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Research article

Overall survival associated with surgery, radiotherapy, and chemotherapy in metastatic vulvar cancer: A retrospective cohort study based on the SEER database

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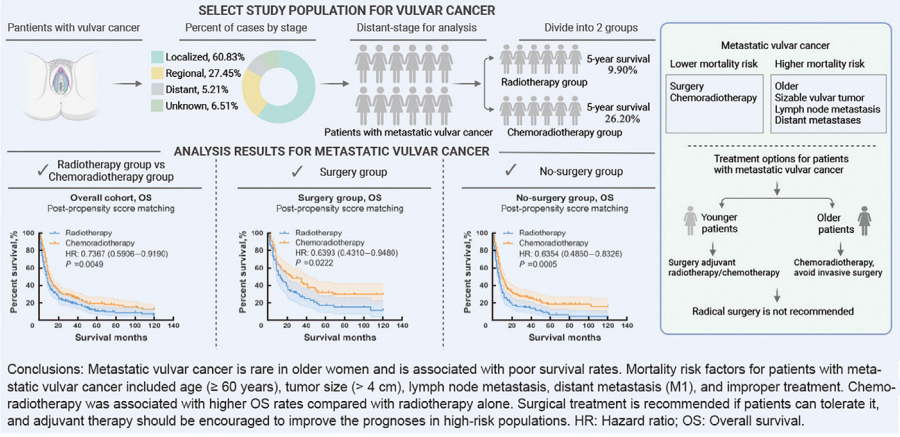
HIGHLIGHTS

- Chemoradiotherapy improved the overall survival of patients with metastatic vulvar cancer compared with radiotherapy.
- Chemoradiotherapy was associated with higher overall survival regardless of surgical intervention.
- Surgery improved overall survival in women with metastatic vulvar cancer but radical surgery is not recommended.
- Surgery is not recommended for patients ≥75 years old, chemoradiotherapy should suffice.
- For younger patients, tumor excision with adjuvant therapy is recommended.

GRAPHICAL ABSTRACT



Conclusions: Metastatic vulvar cancer is rare in older women and is associated with poor survival rates. Mortality risk factors for patients with metastatic vulvar cancer included age (≥ 60 years), tumor size (> 4 cm), lymph node metastasis, distant metastasis (M1), and improper treatment. Chemoradiotherapy was associated with higher OS rates compared with radiotherapy alone. Surgical treatment is recommended if patients can tolerate it, and adjuvant therapy should be encouraged to improve the prognoses in high-risk populations. HR: Hazard ratio; OS: Overall survival.

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ABSTRACT

Background: Large cancer registries help analyze the prognosis of rare malignancies, such as advanced vulvar cancer. This study aimed to compare the overall survival (OS) rates of patients with metastatic vulvar cancer who had undergone chemoradiotherapy and radiotherapy alone and identify prognostic factors using data from the Surveillance, Epidemiology, and End Results (SEER) registry.

Methods: In this retrospective cohort study, we used the SEER database to identify patients with metastatic vulvar cancer diagnosed between 2000 and 2019. Propensity score matching was performed to balance the covariates. Kaplan–Meier curves and Cox models were used to analyze OS.

Results: A total of 685 patients were included and divided into chemoradiotherapy and radiotherapy groups, and 400 patients were included after propensity score matching. The chemoradiotherapy group had higher OS in the

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matched cohort (hazard ratio [HR] = 0.7367; 95% confidence interval [CI]: 0.5906–0.9190; $P = 0.0049$) than the radiotherapy group, which was similar to that in the pre-matched cohort ($P < 0.0001$). Patients who had undergone surgery + radiotherapy with or without chemotherapy showed higher OS rates than those who had received radiotherapy with or without chemotherapy for patients aged <75 years and local tumor excision/destruction or surgical removal of the primary site was the recommended surgical choice ($P < 0.05$). Chemoradiotherapy is sufficient for patients ≥75 years of age.

Conclusions: Patients with metastatic vulvar cancer should undergo surgery if they can tolerate it. Adjuvant chemoradiotherapy should be encouraged because this treatment modality was associated with higher OS than radiotherapy alone.

Introduction

Primary vulvar cancer is a rare gynecological malignancy that accounts for only 4–5% of all gynecological tumors, mainly located in the labia majora, labia minora, clitoris, mons, or perineum, and is common in elderly and postmenopausal females.[1] The predominant pathological type of vulvar cancer is squamous cell carcinoma, which can occur via human papillomavirus (HPV)-dependent and HPV-independent pathways.[2] Due to the increase in high-risk HPV infections, the age of onset of vulvar cancer has gradually decreased in recent years, making the prevention and treatment of vulvar cancer even more urgent.[3–5] Large population-based cancer registries allow the analysis of the treatment and prognosis of rare cancers, such as advanced vulvar cancer.

