The incidence, treatment and prognosis of cervical carcinoma in young women: a retrospective analysis of 4,975 cases in Japan

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Summary

Objective: To determine the clinical characteristics of patients (young women) with cervical carcinoma aged less than 35 years. *Methods:* Data from patients who were treated for cervical carcinomas from 1990 to 2000 in the Kinki District were retrospectively investigated for clinical stage, histologic type, treatment procedure and prognosis. *Results:* Of a total of 4,975 cases, 441 patients were aged less than 35 years old. The incidence of cervical carcinoma in these women was 7.9% from 1990 to 1995, 9.1% from 1996 to 2000, and 9.5% from 2001 to 2005. FIGO Stage I included 374 cases, followed by, 49 in Stage II, 11 in Stage III, and seven in Stage IV. Squamous cell carcinoma incidence was 80.7% and non-squamous cell carcinoma incidence was 19.3%. Several types of surgery were performed in patients with Stage I and II, while patients with Stage III and IV were treated with radiotherapy and/or chemotherapy without any type of surgery. In patients who underwent lymphadenectomy, 21.1% cases had nodal involvement. The 5-year survival rate was 95% for Stage I disease, 73% for Stage II, 68% for Stage III, and 19% for Stage IV. *Conclusion:* The incidence of cervical carcinoma in young women slightly increased from 1990 to 2005. The prognosis of cervical carcinoma tends to be better in young women than in older patients, especially in Stage III disease.

Key words: Young women; Cervical carcinoma; Incidence, prognosis.

Introduction

Cervical cancer is the second most common cancer among women worldwide (GLOBOCAN 2002, http://www.depdb.iarc.fr/blobocan/GLOBOframe.htm). In Japan, the crude mortality rate of cervical cancer is 21.3 per 100,000 women and it was the third most common cause of female deaths in 1960 [1]. The age-standardized uterine cervical cancer incidence based on the world population was 13.4 in 1975 as stated on the website of the Center for Cancer Control and Information Services National Cancer Center in Japan (http://ganjoho.ncc.go.jp/professional/statistics/statistics.html). Widespread use of cervical cancer mass screening was started in Japan by the Japanese Ministry of Health, Labor and Welfare in 1982. The mortality and incidence of cervical cancer decreased up to the mid-1990s. However, the incidence of cervical carcinoma has tended to increase since the late 1990s, especially among young women [2-4].

Several reports have evaluated the effect of cervical cancer screening since national screening programs were initiated. Although the overall incidence of invasive cervical carcinoma has decreased during the last few decades, several studies have demonstrated that cervical carcinoma has been steadily increasing [5-7] or has remained stable in younger women [8]. Histologic analysis revealed that the incidence of adenocarcinoma (AC) has risen in young women, whereas squamous cell carcinoma (SCC) has been reduced [7-10]. In addition, we often have seen unanticipated rapid disease progression in young women despite treatment. Many earlier reports demonstrated poorer prognosis in young women [11-14], while some studies indicated no difference or a better prognosis in young patients [13, 16]. Therefore, it remains controversial whether young patients with invasive cervical carcinoma have a poorer prognosis than older women.

This retrospective study was conducted to examine the trends in the incidence, histologic type, and treatment procedure of invasive cervical carcinoma in Japanese women less than 35 years old since 1990. The purpose of our study was to assess survival rates and to evaluate prognostic factors for cervical carcinoma in young women.

Patients and Methods

The present study was designed by the tumor sectional meeting of the Obstetrical Gynecological Society of the Kinki District of Japan. The medical records of patients with cervical carcinomas treated from 1990 to 2005 were retrospectively reviewed.

Revised manuscript accepted for publication September 22, 2008

Patients were included in the study if primary treatments were carried out in the Kinki District in Japan. The number of institutions included in the study was five from 1990 to 1995, and increased to ten after 1996. Carcinoma in situ of the cervix was not registered, and only cases of invasive cervical cancer were included in the study. The clinical staging and histologic criteria were based on the International Federation of Gynecology and Obstetrics (FIGO). The time of diagnosis was considered to be the date of the primary treatment. Time to recurrence and death or last contact was calculated. Trends in incidence and distribution of clinical stage and histologic type were examined in all ages of women. The treatment types, pathologic risk factors, and prognosis were submitted to date by patients aged less than 35. Informed consent was not deemed necessary for this chart review. We did not request institutional review board approval for this study because of its retrospective nature.

