



Trends in incidence and long-term survival of Japanese women with vulvar cancer: a population-based analysis

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Abstract

Objective The incidence and long-term survival analysis for vulvar cancer, due to its rarity, has not been fully described in Asian population. The objective of the study is to determine the trends in incidence and long-term survival for vulvar cancer in a Japanese population, using a population-based cancer registry data in Osaka, Japan.

Methods The age-standardized incidence rate of 389 cases of vulvar squamous cell carcinoma (SCC) diagnosed between 1976 and 2010 was calculated, using the 1985 model population of Japan. The annual percentage change (APC) of the age-standardized incidence was estimated by the joinpoint regression models. The 5- and 10-year relative survival of 290 cases with vulvar SCC diagnosed between 1976 and 2008 were analyzed, using a cohort or period approach. Using the 10-year relative survival, the conditional 5-year survival for patients who lived for some years after diagnosis was also calculated.

Results We have found that the age-standardized incidence rate for vulvar cancer trended downward during the period of 1979–1992 (APC -6.3% ; 95% confidence interval (CI) $[-11.3\%$ to -1.0%]), whereas it trended upward from 1993 to 2010 (APC 1.9% ; 95% CI $[-0.7\%$ to 4.6%]). There was no statistically significant difference for the 5- and 10-year relative survival between the two periods of 1976–2000 and 2001–2008. A statistically significant increase in the conditional 5-year survival at 2 years after diagnosis was observed (48.4% ; 95% CI $[41.1-55.3]$ versus 75.6% ; 95% CI $[64.0-83.9]$).

Conclusion Despite an increasing trend in vulvar cancer incidence among Japanese population, the relative survival rate for vulvar cancer did not change over the 35 years of this study. We found that the conditional 5-year survival for vulvar cancer, as patients survived additional years, approached within reach of 100%. These data can provide valuable information for both patients and clinicians.

Keywords Cancer registry · Conditional survival · Relative survival · Squamous cell carcinoma · Vulvar cancer

Introduction

Vulvar cancer is a rare gynecologic malignancy, accounting for only approximately 3–5% of all gynecologic cancers [1]. The incidence of vulvar cancer varies by country, and in Japan, vulvar cancer has an incidence of 0.2–0.4 per 100,000 females [2]. In contrast, its incidence in Western countries

is approximately five or ten times higher than that of Asian population [2]. Although it is very important for both clinicians and patients to recognize the trends in vulvar cancer incidence, the trends in Asian population remain unknown.

According to a systematic review of the literature regarding vulvar cancer survival [3], the pooled 5-year overall survival (OS) rate has been 64.9%, and patients with FIGO stage I, II, III, and IV disease had 5-year OS rates of 84.0%, 74.6%, 47.8%, and 9.4%, respectively. The 5-year OS is widely used for survival analysis of cancer patients; however, the long-term (more than 5 years) survival analysis for vulvar cancer, due to its rarity, has not been fully described. Accurate survival statistics not only offer patients an understanding of the disease's nature and course but can also guide oncologists in case counseling and management.

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In the present study, we have analyzed the incidence trends for vulvar cancer and estimated the long-term relative survival using a population-based cancer registry data in Osaka, Japan over the period of 1976 and 2010.

Materials and methods

Data source

The data used in the present study were obtained from the Osaka Cancer Registry for the 35 years from 1976 to 2010. Osaka Cancer Registry has been covering all residents in Osaka Prefecture, and the register collects reports on newly diagnosed cancer patients from all medical institutions in Osaka Prefecture. For scale, the current (2016) population of women in Osaka Prefecture is 4,586,327 [4]. A total of 815 women with vulvar cancer were identified in the registry data.