The Summary Stage system used by the official Surveillance, Epidemiology, and End Results (SEER) program classifies cancer based on how far it has spread from its point of origin. *In situ*, localized, regional, and distant stages are recognized. Distant-stage diseases with poor prognoses include distant site or lymph node involvement or distant metastasis (International Federation of Gynecology and Obstetrics [FIGO] stage IVa, IVb, and IV not otherwise specified [NOS]). Most patients with primary vulvar cancer are diagnosed at the localized stage; the proportion of patients with advanced disease (locally advanced and distant metastases) is low, and the survival prognosis is poor.[6–8]

Clinical treatment for vulvar cancer varies considerably owing to its complex tumor biology and sociodemographic factors, particularly in patients with advanced disease. Therefore, gynecologic oncologists propose a variety of treatment strategies to overcome these factors.[6,9–11] Owing to the rarity and therapeutic complexity of advanced vulvar cancer, evidence for direct comparison of outcomes for different adjuvant therapies for vulvar cancer is scarce.[12] Over the years, the use of chemoradiotherapy to treat advanced vulvar cancer has gradually increased as adjuvant, neoadjuvant, or exclusive therapy.[9,13–16] Treatment for patients with advanced vulvar cancer has not been defined, but chemotherapy can be administered if it is tolerable for patients.[12,17] To date, outcomes of chemoradiotherapy and radiotherapy alone have been compared for primary advanced vulvar cancer, but large-scale cohort studies are still limited. Although single-institution retrospective studies on this subject have been published, the data were mostly obtained from small patient cohorts.[9,11,18] Moreover, the prognosis of rare cancers is difficult to analyze in prospective studies.

Radical surgery is the standard treatment option for vulvar cancer; however, surgery is associated with a high risk of complications and sequelae. The quality of survival of elderly patients with vulvar cancer is a point of concern, and, as a result, conservative and personalized surgical procedures have been developed.[19] Extensive local excision and modified vulvectomy are surgical options for preserving the quality of life of women, with reduced side effects such as lymphedema, urinary complications, sexual dysfunction, and psychological damage. However, studies have compared partial excision and radical vulvectomy, and their safety is comparable.[20]

Managing advanced vulvar cancer, especially stage IV, is complicated by the patient's age, disease stage, oncological characteristics, and curative intent. For example, the treatment modality that achieves satisfactory clinical results in an 80-year-old patient with a sizable vulvar tumor accompanied by lymph node and lung metastases, with aggressive intentions to ease pain and prolong survival, may not be the same treatment modality that achieves satisfactory outcomes in a patient aged 60 years with late-stage vulvar cancer. Even for a minority of elderly patients with late-stage disease, the quality of life and prognosis should be considered. A comparison of different treatment options is urgently needed, as currently, no standard treatment exists.

This study focused on metastatic (distant-stage cases, mainly stage IV) vulvar cancer and evaluated various treatment and surgery options. This study aimed to compare the overall survival (OS) rates of patients with metastatic vulvar cancer who had undergone chemoradiotherapy and radiotherapy alone and identify prognostic factors of metastatic vulvar cancer using data from the SEER cancer registry.

Methods

Data source and study population

The SEER Program (www.seer.cancer.gov) SEER*Stat Database is a population-based tumor registry. All data were obtained from the SEER registry using the Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.4.01. Given that the data released by the SEER registry were publicly available, this study was exempt from approval from the ethics committee. This study retrospectively identified patients diagnosed with metastatic primary vulvar cancers between 2000 and 2019.

Patient selection

The inclusion criteria for patients in this study were as follows: (1) diagnosis of distant-stage disease as defined by the SEER Summary Stage system; (2) having received radiotherapy and/or chemoradiotherapy; and (3) the primary site of the tumor is described according to the SEER Program Coding and Staging Manual (https://staging.seer.cancer.gov/) as the labium majus, labium minus, labium clitoris, overlapping lesion of the vulva, or vulva, NOS with primary site codes C510, C511, C512, C518, or C519, respectively.

The exclusion criteria for patients were as follows: (1) not the first primary tumor; (2) diagnosis of localized, regional, or unknown/unstaged disease as defined by the SEER Summary Stage system; (3) unknown survival period; (4) unknown surgery performed; and (5) absence of radiotherapy or unknown status.

According to the SEER Program Coding and Staging Manual, primary site surgery is defined as a procedure that removes or destroys tissue from the primary site (including local tumor destruction, local tumor excision, simple/partial surgical removal of the primary site, total surgical removal of the primary site, debulking, radical surgery, and unspecified surgery). The surgical codes for local tumor excision/destruction are 10–27; the surgical codes for removal of the primary site are 30–50, including simple/partial/total surgical removal of the primary site and debulking; and the surgical code for radical surgery is 60. A surgical code of 90 means surgery was performed, but the scope of the surgery is not known.

Variables

The collected data included general information, tumor information, and patient survival status. The variables included age (<60, 60–74, or ≥75 years), race (white, black, or other races), marital status (married, single or unmarried, divorced or separated, or widowed), histology (squamous or non-squamous cell carcinoma), grade (grade I, grade II, or grade III/IV), tumor size (≤4 cm or >4 cm), lymph node metastasis (negative or positive), metastasis (M0 or M1), surgery (no or yes), and survival time. International Classification of Diseases-Oncology-3 (ICD-O-3) histology codes 8051–8086 were classified as squamous cell carcinomas, and all the remaining histology codes were considered non-squamous cell carcinomas.