Treatment procedures

Most of the patients were subjected to one or more types of treatment including surgery, radiotherapy, and chemotherapy. Only a few patients had photodynamic therapy or immunotherapy performed. Types of hysterectomy treated with cervical carcinoma were classified into five types by Piver [17]. In Japan, three types of hysterectomy were performed as follows: simple hysterectomy, which corresponds with type I hysterectomy by Piver's classification, extended hysterectomy, which is equivalent to type II, and radical hysterectomy consisting of type III and IV hysterectomy. If women with Stage I disease desire to preserve their fertility, cervical conization is chosen. In Japan, typical primary radiation procedures have consisted of 45-50 Gy with external beam irradiation, followed by a high-dose-rate intracavitary brachytherapy (20-25 Gy), for a total dose of 60-75 Gy to point A. The radiation method used with postoperative cases is 45-50 Gy to the whole pelvis with an external beam. Chemotherapy consists of adjuvant and neoadjuvant treatments, but does not include a maintenance procedure with oral fluoropyrimidines. In this study, concurrent chemoradiotherapy was classified as radiation plus chemotherapy. If women were treated with cervical conization alone, their treatment type was surgery alone. If women underwent cone biopsy without other types of surgery, followed by radiation or chemotherapy, their treatment type was radiation or chemotherapy, not surgery.

Statistical analysis

Trends of incidence, clinical stage, and histologic type among three-year periods were examined for all eligible cases. Descriptive analysis for women aged less than 35 is presented for treatment type, surgical procedure, and pathological prognostic factors. The Fisher exact test was used to estimate the disease-free interval and overall follow-up period. Survival curves were generated using the Kaplan-Meier Method. Univariate analysis of potential prognosis and predictive factors for women aged less than 35 related to clinical stage, histologic type, lymph node metastases, and lymph vascular involvement at the primary treatment was performed using the log-rank test to determine statistical significance. Cox's proportional hazards regression was employed to model the multivariate association of survival. A p value of less than 0.05 was considered to reflect a significant difference.

Table 1. — *Characteristics of cervical carcinoma in the Kinki District in Japan (1990-2005).*

Year periods	1990-95		1996-00		2001-05	
Age group	< 35	Overall	< 35	Overall	< 35	Overall
Stage of FIGO						
I	113	772	129	932	132	965
II	6	367	20	383	23	393
III	1	316	5	234	5	233
IV	0	67	3	82	4	141
Histologic type						
Squamous cell carcinoma	108	1313	129	1420	119	1306
Non-squamous carcinoma	12	209	28	301	45	426

Results

Patient demographics

Between 1990 and 2005, 4,975 women with invasive cervical carcinoma were registered by the tumor sectional meeting of the Obstetrical Gynecological Society of the Kinki District of Japan. Time trends in the distribution of FIGO stage and histologic type are shown in Table 1. The number of all cases of cervical carcinoma has increased since the late 1990s, especially in the population of women aged less than 35. The distribution of FIGO stage did not change in this period. The incidence of adenocarcinoma significantly increased; in the most recent period, there were 426 of 1,306 (24%) cases in all patients and 45 of 164 (27%) cases in the group of young women. Out of a total of 4,975 women, 441 women aged less than 35 were identified and had clinical pathological data analyzed. The characteristics of patients in each age group are given in Table 2. Most of the patients were young women 30-34 years old (69%). Twenty-five out of 441 (5.7%) patients were aged less than 25, and none of the patients was diagnosed with Stage III or IV disease. Patients with FIGO Stage IIIA and more advanced disease were detected in the groups aged over 25. In patients

Table 2. — *Details of characteristics of cervical carcinoma in age groups.*

Age group	< 25	25-29	30-34	All ages
No. of patients	25	111	305	4975
Stage of FIGO				
IA	9 (36)	52 (47)	130 (43)	1027 (21)
IB	14 (56)	42 (38)	127 (42)	1642 (33)
IIA	0	1 (1)	7 (2)	267 (5)
IIB	2 (8)	11 (10)	28 (9)	876 (18)
III	0	2 (2)	9 (3)	873 (18)
IV	0	3 (3)	4 (1)	290 (6)
Histologic type				
Squamous cell carcinoma	20 (80)	92 (83)	244 (80)	4000 (80)
Adenocarcinoma	4 (16)	10 (9)	44 (14)	739 (15)
Adenosquamous carcinoma	0	5 (5)	10 (3)	157 (3)
Other types of carcinoma	1 (4)	4 (4)	7 (2)	79 (2)