The histological subtypes were determined according to International Classification of Diseases for Oncology (ICD-O-3), as approved by the World Health Organization [5]. For data analysis, we categorized the histological subtypes into the following groups: “squamous cell carcinoma” (ICD-O-3 morphology codes: 80513, 80523, 80703, 80713 and 80723), “basal cell carcinoma” (ICD-O-3 morphology codes: 80903 and 80943), “adenocarcinoma” (ICD-O-3 morphology codes: 81403, 83803, 84003, 84103, 84403 and 84803), “extramammary paget’s disease” (ICD-O-3 morphology codes: 85423), “adenosquamous carcinoma” (ICD-O-3 morphology codes: 85603), “malignant melanoma” (ICD-O-3 morphology codes: 87203), “sarcoma” (ICD-O-3 morphology codes: 88003, 88103, 88323, 88503, 88903, 89003, 89103 and 91303) and “others or unclassified” (ICD-O-3 morphology codes: 80003, 80103, 82003 and 82473).

In this database, the extent of the disease at the time of diagnosis was divided into the following five groups: (1) localized, (2) regional lymph node metastasis, (3) adjacent organs, (4) distant metastasis, and (5) unknown.

A written informed consent for participation in the cancer registry database was not obtained from patients, because physicians could transfer data to the cancer registry without the patient’s consent. The institutional review board of Osaka University Hospital and the ethical committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases approved the present study.

Statistical analysis

The age-standardized incidence of vulvar SCC diagnosed between the years of 1976 and 2010 was calculated, using the 1985 model population of Japan as a standard population. The annual percentage change (APC) of the

age-standardized incidence was estimated by the joinpoint regression models using the Joinpoint Regression Program Version 4.3.1.0 [6]. Joinpoint regression model is a statistical method used to identify the years when the statistically significant changes in incidence trends occurred. The model can also estimate whether those trends (APC) are statistically significantly different from zero.

We analyzed the relative survival (RS) for these patients. RS is a ratio of the overall survival in cancer patients versus the expected survival in a comparable set from the general population, which was calculated by the Ederer II method [7] from national life-tables stratified by age, sex and calendar year. In the current study, cases diagnosed from 1976 to 2003 were followed up for 10 years after diagnosis, whereas follow-up was limited to 5 years for those diagnosed from 2004 to 2008. We calculated 10-year relative survival for patients diagnosed between 1976 and 2003, and 5-year relative survival for patients diagnosed between 1976 and 2008 using conventional methods (cohort approach). For patients diagnosed between 2004 and 2008, we applied the period approach [8] to estimate 10-year survival. Usually, we use a cohort approach to report cancer survival. However, long-term survival using the conventional method would be outdated, because we need to wait a long time to follow-up, up to 10 years after diagnosis. The period approach was developed to solve the problem and enabled us to estimate up-to-date long-term survival using recently followed-up data [9].

We also calculated conditional 5-year survival for patients with vulvar SCC who survived for 0–5 years after diagnosis using 10-year cumulative relative survival. Conditional survival analysis is a method to estimate survival rates, with the pre-condition of having already survived a certain length of time [9, 10]. Conditional 5-year survival for an x -year survivor was calculated as previously described [9]: divide the $(x+5)$ -year cumulative survival rate by the x -year cumulative survival, or calculate $(x+5)$ -year cumulative survival, limited to the x -year survivors.

All statistical analyses were performed using the standard statistical package Stata/MP version 13 (StataCorp, College Station, TX, USA).

Results

Patients’ characteristics

389 of the 815 patients were diagnosed as vulvar SCC, extramammary paget’s disease in 163, basal cell carcinoma in 43, adenocarcinoma in 37, malignant melanoma in 28, sarcoma in 14, adenosquamous cell carcinoma in 2, others or unclassified in 139, respectively. The characteristics of the patients with vulvar SCC are shown in Table 1. 322 (82.8%) of the 389 patients were over 60 years old at diagnosis.

Table 1 Characteristics of the 389 patients with vulvar squamous cell carcinoma diagnosed between 1976 and 2010

Number of patients	389
Age at diagnosis	
< 60	67
≥ 60	322
Period (years)	
1976-	34
1981-	48
1986-	50
1991-	45
1996-	48
2001-	71
2006-	93
The extent of disease	
Localized	150
Regional lymph nodes	66
Adjacent organs	77
Distant metastasis	30
Unknown	66
Treatment	
Surgery	176
Non-surgery	174
Unknown	39

The extent of disease included “localized” in 150 patients, “regional lymph nodes” in 66, “adjacent organs” in 77, “distant metastasis” in 30, and “unknown” in 66, respectively.

