

Management of Advanced, Metastatic, and Recurrent Cervical Cancer: Survey of Practice among Thai Gynecologic Oncologists

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Objective: To evaluate the current practice of Thai gynecologic oncologists in the management of patients with advanced, metastatic, and recurrent cervical cancer.

Materials and Methods: This study was a part of the national practice survey on the management of gynecologic cancer in Thailand. All Thai gynecologic oncologists were targeted in the survey. This study retrieved the data regarding the practice of management of advanced-stage cervical cancer and recurrent disease.

Results: Of 170 respondents, 90% used combination platinum/paclitaxel chemotherapy as a first-line treatment for patients with advanced and recurrent diseases. The combination of chemotherapy was used in about 81.8% and 27.6% in first-line and further line treatments, respectively. Single cisplatin was used in 14.1% as the second-line. Palliative treatment without chemotherapy was considered increasingly after first-line treatment and significantly more likely to implement among service hospitals compared to the comparative setting (8.9% vs. 1.2%; $p = 0.030$). Up to 36.6% (30/82) of the respondents who worked in training hospitals preferred to use targeted therapy, i.e. bevacizumab compared to 21.3% (16/75) of respondents who worked in service hospitals ($p = 0.04$).

Conclusion: Combination platinum-based chemotherapy was commonly used as the first-line treatment for advanced and recurrent cervical cancer. The respondents in training hospitals were more likely to use targeted therapy than those in the service hospitals.

Keywords: Cervical cancer, Advanced cervical cancer, Recurrent cervical cancer, Chemotherapy, Targeted therapy, Practice, Survey

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Cervical cancer is the fourth most common female cancer worldwide. From the report of GLOBOCAN 2018, there were approximately 570,000 new cases of cervical cancer with 311,000 deaths from this disease per year. In Thailand, cervical cancer is the second most common malignancy in women with an age-standardized incidence rate of 11.7 per 100,000 women per year resulting in approximately 8,600 new cases and 5,000 deaths annually^(1,2). Nationwide, locally advanced cervical cancer (stage II to IV) accounts for 5 to

54% of the new cases⁽²⁾. Distant metastatic stage or stage IVB is quite uncommon accounting for 2 to 6% of cervical cancer⁽³⁾. Patients with distant metastases have a poor prognosis with highly persistent and recurrent rates after the primary treatment. The median survival of patients initially presented with systemic metastasis was approximately 7 months⁽⁴⁾. The prognosis of patients with locally advanced cervical cancer is also unpleasant; approximately 30 to 70% of them will recur after complete primary treatment^(3,5). The recurrence usually occurs within the first 3 years after primary treatment, almost 50 to 60% of the recurrence was outside pelvis^(4,6).

The patients who experience recurrence may be candidates for comprehensive care with palliative aims such as chemotherapy, radiotherapy to lesions outside the previously irradiated field, pelvic exenteration in selected patients with limited pelvic lesions, or best supportive care⁽⁶⁾.

Chemotherapeutic agents and targeted therapy are

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the options for patients who have good performance status, limited distant metastases, and without contraindications⁽⁷⁾. Single cisplatin or cisplatin-based doublets containing topotecan or paclitaxel, with or without bevacizumab, have been recommended for patients with advanced, metastatic, or recurrent cervical cancer^(7,8).

Despite available standard guidelines, disparities of cervical cancer management among gynecologic oncologists were reported⁽⁹⁾. The diversity of management could be due to some factors e.g. the patients' condition, their health coverage scheme, physicians' experience, and expertise, etc. This national survey was undertaken by the Thai Gynecologic Cancer Society (TGCS) to assess the practice of the Thai gynecologic oncologists on cervical cancer patients focusing on the management of advanced, metastatic, and recurrent diseases.