Table 3. — *Distribution of surgical procedures for FIGO stage.*

Stage of FIGO	IA	IB	II	III	IV
No. of patients	191	183	49	11	7
Types of treatment					
Surgery alone	182 (95)	116 (63)	5 (10)	1 (9)	1 (14)
Surgery + chemotherapy	2 (1)	18 (10)	15 (31)	2 (18)	0
Surgery + radiotherapy	1 (0.5)	34 (19)	9 (18)	0	0
Surgery + chemo + rad	0	14 (8)	15 (31)	3 (27)	0
Radiotherapy alone	0	1 (0.5)	4 (8)	4 (36)	0
Rad + chemo	0	0	0	0	4 (57)
Chemotherapy alone	1 (0.5)	0	1 (2)	0	1 (14)
Others	5 (3)	0	0	1 (9)	1 (14)

Table 4. — *Stage distribution of surgical procedures.*

Stage of FIGO	IA	IB	II
No. of patients	191	183	49
Surgical procedure			
Conization alone	75 (39)	14 (8)	0
Simple hysterectomy	61 (32)	5 (3)	1 (2)
Extended hysterectomy	26 (14)	18 (10)	3 (6)
Radical hysterectomy	23 (12)	145 (79)	40 (82)
No surgery	6 (3)	1 (0.5)	5 (10)

aged 25-29 years old, there were two of 111 cases (1.8%) with Stage IIIB, two (1.8%) cases with Stage IVA, and one (0.9%) case with Stage IVB. In women aged over 30, there was one of 305 (0.3%) cases with Stage IIIA, eight (2.6%) cases with Stage IIIB, three (1.0%) cases with Stage IVA, and one (0.3%) with Stage IVB. The distribution of histologic types among the three age groups was not identified.

Treatment procedures for women aged less than 35

The type of treatment was divided in four types including surgery, chemotherapy, radiotherapy, and other types of treatment. The concurrent chemoradiotherapy (CCRT) was classified as combined treatment with radiotherapy plus chemotherapy. Details of the treatment procedure based on FIGO stage are shown in Table 3. The stage distribution in surgical procedures is addressed in Table 4. In patients with Stage Ia, most of the cases were treated with surgery alone in which conization only was carried out in 39% and simple hysterectomy in 32%. None of the patients underwent radiation therapy alone. Only three patients had combined therapy. Two of them with AC underwent radical hysterectomy followed by systemic chemotherapy. One patient with SCC Stage IA_2 was treated with a simple hysterectomy followed by radiotherapy. One patient with squamous cell carcinoma Stage IA_1 had conization performed followed by chemotherapy. In patients with Stages IB and II disease, 185 of 232 (80%) cases received radical hysterectomy. In patients with Stage III disease, six of 11 (55%) patients underwent radical hysterectomy, while four of 11 patients were treated with radiotherapy alone. Four patients received neoadjuvant chemotherapy (NAC) before surgery. In patients with Stage IV disease, four of seven (57%) cases received CCRT.

Univariate analysis

Among 441 young patients, 53 (12%) patients had tumor recurrence and 36 (8%) patients died of the disease (Table 5). The incidence of recurrent disease was one out of 191 (0.5%) for Stage IA, 27/183 (14.7%) for Stage IB, 17/49 (34.7%) for Stage II, 3/11 (27.3%) for Stage III and 5/7 (71%) for Stage IV. The incidence of tumor death was zero in Stage IA patients, 16/183 (8.7%) for Stage IB, 12/49 (24.5%) for Stage II, 3/11 (27.3%) for Stage III and 5/7 (71%) for Stage IV. The incidence of recurrence and death was 7.9% and 5.1% in squamous cell carcinoma, and 29.4% and 21.2% in non-squamous cancer, respectively. The median follow-up period in young women was

Table 5. — *Univariate analysis related variables with cervical carcinoma in young adult women.*

Variable	No. of patients	No. of recurrences	No. of deaths	Median OAS (months)	5-year survival (%)	*p* value
Stage of FIGO						
I	374	28	16	65 (1-201)	95	< 0.0001
II	49	17	12	43 (1-139)	73	
III	11	3	3	36 (1-101)	68	
IV	7	5	5	12 (1-57)	19	
Histologic type						
Squamous cell carcinoma	356	28	18	65 (1-201)	95	< 0.0001
Non-squamous carcinoma	85	25	18	41 (1-176)	75	
Lymph node metastasis						
Negative	146	16	9	55 (3-187)	93	< 0.0001
Positive	39	17	9	39 (1-139)	74	
Lymph vascular involvement						
Negative	207	8	6	62 (3-187)	97	< 0.0005
Positive	99	26	14	41 (1-145)	83	

OAS: overall survival.

