Descriptive epidemiological study of vaginal cancer using data from the Osaka Japan population-based cancer registry
Long-term analysis from a clinical viewpoint

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Abstract

Vaginal cancer is such a rare tumor that epidemiological and clinical information for it is based mainly on studies of small numbers of cases. The aim of the present study was to perform a descriptive epidemiological analysis of vaginal cancer using a significantly larger population-based dataset from the Japanese Osaka Cancer Registry.

The age-standardized incidence of vaginal cancer per 1,000,000 persons, from 1976 to 2010, was calculated and examined for trends. Relative-survival analysis was applied to estimate a more up-to-date 10-year period calculation, using data from recently followed-up patients. The conditional 5-year survival of patients who survived for 0 to 5 years after diagnosis was calculated.

A total of 481 cases of vaginal cancer were registered in Osaka during the 35-year period from 1976 to 2010. The age-adjusted incidence rate has significantly and consistently decreased over this time [annual percent change (APC) = −1.29, 95% confidence interval (95% CI): −0.3 ∼ −2.2]; however, due to significant population aging, the *raw* incidence of vaginal cancer appeared to have been increasing. The 10-year relative survival of patients with surgery-based treatments was comparable to that of radiation-based treatments, implying that surgery and radiotherapy provide similar therapeutic benefits ($P = .98$). The 10-year relative survival was not significantly different during the period of 1976 to 2000 compared with the period of 2001 to 2008, although there has been, in the latter period, a tendency for improvement of long-term survival, especially for survival longer than 5 years. The longer the time after diagnosis, the higher the conditional 5-year relative-survival at 0 to 4 years after diagnosis.

The age-adjusted incidence of vaginal cancer *has* decreased since 1976. Regrettably, the 10-year survival rate did not similarly improve, and it remained stable during the period from 2001 to 2008, compared with the period from 1976 to 2000, indicating that significant work remains to be done to develop more effective vaginal cancer treatments.

Abbreviations: APC = annual percent change, CCRT = concurrent chemoradiotherapy, CI = confidence interval, DES = diethylstilbestrol, HPV = human papillomavirus, SCC = squamous cell cancer.

Keywords: age-standardized incidence, conditional survival, epidemiological analysis, relative survival, vaginal cancer

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1. Introduction

Vaginal cancer is an unusually rare tumor, as it constitutes less than 1% of all gynecological malignancies. It is so rare that all our current epidemiological and clinical information for it is based on studies with only small numbers of cases. In the United States, only 4620 new cases of vaginal cancer were expected to occur in 2016, but 950 patients were expected to die from it.[1] Early-stage vaginal cancer, usually asymptomatic and thus difficult to detect, has yet to have an effective screening system established for it.

Squamous cell carcinoma (SCC) accounts for approximately 85% of new cases of vaginal cancer, 5% to 10% will be adenocarcinoma,[2] which was once frequently observed in young females whose mothers took diethylstilbestrol (DES) during their pregnancy[3]; however, currently in Japan, few if any new cases can now be accrued to DES. Other rare histological types of vaginal cancer that occur include malignant melanoma, sarcoma, and small cell carcinoma.

SCC, the most frequently observed histological type of vaginal cancer, usually occurs in elderly females; the human papillomavirus (HPV) can be detected in around 80% of these elderly SCC cases.[4] Following a long period of decreasing incidence of uterine cervical cancer in Japan (most of which was caused by

HPV infection), recently cervical cancer incidence has been rising again, especially in younger women.[5] This new and worrisome trend of increasing uterine cervical cancer needs to be analyzed to understand its genesis, to ascertain how poorly it bodes for vaginal cancer as well.

Following the introduction of concurrent chemoradiotherapy (CCRT) for cervical cancer, patient survival prognosis has improved significantly.[6,7] However, a rigorous large-scale examination of the effectiveness of CCRT (or other available treatment modalities) for vaginal cancer has yet to be performed. Largely because of its rare incidence, the long-term survival rate of vaginal cancer patients has yet to be analyzed in any detail. Moreover, the conditional survival of vaginal cancer patients, which would contain useful information about the additional 5-year survival rates at specific lengths of time (0–5 years), has yet to be demonstrated.