Main outcome

OS was adopted as the main outcome and was calculated from the date of diagnosis to the date of death from any cause or the last follow-up visit for surviving women. The OS curves were based on the 10-year survival rates.

Statistical analysis

The chi-square test was used to compare baseline categorical variables in the chemoradiotherapy and radiotherapy alone groups. Age and survival time were expressed as median and interquartile range. The Kaplan–Meier method was used to construct the OS curves at various time points during the follow-up.

Propensity score matching was performed to balance confounding factors between the two groups, and the matched covariates included age, race, marital status, histology, grade, tumor size, lymph node metastasis, metastasis, and surgery.

The Cox proportional hazards model was used to assess the hazard ratio (HR) and 95% confidence interval (95% CI) in the overall cohort population to identify significant factors of OS. We first performed univariate Cox proportional hazards regression models for all factors, and then multivariate Cox regression analysis was performed only for significant variables ($P < 0.05$) in the univariate regression. The effects of various factors on survival and prognosis were evaluated using HR values with 95% CI.

Statistical analyses were performed using the software GraphPad Prism 9 (GraphPad Software, San Diego, California, USA) and IBM SPSS Statistics version 26.0 (IBM, Armonk, New York, USA). Statistical significance was set at $P < 0.05$.

Results

Patient demographics and tumor characteristics

A flowchart of the patient selection is shown in Figure 1. In total, 685 patients were included before propensity score matching, including 227 who received radiotherapy and 458 who received chemoradiotherapy. Four hundred patients were included in the analysis after propensity score matching. The use of chemoradiotherapy gradually increased from 2000 to 2009 and was consistently more frequent than the use of radiotherapy alone [Figure 2].

The baseline demographics and tumor characteristics of patients with metastatic vulvar cancer in the overall and propensity score-matched cohorts are presented in Table 1. The overall cohort included 685 patients with a median age of 66 years (range, 55–77 years) and a median follow-up time of 11 months (range, 5–30 months). The median survival time in the chemoradiotherapy group (14 months) was longer than that in the radiotherapy alone group (7 months). To avoid selection bias in the chemoradiotherapy group as a result of receiving or not receiving surgery, we divided the 685 patients into surgery (232 patients) and no-surgery (453 patients) groups. After propensity score matching, 136 patients remained in the surgery group, and 272 patients remained in the no-surgery group.

Overall survival

The Kaplan–Meier OS curves for the overall and matched cohorts are presented in Figure 3. The curves revealed that OS in the chemoradiotherapy group was significantly higher than that in the radiotherapy group in the overall cohort (HR = 0.5592; 95% CI: 0.4574–0.6836; $P < 0.0001$) [Figure 3A1]. After propensity score matching, OS in the chemoradiotherapy group remained significantly higher than that in the radiotherapy group (HR = 0.7367), 95% CI: 0.5906–0.9190; $P = 0.0049$) [Figure 3A2], which was consistent with the data in the overall population before matching. The overall population was divided into surgery and no-

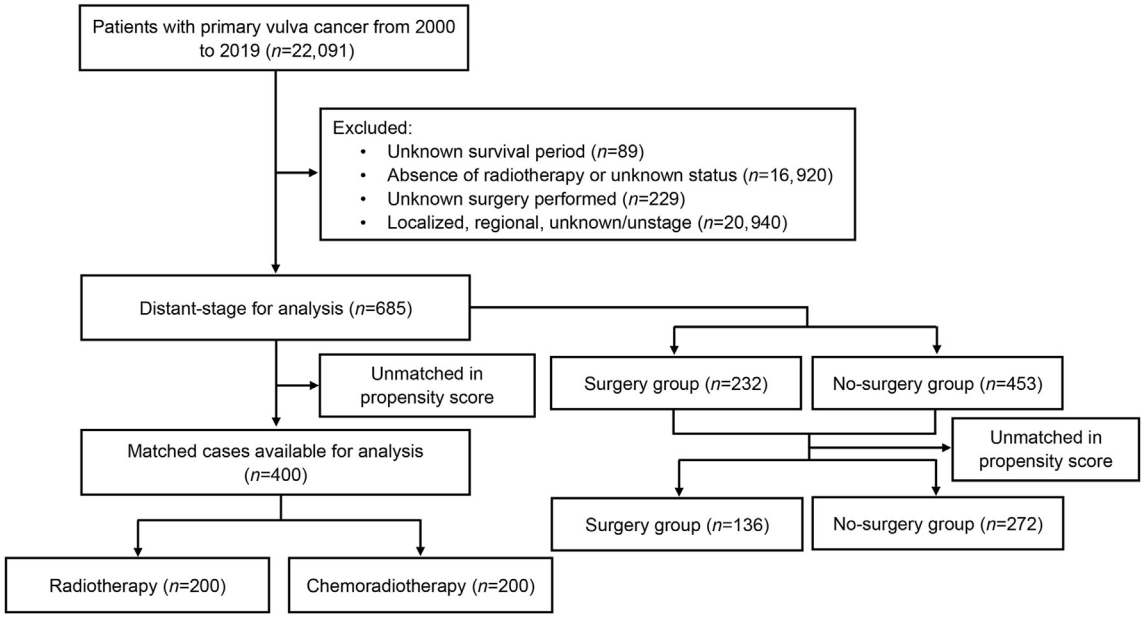

Figure 1. Flowchart of the patient selection procedure. Some patients met more than one of the exclusion criteria, we counted each exclusion criterion separately. Thus the sum case number of excluded patients and analysable patients was greater than 22,091.