Table 6. — *Specific factors on survival as determined by multivariate analysis.*

Variable	Risk ratio	95%CI	*p* value
Early stage (Stage I)	0.298	0.106-0.842	0.022
Non-squamous carcinoma	0.201	0.076-0.527	0.0011
Lymph node metastasis	0.358	0.132-972	0.044

63 months (range 1-201). Kaplan-Meier survival curves and log-rank tests were generated to evaluate the influence of individual prognostic factors on overall survival (Table 5). The 5-year survival rate was also estimated in young women using the Kaplan-Meier method. Earlier stage (Stage I), histologic type (squamous cell carcinoma), the absence of lymph vascular involvement, and no evidence of lymph node metastasis were all associated with significantly improved overall survival rates (Figures 1, 2, 3 and 4). Subset analysis of treatment methods in Stages IB_2 and II disease revealed that patients treated with combined methods including surgery had a better prognosis (5-year survival, 78.9%) than those without surgery (Figure 5). In all patients with Stages IB_2, II, III and IVA, the 5-year survival showed 75.8% with neoadjuvant chemotherapy (NAC) and 68.5% without NAC. NAC showed the potential of improved survival, but there was no significant difference with or without NAC.

Multivariate analysis

The influence of specific factors on survival as determined by univariate analysis may have resulted from selection bias rather than from the variable itself. Therefore, multivariate analysis was performed to account for the potential influence of confounding factors (Table 6). A Cox proportional hazards model was employed. The following variables were considered: early stage (Stage I), histologic type (squamous cell carcinoma), and lymph node metastasis. All factors showed relative risks of less than 1, indicating a favorable effect on survival. These factors were found to have an independent influence on cause-specific survival.

Discussion

Many reports have demonstrated that the incidence of cervical carcinoma has decreased over the past 40 years [6-10]. However, an increased incidence of cervical carcinoma in young women has been well documented. Histologic examination has shown that the incidence of SCC has obviously decreased, while the population of AC has significantly increased. This retrospective study was designed to evaluate the recent trends in cervical carcinoma in Japan. From 1990 to 2005, 7,472 cases with cervical neoplasms were reported in the Kinki District in Japan. Two thousand four hundred and ninety-seven of these were diagnosed as carcinoma in situ, and 4,975 cases were invasive carcinoma. Time trends in the total incidence did not decrease during this period, whereas an increased number of cases in young women aged less than 35 was detected. In Japan, other investigators have reported that the age-standardized incidence of invasive cervical cancer decreased from 13.4 to 7.2 per 100,000 women from 1975 to 1998 [3]. In young women aged less than 30, invasive cervical cancer decreased until 1984, but increased thereafter. Carcinoma in situ (CIS) has rapidly increased by approximately seven times [3]. In our investigation, the rate of CIS was 26.8% from 1990-1995, and was elevated by 36.4% during the next five years and by 36.7% in the most recent five years (data not shown). The incidence of non-SCC has significantly increased since 1990, especially in young women. In our series, the frequency of non-SCC has increased by 1.7 times in all patients and 2.7 times in young women during the past 15 years. This time trend in incidence and histologic type are consistent with many another countries.