The cancer registries of the Japanese prefects of Osaka, Yamagata, Miyagi, Fukui, Niigata, and Nagasaki have records with unusually high data quality; these records have long been used to estimate national statistics for cancer survival in Japan.[8] Among these, the Osaka cancer registry is the largest in scale and has a long history (since 1962). Osaka is the third largest prefecture in Japan, having a population of almost 9,000,000, constituting nearly one-tenth of Japan's population (and nearly equal to that of all of Sweden), and whose cancer registry system is so well established that it is frequently used for epidemiological analyses. In the present study, we have performed a descriptive epidemiological analysis of vaginal cancer using this Osaka prefectural cancer registry data.

2. Methods

2.1. Data sources

Vaginal cancer patients were followed using the death certificate database of the Osaka Cancer Registry for residents of the Osaka Prefecture. To capture the details of patients who may have moved outside the Osaka Prefecture after their diagnosis, resident registries[9] were used, as the death certificate database would have missed them. There were 60,127 cancer cases registered during 1976 to 2010 in the Osaka Cancer Registry database. Of these, 175 cases were diagnosed before 1976 and 14 cases were missing age data. Of the remaining 59,938 cases, 481 were determined to have been diagnosed with vaginal cancer, bearing the medical record code "C52."

For determining age-adjusted incidence, we used data from patients who were diagnosed with vaginal cancer in the period of 1976 to 2008. For survival analysis, we analyzed cases diagnosed from 1976 to 2003 (followed for 10 years) and cases diagnosed from 2004 to 2008 (followed for 5 years).

We investigated changes in survival rates occurring over the time of treatment procedures. We excluded 154 of the 481 available cases. These exclusions included 49 cases with multiple cancers, 103 cases with other-than-newly-diagnosed vaginal cancers, and 2 cases occurring in women older than 100 years. Data were compared between the 2 diagnosis periods, of 1976 to 2000 and 2001 to 2008. These periods were chosen for comparison because radiotherapy, used in the late 90s, is comparably as effective as surgery for treatment for cervical cancer, and CCRT, which was first introduced for cervical cancer treatment in Japan in 2000, were assumed to be utilized, in accordance with cervical cancer treatment guidelines of those times, also for vaginal cancer treatment.

2.2. Variables

Clinical stages of vaginal cancer were classified as "localized," "regional lymph nodes," "adjacent organs," and "distal metastases." Primary treatments were divided into 2 groups: Group 1: surgery (with or without other procedures, including radiotherapy and chemotherapy), Group 2: radiotherapy without surgery, with or without other procedures, including chemotherapy, and Group 3: all other procedures. Vaginal cancer cases registered by the ICD-O3M (International Classification of Diseases for Oncology, 3rd Edition) as 8070/3, 8071/3, 8072/3, 8083/3 or 8051/3 were categorized as SCC.

2.3. Statistical analysis

The 1985 age-distribution population pyramid was used as the standard (model) population for age-standardization. Because vaginal cancer is so rare, the age-standardized incidence rate is presented as "per 1,000,000 population." Using the Joinpoint 4.2.0.2 statistical package (Kim et al, 2000; US National Cancer Institute, 2008), the piecewise log linear regression model was applied to find trends in the age-standardized incidence data.

For survival analysis, we first estimated the 10-year relative-survival using data by periods of diagnosis (1976–2000, and 2001–2008), treatment procedures (Groups 1–3), and 2 histologic types (SCC and non-SCC). Relative survival is a ratio of the observed survival (overall survival) and the survival that would have been expected if the cancer patient had only experienced the normal (background) mortality of the general population in which they lived.[10]

Calculation of long-term survival of cancer patients using previous conventional methods is outdated. We therefore used period analysis to derive more up-to-date long-term survival values using recent follow-up data.[9,11] To estimate the 5-year conditional survival of patients who survived for X number of years, the (X + 5)-year cumulative survival rate is divided by the X-year cumulative survival. In other words, the conditional 5-year survival is the 5-year survival of those patients who are alive several years after diagnosis.[8] Conditional 5-year relative survival rates from 0 to 5 years after diagnosis were calculated thusly.

For statistical analysis based on a relative survival setting, we applied the excess hazard model.[12] We used Fisher exact test to investigate the change-over-time of treatment procedures between the former and the latter diagnosis periods. The level of statistical significance was set at $P = .05$.

