary surgery also serves as the main primary treatment for EMC.

However, most EMC patients are elderly individuals who frequently have other co-morbidities. This results in suboptimal performance status of the patients who are not good candidates for surgery (medically inoperable). Radiation therapy may be considered as a definite treatment in this situation[2-4]. The American Brachytherapy Society reported treatment outcomes after radiation therapy varied directly on stage of disease and modality of radiation. The 5-year survival rates (SVR) were 65 to 85% in stage I, 69% in stage II, and dropped to 14% in stage III in the EMC patients who had brachytherapy alone[5]. With the use of brachytherapy in combination with pelvic radiation, these 5-year SVR increased to 95% in stage I, 88% in stage II, and 57% in stage III[5].

In another scenario when the diseases are far advanced, primary surgery may not be an appropriate option. Generally, the aim of primary surgery is to remove as much cancer as possible. The SVR of the patients was reported to

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be directly associated with the extent and results of surgical cytoreduction[6]. In any patients whose diseases are expected to be surgically inoperable, suboptimally debulked, or when the operative morbidity from immediate surgery will outweigh the benefit, delayed primary surgery after neoadjuvant treatment may be considered[7]. In these circumstances when physical examination demonstrated cancer spread outside the uterus and beyond the pelvis, imaging study would be very useful to evaluate the sites and volume of metastatic diseases to aid in predicting the operability of cancer.

This study aimed to determine the practice of the Thai gynecologic oncologists how they assessed the operability of EMC patients when the diseases deemed to be advanced. The type of neoadjuvant treatment prior to surgery was also studied. We did not include the scenario when the patients had medical illness prohibiting surgery, and when palliative treatment or radiation therapy was considered as the option.

Materials and Methods

This study was a part of the national survey of practice on gynecologic cancer undertaken by the Thai Gynecologic Cancer Society (TGCS). The study was approved by the Ethical Review Committee of all affiliations involving in the research (COAs: Rajavithi Hospital, 104/2562; Faculty of Medicine Chiang Mai University, OBG-2562-06506; Faculty of Medicine Vajira Hospital, 097/2562). Details of materials and methods were described in our main report[8]. In brief, Thai gynecologic oncologists who had worked for at least one year and were currently working in the country were invited to respond to the online questionnaire via https://forms.gle/e1WsBLcX 5jVsXVgG8 from August to October, 2019.

The questionnaire covered demographic data of the respondents, data of primary working hospitals, duration of work, and various aspects of the management of gynecologic cancer. This study abstracted data of the methods that were used to assess the extent of disease to determine the chance of optimal surgery in apparently advanced endometrial cancer. The methods used for an assessment of operability included in the questionnaire were physical examination, imaging study, tumor markers, and any of their combination. Various options of imaging study techniques included ultrasonography (US), computed tomography scan (CT-scan), magnetic resonance imaging (MRI), and positron emission tomography scan (PET scan).The type of neoadjuvant therapy prior to a delayed primary surgery for the patients whose diseases seemed to be inoperable was also assessed.

The association of working features of the respondents and method to assess the operability and options of neoadjuvant therapy was studied. These features included the type of working hospitals, duration of practice, and adequacy of the medical personnel. The hospitals were classified by ownership/administration system (governmental versus private), level/size (secondary- or tertiary-level with $<$ or $\geq$300 in-patient beds, respectively), and mission (service-only versus gynecologic oncology fellowship training). The duration of practice which referred to only practice in gynecologic oncology was divided into $<$ or $\geq$5 years as an indicator of the respondents' experience. The adequacy of gynecologic oncologists and other medical professionals including radiation oncologists and chemotherapy nurses were determined according to the perception of the respondents themselves.

Statistical analyses performed using SPSS computer software version 22.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics used to report patterns of practice in each aspect. Differences between the comparison groups were determined by using the χ^2 and Fisher's exact test, whenever appropriate. All statistical tests were two-sided, and a *p*-value of less than 0.05 was considered statistically significant.

Results

Among 170 gynecologic oncologists who responded, various methods were used to assess the operability in apparently advanced EMC (Table 1). Very limited percentages of the respondents (only 4.7%) accounted for only physical examination whereas nearly half (48.8%) additionally requested for imaging study and the other 20.6% had additional tumor marker assessment. Of interest, approximately one fourth (25.9%) relied only on imaging study to assess the operability.