Materials and Methods

This study was a part of the national survey of practice in gynecologic cancer treatment undertaken by the Thai gynecologic oncologists. The Ethical Review Committee of each affiliating institution approved the study. Details of materials and methods were described in the primary work (COAs/IRBs: Faculty of Medicine Chulalongkorn University, 337/63; Faculty of Medicine Siriraj Hospital Mahidol University, 457/2020; Rajavithi Hospital, 104/2562; Faculty of Medicine ChiangMai University, OBG-2562-06506)⁽¹⁰⁾. In brief, Thai gynecologic oncologists who had worked for at least one year and currently working in the country were invited to respond to the online questionnaire via <https://forms.gle/e1WsBLcX5jVsXVgG8> between August and October 2019.

Data from the respondents regarding their clinical practice in an advanced stage and recurrent cervical cancer were retrieved from the survey database. The information on demographic data of gynecologic oncologists and their hospital setting, current clinical practice of the management of advanced, metastasis and recurrent cervical cancer were retrieved.

Statistical analyses were performed using SPSS computer software version 22 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were summarized by

frequency and percentage, mean and standard deviation (SD), or median and range, according to the distribution of data. The association between interesting treatment options and responders' characteristics was applied by Pearson's Chi-squared or Fisher's exact test when appropriated. A *p*-value of 0.05 was considered as the level of statistical significance.

Results

Among 170 Thai gynecologic oncologists who responded to the questionnaires, about two-thirds were female. The mean age was 41.1±8.3 years. Nearly 90% of the respondents worked in government hospitals, and most of them (over 80%) were tertiary-care hospitals. Eighty-six respondents (50.6%) worked in institutions that had a fellowship training program, training hospital. The median of gynecologic oncologists in each hospital was 6 (ranged from 1 to 19).

For patients with advanced-stage cervical cancer and recurrent diseases, the majority of Thai gynecologic oncologists used platinum-based doublet chemotherapy as the first-line treatment. These included paclitaxel/cisplatin (51.2%: 86/168) followed by paclitaxel/carboplatin (39.9%: 67/168). Single cisplatin was less common (19.6%: 33/168). For second-line treatment, the 2 top-ranked chemotherapy regimens were platinum/gemcitabine (37.4%: 61/163) and paclitaxel/carboplatin (36.8%: 60/163), respectively. Although both cisplatin/paclitaxel (14.7%: 24/163) and single cisplatin (14.1%: 23/163) were uncommonly prescribed, they also reported in the second-line regimen.

Beyond second-line treatment, platinum/gemcitabine was the most common chemotherapy regimen selected by the respondents (22.8%: 37/162). To be noted, a prescription of single cisplatin which was the second most common drug selected in the beyond second-line regimen (14.8%: 24/162). The use of combination cisplatin or carboplatin with paclitaxel in this setting decreased to 4.3% (7/162) and 3.1% (5/162), respectively.

Regarding the palliative treatment without chemotherapy, which was not selected by any respondents as the first-line treatment, increased to 4.9% (8/163) and 57.4% (93/162) for the second- and beyond second-line treatment, respectively. Table 1 shows chemotherapy

Table 1. Chemotherapy regimens chosen by the respondents for the treatment of advanced and recurrent cervical cancer categorized by first-, second-, and beyond second-line treatment

Treatment for cervical cancer	First-line: n (%) n = 168	Second-line: n (%) n = 163	Further line: n (%) n = 162
Cisplatin	33 (19.6)	23 (14.1)	24 (14.8)
Paclitaxel/Carboplatin	67 (39.9)	60 (36.8)	5 (3.1)
Paclitaxel/Cisplatin	86 (51.2)	24 (14.7)	7 (4.3)
Platinum/gemcitabine	1 (0.6)	61 (37.4)	37 (22.8)
Palliative (without chemotherapy)	-	8 (4.9)	93 (57.4)

* One respondent may select more than one treatment option. There are not selected any treatment by two, seven and eight respondents, missing data, for first-, second- and beyond second-line, respectively

regimens categorized by first-line, second-line, and beyond second-line treatment.