Several epidemiological studies have demonstrated that cervical carcinoma in young women has increased steadily in the last few decades [5-7]. Using medical records, we examined the characteristics of clinical status, treatment procedure, and prognosis in young women aged less than 35 since 1990. In our series, the youngest patient was 18 years old, diagnosed with mucinous adenocarcinoma with FIGO Stage IB_2. She underwent radical hysterectomy followed by irradiation with external beam at pole pelvis because multiple lymph node metastases had been observed. Recurrent disease was detected 22 months after primary treatment and she received chemotherapy. It is generally accepted that patients in the younger age group tend to have earlier stage disease. The FIGO annual report indicated that the portion of patients for Stages I, II, III and IV, treated from 1993-1995, was 42.7, 32.3, 20.5, and 3.9%, respectively [20]. In our study, the population of all women treated in 1990-2005 was 53.6% for Stage I, 23.0% for Stage II, 17.5% for Stage III, and 5.8% for Stage IV. Of a total of 441 cases in young women, there were 374 (84.8%) with FIGO Stage I, 49 (11.1%) with Stage II, 11 (2.5%) with Stage III, and seven (1.6%) with Stage IV. No cases with Stages III and IV were observed in the youngest group aged less than 25. Only two patients were diagnosed with FIGO Stage IVB. One was 25 years old with mucinous adenocarcinoma. She has undergone CCRT and is alive without any recurrent diseases. The other patient was 31 years old with other types of carcinoma. Although she had received systemic chemotherapy, she died of primary disease after one month. The population of advanced stages was 4.1% in young women and 23.3% in older women aged over 35; there was a significant increase in the older group. On the other hand, the rate of non-SCC was 19.3% in young women and 18.8% in older women. While the population of non-SCC has been elevated the last 15 years, there is no difference between women aged under 35 and those over 35.

Earlier reports demonstrated that young patients with cervical cancer have a poorer prognosis than older patients [11-13]. Rutledge reported that women aged less than 35 had a poor prognosis as compared with patients