Age-standardized incidence rate of vulvar cancer

Trends in the age-standardized incidence rate of vulvar SCC diagnosed between 1976 and 2010 are shown in Fig. 1. Although the APC between the years of 1976 and 1978 was increased, this period was the dawn of the systematic data collection. Between the years of 1979 and 1992, the APC was -6.3% (95% CI [-11.3% to -1.0%]). We found that the age-standardized incidence rate trended downward during this period, whereas an increasing trend (APC 1.9% ; 95% CI: [-0.7% to 4.6%]) was observed between the years of 1993 and 2010.

Five- and ten-year relative survival

Between the years of 1976 and 2008, the extent of the vulvar SCC was determined as “localized” in 121 cases, “regional lymph nodes” in 58, “adjacent organs” in 59, “distant metastasis” in 26, and “missing” in 26, respectively. We compared the 5- and 10-year RS by the year-date at diagnosis (1976–2000 versus 2001–2008); Fig. 2 shows the results. Unfortunately, there was no statistically significant difference in 5- and 10-year RS between the two groups, regardless of the extent of the diseases.

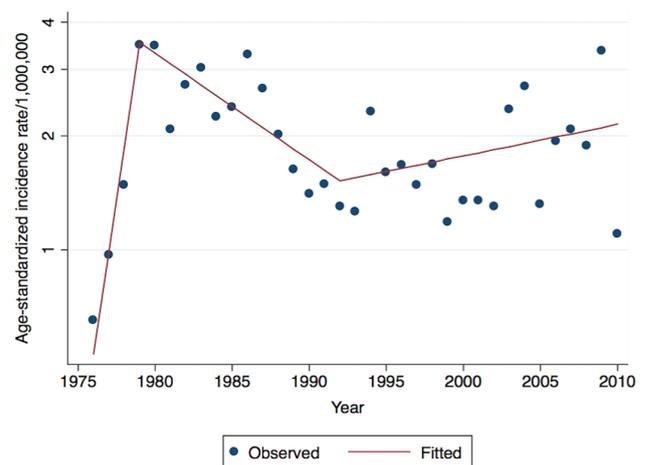


Fig. 1 Age-standardized incidence of vulvar squamous cell carcinoma. Between the years of 1979 and 1992, the APC was -6.3% (95% confidence interval (CI) [-11.3% to -1.0%]). In contrast, an increasing trend (APC 1.9% ; 95% CI [-0.7% to 4.6%]) was observed between the years of 1993 and 2010. APC annual percentage change

Conditional 5-year relative survival

The conditional 5-year relative survival of 290 vulvar SCC cases was analyzed. There was a continuous increase in the conditional 5-year survival, as shown in Fig. 3. A statistically significant increase in the conditional 5-year survival during the first 2 years after diagnosis was observed (48.4% ; 95% CI [$41.1\text{--}55.3$] versus 75.6% ; 95% CI [$64.0\text{--}83.9$], respectively). We found that, as patients survived additional years, the conditional 5-year survival came within reach of 100%.

Discussion

In the current study, we focused on conditional survival, which was a relatively new approach for examining cancer survival. For a wider perspective on our findings, we searched, using PubMed, for English-language articles published before June 2016, using as key words “vulvar cancer”, “survival”, “relative survival”, and “conditional survival”. We found that only a limited amount of information is available regarding conditional survival for vulvar cancer [11]. Although clinicians who care for gynecologic cancer patients usually report 5-year survival rates, even some patients with advanced vulvar cancer survive more than 5 years after diagnosis [3]. The 5-year overall survival thus does not reflect the survival rates of patients having already survived a certain length of time [9, 10]. Conditional survival can provide valuable predictive information for both patients and clinicians, and new insights into traditional survival analysis in gynecologic oncology.