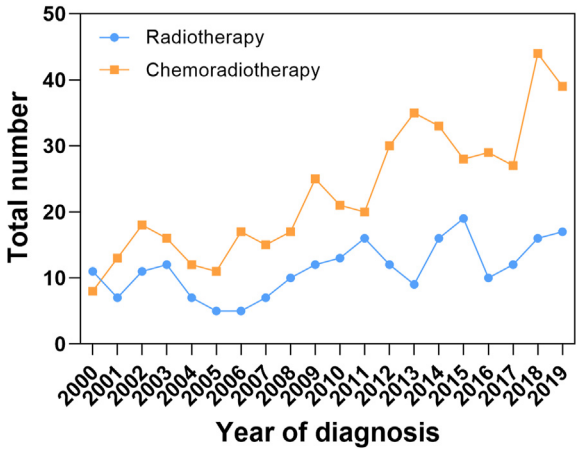

Figure 2. Numbers of patients receiving chemoradiotherapy and radiotherapy per year from 2000 to 2019.

surgery groups, and propensity score matching was performed separately. We compared the OS rates of patients treated with chemoradiotherapy with those treated with radiotherapy alone in the surgery and no-surgery groups. For patients who had undergone surgery, chemoradiotherapy conferred a higher survival advantage than radiotherapy in both the pre-matched (HR = 0.6114; 95% CI: 0.4288–0.8717; $P = 0.0022$) and post-matched cohorts (HR = 0.6393; 95% CI: 0.4310–0.9480; $P = 0.0222$) [Figure 3B1 and B2]. In patients who had not undergone surgery, OS rates in the pre-matched cohort (HR = 0.5291; 95% CI: 0.4143–0.6758; $P < 0.0001$) and post-matched cohort (HR = 0.6354; 95% CI: 0.4850–0.8326; $P = 0.0005$) were significantly higher in the chemo-radiotherapy group [Figures 3C1 and 3C2].

One-, three, and five-year overall survival rates

As shown in Table 2, the 1-, 3-, and 5-year OS rates were higher in the chemoradiotherapy group than in the radiotherapy group. The 5-year OS rates for patients who had received chemoradiotherapy and radiotherapy were 26.2 (21.7–30.7) months and 9.9 (5.4–14.4) months, respectively.

Multivariate Cox analysis and survival curves in the overall cohort

Multivariate Cox analysis was performed only for significant variables ($P < 0.05$) in the univariate analysis, and the results of the multivariate regression analysis are presented in Table 3. Age (≥60 years), tumor size >4 cm, lymph node metastasis, distant metastases (M1), the absence of surgery, and radiotherapy alone were associated with lower OS rates. Age (≥75 years) was significantly associated with lower OS rates

Table 1
Baseline characteristics of patients with metastatic vulvar cancer in the overall cohort and propensity-matched cohort.

