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Trends in gynecologic cancer mortality in East Asian regions

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Objective: To evaluate uterine and ovarian cancer mortality trends in East Asian countries.

Methods: For three Asian countries and one region (Japan, Korea, Singapore, and Hong Kong), we extracted number of deaths for each year from the World Health Organization (WHO) mortality database, focusing on women ≥20 years old. The WHO population data were used to estimate person-years at risk for women. The annual age-standardized, truncated rates were evaluated for four age groups. We also compared age-specific mortality rates during three calendar periods (1979 to 1988, 1989 to 1998, and 1999 to 2010). Joinpoint regression was used to determine secular trends in mortality. To obtain cervical and uterine corpus cancer mortality rates in Korea, we re-allocated the cases with uterine cancer of unspecified subsite according to the proportion in the National Cancer Incidence Databases.

Results: Overall, uterine cancer mortality has decreased in each of the Asian regions. In Korea, corrected cervical cancer mortality has declined since 1993, at an annual percentage change (APC) of −4.8% (95% confidence interval [CI], −5.3 to −4.4). On the other hand, corrected uterine corpus cancer mortality has abruptly increased since 1995 (APC, 6.7; 95% CI, 5.4 to 8.0). Ovarian cancer mortality was stable, except in Korea, where mortality rates steadily increased at an APC of 6.2% (95% CI, 3.4 to 9.0) during 1995 to 2000, and subsequently stabilized.

Conclusion: Although uterine cancer mortality rates are declining in East Asia, additional effort is warranted to reduce the burden of gynecologic cancer in the future, through the implementation of early detection programs and the use of optimal therapeutic strategies.

Keywords: Mortality, Ovarian neoplasms, Time trends, Uterine neoplasms

INTRODUCTION

Uterine and ovarian cancers are responsible for 10% and 2% of all cancer deaths worldwide, respectively, causing an estimated 489,000 deaths annually. Indeed, cancers of the cervix and ovary are respectively the fifth and seventh most common causes of death from cancer in Asia [1]. It has been estimated that the number of deaths due to uterine and ovarian cancer will reach approximately 347,100 by 2020 in Asia alone [1].

Mortality from cancers of the uterus and ovaries has been declining in Western countries for decades [2-5]. The incidence and mortality rates of gynecologic cancers in Asian countries differ from those in Western countries. Cervical cancer remains a major health problem in East Asia, although incidence rates have been decreasing [6,7]. In recent decades, East Asia has experienced rapid economic growth and social transformation. These socioeconomic changes have resulted in improved treatments and advances in screening. In particular, cervical

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cancer screening programs were introduced as early as the 1980s, and routine gynecologic examination has become popular in East Asian countries. In addition, behavioral factors such as delayed and reduced childbearing, use of hormone-replacement therapy, and reduced physical activity have also become more prevalent among East Asian women. These reproductive and lifestyle changes are associated with higher incidences of uterine corpus and ovarian cancer [8,9]. However, there are few studies on temporal trend in gynecologic cancer mortality in East Asian regions.

Specific trends in gynecologic cancer mortality differ widely by geographic region, age group, and time period. The aim of this study was to report and compare secular trends of uterine and ovarian cancer in Hong Kong, Japan, Korea, and Singapore. We designed our study to fully investigate the different cancer trends that are present in different regions, age groups, and time periods. In addition, we used national cancer incidence data from Korea to correct cervical and uterine corpus cancer mortality rates, which are otherwise substantially biased by missing cancer subsite information in mortality databases.

MATERIALS AND METHODS

1. Data source

The World Health Organization (WHO) obtains data on deaths by age, sex, and cause of death, as reported annually by member states based on their civil registration systems. WHO compiles these data in the WHO mortality database. The 4 East Asian regions with data available for longest period were Japan, Singapore, Korea, and Hong Kong. The coverage of cause of death in the registration systems had increased over 85% since 1990. We extracted annual uterine cancer mortality data for women aged ≥20 years in Hong Kong (1966 to 2009), Japan (1955 to 2010), Korea (1985 to 2010), and Singapore (1966 to 2009) from the WHO mortality database [10]. Ovarian cancer mortality data were also extracted from the same database for Hong Kong (2001 to 2009), Japan (1979 to 2010), Korea (1985 to 2010), and Singapore (1979 to 2009). To obtain estimates of person-years at risk, we used WHO population data [10].

Uterine cancer mortality was defined as deaths in the WHO mortality database that were coded as C53 (uterine cervical cancer), C54 (uterine corpus cancer), or C55 (unspecified uterine cancer), according to the International Statistical Classification of Disease and Related Health Problems, 10th revision (ICD-10) [11]. Assessment of ovarian cancer mortality was based on the ICD-10 code C56. Uterine cervical cancer and uterine corpus cancer have different etiologies and prognoses, and the ICD-10 code C55 (which is, "uterus, unspecified site") makes it difficult to determine the exact cervical and uterine corpus cancer mortality trends [12-15]. To solve this problem, we corrected the number of cervical cancer and uterine corpus cancer deaths using death certificate data during 1993 to 2010 from the Statistics Korea and data on cases of unspecified uterine cancer from the National Cancer Incidence Databases (NCIDB) of Korea [16]. To obtain a corrected count of cervical cancer deaths, we multiplied the total number of registered unspecified uterine cancer deaths (ICD-10: C55) by the proportion of registered, incident uterine cancer cases that were specifically coded as cervical cancer (ICD-10: C53). We then added the result to the deaths known to cause cervical cancer, thereby achieving at a corrected total of cervical cancer deaths. Analogous methods were applied to obtain a corrected estimate of uterine corpus deaths. The details of this correction procedure have been described in a previous report [17]. As the personal identification number used for data was deleted, this study did not require the ethical approval of the Institutional Review Board.

2. Statistical analysis

Annual age-standardized mortality rates were estimated using the world standard population [18]. Rates were age-standardized to the Segi's 1960 world standard, using the direct method. Annual percentage change (APC) was used to compare changes in gynecologic cancer mortality by age group within each time period. We also compared age-specific mortality rates across three calendar periods (1979 to 1988, 1989 to 1998, and 1999 to 2010). Trends in gynecologic cancer mortality were assessed using joinpoint regression model. This analysis was performed using the Joinpoint software ver. 3.5.3 from the Surveillance Research Program of the US National Cancer Institute (Bethesda, MD, USA) [19]. The joinpoint method identifies the best-fit lines through several years of data. The method proceeds by fitting a series of joined lines, which are straight on a logarithmic scale, to trends in the annual age-adjusted cancer mortality rates. The line segments are joined at points called joinpoints, each of which indicates a statistically significant change in trend.

RESULTS

1. Uterine and ovarian cancer mortality rates

Table 1 presents age-standardized uterine and ovarian cancer mortality rates per 100,000 women for each region. In general, mortality rates due to uterine cancer are higher than those due to ovarian cancer. During 1966 to 2009, Singapore

experienced the highest uterine cancer mortality rates among the four regions. In 2009, Korea had the lowest uterine cancer mortality rates among these regions. Between 2000 and 2009, Singapore had the highest ovarian cancer mortality rates. Furthermore, Korea and Hong Kong had the lowest ovarian cancer mortality rates.

2. Trends in uterine cancer mortality rates

Fig. 1A presents overall trends in uterine cancer mortality rates for each of the four East Asian regions. When certified uterine cancer deaths (ICD-10: C53, C54, and C55) are plotted, a significantly decreasing trend is evident throughout the entire study period.

Indeed, overall, uterine cancer mortality rates significantly declined across the study period for each of the four regions (**Table 2**, **Fig. 1A**). During the entire study period, Singapore had the highest uterine cancer mortality of the four regions, although there has been a trend of decreasing uterine cancer mortality in Singapore since 1966 (APC, −2.3%; 95% confidence interval [CI], −2.6 to −2.1). In Hong Kong, there was an overall trend of decrease of uterine cancer mortality since at least 1966 (APC, −4.0%; 95% CI, −4.6 to −3.5). More rapid reductions in uterine cancer mortality occurred in Japan between 1970 and 1990 (APC, −4.9%; 95% CI, −5.1 to −4.8) and in Korea between 1994 and 2010 (APC, −4.4%; 95% CI, −4.8 to −4.0). After 1990, however, the trend of decreased mortality began to slow in Japan. In the three Asian countries and Hong Kong, uterine cancer mortality rates have been declining significantly in almost all age groups. **Fig. 2A** presents changes in mortality rates by age group. Interestingly, the uterine cancer mortality rates tended to increase among women 20 to 34 years of age in Japan and among women over 70 years of age in Korea.