3. Results

3.1. Vaginal cancer case characteristics

In the Osaka Cancer Registry, 481 cases of vaginal cancer were registered during the period of analysis, 1976 to 2010. The number of vaginal cancers registered per 5-year increment has increased recently: 42 in 1976 to 1980, 59 in 1981 to 1985, 55 in 1986 to 1990, and then 85 in 1991 to 1995, 82 in 1996 to 2000, 76 in 2001 to 2005, and 82 in 2006 to 2010 (Table 1). Of these 481 cases, the SCC-type of vaginal cancer was observed in 25 females aged 49 years or younger, in 59 cases aged 50 to 59 years, in 65 cases aged 60 to 69 years, in 89 cases aged 70 to 79 years, and in 49 cases aged 80 to 89 years, peaking in the age group of 70 to 79 years. On the contrary, a non-SCC type of vaginal cancer, including adenocarcinoma, adenosquamous carcinoma, etc, was observed in 25 females aged 49 years or younger, in 41 aged 50 to 59 years, in 40 aged 60 to 69 years, in 40 aged 70 to 79 years, and in 45 aged 80 to 89 years,

Table 1

Characteristics of vaginal cancer cases in Osaka Cancer Registry, Japan in 1976–2010.

	1976-	1981-	1986-	1991-	1996-	2001-	2006–2010	Total
Total	42 (8.7%)	59 (12.3%)	55 (11.4%)	85 (17.7%)	82 (17.0%)	76 (15.8%)	82 (17.1%)	481 (100.0%)
SCC	24 (57.1%)	35 (59.3%)	36 (65.5%)	53 (62.4%)	44 (53.7%)	49 (64.5%)	48 (58.5%)	289 (60.1%)
Non-SCC	18 (42.9%)	24 (40.7%)	19 (34.5%)	32 (37.6%)	38 (46.3%)	27 (35.5%)	34 (41.5%)	192 (39.9%)

	1976–2000 (n = 323)	2001–2010 (n = 158)	Total
Stage			
Localized	109 (33.7%)	36 (22.8%)	145 (30.1%)
Regional lymph nodes	20 (6.2%)	10 (6.3%)	30 (6.2%)
Adjacent organs	74 (22.9%)	36 (22.8%)	110 (22.9%)
Distant	23 (7.1%)	17 (10.8%)	40 (8.3%)
Unknown/Missing	97 (30.0%)	59 (37.3%)	156 (32.4%)
SCC (n = 289)			
<49	17 (8.9%)	8 (8.3%)	25 (8.7%)
50–59	40 (20.8%)	19 (19.6%)	59 (20.4%)
60–69	53 (27.6%)	12 (12.4%)	65 (22.5%)
70–79	57 (29.7%)	32 (33.0%)	89 (30.8%)
80-	25 (13.0%)	26 (26.8%)	51 (17.6%)
Non-SCC (n = 192)			
<49	23 (17.6%)	2 (3.3%)	25 (13.0%)
50–59	33 (25.2%)	8 (13.1%)	41 (21.4%)
60–69	24 (18.3%)	16 (26.2%)	40 (20.8%)
70–79	25 (19.1%)	15 (24.6%)	40 (20.8%)
80-	26 (19.8%)	20 (32.8%)	46 (24.0%)

SCC = squamous cell cancer.

forming a broader plateau beginning at age 50, compared with the age peak of 70 to 79 for SCC.

3.2. Trends in age-adjusted incidence rate

In order to evaluate the trends of vaginal cancer incidence, the age-adjusted incidence of vaginal cancer was analyzed using the Japanese model population for 1985. The result of a Joinpoint regression analysis is shown in Fig. 1. Although the number of occurrences of vaginal cancer has increased, the age-adjusted incidence rate per 1,000,000 was significantly and consistently decreased [annual percent change (APC) = −1.29, 95% confidence interval (95% CI): −0.3 ~ −2.2].
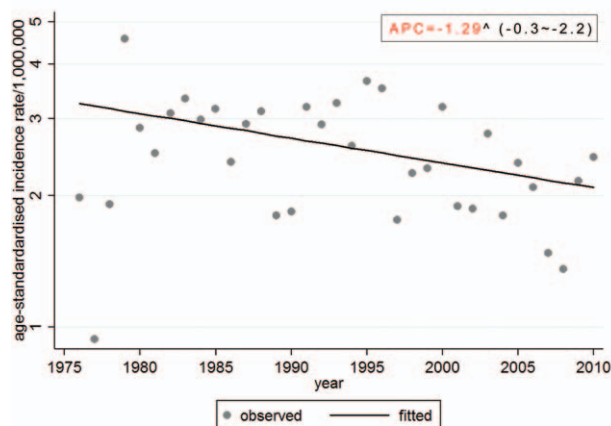

Figure 1. Age-adjusted incidence rate of vaginal cancer. Age-adjusted incidence rate of vaginal cancer was analyzed using the Japanese model population for 1985. The age-adjusted incidence rate per 1,000,000 was significantly and consistently reduced over time. APC: −1.29, 95% CI: −0.3 ~ −2.2, by the Joinpoint regression model.