Fig. 1

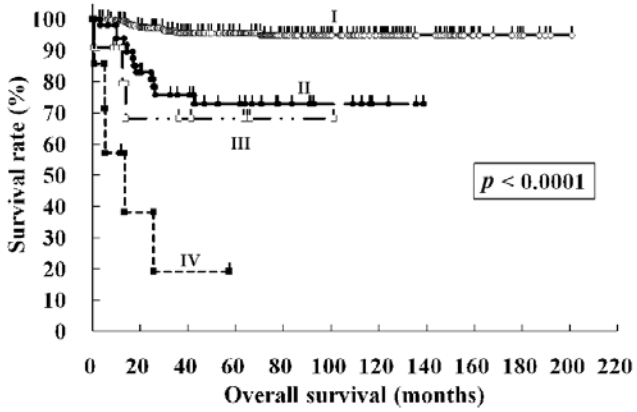

Fig. 2

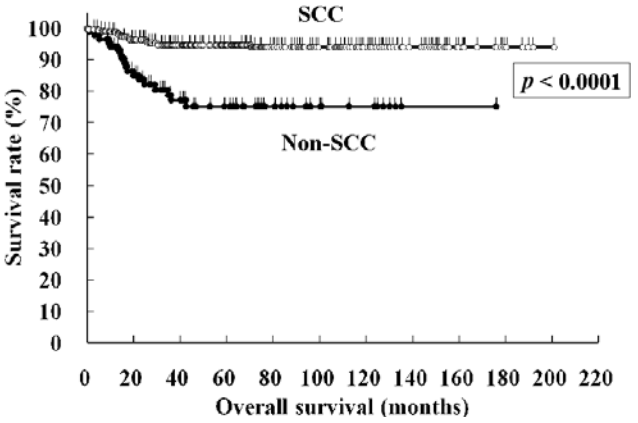

Fig. 3

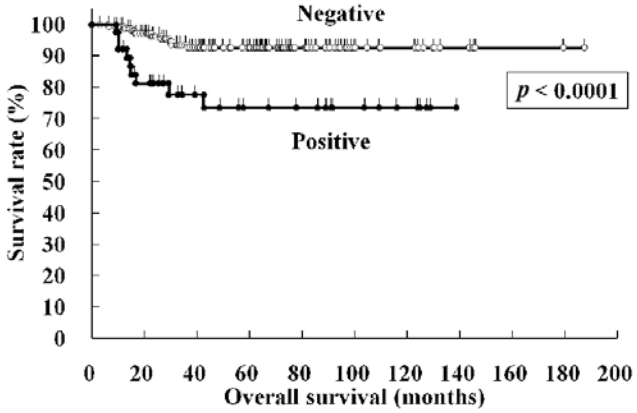

Fig. 4

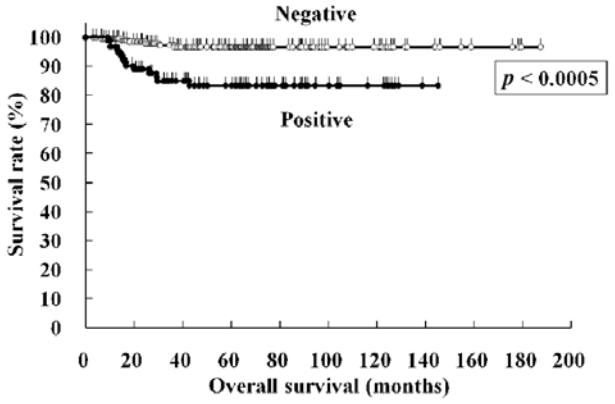

Fig. 5

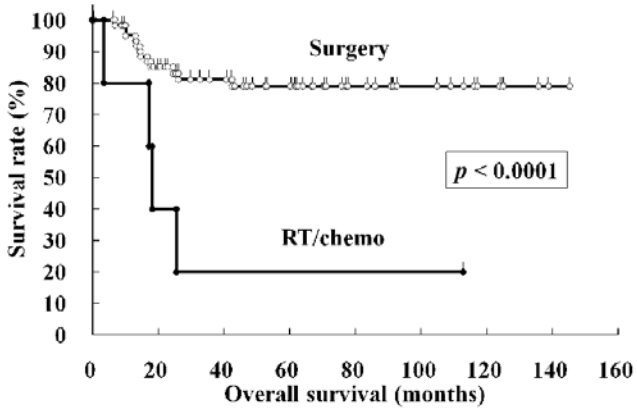

Figure 1. — Kaplan-Meier analysis of overall survival related to FIGO stage in young women. The x-axis indicates overall survival in months after primary treatment. The y-axis indicates the proportion of patients surviving with uncensored data.
I; FIGO Stage I, II; FIGO Stage II, III; FIGO Stage III and IV; FIGO Stage IV.
Figure 2. — Kaplan-Meier analysis of overall survival related to histologic types in young women. The x-axis indicates overall survival in months after primary treatment. The y-axis indicates the proportion of patients surviving with uncensored data.
SCC; squamous cell carcinoma, non-SCC; non-squamous carcinoma.
Figure 3. — Kaplan-Meier analysis of overall survival related to lymph node metastasis in young women. The x-axis indicates overall survival in months after primary treatment. The y-axis indicates the proportion of patients surviving with uncensored data.
Negative; absence of lymph node metastasis, Positive; presence of lymph node metastasis.
Figure 4. — Kaplan-Meier analysis of overall survival related to lymph vascular involvement in young women. The x-axis indicates overall survival in months after primary treatment. The y-axis indicates the proportion of patients surviving with uncensored data.
Negative; absence of lymph vascular involvement, Positive; presence of lymph vascular involvement.
Figure 5. — Kaplan-Meier analysis of overall survival related to treatment procedure for FIGO Stages IB_2-IIB in young women. The x-axis indicates overall survival in months after primary treatment. The y-axis indicates the proportion of patients surviving with uncensored data.
Surgery; patients treated with surgery alone and in combination, RT/chemo; patients treated without surgery.

over 35 in a stage- and treatment-matched analysis [12]. Serur *et al.* indicated that women with FIGO Stages IIB and III had a poorer prognosis in patients aged less than 50 than in older patients [14]. In addition, we have often seen unanticipated rapid disease progression in young women, although aggressive and combined treatments had been received. However, some reports indicated that the prognosis by FIGO stage at diagnosis was poorer in older aged women than that in young women. Kosary demonstrated that the 5-year survival rate was highest in women aged less than 30 and declined steadily as age increased in patients both overall and within stage [17]. Another study indicated that the stage-matched 5-year survival rates were better for young women aged less than 40 than older patients with FIGO Stages I and II [16]. In Japan, the 5-year survival rates for FIGO Stages I, II, III, and IV were 84.7, 60.6, 36.3, and 11.1%, respectively. In our study, patients aged less than 35 had a better prognosis within each stage. The FIGO annual report showed that 5-year survival rates for Stages Ib, IIb, IIIb, and IVa patients treated from 1993-1996 were 80.7, 73.3, 46.4 and 29.6%, respectively [19]. In our analysis, 5-year survival rates for Stages IB, IIB, IIIB, and IVA were 90.3, 73.4, 64.3, and 20.0, respectively. Therefore, the present retrospective study indicates that the younger the patient is, the better their prognosis. However, it is doubtful whether younger patients have a better prognosis than older patients. In our cases, young patients tended to be more willing to undergo surgery and combined aggressive treatment. It is generally accepted that radical hysterectomy with lymph node dissection or CCRT should be considered for patients with Stage IB or IIA. It is recommended that patients with Stage IIb and more advanced disease should be treated with CCRT, not radical surgery [20]. In Japan, a report in 2005 demonstrated that the population of primary treatment including surgery was 1,026 of 1,490 (68.9%) for Stages IB_2 and II disease, and 79 of 719 (11%) for Stage III. In our cases aged less than 35, primary treatment including surgery was 64 of 69 (92.8%) patients with Stages IB_2 and II, and six of 11 (54.5%) women for Stage III [21]. While primary treatment without surgery for Stages IB_2 to IVA was 1,156 of 2,366 (48.8%) cases in Japan in 2005, 14 of 87 (16.1%) women underwent radiotherapy or chemotherapy without surgery in our young patients. The 5-year survival rate for Stages IB_2 and II was 78.9% with surgery, but 20.0% without surgery. Therefore, it is possible that the distribution of treatment methods affects the better prognosis observed in our young patients.