3. Trends in ovarian cancer mortality rate

Overall, no significant changes in ovarian cancer mortality were observed, except in Korea and Japan (**Table 2**). In Korea, ovarian cancer mortality rates significantly increased (APC,

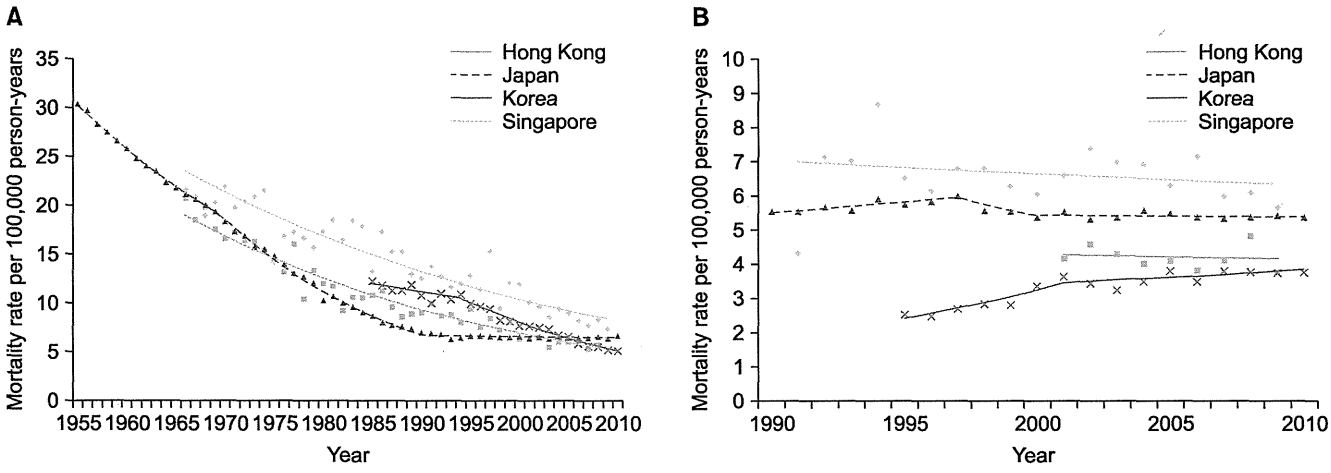

Fig. 1. Trends in uterine* and ovarian cancer mortality rates (age-standardized, women ≥20 years) obtained by joinpoint regression for 4 female Asian populations. (A) Uterine cancer. (B) Ovarian cancer. *Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55).

Table 1. Gynecologic cancer deaths and age-adjusted mortality rates among women ≥20 years according to region and calendar year

Country	Period	Age-adjusted uterine cancer* death rate (≥20 yr) per 100,000 women					Period	Age-adjusted ovarian cancer death rate (≥20 yr) per 100,000 women			
		1970	1980	1990	2000	2009		1980	1990	2000	2009
Hong Kong	1966–2009	16.7	12.1	9.0	6.3	6.0	2001–2009	–	–	–	3.8
Japan	1955–2010	18.4	11.3	6.9	6.5	6.2	1979–2010	4.6	5.5	5.3	5.3
Korea	1985–2010	–	–	10.9	7.8	5.3	1985–2010	–	–	3.4	3.8
Singapore	1966–2009	21.7	17.1	12.5	11.9	7.2	1979–2009	–	–	6.1	5.7

*Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55).

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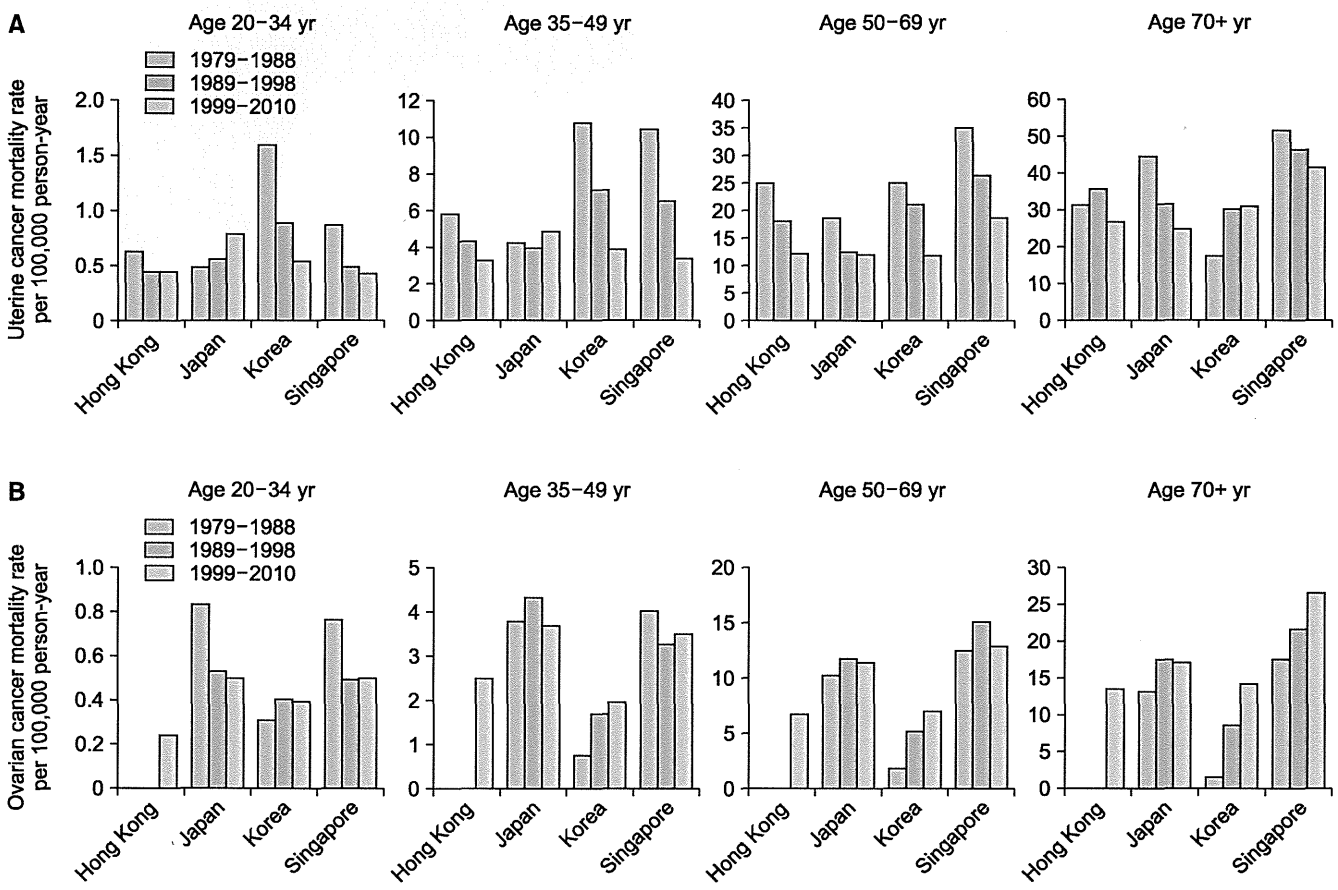

Fig. 2. Uterine and ovarian cancer mortality by age group, period, and region. (A) Uterine cancer. (B) Ovarian cancer. *Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55).

Table 2. Estimated annual percentage change of gynecologic cancer death rates, with 95% CIs

	Trend 1			Trend 2			Trend 3		
	Year	APC	95% CI	Year	APC	95% CI	Year	APC	95% CI
Uterine cancer*									
Hong Kong	1966–2009	−4.0†	−4.6, −3.5						
Japan	1955–1970	−3.2†	−3.4, −3.0	1970–1990	−4.9†	−5.1, −4.8	1990–2010	−0.2†	−0.4, −0.1
Korea	1985–1994	−1.4†	−2.3, −0.5	1994–2010	−4.4†	−4.8, −4.0			
Singapore	1966–2009	−2.3†	−2.6, −2.1						
Ovarian cancer									
Hong Kong	2001–2009	−0.4	−3.1, 2.3						
Japan	1990–1997	1.1†	0.4, 1.8	1997–2000	−3.1	−7.9, 2.0	2000–2010	0.0	−0.4, 0.4
Korea	1995–2000	6.2†	3.4, 9.0	2000–2010	1.1	0.0, 2.3			
Singapore	1991–2009	−0.5	−1.6, 0.5						

APC, annual percentage change; CI, confidence interval.
*Uterine cancer includes cervix uteri (International Statistical Classification of Disease and Related Health Problems, 10th revision [ICD-10] code C53); corpus uteri (ICD-10 code C54); and uterus, unspecified (ICD-10 code C55). †The APC is significantly different from zero ($p<0.05$).