3.3. Change over time of primary treatment procedure

We compared the different treatment procedures used between the 2 time periods, 1976 to 2000 and 2001 to 2008, for the 289 cases for which a primary treatment was accurately recorded in the registry. During the first time period, 36.1% of the patients were in Group 1 (i.e., underwent surgery, with or without other treatment procedures), 47.0% were in Group 2 (i.e., received radiotherapy without surgery), and the remaining 16.9% were in Group 3 (all other treatments). The proportion of cases having surgery (Group 1) in the second period decreased significantly, from 36.1% to 15.7% ($P < .05$). On the contrary, the use of radiotherapy without surgery (Group 2) increased from 47.0% to 55.7% in the second period. When considering only SCC cases, radiotherapy without surgery (Group 2) was preferably performed, occurring in 56.1% of all SCC cases. In contrast, the proportion of cases where surgery (Group 1) was the preferred treatment was significantly higher (41.4%) in the non-SCC cases (data not shown).

3.4. Relative survival

The goodness-of-fit of the excess hazard model was evaluated for relative survival analysis. The 5-year and 10-year relative-survival rates were calculated. These rates were not significantly different between the first (1976–2000) and second (2001–2008) time periods, although there was a tendency for improvement in long-term survival, especially for survival longer than 5 years, in the more recent period (Fig. 2). The 10-year survival rate was significantly better in cases of localized tumor than more progressed cases ($P < .001$) (Fig. 3).

With regards to treatment procedures, the relative survival rate of Group 1 was closely similar to that of Group 2, implying that surgery and radiotherapy provided comparable therapeutic benefits ($P = .98$) (Fig. 4). On the contrary, cases where only "other treatments" were performed (Group 3) demonstrated a significantly worse prognosis ($P < .001$). The 92 non-SCC cases also demon-
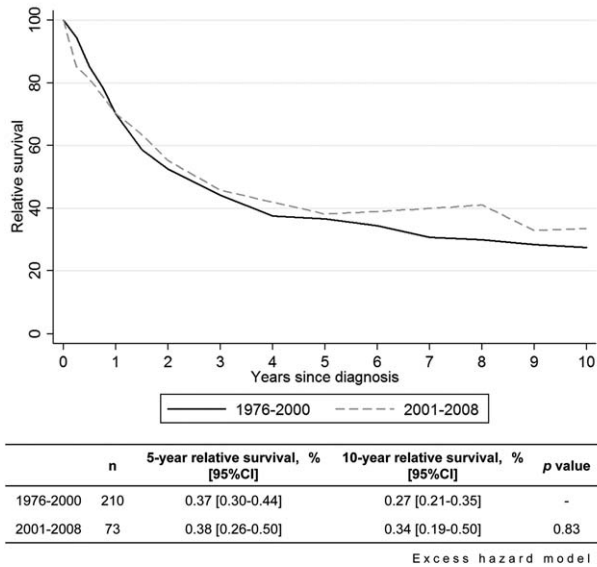
Figure 2. Relative survival in the periods of 1976 to 2000 and 2001 to 2008. The 10-year relative survival rates were not significantly different between the 2 periods (P = .83; excess hazard model).

Figure 3. Relative survival by tumor stage. The 10-year survival rate was significantly better in cases of localized lesions than in the more progressed cases ($P < .001$).

strated a worse 10-year relative-survival rate, of 0.20 (0.11–0.31), than did the 211 SCC cases, 0.33 (0.25–0.41) (P = .005) (Fig. 5).