The respondents reported best supportive care without chemotherapy in the patients who failed first-and second-line treatment at 4.9% and 57.4%, respectively. Palliative treatment was significantly common in the patients who failed first-line chemotherapy in the service hospitals compared to training hospitals (8.9% vs. 1.2%, $p = 0.030$). No difference among the respondents' characteristics and the response of palliative treatment only in the patients who failed second-line chemotherapy (Table 2).

Among 170 respondents, 157 responded to the query of targeted therapy. The targeted therapy, bevacizumab, had ever been used by 46 respondents (29.3%) with the median frequency of 5% (range 1 to 50%) of their patients. The use of bevacizumab was significantly higher among the respondents who worked in training hospitals than those in service-only hospitals: 36.6% (30/82) versus 21.3% (16/75) respectively, $p = 0.04$. The respondents had ever been used targeted therapy significantly higher in hospitals which had the number of gynecologic oncologists more than six: 15.9% (11/69) versus 39.8% (35/88) respectively, $p < 0.01$ (Table 3).

Discussion

This study represents a practice of Thai gynecologic oncologists focusing on the management of patients with advanced, metastatic, and recurrent cervical cancer. Chemotherapy regimens were variously selected in different settings. Platinum-based doublets were prescribed in nearly 90% of the respondents as the first-line regimen

whereas one-fifth of the respondents considered single cisplatin in this setting.

The more common use of doublets over single agent in this survey was probably based on the awareness of the Thai gynecologic oncologists regarding a superior clinical benefit in terms of progression-free survival (PFS) or overall survival (OS) of cisplatin-based chemotherapy combined drugs over single cisplatin from previous studies^(11,12). Data from the 2 large trials by the Gynecologic Oncology Group (GOG 169, GOG 179) demonstrated that PFS of the patients with advanced/recurrent cervical cancer was significantly higher with cisplatin combined with paclitaxel or with topotecan than cisplatin alone^(11,12). Additional significant benefit on OS was also demonstrated with the cisplatin/topotecan⁽¹²⁾.

Among the combination chemotherapy used in the first-line setting, almost half of the respondents in this survey reported cisplatin/paclitaxel as the most common chemotherapy regimen. This finding may be due to the well-recognized evidence-based data as described above and the recommendation by the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines^(7,8). Although cisplatin/topotecan which deemed to be more useful than cisplatin/paclitaxel because of the additional benefit on OS, this doublet was not selected by any respondents in any settings of treatment. Few obvious reasons for this finding were because this regimen was associated with a high rate of adverse events especially hematologic toxicity which may not be appropriate for this particular group of patients who had frequently been treated with radiation therapy.

Table 2. Palliative treatment without chemotherapy chosen for the patients who failed first- or second-line chemotherapy by characteristics of the respondents

Respondents' characteristics	The setting of the patients					
	Failed first-line chemotherapy, n = 163			Failed second-line chemotherapy, n = 162		
	Palliative n = 8	Chemotherapy n = 155	p-value	Palliative n = 93	Chemotherapy n = 69	p-value
Hospital setting						
Government	7 (4.7)	141 (95.3)	0.55	84 (57.1)	63 (42.9)	0.83
Private	1 (6.7)	14 (93.3)		9 (60.0)	6 (40.0)	
Level of hospital						
Secondary	2 (8.3)	22 (91.7)	0.33	11 (45.8)	13 (54.2)	0.21
Tertiary	6 (4.3)	133 (95.7)		82 (59.4)	56 (40.6)	
Mission of hospital						
Training	1 (1.2)	83 (98.8)	0.03	49 (58.3)	35 (41.7)	0.81
Service	7 (8.9)	72 (91.1)		44 (56.4)	34 (43.6)	
Experience of respondents						
<5 years	3 (4.3)	66 (95.7)	1.00	34 (49.3)	35 (50.7)	0.07
≥5 years	5 (5.3)	89 (94.7)		59 (63.4)	34 (36.6)	
Number of gynecologic oncologists						
<6	6 (8.2)	67 (91.8)	0.14	39 (54.2)	33 (45.8)	0.46
≥6	2 (2.2)	88 (97.8)		54 (60.0)	36 (40.0)	