Table 3. Calculation of the corrected cervical cancer and uterine corpus cancer deaths in Korea (1993 to 2010)

Year	No. of deaths by cause of death*						Proportion among all cancer (%)		Corrected deaths	
	Uterine, cervix (C53) (A)	Uterine, corpus (C54) (a)	Uterine, unspecified (C55)							
			Uterine, unspecified (C55) (B)	Registered as cancer incidence cases†						
				Registered as cancer of all sites (C)*	Uterine, cervix (C53) (D)	Uterine, corpus (C54) (d)	Uterine, cervix (E)=(D)/(C)×100	Uterine, corpus (e)=(d)/(C)×100	Uterine, cervix (G)=(A)+(B)×(E)/100	Uterine, corpus (g)=(a)+(B)×(e)/100
1993	416	4	944	542	419	22	77.3	4.1	1,125	50
1994	548	8	925	575	450	27	78.3	4.7	1,268	55
1995	544	29	839	576	448	26	77.8	4.5	1,192	69
1996	656	29	714	483	382	26	79.1	5.4	1,213	65
1997	680	30	709	507	384	28	75.7	5.5	1,216	67
1998	606	37	665	511	395	31	77.3	6.1	1,116	78
1999	690	38	593	476	345	40	72.5	8.4	1,118	85
2000	726	50	534	431	328	33	76.1	7.7	1,134	87
2001	807	56	495	419	313	37	74.7	8.8	1,177	96
2002	1,009	120	252	166	104	17	62.7	10.2	1,168	143
2003	1,111	146	140	94	54	9	57.4	9.6	1,192	157
2004	1,078	125	122	72	28	14	38.9	19.4	1,135	144
2005	1,066	151	128	84	42	22	50.0	26.2	1,133	183
2006	1,002	146	92	60	28	11	46.7	18.3	1,045	163
2007	987	165	89	63	22	21	34.9	33.3	1,019	195
2008	954	210	97	77	41	21	53.2	27.3	1,007	236
2009	949	221	87	66	24	13	36.4	19.7	982	238
2010	956	222	94	67	25	23	37.3	34.3	995	249
Total	14,785	1,787	7,519	5,269	3,832	421	61.5	14.1	20,235	2,360

*National death certificate data, Statistics Korea. †Korea National Cancer Incidence Databases.

2.6%; 95% CI, 1.8 to 3.5) across the entire period (1995 to 2010). Especially, rapid increase in ovarian cancer mortality occurred during 1995 to 2000 (APC, 6.2%; 95% CI, 3.4 to 9.0). In Japan, ovarian cancer mortality rates began to increase during 1990 to 1997 (APC, 1.1%; 95% CI, 0.4 to 1.8). Subsequently, the mortality rates appeared to decline, but the reduction was not statistically significant. **Fig. 1B** presents overall trends in ovarian cancer mortality rates for the four regions that were investigated in the current study. **Fig. 2B** presents ovarian cancer mortality by age group, again for each of these four regions. Among women older than 70 years, prominent increasing trends were found in Japan, Korea, and Singapore.

4. Corrected trends in uterine cervix and corpus mortality rates in Korea

Table 3 presents our method of correcting the number of annual deaths due to uterine cervix and uterine corpus cancer, based on the NCIDB in Korea. The proportion of all uterine cancer deaths with unspecified subtype was the highest in 1993 (69.2%) and gradually diminished until 2010 (7.4%), which suggest significant improvement of quality of the death certificate over the past two decades.

Fig. 3 presents the overall trends in cervical and uterine corpus cancer mortality rates in Korea, using the corrected estimates of mortality. After corrections, it was evident that overall age-standardized cervical cancer mortality rates significantly declined during 1993 to 2010 (APC, −4.8%; 95% CI, −5.3 to −4.4). On the other hand, increase in corrected uterine corpus mortality rates were observed during 1995 to 2010 (APC, 6.7%; 95% CI, 5.4 to 8.0). **Suppl. Table 1** and **Fig. 1** present changes in mortality rates by age group. Whereas cervical cancer mortality rates have been declining significantly in almost all age groups, a nonsignificant trend of increasing mortality rates was found among women 20 to 34 years of age after 2004 (APC, 6.4%; 95% CI, −2.6 to 16.2).

DISCUSSION

In the present study, we compared and assessed secular

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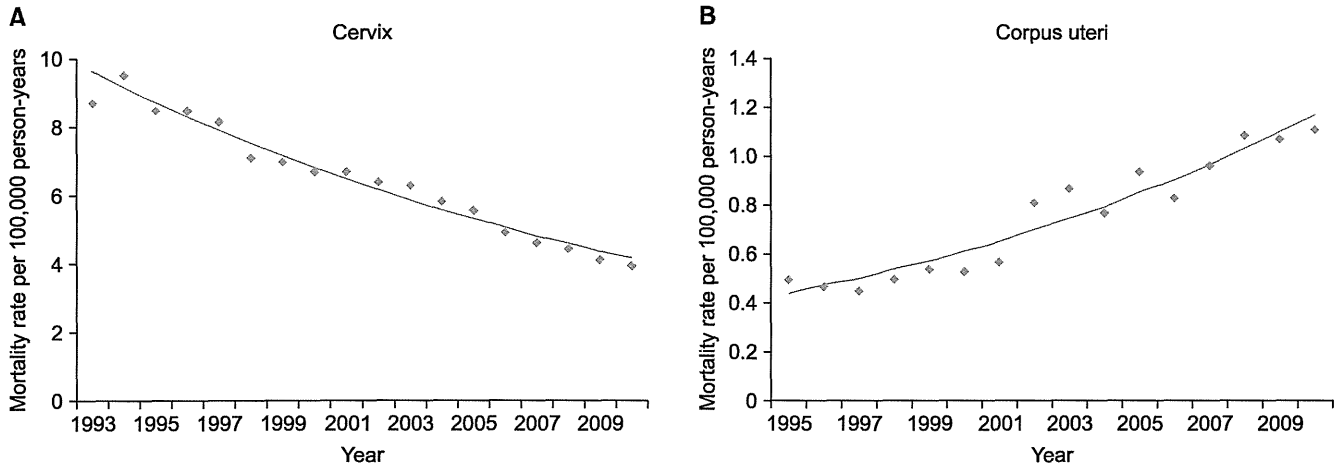

Fig. 3. Corrected trends in cervical and uterine corpus cancer mortality in Korea (age-standardized, women ≥20 years) obtained by joinpoint regression. (A) Cervix. (B) Corpus uteri.

trends of gynecologic cancer mortality among four East Asian female populations, including specific examinations of age-specific mortality. In some European countries, over 70% of deaths from uterine cancer were allotted to "uterus unspecified" during 1960; however, this proportion had reduced to 30% by around 1995 [14]. In Korea, a proportion of classification of "uterus, unspecified" has decreased from 69.1% of uterine cancer deaths in 1993 to 18.4% of uterine cancer deaths in 2002 [17]. We corrected the counts of cervical cancer and uterine corpus cancer deaths by referencing NCIDB in Korea. Our correction procedure allowed us to estimate separate mortality rates for cervical and uterine corpus cancer. After correcting the WHO mortality data, we found that cervical cancer mortality rates had decreased since at least 1993. On the other hand, the corrected data also revealed a trend of increasing uterine corpus cancer mortality rates, which began during or before 1995.

Considering the similar cancer mortality patterns that we observed across the four Asian regions, it is likely that the majority of deaths registered as "uterus, unspecified site" are the result of cervical cancer, as we found in Korea. Therefore, the overall trend of declining uterine cancer mortality might be attributed to the specific decline in cervical cancer mortality. This finding is also confirmed by gynecologic cancer mortality statistics from the Singapore Cancer Registry (**Suppl. Fig. 2**) [20].

Cervical cancer mortality has been decreasing in most developed countries, possibly as a result of early diagnosis and improved treatments [12,21-23]. Two causes likely explain the majority of the trend of decreasing cervical cancer mortality that we found in the four East Asian regions. First, mortality reductions have resulted from trends of decreasing incidence. Particularly, cervical cancer incidence has decreased as lesions have been detected increasingly early, when they are precancerous. The value of cervical cancer screening programs is widely accepted, and national screening programs for cervical cancer have been introduced in Japan (1983), Korea (1988), Taiwan (1995), and Hong Kong (2004). Cervical cancer screening programs have led to decreases in the incidence of invasive cervical cancer in Japan [7], Korea [24], and Taiwan [25]. Further, successful treatment of precancerous lesions (such as intraepithelial neoplasm and carcinoma *in situ*) has resulted in a decreasing trend of invasive cervical cancer. Second, mortality reductions have resulted from advances in cervical cancer therapy, particularly the introduction of concurrent chemoradiation. In 1999, Keys et al. [26] demonstrated that concurrent chemoradiation is associated with better outcomes than radiation alone. Since then, concurrent chemoradiation has been accepted as a standard treatment in the form of either a primary treatment or adjuvant treatment after surgery.

A worrying finding of our study was that uterine cancer mortality rates appeared to be increasing among women <50 years in Japan. Most deaths from uterine cancer among women <50 years can be attributed to cervical cancers [14]. Accordingly, the trend of increasing uterine cancer among younger women in Japan may reflect the trend of increasing cervical cancer incidence in this same population [27-29]. In Korea, cervical cancer mortality rates tended to increase among women 20 to 34 years of age after 2004. Although this increase was not statistically significant (APC, 6.4%; 95% CI, −2.6 to 16.2), further efforts are required to improve the outcomes in this young age group.

Despite decreasing trends of cervical cancer mortality in

Asian countries, cervical cancer still has the second greatest incidence of all cancers among young women in East Asian countries [30]. Because cervical cancer has been demonstrated to be a preventable disease, additional efforts are warranted in East Asia. Specific strategies to prevent cervical cancer are required, including both primary and secondary preventive measures, such as human papillomavirus vaccination and national cervical cytology screening.