Patient characteristics	Overall cohort				Propensity-matched cohort			
	Total	Radiotherapy	Chemoradiotherapy	*P*	Total	Radiotherapy	Chemoradiotherapy	*P*
N	685	227	458		400	200	200	
Age (years)								
Median (IQR)	66 (55.0–77.0)	74 (61.0–84.0)	63 (54.0–74.0)		70.5 (58.0–81.0)	71.5 (59.0–83.0)	68.5 (57.3–78.0)	
Age, *n* (%), years								
<60	233 (34.0)	54 (23.8)	179 (39.1)	<0.001	109 (27.3)	53 (26.5)	56 (28.0)	0.777
60–74	238 (34.7)	63 (27.8)	175 (38.2)		122 (30.5)	59 (29.5)	63 (31.5)	
≥75	214 (31.3)	110 (48.4)	104 (22.7)		169 (42.2)	88 (44.0)	81 (40.5)	
Marital status, *n* (%)								
Single, unmarried	151 (22.0)	46 (20.3)	105 (22.9)	0.031	85 (21.3)	42 (21.0)	43 (21.5)	0.794
Married	222 (32.4)	68 (30.0)	154 (33.6)		124 (31.0)	60 (30.0)	64 (32.0)	
Divorced, separated	126 (18.4)	36 (15.9)	90 (19.7)		72 (18.0)	33 (16.5)	39 (19.5)	
Widowed	155 (22.6)	68 (30.0)	87 (19.0)		102 (25.5)	56 (28.0)	46 (23.0)	
Unclear	31 (4.6)	9 (3.8)	22 (4.8)		17 (4.2)	9 (4.5)	8 (4.0)	
Race, *n* (%)								
Black	69 (10.1)	23 (10.1)	46 (10.0)	0.007	42 (10.5)	23 (11.5)	19 (9.5)	0.198
White	590 (86.1)	188 (82.8)	402 (87.8)		344 (86.0)	167 (83.5)	177 (88.5)	
Others	26 (3.8)	16 (7.1)	10 (2.2)		14 (3.5)	10 (5.0)	4 (2.0)	
Histology, *n* (%)								
Squamous cell carcinoma	604 (88.2)	184 (81.1)	420 (91.7)	<0.001	358 (89.5)	183 (91.5)	175 (87.5)	0.192
Non-squamous cell carcinoma	81 (11.8)	43 (18.9)	38 (8.3)		42 (10.5)	17 (8.5)	25 (12.5)	
Grade, *n* (%)								
Grade I	82 (12.0)	29 (12.8)	53 (11.6)	0.758	57 (14.2)	29 (14.5)	28 (14.0)	0.329
Grade II	238 (34.7)	75 (33.0)	163 (35.6)		132 (33.0)	74 (37.0)	58 (29.0)	
Grade III/IV	177 (25.8)	56 (24.7)	121 (26.4)		104 (26.0)	49 (24.5)	55 (27.5)	
Unclear	188 (27.5)	67 (29.5)	121 (26.4)		107 (26.8)	48 (24.0)	59 (29.5)	
Tumor size, *n* (%)								
≤4 cm	149 (21.8)	54 (23.8)	95 (20.7)	0.577	89 (22.3)	47 (23.5)	42 (21.0)	0.810
>4 cm	340 (49.6)	107 (47.1)	233 (50.9)		193 (48.3)	96 (48.0)	97 (48.5)	
Unclear	196 (28.6)	66 (29.1)	130 (28.4)		118 (29.4)	57 (28.5)	61 (30.5)	
Lymph node metastasis, *n* (%)								
Negative	157 (22.9)	60 (26.4)	97 (21.2)	0.154	100 (25.0)	56 (28.0)	44 (22.0)	0.071
Positive	488 (71.2)	151 (66.5)	337 (73.6)		281 (70.3)	131 (65.5)	150 (75.0)	
Unclear	40 (5.9)	16 (7.1)	24 (5.2)		19 (4.7)	13 (6.5)	6 (3.0)	
Metastasis, *n* (%)								
No (M0)	251 (36.6)	79 (34.8)	172 (37.6)	0.040	145 (36.3)	75 (37.5)	70 (35.0)	0.603
Yes (M1)	431 (62.9)	145 (63.9)	286 (62.4)		255 (63.7)	125 (62.5)	130 (65.0)	
Unclear	3 (0.5)	3 (1.3)	0 (0)					
Surgery, *n* (%)								
No	453 (66.1)	156 (68.7)	297 (64.8)	0.313	276 (69.0)	139 (69.5)	137 (68.5)	0.829
Yes	232 (33.9)	71 (31.3)	161 (35.2)		124 (31.0)	61 (30.5)	63 (31.5)	
Survival time (months)								
Median (IQR)	11 (5.0–30.0)	7 (3.0–18.0)	14 (6.0–38.0)		9 (4.0–20.0)	7 (3.0–18.8)	10 (5.0–21.8)	

IQR: Interquartile range.