Table 3. Association between the targeted therapy prescription and respondents' characteristics

Respondents' characteristics	Total number	Targeted therapy prescription: n (%)		p-value
		Ever prescribed: n = 46	Never prescribed: n = 111	
Hospital setting				
Government	140	41 (29.3)	99 (70.7)	1.00
Private	17	5 (29.4)	12 (70.6)	
Level of hospital				
Secondary	24	8 (33.3)	16 (66.7)	0.64
Tertiary	133	38 (28.6)	95 (71.4)	
Mission of hospital				
Academic	82	30 (36.6)	52 (63.4)	0.04
Service		16 (21.3)	59 (78.7)	
Experience				
<5 years	67	16 (23.9)	51 (76.1)	0.20
≥5 years	90	30 (33.3)	60 (66.7)	
Number of staff				
<6	69	11 (15.9)	58 (84.1)	<0.01
≥6	88	35 (39.8)	53 (60.2)	

Furthermore, this regimen had a high cost and could be reimbursed only by the government or state enterprise officers.

The second most common chemotherapy regimen reported as the first-line drugs were carboplatin/paclitaxel (39%). The main reasons for this finding were evidence-based data from the Japanese trial (JCOG 0505) showing comparable OS in metastatic/recurrent cervical cancer by the use of carboplatin/paclitaxel or cisplatin/paclitaxel: OS of 18.3 months vs. 17.5 months, respectively (hazard ratio of 0.99; 90% CI 0.79 to 1.25)⁽¹³⁾. Subsequently, this carboplatin/paclitaxel was also included in the NCCN and ESMO guidelines as the other recommended first-line combination therapy regimens for patients with metastatic/recurrent cervical cancer^(7,8). Lastly, this carboplatin/paclitaxel was easy to administer, had tolerable and manageable toxicities, and was more familiar to the gynecologic oncologists due to its common use in ovarian cancer.

The present study demonstrated that nearly 20% of the respondents selected cisplatin as first-line chemotherapy. This was following the NCCN guideline which recommended cisplatin as the preferred first-line single-chemotherapeutic agent for metastatic/recurrent cervical cancer⁽⁸⁾. Being a survey study with a general question, this study did not explore the reason why or specific scenarios that the respondents considered specific chemotherapy regimen for the patients.

Approximately one-third of the patients with metastatic/recurrent cervical cancer will respond to first-line chemotherapy, however, the response will be of short duration, and other episodes of recurrences frequently occur. Subsequent treatment is usually tailored by the patients' status, co-morbidities, and prior treatments. To date, there

had been no shreds of evidence supporting the promising chemotherapy for metastatic/recurrent cervical cancer which progressed after the first-line chemotherapy; the response rates from various drugs varied from 5 to 29%⁽⁶⁾. Hence, various second- or further-line chemotherapy regimens were demonstrated in this survey study. As described earlier that this survey study did not specify the condition in which chemotherapy would be used e.g. progression- or recurrence-free interval especially the platinum-free period which may impact the subsequent regimen selected. So combined paclitaxel/carboplatin was still selected as second-line drugs as high as 35.9%. Another chemotherapy regimen which was selected as high as 35.9% and 21.8% in the second- and further-line settings was platinum/gemcitabine. This finding may be based on evidence-based data showing its efficacy in advanced and recurrent cervical cancer⁽¹⁴⁾ and its relatively low cost, widely available, and be included in most reimbursement systems. Although several recent updated guidelines suggest several single-agents as second-line drugs, such as pembrolizumab, bevacizumab, albumin-bound paclitaxel, docetaxel, gemcitabine, ifosfamide, and topotecan^(3,6-8), this survey found that cisplatin was the only single-agent reported by the respondents. This may be because of the acceptable toxicity, low cost, and coverage of the reimbursement systems.