Although the trends of decreasing cervical cancer mortality are promising, our results show an abrupt increase in uterine corpus cancer mortality in Korea. This finding should be interpreted in the context of the abruptly increasing incidence of endometrial cancer in East Asia [7,31]. Uterine cancer is mainly diagnosed among postmenopausal women. Endometrial cancer constitutes the majority of cases, while uterine sarcoma is a rare malignancy that accounts for approximately 3% of all uterine cancers [32]. Although endometrial cancer is the most common malignancy of the female genital tract in Western countries, its incidence is rather low in East Asia [33]. Changes in risk factors, especially those associated with lifestyle, have been suggested as the principal cause of the increasing endometrial cancer incidence in East Asia [31]. In particular, one of the established risk factors for endometrial cancer is an increase in unopposed estrogen, which can result from obesity or diabetes mellitus. Based on the trend of increasing uterine corpus cancer incidence that has been reported [34], we suggest that the burden of mortality from uterine corpus cancer will also increase in East Asia within the near future.

A troubling finding of the present study was the persistently high pattern of ovarian cancer mortality rates in Hong Kong, Japan, and Singapore, along with the trend of increased mortality in Korea. In Korea, increases in ovarian cancer mortality rates were found for all age groups, except women 20 to 34 years of age. In Japan and Singapore, it appeared that past age-specific decreases ovarian cancer mortality were reversing.

In the United States, ovarian cancer mortality rates leveled off during the 1980s and declined during the 1990s, with an annual average change of 0.9% [35]. Three or more years of oral contraceptive use reduces the risk of ovarian cancer, and consequently, widespread use of oral contraceptives has contributed to the trend of declining mortality [36]. Although oral contraceptives have long been the most common method of contraception for women in the United States and European countries, the rate of contraceptive use in East Asia has been substantially lower. The proportion of the Chinese women who used pills was only 2.1% in 2006 [37], while approximately 30% of European women used oral contraceptives in 2003 [38]. Therefore, the protective effects of oral contraceptives only contribute minimally to population cancer rates in Korea. In addition, early age at menarche, late age at menopause, lower fertility rates, and other reproductive factors are also risk factors for ovarian cancer. Korea and Japan are among the countries that have the lowest total fertility rates. Indeed, the total fertility rate has remained below 1.3 in Korea since 2005 [39]. East Asia underwent rapid industrialization during the 1960s, and Asian women born after the 1960s have tended to undergo menarche at earlier, delay childbirth, and have reduced fertility rates. The very low fertility rate and the low use of oral contraceptives will presumably sustain the trend of increasing ovarian cancer rates in East Asia [40]. Considering that epithelial ovarian cancer is mostly found at an advanced stage, and has low survival rates, we expect the burden from ovarian cancer to increase in Asian countries. Therefore, improvements to optimal cytoreductive surgery and new therapeutic modalities are urgently required for ovarian cancer.

In the current study, most of the deaths due to ovarian cancer occurred in women older than 50 years. Mortality rates for women over 70 years of age showed an increasing trend in Asian countries, while rates for women younger than 35 years remained stable or decreased. The present study shows that mortality rates for women over 70 years of age have doubled in past 20 years in Korea and Singapore. Considering that ovarian cancer incidence has not increased abruptly during the same period (and indeed has remained stable) [34], the increasing trend of mortality in old age groups could be the result of under treatment of ovarian cancer [41]. Elderly patients have been less likely to undergo standard treatments for ovarian cancer, such as optimal debulking surgery, and have been less likely to complete chemotherapy. Indeed, it has been reported that, among patients who do receive optimal treatment, old age is not an independent poor prognostic factor [42].

The main limitation to this study is the presence of "uterus, unspecified site" as the cause of death on many death certificates. This made it impossible to evaluate cervical and uterine corpus cancer trends separately, based on the WHO mortality database alone. We corrected Korean cervical and uterine corpus cancer mortality rates using Korea NCIDB. However, we were unable to correct the mortality rates for other regions. In addition, this study is limited by several problems that are inherent to the WHO mortality database. Specifically, some mortality data are incomplete and the database does not include full coverage of all deaths in every region. Inaccuracies in death registration coverage and cross-national differences in coding practices should be considered when applying the results of this study.

In conclusion, uterine cancer mortality has decreased in Hong Kong, Japan, Korea, and Singapore. After correcting the

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cervical and uterine corpus mortality rates in Korea, a significant trend of decreasing mortality was found for cervical cancer, and a trend of rapidly increasing mortality was observed for uterine corpus cancer. The most important contributor to declines in cervical cancer mortality has been the early diagnosis and improved treatments. Overall, ovarian cancer mortality was stable in East Asia, with the exception of Korea. A continuing increase in ovarian cancer mortality should be expected because of trend of increasing incidence in East Asia. Preventive measures, early detection programs, and standard use of optimal therapeutic strategies are urgently required, particularly for older age groups. Such improvements could include obesity control programs, increases in fertility, wider oral contraceptive use, optimal cytoreductive surgery, and novel target agents.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMETARY MATERIALS

Visit the following URLs for supplementary materials.

Supplementary Table 1.
http://ejgo.org/src/sm/jgo-25-174-s001.pdf

Supplementary Figure 1.
http://ejgo.org/src/sm/jgo-25-174-s002.pdf

Supplementary Figure 2.
http://ejgo.org/src/sm/jgo-25-174-s003.pdf

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Clinicopathological study on para-aortic lymph node metastasis without pelvic lymph node metastasis in endometrial cancer

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Abstract

Aim: One of the important risk factors for recurrence of endometrial cancer is lymph node metastasis. The regional lymph nodes are pelvic lymph nodes (PLN) and para-aortic lymph nodes (PAN). PAN metastasis was often detected in the cases with PLN metastasis. However, PAN metastasis not associated with PLN metastasis was identified in a few cases. We focused on nine cases with PAN metastasis and without PLN metastasis.

Material and Methods: The subjects of this study were 260 cases that were diagnosed with endometrial cancer. The initial treatments were surgery, including pelvic and para-aortic lymphadenectomy. Nine of these cases had PAN metastasis but did not have PLN metastasis. We retrospectively analyzed the clinicopathological factors and prognosis in cases with PLN–PAN+ cases.

Results: A total of 91 (35%) cases were identified as positive for either PLN or PAN. PAN metastases were detected in 62.6% of the cases that had some regional lymph node metastases and 3.5% of all cases were PLN– and PAN+. In all PLN–PAN+ cases, PAN swelling was not detected by preoperative chest-abdominal computed tomography scan. There were no clear trends among risk factors of regional lymph node metastasis. The 5-year progression-free survival was 87.1% for PLN–PAN– cases, 67.5% for PLN+PAN– cases, 44.4% for PLN–PAN+ cases, and 33.2% for PLN+PAN+ cases.

Conclusion: During diagnosis and treatment for endometrial cancer, PLN–PAN+ cases should also be considered because the prognosis in PLN–PAN+ cases tended to be lower than that in PLN–PAN– cases and PLN+PAN– cases.

Key words: endometrial cancer, para-aortic lymph node metastasis, pelvic lymph node metastasis.

Introduction

Endometrial cancer is characterized by malignant tumors with increasing prevalence in Japan and has a relatively more favorable prognosis than other gynecologic cancers. The initial treatment for endometrial cancer is surgery, including hysterectomy and bilateral salpingo-oophorectomy (BSO).[1] The risk factors for recurrence are deeper myometrial invasion (MI),[2] endometrioid adenocarcinoma grade 3 (G3),[2,3] histological type except endometrioid adenocarcinoma,[4,5] lymphovascular space invasion,[4,6] adnexal metastasis,[7] cervical involvement,[7,8] lymph node metastasis,[9,10] and distant metastasis.

After conducting an assessment for the risk of recurrence on the basis of a pathological diagnosis of a

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surgical specimen, it is common to consider the need for postoperative adjuvant therapy. Among the risk factors associated with endometrial cancer, prognosis is particularly relevant to the presence or absence of lymph node metastasis.[1] Because lymphogenous metastasis is observed more often with endometrial cancer, it is desirable to perform retroperitoneal lymphadenectomy (pelvic lymph nodes [PLN] and para-aortic lymph nodes [PAN]) or biopsies for cases that are predicted to progress to extrauterine cancer.

Although the diagnostic significance of lymphadenectomy has been established, its therapeutic significance remains controversial. Therefore, the indication for retroperitoneal lymphadenectomy may not be firm in each institution at present. In particular, the indication for para-aortic lymphadenectomy may differ between institutions because of the difficulty and invasiveness of the surgical procedure.

However, stage IIIC, which includes cases with regional lymph node metastasis, was subclassified as IIIC1 and IIIC2 on the basis of the presence or absence of PAN metastasis in International Federation of Gynecology and Obstetrics (FIGO) 2008 staging.[11] Therefore, there is a need to perform para-aortic lymphadenectomy for exact endometrial cancer staging. We considered the indication of para-aortic lymphadenectomy more thoroughly.

It is commonly considered that a case with PLN metastasis also has PAN metastasis.[12–14] There is the notion that para-aortic lymphadenectomy should be performed in patients who are strongly suspected to have PLN metastasis. However, at our institution, we encountered some patients who had PAN metastasis but did not have PLN metastasis. If para-aortic lymphadenectomy was not performed in these cases, staging may have been underestimated.

We report PAN metastasis in endometrial cancer and focus on nine cases with PAN metastasis and without PLN metastasis.

Methods

The subjects of this study were 260 cases that were diagnosed with endometrial cancer during 1990–2012 at our institution. The initial treatments were surgery, which included hysterectomy, BSO, pelvic lymphadenectomy, and para-aortic lymphadenectomy. Nine of these cases had PAN metastasis but did not have PLN metastasis.