3.5. Conditional 5-year relative survival

The conditional 5-year relative survival for all stages of patients was calculated (Fig. 6). The longer the time after diagnosis, the higher was the conditional 5-year relative-survival of 0 to 4 years after diagnosis. However, the conditional 5-year relative survival rate of the cases who survived for 5 years after diagnosis was not increased compared with those who survived for 4 years.
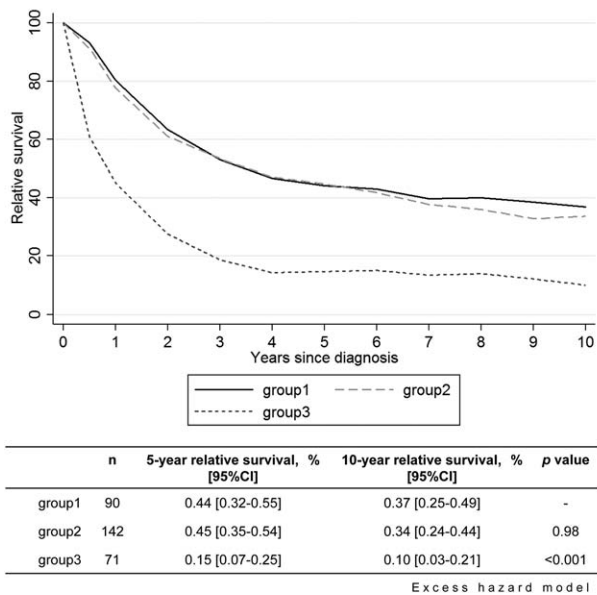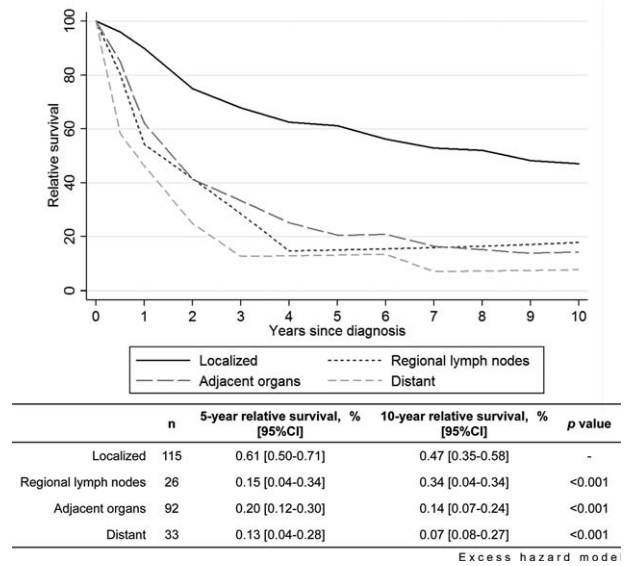
4. Discussion

Vaginal cancer is such an extremely rare tumor that there are only a limited number of reports concerning its epidemiological analysis. Clinical information, usually based on studies of small numbers of cases, is also sparse. According to the Cancer Registry and Statistics,[13] vaginal cancer's crude incidence rate during 2008 to 2011 is estimated to be only 0.7 cases per 100,000. In our study, the age-adjusted incidence rate per 1,000,000, using the Japanese model population of 1985, was 2.5 in 2010, which converts to 0.25 per 100,000. For comparison, Wu et al[14] reported that the age-adjusted incidence rate per 100,000 in the

Figure 4. Relative survivals by treatment procedures. The 10-year relative survival rate of Group 2 was comparable to that of Group 1 (P = .98), and Group 3 demonstrated significantly worse survival than Group 1 ($P < .001$; excess hazard model).
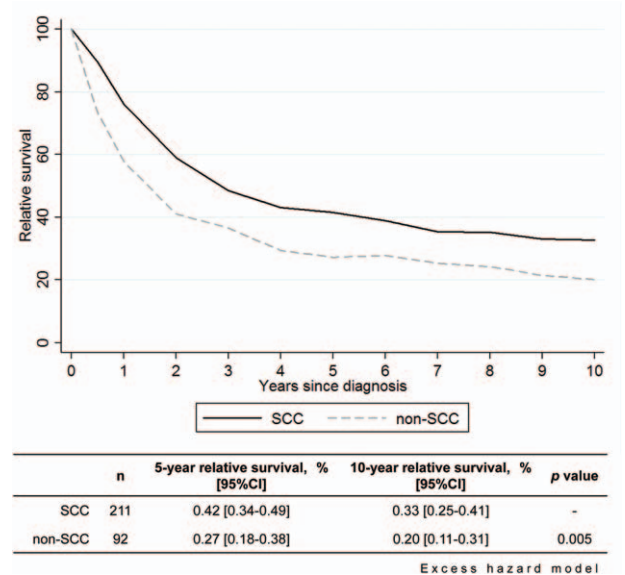