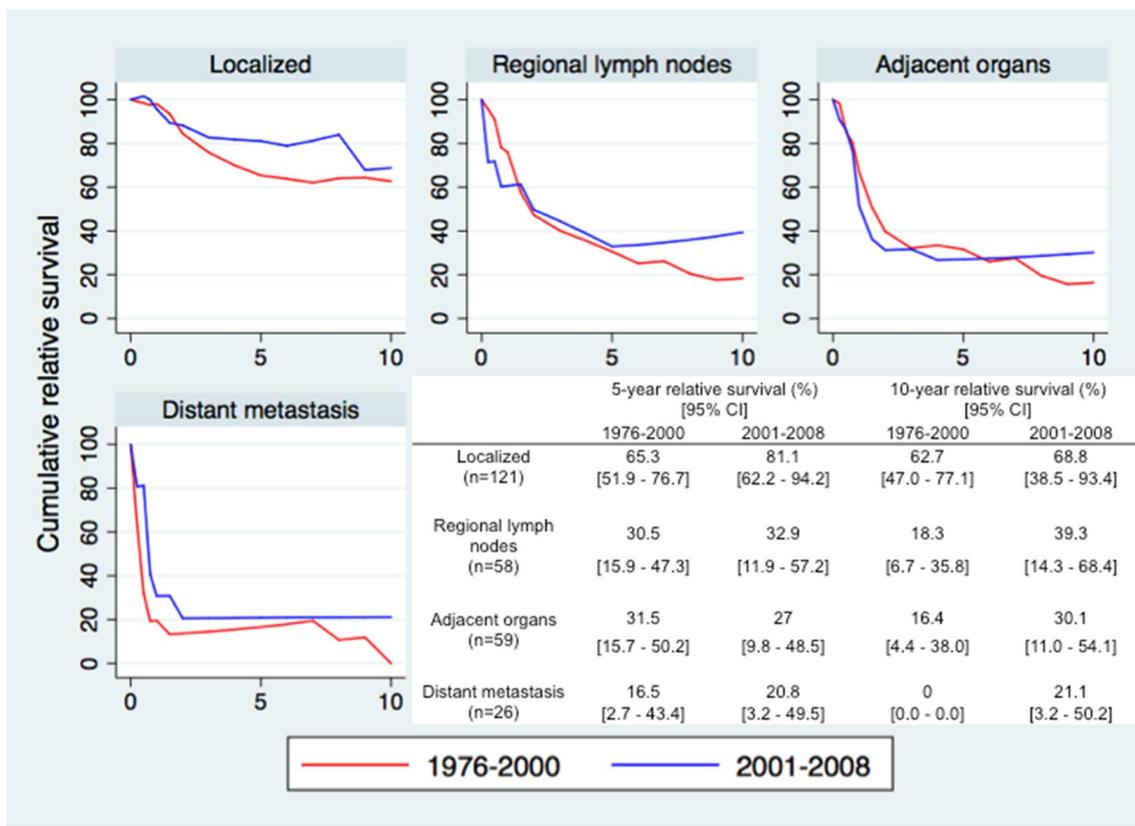


Fig. 2 Relative survival for patients with vulvar squamous cell carcinoma. There was no statistically significant difference between the two groups (1976–2000 versus 2001–2008) regarding 5- and 10-year relative survival

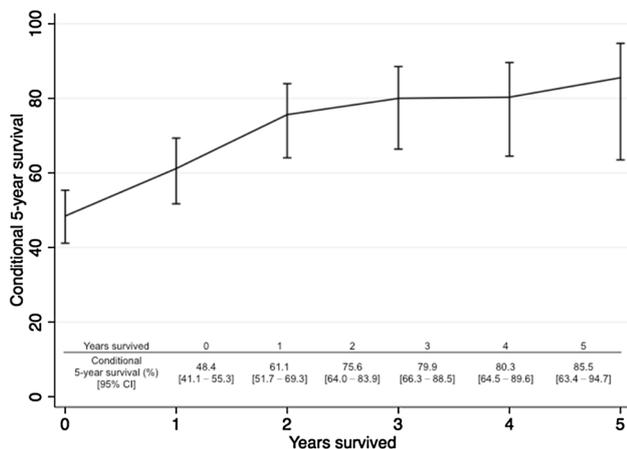


Fig. 3 Conditional 5-year relative survival for patients with vulvar squamous cell carcinoma