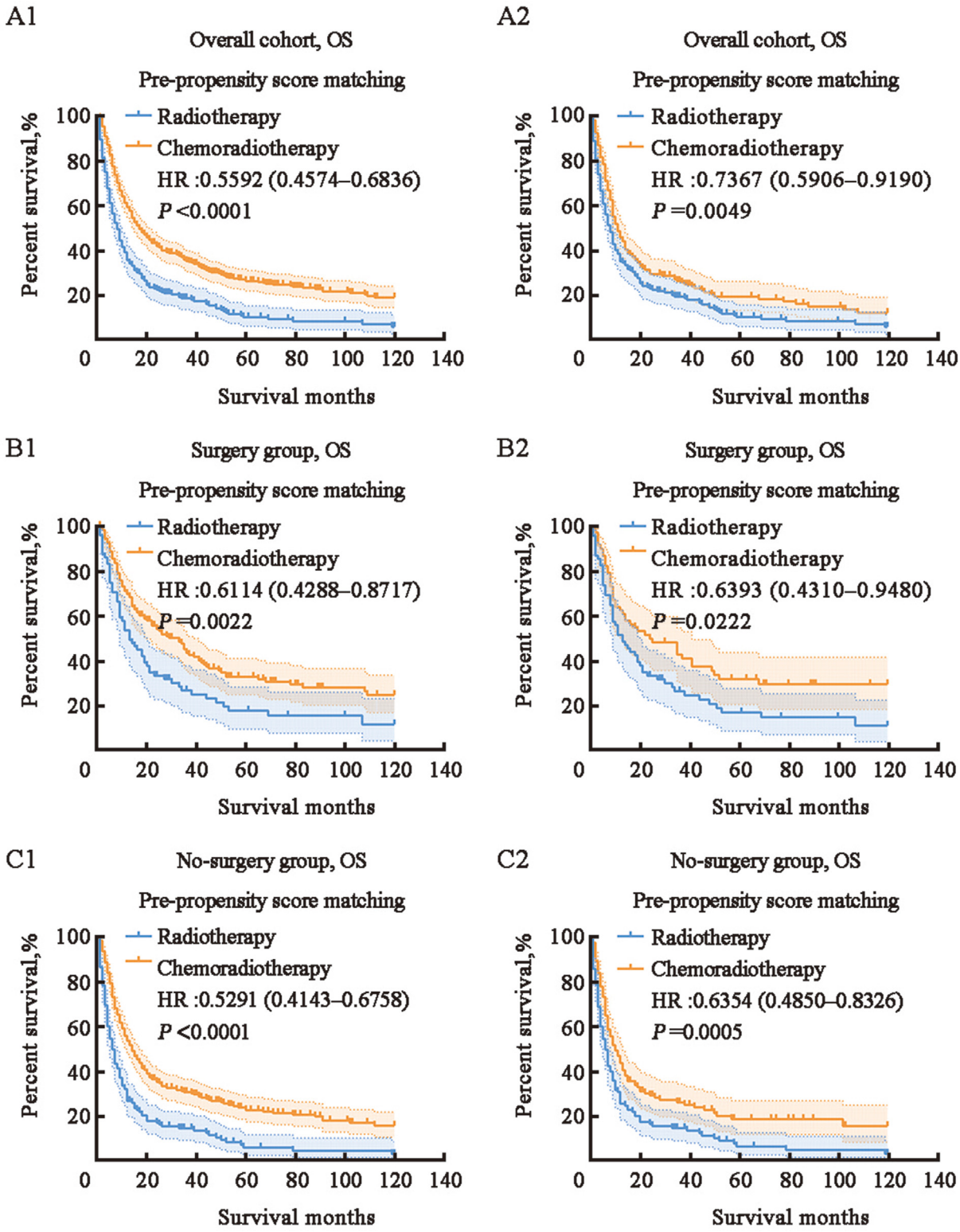

Figure 3. Kaplan–Meier survival curves for patients with metastatic vulvar cancer who had undergone chemoradiotherapy or radiotherapy alone, pre- and post-propensity score matching. Overall cohort (A1) pre- and (A2) post-propensity score matching. Surgery group (B1) pre- and (B2) post-propensity score matching. No-surgery group (C1) pre- and (C2) post-propensity score matching. OS: Overall survival. HR: Hazard ratio.

(HR = 1.78; 95% CI: 1.38–2.30; $P < 0.001$). Tumor size >4 cm was also significantly associated with worse OS (HR = 1.28; 95% CI: 1.01–1.64; $P = 0.042$). Lymph node metastasis and distant metastasis (M1) were also significantly associated with lower OS rates (lymph node metastasis positive *vs.* negative: HR = 1.3; 95% CI: 1.03–1.64; $P = 0.025$; M1 *vs.* M0: HR = 1.53; 95% CI: 1.26–1.85; $P < 0.001$). Moreover, the HR of the patients who underwent surgery was significantly lower (HR = 0.67; 95% CI: 0.55–0.82; $P < 0.001$), and those treated with chemoradiotherapy had a significantly lower mortality risk than those who received radiotherapy alone (HR = 0.57; 95% CI: 0.47–0.69; $P < 0.001$).

We used Kaplan–Meier curves to further assess age, tumor size lymph node metastasis, distant metastasis, and treatment-related survival

Table 2
One-, three-, and five-year overall survival for patients with metastatic vulvar cancer in overall and matched cohorts.

Time points	Overall cohort		Propensity-matched cohort	
	Radiotherapy % survival, HR (95% CI)	Chemoradiotherapy % survival, HR (95% CI)	Radiotherapy % survival, HR (95% CI)	Chemoradiotherapy % survival, HR (95% CI)
1-year	34.9 (28.6–41.2)	59.1 (54.4–63.8)	34.7 (28.0–41.4)	45.8 (38.7–52.9)
3-year	17.6 (12.3–22.9)	35.1 (30.4–39.8)	18.5 (12.8–24.2)	25.7 (19.0–32.4)
5-year	9.9 (5.4–14.4)	26.2 (21.7–30.7)	10.2 (5.5–14.9)	18.4 (11.9–24.9)

CI: Confidence interval.

benefit/risk [Figure 4]. These curves corroborated the results of the Cox analysis.