Among options of imaging studies, CT scan was most commonly selected (84.1%) followed by MRI (32.4%) and US (26.5%). Of note, CT scan was selected as the only imaging technique in 81 respondents (47.6%) whereas MRI, PET scan, or US was selected as the sole option in 16 respondents for MRI or PET scan (8 or 4.7% each) and 9 for US (5.3%). The other 34 (20.0%) selected either CT scan, MRI, or US whereas 22 (12.9%) required either only

Table 1. Methods used in the assessment of operability in apparently advanced endometrial cancer (n = 170)

Assessment of operability	n (%)
Methods to assess the operability	
Physical examination only	8 (4.7)
Physical examination and imaging study	83 (48.8)
Physical examination, imaging study, and tumor markers	35 (20.6)
Imaging study only	44 (25.9)
Imaging study used to assess the operability*	
Ultrasonography	45 (26.5)
Other special imaging	153 (90.0)
CT-scan	143 (84.1)
MRI	55 (32.4)
PET scan	8 (4.7)

* One respondent may select ≥1 imaging studies

Table 2. A special imaging study to assess operability in clinical advanced endometrial cancer by working features of the respondents (n = 170)

Features of respondents	Imaging study		*p*-value
	Only ultrasonography or no imaging, n = 17	Other special imaging studies, n = 153	
Hospital setting			0.221
Government, n = 152	17 (11.2)	135 (88.8)	
Private, n = 18	-	18 (100.0)	
Level of hospital			0.742
Secondary, n = 28	2 (7.1)	26 (92.9)	
Tertiary, n = 142	15 (10.6)	127 (89.4)	
Type of service			0.022
Service/training, n = 86	4 (4.7)	82 (95.3)	
Service only, n = 84	13 (15.5)	71 (84.5)	
Duration of practice			0.641
<5 years, n = 71	8 (11.3)	63 (88.7)	
≥5 years, n = 99	9 (9.1)	90 (90.9)	

Table 3. Options of neoadjuvant treatment in endometrial cancer patients who seemed to be inoperable

Type of neoadjuvant treatment	n = 167* (%)
Radiation	56 (33.5)
Chemotherapy	98 (58.7)
Radiation/chemotherapy	70 (41.9)

* Three respondents who chose only supportive care without any neoadjuvant therapy were not included and one respondent may select one or more options of neoadjuvant therapy

CT scan or MRI.

Because US is the most accessible (available bedside in most hospitals) and most frequent imaging study in gynecologic practice, the use of other special imaging studies were compared between the respondents by their US use. The respondents who did not perform US (n = 125) tended to request for a special imaging study to screen the operability more frequently than the respondents who used US (n = 45): 92.8% (116/125 respondents) vs. 82.2% (37/45) respectively (p = 0.077). On the other hand, 7.2% of respondents (9/125) who did not perform US neither requested other imaging studies.

The methods of pre-operative assessment for operability according to work setting and duration of practice of the respondents were studied (Table 2). We found the respondents who worked in private, secondary-level, and training hospitals used special imaging more frequently. The difference was statistically significant only between those working in training compared to a service-only hospital.

Regarding the treatment for the patients who deemed to be inoperable, neoadjuvant chemotherapy was the most common selected mode of treatment (58.7%), followed by chemotherapy combined with radiation (41.9%), and radiation therapy alone (33.5%) (Table 3). To be noted, chemotherapy alone was selected as the sole therapeutic option in 34.7% (n = 58) whereas radiation plus chemotherapy or radiation therapy alone was selected in 27.5% (n = 46) and 12.0% (n = 20) respectively.

The type of neoadjuvant treatment selected by the gynecologic oncologists was assessed by their working features (Table 4). The respondents who worked in government and training hospitals used radiation therapy significantly more frequently than their comparative groups. On the other hand, those who worked in a private hospital or had been practicing for <5 years used combined radiation and chemotherapy more frequently (significant only for the duration of practice).

The influence of personnel adequacy on the type of treatment was also analyzed. We did not find any impact on the adequacy of gynecologic oncologists, radiation oncologists, and chemotherapy nurses on the option of neoadjuvant treatment (Table 5).