Many international guidelines preferred a combination of platinum-based doublets of topotecan or paclitaxel with the addition of bevacizumab⁽¹⁵⁾. This was based on evidence-based data from a large phase III clinical trial (GOG 240) which demonstrated a significant improvement of OS (17.0 months vs. 13.3 months; HR 0.71, $p = 0.004$) and PFS (8.2 months vs. 5.9 months; HR 0.67, $p = 0.002$) by adding bevacizumab to back-bone

chemotherapy⁽¹⁵⁾. The benefit from incorporating bevacizumab to standard chemotherapy remained sustained after a longer period of follow-up, OS of 16.8 months vs. 13.3 months (HR 0.77, $p = 0.007$)⁽¹⁶⁾. Despite this obvious benefit and guideline recommendation of adding bevacizumab to standard chemotherapy, only 29% of the respondents in this survey had experiences in using bevacizumab in their practice with a low frequency of use of only 10%. The main reason for its limited use was its high cost and not included in the National List of Essential Medicines (NLEM) of Thailand. Nevertheless, some patients may be able to subsidize for the cost of bevacizumab themselves especially those seeking medical service in a large and training hospital which usually located in urban areas with higher financial status than the service hospitals which frequently located in suburban areas with lower financial privileges. This was found in this study that the respondents in training hospitals, had fellow training and had the number of gynecologic oncologists more than six, used bevacizumab significantly more frequent than the respondents in the other comparative settings. The possible reasons were the respondents in these academic hospitals were more familiar with this drug as well as its toxicities, and with a greater number of colleagues with the team, the discussion might have led to more frequent use.

Palliation with the best supportive care is one of the crucial parts of treatment for any advanced-stage cancer. The goals of palliative care are to relieve symptoms and maintain quality of life during the terminal stage. Palliative care should be started early in treatment and can be changed along with the course of the disease⁽¹⁷⁾. One literature showed that only 1% of the health care providers reported referring patients for palliative care⁽¹⁸⁾. Upon this survey, service hospital staff tend to implement palliative care earlier than the academic hospital staff ($p = 0.02$) when progressive/persistent diseases occurred after the first-line regimen. Limited access to further-line chemotherapy might be another possible reason. Eventually, when the diseases are incurable, both academic and service hospital staff consider palliative care in their practice.

The fundamental limitation of this study was the nature of the survey research. Findings of this survey research were vulnerable to various biases, especially social desirability and recall biases. In addition, the survey findings were summarized based on self-reported data and it thus might not indicate their real practices. The relatively high response rate is a strength of this survey.

Conclusion

This study reported the practice of Thai gynecologic oncologists in the management of cervical cancer focusing on advanced, metastatic, and recurrent diseases. Combination platinum-based chemotherapy was commonly used in metastatic/recurrent cervical cancer for the first-, second-, and further-line treatment, while single cisplatin was used in 13.5 to 19.4%. The respondents working in academic hospitals tended to use targeted therapy more than those working in service hospitals.

What is already known on this topic?

Chemotherapy and palliative treatment are the mainstays of advanced, metastatic, and recurrent cervical cancer management. There were many evidence-based data demonstrated survival benefits from combination chemotherapy and targeted therapy in good performance patients. The platinum-based regimen was commonly used in current practice especially in first-line treatment. However, the standard treatment beyond the second line was controversy regarding survival benefit.

What this study adds?

The Thai gynecologic oncologists commonly used combination platinum-based regimen as the first-line treatment for advanced, metastatic, and recurrent cervical cancer. Palliative without chemotherapy was implemented in beyond second-line treatment in more than half of respondents. Although, the addition of targeted therapy to standard chemotherapy demonstrated survival benefit, Thai gynecologic oncologists humbly used this regimen. The variation of these practices was associated with hospital features.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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การดูแลรักษามะเร็งปากมดลูกระยะลุกลามแพร่กระจายและมะเร็งปากมดลูกกลับเป็นซ้ำ: การสำรวจแนวปฏิบัติของแพทย์มะเร็งเร็งนรีเวชไทย