Surgical management of the primary site

We further clarified the effect of surgery on the OS of patients with metastatic vulvar cancer. The percentage of patients who had undergone surgery + radiotherapy with or without chemotherapy was lower than that of patients who had undergone radiotherapy with or without chemotherapy [Figure 5A]; however, patients who had undergone surgery + chemoradiotherapy had a better prognosis [Figure 4A and B]. The frequency of surgery + chemoradiotherapy gradually decreased in patients with increasing age, whereas the use of radiotherapy alone gradually increased [Figure 5B]. In addition, we analyzed the prognoses associated with different treatment modalities in patients of different ages. For patients ≥75 years old, although the frequency of radiotherapy was comparable to that of chemoradiotherapy [Figure 5B], the OS rates of patients who had undergone chemoradiotherapy were significantly higher than those of patients who had undergone radiotherapy alone [Figure 5E, $P < 0.05$]. In patients aged <75 years, although chemoradiotherapy was more common [Figure 5B], surgery supplemented with radiotherapy with or without chemotherapy resulted in higher OS rates [Figure 5C and D].

The OS rates associated with different surgical modalities in the overall cohort did not differ significantly [Figure 6C, $P = 0.7410$]. Considering the improvement in OS rates associated with comprehensive treatment (surgery + chemoradiotherapy) [Figures 4A and B], we further investigated surgical procedure options in patients for whom comprehensive treatment is recommended. During 2000–2019, the frequency of radical surgery gradually declined [Figure 6A]. A gradual increase was observed in the frequency of primary site surgical removal with age, whereas that of radical surgery decreased [Figure 6B]. Radical surgery did not improve the OS rates of any age group [Figures 6D–F]. For patients ≥75 years of age, the highest OS was observed in patients who had undergone chemoradiotherapy [Figure 5E]. Local tumor excision/destruction and surgical removal of the primary site were associated with a significantly higher OS rate than radical surgery [Figure 6F, $P = 0.0023$]. For patients aged <60 years, local tumor excision/destruction surgery with adjuvant chemoradiotherapy was associated with higher OS rates [Figures 5C and 6D]. More extensive surgical removal of the primary site with adjuvant radiotherapy with or without chemotherapy was associated with higher OS rates in patients aged 60–74 years [Figures 5D and 6E].

Table 3
Multivariate Cox analysis in the overall cohort.

Characteristics	Overall survival	
	HR (95% CI)	*P*
Age (years)		
<60	1	Ref.
60–74	1.30 (1.04–1.63)	0.023
≥75	1.78 (1.38–2.30)	<0.001
Marital status		
Single or unmarried	1	Ref.
Married	1.04 (0.81–1.34)	0.741
Divorced or separated	0.93 (0.70–1.24)	0.631
Widowed	1.13 (0.85–1.50)	0.404
Tumor size		
≤4 cm	1	Ref.
>4 cm	1.28 (1.01–1.64)	0.042
Lymph node metastasis		
Negative	1	Ref.
Positive	1.30 (1.03–1.64)	0.025
Metastasis		
No (M0)	1	Ref.
Yes (M1)	1.53 (1.26–1.85)	<0.001
Surgery		
No	1	Ref.
Yes	0.67 (0.55–0.82)	<0.001
Radiotherapy and chemotherapy		
Radiotherapy alone	1	Ref.
Chemoradiotherapy	0.57 (0.47–0.69)	<0.001

CI: Confidence interval; HR: Hazard ratio; Ref: Reference. Multivariate Cox analysis was performed only for significant variables in the univariate analysis. Patient demographic data are shown in Table 1.

Discussion

Summary of the main results

Our results indicate that the use of chemoradiotherapy as a treatment option has gradually increased from 2000 to 2009 in patients with metastatic vulvar cancer. Chemoradiotherapy improved OS rates compared with the use of radiotherapy alone. Additionally, in patients who had undergone surgery, higher OS rates were associated with chemoradiotherapy than with radiotherapy alone ($P < 0.05$). In the no-surgery group, most patients were not able to tolerate surgery, which made the combination of radiotherapy and chemotherapy more advantageous than that of radiotherapy alone. Chemoradiotherapy is also a more advantageous treatment option for these women compared with radiotherapy alone. Baseline data showed that the median survival time of patients was only 11 months, patients who had undergone chemoradiotherapy were younger, and after propensity score matching, metastatic vulvar cancer was more common in women aged ≥75 years, which was characterized as mostly squamous cell carcinoma, grade II cancer, a tumor diameter >4 cm, lymph node metastasis, and M1 status. Finally, significant prognostic factors of metastatic vulvar cancer were identified. Mortality risk factors included age (≥60 years), tumor size (>4 cm), lymph node metastasis, distant metastasis (M1), the absence of surgery, and radiotherapy alone, which is consistent with previous studies on locally advanced vulvar cancer (stages I–IV).[18,21] Our results suggest that patients aged ≥75 years had the highest HR, which is consistent with the results of previous studies.[22,23] In our study population, most patients had not undergone surgical procedures at the primary site. However, surgical treatment still affected prognoses, and a combined treatment regimen of surgery, radiotherapy, and chemotherapy was associated with the most favorable prognosis. Surgical treatment with aggressive adjuvant radiotherapy and chemotherapy should be considered primarily for patients aged <75 years. For patients ≥75 years, surgery is not recommended, and more conservative treatments such as a combination of radiotherapy and chemotherapy should be used to improve long-term OS rates and the quality of life. Invasive surgery should be avoided in older patients as various complications may ensue. For patients aged <75 years, local tumor excision/destruction or surgical removal of the primary site supplemented with radiotherapy or chemotherapy may