Discussion

When the benefit of optimal cytoreduction in EMC had become recognized, the aim of surgery in EMC is similar to that of ovarian cancer to remove tumors as much as possible[6]. In a circumstance when the optimal surgery for EMC was doubtful, preoperative judgment is critical to guide whether the standard primary surgery should be proceeded or an alternative option of neoadjuvant therapy should be given.

From this survey, various methods were used by the gynecologic oncologists to assess the extent of disease to determine the chance of optimal surgery. Most respondents had radiologic assessment along with physical examination (nearly 50%). Additional tumor markers were measured in the other 21%. Surprisingly, 26% did not rely on findings from physical examination to judge the operability, but only imaging study. Being a survey study, the actual practice

Table 4. Type of neoadjuvant treatment according to working feature of the respondents (n = 167)

Clinical setting	Neoadjuvant treatment					
	RT	*p*-value	CMT	*p*-value	Combined RT/CMT	*p*-value
Hospital setting		0.009		0.753		0.069
Government, n = 152	55 (36.2)		87 (57.2)		59 (38.8)	
Private, n = 18	1 (5.6)		11 (61.1)		11 (61.1)	
Level of hospital		0.328		0.719		0.537
Secondary, n = 28	7 (25.0)		17 (60.7)		13 (46.4)	
Tertiary, n = 142	49 (34.5)		81 (57.0)		57 (40.1)	
Type of service		0.022		0.625		0.420
Service/training, n = 86	35 (40.7)		48 (55.8)		38 (44.2)	
Service only, n = 84	21 (25.0)		50 (59.5)		32 (38.1)	
Experience		0.840		0.111		0.022
<5 years, n = 71	24 (33.8)		46 (64.8)		22 (31.0)	
≥5 years, n = 99	32 (32.3)		52 (52.5)		48 (48.5)	

CMT = chemotherapy, RT = radiation therapy

Table 5. Type of neoadjuvant treatment according to personnel factor

Personnel	Neoadjuvant treatment (n = 167)					
	RT n (%)	*p*-value	CMT n (%)	*p*-value	Combined CMT/RT n (%)	*p*-value
Adequacy						
Gynecologic oncologist		0.248		0.251		0.541
Adequate, n = 122	37 (30.3)		67 (54.9)		52 (42.6)	
Inadequate & not available, n = 48	19 (39.6)		31 (64.6)		18 (37.5)	
Radiation oncologist		0.324		0.571		0.984
Adequate, n = 87	30 (34.5)		51 (58.6)		36 (41.4)	
Inadequate & not available, n = 34	15 (44.1)		19 (55.9)		14 (41.2)	
Chemotherapy nurse		0.777		0.174		0.316
Adequate, n = 97	33 (34.0)		60 (61.9)		37 (38.1)	
Inadequate & not available, n = 72	23 (31.9)		37 (51.4)		33 (45.8)	
Total	56 (33.5)		98 (58.7)		70 (41.9)	

CMT = chemotherapy, RT = radiation therapy

whether they absolutely precluded physical examination or rather regarded it as not useful regardless of its findings could not be clarified.

In the modern era of medical practice, imaging study has many important roles in various settings: diagnosis, response assessment, and surveillance. In the patients whose diseases seem to be advanced, sites of cancer metastasis and involvement or invasion to other viscera can be screened whether the surgery is possible, safe, and successful[9]. Among several technologies of imaging, a CT scan was most commonly selected in this survey (84%). Although US is generally the most common imaging study in gynecologic practice, this survey found that only 27% of the respondents selected US to evaluate the operability. US has the benefit that it can be performed bedside and could be correlated with findings from the pelvic examination, however, some limitations are recognized. Ultrasonography certainly requires the skills of the operator. Furthermore, it may be difficult to assess the anatomical relationship of the lesion with other viscera, especially in the upper abdomen. Another possible reason in real clinical practice was the regulation in some hospitals that all imaging studies had to be performed by a radiologist. In these circumstances, some gynecologic oncologists might tempt to skip this US study and directly requested special imaging studies. As demonstrated in this survey that CT scan, MRI or PET scan was used as high as 90%.

From subgroup analyses, the respondents who were in training hospitals used special imaging studies significantly more frequently than those in service-only

hospitals. This was probably because these training hospitals were likely to be the referral center for a difficult case (more advanced). Furthermore, these training hospitals were usually well equipped with high technology instruments, so more accessible to special studies.