Survivors of cancer treatment are at high risk for fear of recurrence, distress, anxiety, and depression due to the multiple challenges they face. Fear of recurrence can lead to increased symptoms when surveillance testing or follow-up appointments are scheduled, and increased anxiety when

physical symptoms occur that may or may not be similar to those experienced during the cancer diagnosis [12]. Therefore, we believe that a statistical analysis focused on conditional survival would be highly useful in support of a cancer patient’s peace of mind.

As shown in Fig. 3, the conditional 5-year survival of vulvar cancer increases according to years already survived after diagnosis, reaching to 100%. This means that patients with the most unfavorable stage died relatively shortly after diagnosis, but the remaining patients (those who survived more than 5 years) have almost the same probability of living a full life as the general population [9]. They could, therefore, be considered as cured.

A recent report from Canada, concerning the period between 1992 and 2008, described their increasing trends in vulvar cancer incidence [13]. Another report from Netherlands [14] revealed a statistically significant annual increase in incidence of vulvar SCC of 5% between 2002 and 2010, while during the earlier years of 1989–2002 no increase was observed. Most of the recent literatures regarding the epidemiology of vulvar cancer have been reported from Western countries [13–15]. It is worth noting that the incidence of vulvar cancer in Asian populations is completely different

from that of North America or Europe [2], and that, to our knowledge, the trends of its incidence in Asian populations have never been previously discussed. In the current study, we have found, for the first time, an increasing trend in vulvar cancer incidence in Asian population, but which, considering genetic and lifestyle similarities, we predict to extend much more widely to other Asian countries.

Lower socioeconomic status is associated with a higher vulvar cancer incidence rate [16]. Our results show that the incidence of vulvar cancer decreased from 1979 through 1992. In Japan, rapid economic growth started in the late 1950s, and the gross domestic product (GDP) had doubled from 1970 to 1990 [17]. Thus, the decreased incidence of vulvar cancer of that period might have resulted from the generally improved socioeconomic status of Japanese females. In contrast, as shown in Fig. 1, the incidence of vulvar cancer increased from 1993 through 2010. Although the reason for the increasing trend in vulvar cancer remains unknown, it may result from the increasing incidence of HPV infection subsequent to increased sexual activity among Japanese women.

Currently, there is limited literature regarding the trends in relative survival for vulvar cancer [13, 14, 18]. Data from the Eastern part of Netherlands described that there was no statistically significant differences in the 5- and 10-year RS in 2000–2008, compared to that in 1989–1999 [18]. The nationwide data from the USA and Canada (1973–2010 for US., and 1992–2008 for Canada) demonstrated that 5-year RS decreased over time for all age groups (particularly for the older age groups), suggesting that the increased incidence rate of invasive vulvar cancer over time may be one of the reasons for this phenomenon [13]. According to analysis data from the Netherlands Cancer Registry for the years of 1989–2010, 5-year RS of vulvar SCC did not change over time, varying between 70 and 72%. Women aged below 60 years had a considerably higher 5-year RS compared to women aged 60 and older [14]. Sadly, based on these findings combined with our data, we find that clinicians have not significantly improved the 5-year survival for vulvar cancer patients over the past 4 decades.

In conclusion, we demonstrated the increasing trends in incidence and the long-term survival for vulvar cancer among Japanese population. RS has not been improved during the last 10 years, despite the increased incidence of vulvar cancer. More optimal treatment strategies and screening methods will be required to decrease vulvar cancer mortality. Compared with traditional survival estimates, such as overall survival from the time of diagnosis, conditional survival estimates provide more relevant quantitative information for cancer survivors and their families, as their risk profiles change over time. This information will also be useful for clinicians, when considering post-treatment surveillance intervals after treatment.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki. A written informed consent for participation in the cancer registry database was not obtained from patients, because physicians could transfer data to the cancer registry without the patient's consent.

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