Since the US National Cancer Institute alert in 1999 stated that concurrent chemoradiotherapy (CCRT) should be considered for locally advanced cervical carcinoma, it is recommended that patients with Stage IB_2 and greater should be treated with CCRT [20, 22, 23]. Although CCRT has tended to increase, the population of CCRT is only 5-10% for Stage IIB-IVA [20]. On the other hand, in Stage Ib disease, the rate of CCRT has decreased, and NAC plus surgery was significantly increased from 1993-95 compared to that from 1990-92 [20]. Several studies have indicated that NAC has been useful in the control of locally advanced cervical carcinoma [24, 25]. It is thought that the major theoretical advantages of NAC may be to promote the efficacy of surgery on local control by down-staging the disease, and to contribute to micro-metastasis control. We have shown that CDDP-based chemotherapy results in transient increases in apoptosis in locally advanced cervical cancer [26]. We also demonstrated that patients with FIGO IIIB stage cervical carcinoma treated with CPT-11 plus MMC showed remarkable reduction of tumor size, and could successfully undergo radical hysterectomy [27]. In general, the response rate has been reported to be approximately 70-80% for NAC with a CDDP-based regimen [28-30]. Sardi et al. reported that NAC followed by surgery was associated with a significant improvement in 8-year survival rates compared with surgery alone in patients with FIGO Ib disease [28]. Benedetti-Panici et al. demonstrated that FIGO IB_2-IIB patients treated with NAC followed by surgery showed a better prognosis than those with RT alone [29]. Our previous study demonstrated that 5-year survival rates for Stages IIA, IIB, III disease treated with NAC were 100%, 74%, and 75%, respectively [30]. In this study, the 5-year survival for Stages IB_2-IVA was 75.8% in patients treated with NAC and 68.5% without NAC. Other reports, however, have noted that NAC followed by RT for advanced disease did not result in an improvement in the overall survival compared with RT alone [31, 32]. Therefore, the effectiveness of NAC for prolonged survival in patients with locally advanced cervical carcinoma is controversial.

In conclusion, the incidence of invasive cervical carcinoma in young women aged less than 35 has steadily increased from 1990 to 2005, especially in patients with non-SCC. Most of the patients tended to choose radical surgery or combined treatment including surgery. The prognosis was better in young women than in the overall population. The reasons for this better survival may be associated with an earlier diagnosis and aggressive combined treatment with surgery, but additional studies are required to confirm this possibility.

Acknowledgments

The following institutions participated in this study and the principal investigators are shown in parentheses: Hyogo Medical Center for Adults (S. Takekida), Hyogo College of Medicine (K. Koyama), Kansai Medical University (J. Saito), Kobe City General Hospital (M. Kita), Kyoto University Graduate School of Medicine (S. Horie), Nara Medical University (R. Kawaguchi), Osaka Medical Center for Cancer and Cardiovascular Diseases (S. Kamiura), Osaka University Graduate School of Medicine (T. Enomoto), Osaka Medical College (K. Nishiyama), Takatsuki Red Cross Hospital (K. Kumagai), and Wakayama Medical University (N. Umesaki)

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