Surgical procedures for hysterectomy included simple hysterectomy, modified radical hysterectomy (type II), or radical hysterectomy (type III), which were determined on the basis of the cervical involvement and MI.[15] BSO was performed in all cases. Pelvic lymphadenectomy was performed for all cases except stage IA and endometrioid adenocarcinoma G1 without MI. Para-aortic lymphadenectomy was performed for the following cases: MI greater than half its thickness; histological type was endometrioid adenocarcinoma G3 except endometrioid; adnexal metastasis; PLN metastasis; or PAN swelling.

Surgical specimens were diagnosed by pathologists at our institution. Postoperative adjuvant therapy was administered in cases with the following risk factors for recurrence: MI; worse histological type and grade; adnexal metastasis; cervical stromal invasion; vaginal metastasis; parametrial invasion; regional lymph node metastasis; and distant metastasis. Adjuvant therapies were multidrug chemotherapy or radiotherapy. Multidrug chemotherapy using anthracycline or taxane and platinum was administered in three to six cycles as adjuvant chemotherapy. The follow-up period was 10–15 years after treatment, which included gynecological examination, cytology, computed tomography (CT), and tumor markers to investigate recurrence.

PLN included suprainguinal, obturator, inner iliac, external iliac, common iliac, sacral, and cardinal lymph nodes. PAN are lymph nodes around the aorta and the inferior vena cava from the renal vein bifurcation to the common iliac arterial bifurcation. PAN are divided into two parts on the boundary of the inferior mesenteric artery: the upper region is 326b1 and the lower is 326b2.

This study was conducted with approval from the ethics committee of the School of Medicine, Keio University (approval number: 20120243).

Statistical analysis

SPSS version 20 was used for statistical analysis. Statistical analysis was performed with Fisher's exact test and with χ^2 analysis to test for relations between pairs of categorical variables. Kaplan–Meier survival curves were generated for event outcome measures and were compared with standard log–rank tests. A *P*-value less than 0.05 was considered statistically significant.

Results

Patients' characteristics

The clinicopathological characteristics of these cases are shown in Table 1. The patients' median age was 57 years (range: 13–79 years). The median follow-up

Table 1 Patients' characteristics

Age (years, median)		57	(28–79)
Follow-up period (days, median)		1711	(20–6293)
		n	%
Pregnant history	Nullipara	83	31.9
	Multipara	164	63.1
	Unknown	13	5.0
Body mass index	<25	190	73.1
	≥25	49	18.8
	Unknown	21	8.1
Surgical staging (FIGO 2008)	Stage I	123	47.3
	Stage II	17	6.5
	Stage III	102	39.2
	Stage IV	18	6.9
Histological type	Endometrioid	217	83.5
	Serous	14	5.4
	Clear	8	3.1
	Carcinosarcoma	12	4.6
	Others	9	3.5
Histological grade	G1	78	30.0
	G2	84	32.3
	G3	55	21.2
Operative procedure			
Hysterectomy	Simple	41	15.8
	Modified radical	157	60.4
	Radical	59	22.7
	Others	3	1.2
Lymphadenectomy	PLN+PAN	260	100.0
Adjuvant therapy	None	53	20.4
	Chemotherapy	177	68.1
	Radiation	24	9.2
	Unknown	6	2.3

period was 1711 days (range: 20–6293 days). During surgical staging, 120 cases (46.2%) were classified as stages III and IV because the subjects included those who underwent pelvic and para-aortic lymphadenectomy. For the same reason, 37.7% of the cases were histological G3 or special histological types.

Sites of lymph node metastases

A total of 91 (35%), 83 (32%), and 57 cases (22%) were identified as positive for either PLN or PAN, PLN (PLN+), and PAN (PAN+), respectively. PAN metastases were detected in 62.6% of the cases that had some regional lymph node metastases.

PAN+ cases included nine PLN– cases and 48 PLN+ cases. Among these, 15.8% of PAN+ cases had no PLN metastasis, and 3.5% of all cases were PLN– and PAN+.

The sites of PAN metastases were: left-326b1 ($n = 21$), left-326b2 ($n = 17$), right-326b1 ($n = 15$), and right-326b2 ($n = 17$). The sites of PAN metastases in PLN–PAN+ cases were: left-326b1 ($n = 4$), left-326b2 ($n = 3$), right-326b1 ($n = 1$), and right-326b2 ($n = 7$).

Regional lymph node metastases and pathological factors

Figure 1 shows the relations between PAN metastases and the pathological factors that were considered risk factors for recurrence. There was significantly more PAN metastasis observed in patients with deeper MI (greater than two-thirds; $P = 0.004$), adnexal metastasis ($P = 0.001$), positive peritoneal cytology ($P = 0.002$), cervical involvement ($P = 0.002$), and parametrial metastasis ($P = 0.03$). In particular, 44.1% of positive peritoneal cytology cases and 42.9% of adnexal metastasis cases had PAN metastases.

Figure 2 shows the relations between PLN and/or PAN metastases and the pathological factors that were considered risk factors for recurrence. There was a lower percentage of MI > 2/3 and adnexal metastasis in

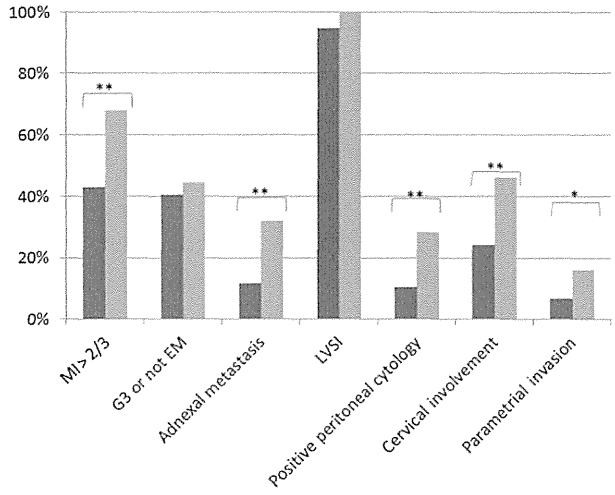

Figure 1 Relations between para-aortic lymph node (PAN) metastases and the pathological risk factors predicting recurrence: myometrial invasion (MI) greater than two-thirds the thickness; G3 or special histological type; adnexal metastasis; lymphovascular space involvement (LVSI); positive peritoneal cytology; cervical involvement; and parametrial invasion. Statistical analysis was performed with Fisher's exact test and with χ^2 analysis. *$P < 0.05$, **$P < 0.01$. (■) PAN–, (■) PAN+. EM, endometrioid adenocarcinoma.

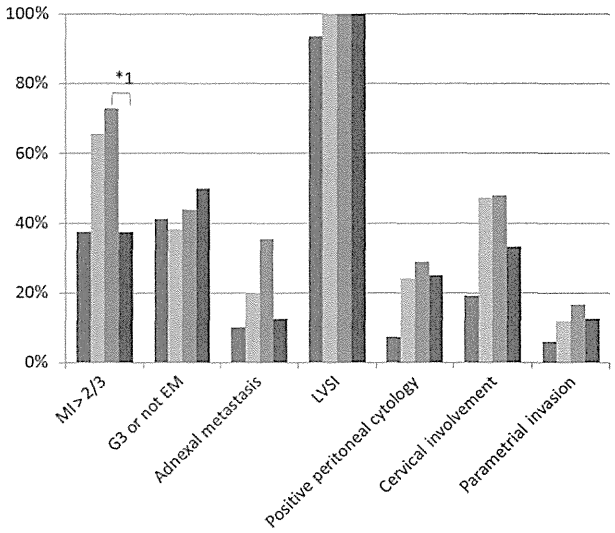

Figure 2 Relations between para-aortic lymph node (PAN) metastases and the following seven pathological risk factors: myometrial invasion (MI) greater than two-thirds the thickness; G3 or special histological type; adnexal metastasis; LVSI; positive peritoneal cytology; cervical involvement; and parametrial invasion. Statistical analysis was performed with Fisher's exact test and χ^2 analysis. (*1$P = 0.09$). (■) Pelvic lymph node (PLN)–PAN–, (■) PLN+PAN–, (■) PLN+PAN+, (■) PLN–PAN+. EM, endometrioid adenocarcinoma; LVSI, lymphovascular space involvement.

PLN–PAN+ than in PLN+PAN+ cases. The risk factors of PAN metastasis were deeper MI, adnexal metastasis, positive peritoneal cytology, cervical involvement and parametrial invasion. However, PLN–PAN+ patients did not tend to have these risk factors.

Analysis of PLN–PAN+ cases

The clinical characteristics of PLN–PAN+ cases are shown in Table 2. Pelvic magnetic resonance imaging (MRI) and chest–abdomen CT were performed as preoperative examinations for all cases. However, PAN swelling was not detected in all cases, and 44.4% of these cases were identified on the basis of tumor marker (cancer antigen 125) levels higher than the standard value.

The pathological characteristics of PLN–PAN+ cases are shown in Table 3. Among these nine cases, five were identified as endometrioid adenocarcinomas and four were identified as special histological types. Five cases had greater than half MI, all cases had lymph venal space involvement (LVSI), two had cervical involvement, and one had adnexal metastasis.