Generally, the diagnostic performances of these imaging studies are comparable except MRI which may yield better resolution for soft tissue invasion whereas PET scan can provide images of most viscera in the body[10,11]. The present study found a CT scan to be the most common special imaging study selected. This was probably because it was more widely available than an MRI or PET scan.

Regarding the therapy before surgery, this survey found chemotherapy was the most common option (58%) followed by combined chemotherapy and radiation (41%) and radiation therapy alone (33%). With the expanding role of chemotherapy from salvage to adjuvant treatment, its role as a neoadjuvant treatment in EMC was also reported. Several cases series or retrospective studies demonstrated good survival outcomes of advanced stage EMC patients receiving neoadjuvant chemotherapy[12-16]. One large retrospective study which included 426 patients with stage IV EMC patients who had primary surgery or neoadjuvant chemotherapy before surgery reported comparable survival of the patients in both groups[16]. The only prospective study of neoadjuvant chemotherapy including 30 stage IV EMC patients with transperitoneal spread (the majority having serous carcinoma) also demonstrated successful outcomes: 74% responded to neoadjuvant chemotherapy and 20% had stable disease and 80% achieved optimal cytoreduction[17].

Regarding the option of neoadjuvant treatment, there were no differences in the frequency of neoadjuvant chemotherapy treatment among the respondents working in different hospital settings or experience were demonstrated. This was probably because chemotherapy is available in all hospitals serving cancer patients and the ease of administration system. Albeit less than chemotherapy use, radiation therapy was also used by the respondents working in government and training hospitals more frequently than their comparative groups. This was likely because the radiation machine is a specialized and costly instrument requiring radiation oncologists along with radiotherapy technicians, so it is available only in large medical centers. On the other hand, combined chemotherapy and radiation treatment was used more frequently among the respondents who worked in a private hospital or had worked ≥5 years (significant only for the longer work duration). One possible reason was that there were data from some studies showing activity of combined chemotherapy and radiation as adjuvant treatment, so the gynecologic oncologists in a private or longer duration of practice tended to be more alert and expected the best of outcomes with this modern modality of neoadjuvant treatment.

Conclusion

Most Thai gynecologic oncologists used imaging study with or without tumor markers to assess the operability in advanced endometrial cancer. The most common pre-operative imaging used was a CT scan. Chemotherapy alone or combined with radiation was more commonly used as neoadjuvant therapy than radiation alone which tends to have a more definite role in the patients who were less likely to be able to undergo surgery. A retrospective study with data collection in a multicenter fashion or prospective study is warranted to obtain a clear benefit of this neoadjuvant treatment.

What is already known on this topic?

Surgery is the mainstay of treatment for endometrial cancer patients. A gynecologic oncologist may use imaging study aside from physical examination among the patients with the advanced-stage disease to evaluate the extent of disease and the chance of optimal surgery. In the patients whose diseases are extensive and are expected to have suboptimal surgery, various types of neoadjuvant therapy i.e. radiation, chemotherapy, or both may be used to reduce tumor burden before considering surgery.

What this study adds?

Approximately 75% of the Thai gynecologic oncologists reported the use of imaging study to evaluate the chance of optimal debulking surgery in advanced stage endometrial cancer. CT scan as the most common mode of study. The rates of imaging study use were different among the Thai gynecologic oncologists who worked in various hospital settings. In the patients who deemed inoperable, chemotherapy with radiation or without radiation was more frequently used than radiation therapy alone as neoadjuvant therapy. The option of neoadjuvant treatment varied among the gynecologic oncologists working with different hospital features and with different duration of practice.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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การประเมินก่อนผ่าตัดและการรักษาที่ใช้ก่อนการผ่าตัดสำหรับมะเร็งเยื่อบุโพรงมดลูกระยะลุกลาม: การสำรวจแนวปฏิบัติของแพทย์มะเร็งนรีเวชไทย

ศุภกร พิทักษ์การกุล, ศรัญญา ชาญพานิชกิจโชติ, จตุพล ศรีสมบูรณ์, ศิริวรรณ ตั้งจิตกมล, สมาคมมะเร็งนรีเวชไทย

วัตถุประสงค์: เพื่อศึกษาวิธีการที่แพทย์มะเร็งนรีเวชไทยใช้ในการประเมินผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะลุกลามก่อนการผ่าตัดและวิธีการรักษาที่ใช้ก่อนการผ่าตัด