Figure 5. Five-year and 10-year relative survivals by histological type. The relative survival rate of non-SCC vaginal cancer was demonstrated to be worse than that of SCC (P = .005; excess hazard model).
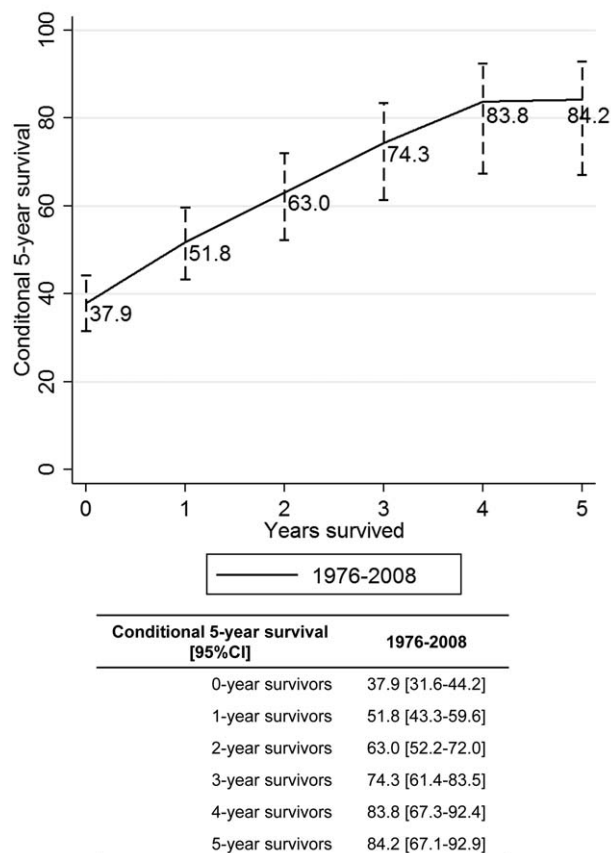
Figure 6. Conditional 5-year relative survival in the 2 diagnostic periods. The conditional 5-year relative survival of 0 to 5 years after diagnosis was calculated.

Conditional 5-year survival [95%CI]	1976-2008
0-year survivors	37.9 [31.6-44.2]
1-year survivors	51.8 [43.3-59.6]
2-year survivors	63.0 [52.2-72.0]
3-year survivors	74.3 [61.4-83.5]
4-year survivors	83.8 [67.3-92.4]
5-year survivors	84.2 [67.1-92.9]

United States, using the US standard population of 2000, was much higher, 0.69 (95% CI: 0.67–0.71).

Our analysis of the Osaka Cancer Registry data found that there has been a significant recent increase in the number of vaginal cancers registered per 5-year increment in the Osaka/Japanese population. One obvious explanation for this increase is that the number of those aged 70 years or older has been increasing year to year, as crude rates are influenced by the underlying age distribution of the study population. Even if 2 populations have the same age-adjusted rates, the group with the relatively older population generally will have higher crude rates because incidence or death rates for most cancers increase with increasing age. The age distribution of a population can change over time, as it has done significantly in Japan, with our steadily dropping birth rate. Calculating and using age-adjusted rates ensures that differences in incidence or deaths noted from one time period to another are not due to differences in the age-distribution of the populations being compared.[15] In fact, in the present study, we demonstrate for the first time that the age-adjusted incidence rate per 1,000,000, using the Japanese model population of 1985, has actually been significantly and consistently dropping from 1976 to 2010 (APC=−1.29, 95% CI: −0.3 ∼ −2.2) (Fig. 2), suggesting that the increase of crude incidence others have noted was in fact caused by the aging of the Osaka/Japanese population. These results are consistent with a report that the European age-standardized incidence of vaginal cancer also decreased, by 14%, during 1975 to 2013, in parallel with a decrease of cervical cancer in Great Britain.[16]

Most vaginal cancers, similar to cervical cancers, are associated with HPV infection.[17–19] In Japan, a trend for the lowering of the age of first cervical cancer diagnosis has been observed, and the age-adjusted mortality rate for those under 50 was noted, as increasing.[20] Vaginal cancer has had a parallel history of earlier age at diagnosis. Both cancer increases correspond to upsurges in cases of HPV infection in younger women (a direct result of Japan's suspended HPV vaccination program), and both are predicted to further mushroom in the near future; therefore, more attention should be paid to vaginal cancers and more HPV vaccinations should be heavily encouraged.