The median number of PLN was 50 (range: 33–90) and the median number of PAN was 22 (range: 1–38). For each case, the region of positive PAN metastasis was 1–2 and the median number of positive PAN metastasis was 1 (range: 1–4). The number of risk factors for PAN metastasis was 0–2 in PLN–PAN+ cases, which tended to be less than in PLN+PAN+ cases. There were no clear trends among these factors.

Regional lymph node metastases and survival periods

Figure 3 shows the Kaplan–Meier curves for progression-free survival (PFS). The 5-year PFS was 87.1% for PLN–PAN– cases, 67.5% for PLN+PAN– cases, 44.4% for PLN–PAN+ cases, and 33.2% for PLN+PAN+ cases. The prognoses for PLN+PAN–, PLN+PAN+, and PLN–PAN+ cases were significantly shorter than those for cases without metastases. In particular, the prognosis for PLN+PAN+ cases was the worst. Because there were few PLN–PAN+ cases, there was no significant difference. The prognosis for PLN–PAN+ cases tended to be shorter than that for PLN+PAN– cases ($P = 0.16$).

Table 2 Clinical factors of the patients with PLN–PAN+

No.	Age	BMI	Parity	CA125 / CA602	Method of hysterectomy	Method of LN resection	Statement	PFS (M)	OS (M)	Part of recurrence
1	66	22.5	3	WNL	M-radical	PLN+PAN	DOD	9	20	Lung, multiple LN
2	53	22.4	2	WNL	M-radical	PLN+PAN	NED	—	3	—
3	67	20.2	2	WNL	M-radical	PLN+PAN	NED	—	3	—
4	63	23.6	3	High	Simple	PLN+PAN	AWD	11	128	Liver
5	58	20.3	2	High	Radical	PLN+PAN	NED	—	146	—
6	49	22.7	3	High	Radical	PLN+PAN	NED	—	124	—
7	62	31.2	2	High	M-radical	PLN+PAN†	NED	—	19	—
8	55	21.4	2	WNL	Simple	PLN+PAN	NED	—	25	—
9	67	20.6	2	WNL	Radical	PLN+PAN	AWD	11	15	Vagina

†PAN biopsy only. AWD, alive with disease; BMI, body mass index; CA, cancer antigen; DOD, died of disease; LN, lymph nodes; M-radical, modified radical; NED, no evidence of disease; OS, overall survival; PAN, para-aortic lymph node; PFS, progression-free survival; PLN, pelvic lymph nodes; WNL, within normal limit.

Table 3 Pathological factors of the patients with PLN–PAN+

No.	Histological type	MI	LVSI	CI	AM	pT	pM	No. of PLN	No. of PAN metastasis				
									Left 326		Right 326		Total
									b1	b2	b1	b2	
1	CS†	<1/2	+	–	–	1A	0	0/35	0/5	1/3	0/4	0/1	1/13
2	EM G2	1/2–2/3	+	–	–	1B	0	0/53	0/20	0/2	2/6	2/8	4/36
3	Serous	>2/3	+	–	–	3A	0	0/43	0/2	2/13	0/2	0/7	2/24
4	EM G1	<1/2	+	–	+	3A	0	0/33	1/8	0/7	–	0/2	1/17
5	EM G2	>2/3	+	+	–	3B	0	0/39	1/6	0/14	0/1	0/3	1/24
6	EM G2	>2/3	+	+	–	2	0	0/59	0/8		0/2	1/11	1/21
7	EM G1	>2/3	+	–	–	1B	0	0/90	–	–	–	1/1	1/1
8	Serous	<1/2	+	–	–	3A	0	0/57	0/1	0/9	0/1	2/11	2/22
9	Mixed‡	>2/3	+	–	–	1B	0	0/50	1/24	0/8	0/4	0/2	1/38

†Serous + clear + EMG3 + ESS. ‡Serous + EMG3. AM, adnexal metastasis; CI, cervical involvement; CS, carcinosarcoma; EM, endometrioid adenocarcinoma; ESS, endometrial stromal sarcoma; LVSI, lymphovascular space involvement; MI, myometrial invasion; PAN, para-aortic lymph node; PLN, pelvic lymph node.

Discussion

PAN metastasis is reported to be one of the most important prognostic factors for endometrial cancer. Regarding risk factors for PAN metastasis, Yokoyama *et al.*[16] reported deeper MI and positive PLN metastasis, Hiratake *et al.*[17] reported positive PLN metastasis, and Nomura *et al.*[14] reported greater than 50 years, positive LVSI, and positive PLN metastasis. These reports indicated that PLN metastasis was the most important risk factor for PAN metastasis.

In our study, 88.9% of PAN+ cases had PLN metastasis and 59.0% of PLN+ cases had PAN metastasis. However, PAN+ cases without PLN metastasis have been reported. Mariani *et al.*,[18] Ayhan *et al.*,[19] and Abu-Rustum *et al.*[20] reported 3.6%, 2.7% and 1.6% of cases as PLN–PAN+. The percentages of PLN–PAN+ cases in these reports were nearly the same as that in our study (3.4%).

Because retroperitoneal lymph node metastasis is one of the risk factors with endometrial cancer, the diagnostic significance for performing lymph node biopsy or lymphadenectomy has been established. In FIGO 2008 staging, stage IIIc was subclassified into stage IIIC1 and stage IIIC2 on the basis of the presence or absence of PAN metastasis.

However, the therapeutic significance has not been established. The conclusion from the ASTEC trial reported in 2009 was that survival was not different on the basis of the presence or absence of pelvic lymphadenectomy.[21] However, Todo *et al.* reported that the prognosis of a group that underwent pelvic and para-aortic lymphadenectomy was significantly better than that of a group that underwent pelvic lymphadenectomy.[22]

It is important to diagnose PAN metastasis for exact staging. However, PAN biopsy and lymphadenectomy require an expert gynecological oncologist for the

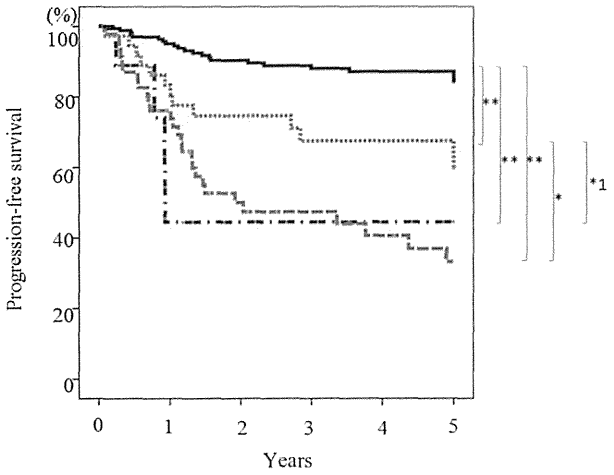

Figure 3 Kaplan–Meier curves for 5-year progression-free survival. (—) Pelvic lymph node (PLN)–para-aortic lymph node (PAN)–, (·····) PLN+PAN–, (-·-) PLN–PAN+, (----) PLN+PAN+. Statistical analysis was performed with the log–rank test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{*1}P = 0.16$.

operation because of the high frequency of complications that may occur when removing tissue from around the aorta. Some authors[21,23,24] insist that PAN biopsy and lymphadenectomy cannot be applied to all cases due to the following reasons: (i) when these procedures are carried out near the large artery they are highly prone to complications and the gynecologic neoplasm surgeon should have expert skills; (ii) these procedures require a large surgical wound so that the lower extreme of the renal vein can be observed; and (iii) the treatment significance of these procedures has not yet been established.

Positron emission tomography (PET)-CT is suggested for preoperative identification of metastatic lymph node instead of CT used in the past; however, the specificity is high and the sensitivity is not very high in PET-CT. Chang *et al.*[25] reported that PET-CT demonstrated a sensitivity of 63.0%, specificity of 94.7%, and diagnosis rate of 89.5%. Kitajima *et al.*[26] indicated a sensitivity of 50%, specificity of 90.9%, and negative predictive value of 16.7%. Moreover, the size of the metastatic lymph node was related to the sensitivity, and preoperative diagnosis for micrometastasis was difficult. For example, 2–4-mm size showed 12.5% sensitivity, 5–9 mm showed 66.7%, and 10–12 mm showed 100%. PET-CT was not a tool to identify the PAN metastasis with accuracy because the sensitivity and negative predictive value were not sufficiently high.

Some studies for sentinel lymph node navigation surgery (SNNS) reported a positive result in endometrial cancer; however, the regional lymph node is widely expanded from the pelvis to the PAN area, thus observation should be performed in a wider area. Insufficient evidence is present for SNNS as a standard treatment and its efficacy should be further investigated.[27,28] However, there were some reports that the sensitivity and negative predictive value of SNNS were sufficiently high. SNNS may be enabled for an accurate diagnosis for lymph node metastasis in the future.

In this study, the predictive factors for PLN–PAN+ were not able to be re-evaluated. In case PLN was positive (+), MI was >1/2, histological type was endometrioid adenocarcinoma G3 or the special histological type, and adnexal metastasis was positive, then PAN biopsy or lymphadenectomy was performed for pathological investigation of metastasis under the circumstances. By doing that, it is thought that PLN–PAN+ cases would not be overlooked.