วัสดุและวิธีการ: การศึกษานี้เป็นส่วนหนึ่งของโครงการสำรวจระดับประเทศโดยสมาคมมะเร็งนรีเวชไทย เกี่ยวกับแนวปฏิบัติในการดูแลรักษามะเร็งนรีเวชของแพทย์มะเร็งนรีเวชไทย ที่ปฏิบัติงานมาแล้วอย่างน้อย 1 ปี การศึกษารวบรวมข้อมูลจากการตอบแบบสอบถามออนไลน์ตั้งแต่เดือนสิงหาคมถึงเดือนตุลาคม พ.ศ. 2562 รายงานนี้นำข้อมูลที่เกี่ยวกับวิธีการ ที่แพทย์ใช้ในการประเมินผู้ป่วยก่อนการผ่าตัด และวิธีการรักษาต่างๆ ที่ใช้ก่อนการผ่าตัดในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะลุกลามมาศึกษาวิเคราะห์

ผลการศึกษา: จากผู้ตอบแบบสอบถามทั้งหมด 170 ราย พบว่า ร้อยละ 48.8 ของผู้ตอบใช้วิธีการตรวจร่างกายร่วมกับการใช้รังสีวินิจฉัย ในขณะที่ร้อยละ 25.9 ใช้รังสีวินิจฉัยอย่างเดียวในการประเมินก่อนผ่าตัด วิธีทางรังสีวินิจฉัยที่ใช้มากที่สุด คือ เอกซเรย์คอมพิวเตอร์ซีทีสแกน คือ ร้อยละ 84.1 ผู้ตอบแบบสอบถามที่ปฏิบัติงานในโรงพยาบาลที่มีการฝึกอบรมมีสัดส่วนการใช้รังสีวินิจฉัยเทคนิคพิเศษ (ที่ไม่ใช่การตรวจคลื่นเสียงความถี่สูง) มากกว่าผู้ที่ปฏิบัติงานในโรงพยาบาลที่ให้บริการเพียงอย่างเดียว คือ ร้อยละ 95.3 เทียบกับร้อยละ 84.5 (p = 0.022) สำหรับวิธีการรักษาก่อนการผ่าตัดพบว่า ผู้ตอบแบบสอบถามใช้วิธีการรักษาด้วยยาเคมีบำบัดมากที่สุด คือ ร้อยละ 58.7 ตามด้วยวิธีเคมีบำบัดร่วมกับรังสีรักษา ร้อยละ 41.9 และรังสีรักษาอย่างเดียว ร้อยละ 33.5 พบว่า ผู้ตอบแบบสอบถามที่ปฏิบัติงานในโรงพยาบาลรัฐ และโรงพยาบาลที่มีการฝึกอบรมให้การรักษาด้วยรังสีรักษาก่อนการผ่าตัดมากกว่าผู้ที่ปฏิบัติงานในโรงพยาบาลเอกชนและโรงพยาบาลที่ให้บริการเพียงอย่างเดียว คิดเป็นร้อยละ 36.2 เทียบกับร้อยละ 5.6 (p = 0.009) และร้อยละ 40.7 เทียบกับร้อยละ 25.0 (p = 0.022) ตามลำดับ ผู้ตอบแบบสอบถามที่มีประสบการณ์การทำงานมากกว่าหรือเท่ากับ 5 ปี มักให้การรักษาด้วยเคมีบำบัด ร่วมกับรังสีรักษาบ่อยกว่าผู้ที่มีประสบการณ์การทำงานน้อยกว่า คือ ร้อยละ 48.5 เทียบกับ 5 ปี ร้อยละ 31.0 (p = 0.022)

สรุป: แนวปฏิบัติในการประเมินผู้ป่วยก่อนการผ่าตัดและวิธีการรักษาต่างๆ ก่อนการผ่าตัดในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะลุกลามของแพทย์มะเร็งนรีเวชในประเทศไทยมีความแตกต่างกัน ซึ่งปัจจัยที่มีผลในการเลือกวิธีการรักษาได้แก่ ลักษณะของโรงพยาบาลที่ปฏิบัติงานรวมถึงประสบการณ์การทำงานของแพทย์