Farther into the future, re-energizing the anti-HPV vaccine program will potentially prevent most vaginal cancers. However, the current HPV vaccination rate in Japan is in a dramatic slump. In Japan, the government's recommendation for HPV vaccination has now been suspended since mid-2013. The news of Japan's suspension of the HPV vaccine recommendation has traveled widely through online and social media networks, seriously impairing the global battle against vaginal cancer.[21]

There has yet to be a large-scale randomized study of treatments for vaginal cancer, so only a few small retrospective studies have been shaping all our decisions for treatment strategy. For example, CCRT is a well-established treatment option for cervical cancer, yet there are only retrospective studies with relatively small numbers cases analyzing its efficacy and safety for vaginal cancer treatment.[22–24] Similarly, a standard chemotherapy for vaginal cancer has not yet been established. According to the National Cancer Database of the United States, radiotherapy provides a better prognosis for stage I and stage II patients than does surgery, although effects on the analysis from age and health conditions could not be excluded.[24,25] For adenocarcinoma, which is usually resistant to radiotherapy, surgical treatment has been recommended.[26,27]

Our present analysis shows that radiation-based therapy (Group 2) has been increasingly utilized. The possible reasons for increased use of radiotherapy over surgery include the fact that recently CCRT has been applied for both cervical and vaginal cancers, and that vaginal cancer usually occurs more often in elderly patients, leading to an avoidance of invasive surgery. Fortunately, radiotherapy appears to be an appropriate option for the majority of vaginal cancers, as SCC, the predominant histological type of vaginal cancer, responds well to CCRT. This is corroborated in the present study, where we found that radiation-based treatment (Group 2) provided a better survival prognosis for SCC cases than for non-SCC cases ($P < .001$, 95% CI: 0.084–0.290, data not shown).

We were surprised, and discouraged, to find that the 10-year survival rate during the most recent period, from 2001 to 2008, was not significantly improved compared with the period from 1976 to 2000 (Fig. 2). The 10-year survival rate was also not significantly different between surgery-based (Group 1) and radiation-based (Group 2) treatments. However, in cases where the cancer lesion is located in the upper third of the vagina, surgical treatment is still preferable.

In our present analysis, there is a possibility that certain unspecified clinical characteristics were different between the cases where surgery-based treatment was performed and those where radiation-based treatment was. In fact, a previous study showed that stage I and II cases, whose lesions were localized in the upper third of the vagina, and surgery-based treatment was performed, the cases exhibited a better prognosis than radiation-based treatment.[28] Radiation might be preferable in cases whose lesions progressed beyond the upper third of the vagina.

Although the 10-year survival rate has not been significantly improved over the years, the survival rate after the fifth year *has* recently tended to improve (Fig. 2), implying a possible decrease of late recurrence due to changes in treatment strategy and possible improvement of treatment for recurrent diseases; however, this was not analyzed for in the present study.

In our study, the 10-year survival rate was different by tumor stage. Localized cases exhibited a good prognosis, of 47% (95% CI: 35~58%), whereas, not surprisingly, the more progressed cases exhibited a worsened prognosis (Fig. 3). These findings are consistent with a previous study.[16]

The present study demonstrated, for the first time, an accurate survival rate for vaginal cancers. The conditional 5-year relative survival rate did become longer in proportion with the years the patients survived (Fig. 6); however, the rate for patients who survived for 5 years was similar to that of those who survived for 4 years, implying that a late recurrence, and late death, cannot yet be avoided. This result is consistent with a previous study showing that 70% to 80% of recurrence occurred within 2 years, but that late recurrence also was still observed—even after 5 years.[29,30]

In conclusion, our epidemiological and clinical analyses using the well-established Japanese Osaka Cancer Registry database have demonstrated that the age-adjusted incidence rate of vaginal cancer has been significantly and consistently dropping over the years, that radiation-based therapy for vaginal cancer has recently been the preferred treatment, and has this treatment has been exhibiting an improved prognosis. The conditional 5-year relative survival rate for survivors should be an encouraging bit of information for our vaginal cancer patients. Tragically, however, our study suggests that death from recurrence can still occur even after 4 or 5 years of survival, proving that more effective treatments for vaginal cancers should be investigated.

Acknowledgment

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