Insufficient comparison tests for prognosis between PLN+PAN+ and PLN–PAN+ metastasis were performed because PLN–PAN+ patients were few. PLN+PAN+ patients showed significantly poorer prognosis than PLN+PAN– patients in this study. PLN–PAN+ patients also tended to have poorer prognosis than PLN+PAN– patients, but did not show a significant difference. The reason was not clear; however, it is thought that PAN metastasis is a stronger risk factor than PLN metastasis. It is consistent with the new FIGO 2008 staging that stage IIIC2 cases include PLN–PAN+ cases and PLN+PAN+ cases.

Most of the patients with retroperitoneal lymph node metastases received postoperative treatments. Note that the additional treatment might not be applied for PLN–PAN+ patients because PAN metastasis was missed and diagnosed as stage I–II if PAN biopsy or lymphadenectomy was not performed.

During diagnosis and treatment for endometrial cancer, PLN–PAN+ cases should also be considered.

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Disclosure

The authors have declared no conflicts of interest.

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A retrospective study on combination therapy with ifosfamide, adriamycin and cisplatin for progressive or recurrent uterine sarcoma

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Abstract. There is currently insufficient evidence to recommend a specific chemotherapeutic regimen as standard treatment for uterine sarcomas. In this study, we investigated the toxicity and effectiveness of ifosfamide, adriamycin and cisplatin (IAP therapy) in patients with progressive and recurrent uterine sarcoma. A total of 11 patients with progressive or recurrent uterine sarcoma containing leiomyosarcoma (LMS), undifferentiated endometrial sarcoma (UES) or adenosarcoma, who were diagnosed at our institution, were retrospectively investigated. We recorded the adverse events, response rate and progression-free survival in these cases. The histological types included LMS (54.5%), adenosarcoma (27.3%) and UES (18.2%). Grade ≥3 leukopenia or neutropenia were observed in all the cases, febrile neutropenia developed in 45.5% of the patients and grade 4 thrombocytopenia developed in 3 cases (27.3%). With IAP therapy, the response rate was 36.4% and the disease control rate was 90.9%. Therefore, IAP therapy may be a viable option as chemotherapy for uterine sarcoma.

Introduction

Uterine sarcomas are extremely rare, non-epithelial malignant uterine tumors. Uterine sarcomas account for 8% of all malignant tumors of the corpus uteri and the most common histological types are carcinosarcoma (CS), leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), in decreasing order of frequency (1). In Japan, it was reported that the most common histological types are CS (46%), LMS (36%) and ESS (13%) (2). CS is a malignant tumor consisting of an epithelial and a non-epithelial component, which mainly affects postmenopausal women. A combination tumor theory suggested that the majority of CSs originate from a single cell and differentiate into epithelioid-like and stromal-like components, whereas they are considered to exhibit cellular characteristics and progression similar to those of poorly differentiated endometrioid adenocarcinoma (3). Therefore, CSs tend to be treated in accordance with the treatment for epithelial endometrial cancer. However, LMS and ESS possess totally different properties compared to epithelial endometrial cancer.

LMS and ESS are malignant tumors that are mainly encountered during the perimenopausal period. Uterine leiomyomas may exhibit malignant transformation to LMS in 0.13-0.81% of the cases (4). These tumors are diagnosed based on the number of mitoses, degree of cellular atypia and presence of coagulation necrosis. ESS may be classified as low- or high-grade, based on the number of mitoses. However, these sarcomas are currently considered as different types of tumors. High-grade ESS, in particular, is referred to as undifferentiated endometrial sarcoma (UES). Total hysterectomy and bilateral salpingo-oophorectomy (BSO) are currently considered the first choice for the treatment of uterine sarcomas, although a consensus has not been reached regarding retroperitoneal lymphadenectomy (5,6). However, these tumors cannot be sufficiently controlled by surgical treatment alone, since a number of patients develop progression and recurrence of uterine sarcoma. As LMS often develops distant hematogenous metastases to the lungs and the liver, chemotherapy is commonly required as a systemic treatment. However, there is insufficient evidence to recommend a specific chemotherapeutic regimen as standard treatment for uterine sarcomas, as these are rare tumors and the number of reported cases is limited.

We administered a combination of ifosfamide (IFM), adriamycin (ADM) and cisplatin (CDDP) (IAP therapy) to patients with progressive and recurrent uterine sarcomas and retrospectively investigated treatment effectiveness and toxicity.

Patients and methods

Patients. We investigated 11 patients who were diagnosed with uterine sarcoma and treated with IAP between 1990 and 2010 at the Keio University Hospital, Tokyo, Japan.

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Total hysterectomy and BSO or tumorectomy were performed in our hospital. The pathological diagnosis in all the cases was LMS, UES or adenosarcoma. The median follow-up period was 298 days (range, 36-2,757 days). Remission induction chemotherapy was performed in all the cases, as 8 of the patients had progressive disease (PD) and 3 patients had recurrent disease.

This study was approved by the Keio University School of Medicine Ethics Committee (approval no. 20120236) and all the patients provided informed consent.

Treatment plan. The treatment schedule was based on a case report of uterine sarcoma that was treated with IAP (7,8). The administration was every 3 weeks as follows: IFM 1.5 g/body on days 1-5, mesna 900 mg/body on days 1-5, ADM 50 mg/m^2 on day 1 and CDDP 50 mg/m^2 on day 1, intravenously. Granulocyte colony-stimulating factor (G-CSF) was used according to the criteria of the American Society of Clinical Oncology. This treatment schedule was repeated every 3 weeks until disease progression or until discontinuation due to adverse events.

Evaluation of response and toxicity. The adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0, based on the interviews and blood tests conducted once a week or more frequently after each cycle. The subsequent cycle was initiated after the adverse events were resolved. As regards hematotoxicity, if patients presented with grade 4 leukopenia or neutropenia for >7 days, grade 3-4 thrombocytopenia, or febrile neutropenia, we considered reducing the dose or withdrawing drugs for the subsequent cycle.

We assessed the overall response rate of 11 cases who had received remission induction therapy and had evaluable lesions in accordance with the World Health Organization evaluation criteria and recorded the progression-free survival. The tumors were measured by computed tomography after every 2 cycles. After the product of the two longest perpendicular diameters was calculated, the response was assessed as follows: complete response (CR), complete disappearance of all known lesions for a minimum of 4 weeks; partial response (PR), >50% reduction in the sum of the length x width of each measurable lesion for a minimum of 4 weeks; PD, >25% increase in the sum of the products of all measurable lesions or appearance of any new lesions; no change (NC), any outcome that did not qualify as response or progression.

Statistical analysis. SPSS software, version 20 (IBM-SPSS Software, Chicago, IL, USA) was used for statistical analysis, using Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference. Kaplan-Meier curves were used for the estimation of progression-free survival and were compared with standard log-rank tests.

Results

Clinicopathological characteristics. The clinicopathological characteristics of the 11 cases who underwent IAP therapy are presented in Tables I and II. The median age at IAP therapy was 50 years (range, 34-72 years). The primary tumor sites were the uterus (10 cases, 90.9%) or the retroperitoneum (1 case, 9.1%). The histological types were LMS (6 cases, 54.5%), adenosarcoma (3 cases, 27.3%) and UES (high-grade ESS; 2 cases, 18.2%).

Table I. Clinicopathological characteristics of the 11 cases.

Characteristics	No.
Age (years)	
<50	5
≥50	6
Origin	
Uterus	10
Retroperitoneum	1
Histological type	
Leiomyosarcoma	6
Adenosarcoma	3
Undifferentiated endometrial sarcoma	2
Stage (FIGO 1988)	
I	4
II	0
III	1
IV	5
Other	1
Type of disease	
Progressive	6
Recurrent	5
Initial treatment	
Surgery	11
Chemotherapy	0
Type of surgery	
Hysterectomy + BSO (USO)	7
Other	4
Chemotherapy prior to IAP[a]	
None	9
CYVADIC[b]	1
DOC + GEM	1

[a]Ifosfamide, adriamycin and cisplatin. [b]Cyclophosphamide, vincristine, adriamycin and dacarbazine. FIGO, International Federation of Gynecology and Obstetrics; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy; DOC, docetaxel; GEM, gemcitabine.

Treatment. A total of 2 cases (18.2%) had received pretreatment; 1 case had received cyclophosphamide, vincristine, ADM and dacarbazine (DTIC) (CYVADIC therapy) and 1 case had received docetaxel (DOC) + gemcitabine (GEM).

The median number of cycles of IAP therapy was 6 (range, 1-8 cycles). In 72.7% of the cases, a dose reduction was required. Among cases who received >6 cycles, in particular, 71.4% required a dose reduction. The chemotherapy was interrupted after 1 to 2 cycles for the patients who requested treatment discontinuation due to intolerable adverse events.

Adverse events. The adverse events of IAP therapy are summarized in Table III. Hematotoxicity, particularly grade ≥3

Table II. Clinicopathological and treatment details of the 11 cases.