วุดินันท์ อัจฉริยะโพธา, ณัฐกฤตา โพธิ์พรธวัช, พีรพงศ์ อินทสร, วิชัย เดิมรุ่งเรืองเลิศ, จตุพล ศรีสมบูรณ์, ศรัณยูชา ชาญพานิชกิจโชติ, ชื่นกมล ชรากร, กิตติศักดิ์ เจริญขวัญ, สมาคมมะเร็งนรีเวชไทย

วัตถุประสงค์: เพื่อศึกษาแนวทางเวชปฏิบัติของแพทย์มะเร็งนรีเวชไทยในการรักษามะเร็งปากมดลูกระยะลุกลามแพร่กระจายและมะเร็งปากมดลูกที่กลับเป็นซ้ำ

วัตถุประสงค์และวิธีการ: การศึกษานี้เป็นส่วนหนึ่งของการสำรวจระดับประเทศที่เกี่ยวข้องกับแนวทางปฏิบัติสำหรับมะเร็งนรีเวช จัดทำโดยสมาคมมะเร็งนรีเวชไทยโดยมุ่งเป้าไปที่แพทย์มะเร็งนรีเวชทั้งหมด การศึกษานี้ได้ทำการวิเคราะห์ข้อมูลที่เกี่ยวข้องกับการรักษามะเร็งปากมดลูกระยะลุกลามแพร่กระจายและมะเร็งปากมดลูกที่กลับเป็นซ้ำ

ผลการศึกษา: สำหรับผู้ตอบแบบสอบถาม 170 คน พบว่าประมาณร้อยละ 90 พิจารณาเลือกใช้ยาเคมีบำบัดชนิด platinum (cisplatin หรือ carboplatin) ร่วมกับ paclitaxel เป็นการรักษาขนานแรกในผู้ป่วยมะเร็งปากมดลูกระยะลุกลามแพร่กระจายและมะเร็งปากมดลูกที่กลับเป็นซ้ำ ในขณะที่ผู้ตอบแบบสอบถามประมาณร้อยละ 81.8 และ ร้อยละ 27.6 จะพิจารณาให้ยาเคมีบำบัดหลายชนิดร่วมกันในการรักษาผู้ป่วยเป็นขนานที่สองและขนานที่สาม ตามลำดับ ยาเคมีบำบัด cisplatin ถูกนำมาใช้ในการรักษาขนานที่สองร้อยละ 14.1 การรักษาแบบประคับประคองโดยไม่ให้ยาเคมีบำบัดถูกนำมาใช้เพิ่มขึ้นภายหลังการรักษาขนานแรกโดยเฉพาะอย่างยิ่งในผู้ตอบแบบสอบถามที่ทำงานในโรงพยาบาลที่ไม่มีการฝึกอบรม (ร้อยละ 8.9) เทียบกับ ร้อยละ 1.2 ในกลุ่มเปรียบเทียบ ($p = 0.030$) ผู้ตอบแบบสอบถามที่ทำงานในโรงพยาบาลที่มีการฝึกอบรมมีประสบการณ์ในการใช้การรักษาแบบมุ่งเป้าเช่น bevacizumab ประมาณ ร้อยละ 36.6 ในขณะที่ผู้ตอบแบบสอบถามที่ทำงานในโรงพยาบาลด้านบริการที่เคยใช้การรักษาแบบมุ่งเป้าร้อยละ 21.3 เท่านั้น ($p = 0.036$)

สรุป: การให้ยาเคมีบำบัดแบบหลายขนานที่มียา platinum รวมด้วยเป็นการรักษาที่ใช้อย่างแพร่หลายที่สุดในผู้ป่วยมะเร็งปากมดลูกระยะลุกลามแพร่กระจายและมะเร็งปากมดลูกที่กลับเป็นซ้ำทั้งในการรักษาขนานที่หนึ่ง สองและสาม ผู้ตอบแบบสอบถามที่ทำงานในโรงพยาบาลที่มีการฝึกอบรมมีประสบการณ์ในการใช้การรักษาแบบมุ่งเป้ามากกว่าผู้ที่ทำงานในโรงพยาบาลด้านบริการ