Age at diagnosis (years)	Age at IAP[a] therapy (years)	Histological type	Disease status	Initial treatment	Prior chemotherapy	No. of cycles	Effectiveness	Recurrence after IAP[a] therapy	PFS (days)
33	34	Leiomyosarcoma	Recurrent	ATH + BSO	CYVADIC[b]	8	SD	Yes	1,321
67	72	Adenosarcoma	Recurrent	ATH + BSO	-	2	SD	No	-
51	51	Leiomyosarcoma	Recurrent	Tumorectomy + BSO	-	3	CR	Yes	213
62	62	Leiomyosarcoma	Progressive	Tumorectomy	-	8	SD	Yes	125
57	56	ESS, high-grade	Progressive	Virchow LN biopsy	-	1	SD	Yes	307
43	43	Adenosarcoma	Progressive	ATH + BSO + PLN + OMT + tumorectomy	-	6	SD	Yes	44
50	50	ESS, high-grade	Progressive	ATH + BSO	-	2	SD	Unknown	-
40	40	Leiomyosarcoma	Progressive	ATH + BSO + PLN + tumorectomy	-	8	PD	Yes	25
38	39	Adenosarcoma	Progressive	ATH + tumorectomy	-	6	PR	Yes	80
35	35	Leiomyosarcoma	Progressive	ATH + BSO	DOC + GEM	6	CR	No	-
56	57	Leiomyosarcoma	Progressive	Tumorectomy	-	6	CR	Yes	1,539

[a]Ifosfamide, adriamycin and cisplatin. [b]Cyclophosphamide, vincristine, adriamycin and dacarbazine. PFS, progression-free survival; ESS, entometrial stromal sarcoma; ATH, abdominal total hysterectomy; BSO, bilateral salpingo-oophorectomy; LN, lymph node; PLN, pelvic lymphadenectomy; OMT, omentectomy; DOC, docetaxel; GEM, gemcitabine; SD, stable disease; CR, complete response; PD, progressive disease; PR, partial response.

leukopenia or neutropenia, developed in all the cases during the first cycle. Febrile neutropenia developed in 45.5% of the cases and resolved with administration of antibiotics and G-CSF. Grade 4 thrombopenia developed in 3 cases (27.3%), one of which required a platelet transfusion. Non-hematological adverse events other than anorexia, nausea and vomiting were not reported. Hemorrhagic cystitis or cardiotoxicity, which are adverse events characteristic of IFM and ADM, were also not reported.

Effectiveness. The therapeutic effects of remission induction chemotherapy are presented in Fig. 1. The sum of CR + PR was 36.4% (95% CI: 8.0-64.8%) and that of CR + PR + NC was 90.9% (95% CI: 73.9-100%). The median progression-free survival was 307 days (95% CI: 168-446 days).

Table III. Adverse events following IAP[a] therapy.

Adverse events	Grade	N	%
Hematological			
Leukopenia	3	2	18.2
	4	9	81.8
Neutropenia	3	2	18.2
	4	9	81.8
Febrile neutropenia	3	5	45.5
Thrombocytopenia	4	3	27.3
Non-hematological	3	0	0
	4	0	0

[a]Ifosfamide, adriamycin and cisplatin.

Discussion

Although several chemotherapeutic options for uterine sarcoma were previously suggested, the number of large-scale studies on uterine sarcomas is limited, as this type of tumor is relatively rare. The overall rate of response to single-agent chemotherapy is presented in Table IV. The response rate for ADM, IFM and gemcitabine (GEM) was 25.0, 17.0 and 21.0%, respectively (9-11); these are considered to be the key drugs in the treatment of uterine sarcoma. However, the response rate with paclitaxel and CDDP was 9.0 and 3.0%, respectively (12,13); thus, these drugs are considered to be less effective.

The efficiency of multi-agent chemotherapy for uterine sarcoma is summarized in Table V. Omura *et al* (9) investigated the efficiency of ADM + DTIC therapy and reported that, among 66 cases with measurable lesions of uterine sarcoma, 16 (24.2%) achieved a remission (CR + PR). Specifically, the response rate was 30.0% (6/20) in cases with LMS.

Sutton *et al* (14) investigated ADM + IFM therapy in 33 patients with LMS. As regards adverse events, grade >3 neutropenia developed in 17 cases (48.6%), of which 2 developed febrile neutropenia. Grade ≥3 thrombocytopenia was observed in 2 cases and nephrotoxicity in 1 case. There were 2 reported deaths due to the development of severe adverse events, specifically sepsis and cardiotoxicity. CR was achieved in 1 case and PR in 9 cases. The overall response rate was 30.3% and the disease control rate (CR + PR + SD) was 82.0%.

Piver *et al* (15) investigated CYVADIC therapy in 26 patients with intrapelvic sarcoma. As regards adverse events, neurotoxicity was observed in 8 cases (30.7%), including 6 mild-to-moderate and 2 severe cases. No patient developed cardiotoxicity. However, sepsis developed in 4 cases (15.3%) and 1 patient succumbed to the complications. The effectiveness was determined in 10 uterine sarcoma cases. The overall response rate and disease control rate were 20.0 and 60.0%, respectively.

Table IV. Overall rate of response to single-agent chemotherapy.

Agents	Dose and regimen	Response rate (%)	First author	Refs.
ADM	60 mg/m^2 day 1	25	Omura	(9)
Etoposide	100 mg/m^2 day 1-3	11	Slayton	(19)
CDDP	50 mg/m^2 day 1	3	Thigpen	(13)
Ifosfamide	1.5 g/m^2 day 1-5	17	Sutton	(10)
Paclitaxel	175 mg/m^2 day 1	9	Sutton	(12)
Gemcitabine	50 mg/m^2 day 1, 8 and 15	21	Look	(11)
Liposomal doxorubicin	50 mg/m^2 day 1	14	Sutton	(20)
Topotecan	1.5 mg/m^2 day 1-5	11	Miller	(21)
Trabectedin	1.5 mg/m^2 day 1	10	Monk	(22)

ADM, adriamycin; CDDP, cisplatin.

Table V. Overall rate of response to multi-agent chemotherapy.

Agents	Dose and regimen	Cases	Response rate (%)	Disease control rate (%)	First author	Refs.
ADM + DTIC	ADM 60 mg/m^2 day 1 DTIC 250 mg/m^2 days 1-5	20	30.0		Omura	(9)
IFM + ADM	IFM 5 g/m^2 day 1 ADM 50 mg/m^2 day 3	33	30.3	81.8	Sutton	(14)
CYVADIC	CPA 400 mg/m^2 day 2 Vicristine 1 mg/m^2 days 1-5 ADM 40 mg/m^2 day 2 DTIC 200 mg/m^2 days 1-5	10	20.0	60.0	Piver	(15)
GEM + DOC	GEM 900 mg/m^2 day 1 DOC 100 mg/m^2 days 1 and 8	42	35.8	62.0	Hensley	(16,17)
MAID	Mesna 1.5 g/m^2 days 1-4 IFM 1.5 g/m^2 days 1-3 ADM 15 mg/m^2 days 1-3 DTIC 250 mg/m^2 days 1-5	6	33.3	50.0	Pearl	(18)
IAP	IFM 1.5 g/body days 1-5 ADM 50 mg/m^2 day 1 CDDP 50 mg/m^2 day 1	11	36.4	90.9	Present study	

ADM, adriamycin; CPA, cyclophosphamide; GEM, gemcitabine; DTIC, dacarbazine; DOC, docetaxel; IFM, ifosfamide; CDDP, cisplatin.

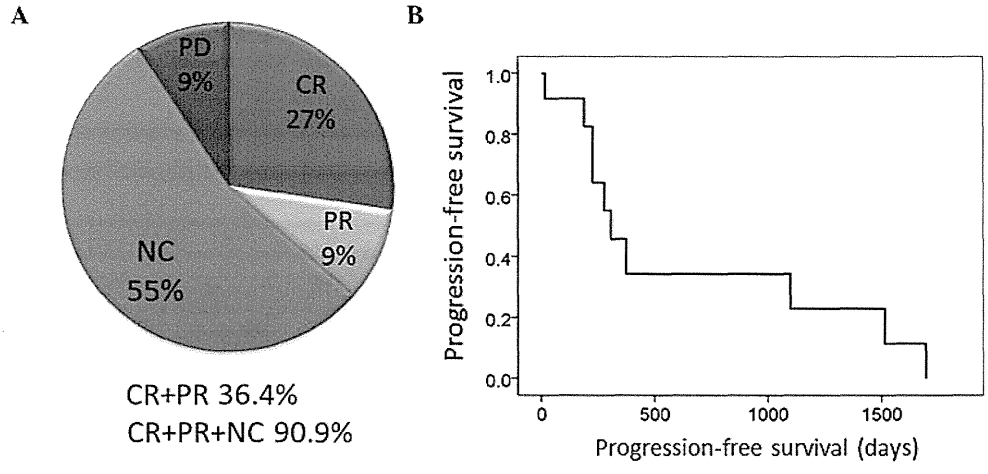

Figure 1. Therapeutic effects of remission induction chemotherapy. (A) The overall response rate was 36.4% and the disease control rate, including NC, was 90.9%. (B) The median progression-free survival was 307 days (95% CI: 168-446 days). NC, no change; CR, complete response; PR, partial response; PD, progressive disease.