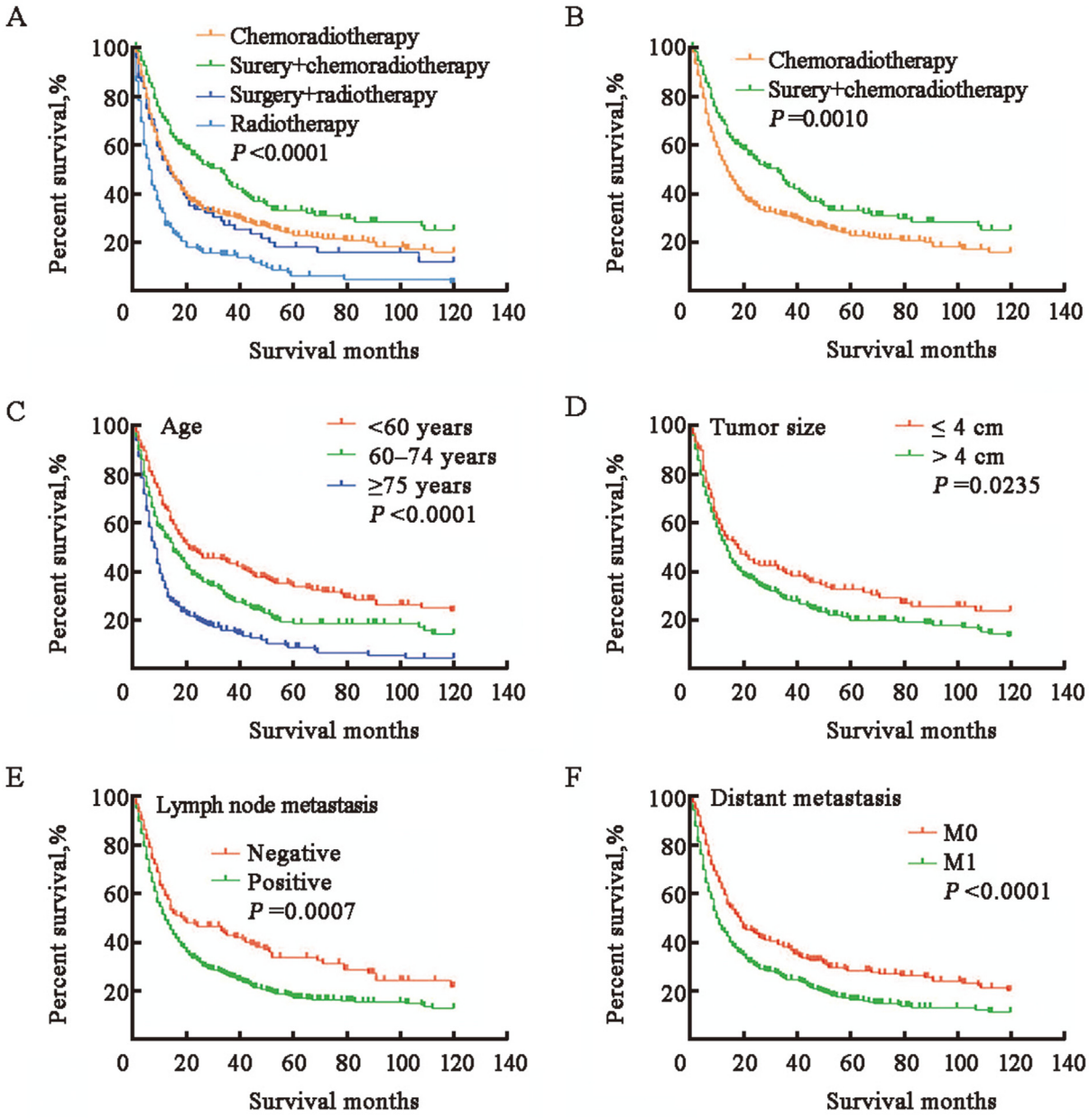

Figure 4. Kaplan–Meier survival curves for the factors age, tumor size, lymph node status, distant metastases, and treatment-related survival benefit or risk in patients with metastatic vulvar cancer in the overall cohort. (A) Different treatment regimens; (B) Chemoradiotherapy, with or without surgery; (C) Age; (D) Tumor size; (E) Lymph node metastasis; and (F) Distant metastasis.

improve OS rates. Considering the risk of serious complications, such as infection, radical surgery is not recommended for patients with predominantly stage IV metastatic vulvar cancer.

Results in the context of published literature

Previous studies have suggested that chemoradiotherapy should be used as an adjunct therapy to surgery. In contrast, other studies have supported chemoradiotherapy as the definitive treatment for advanced vulvar cancer. A large retrospective study of patients with stage I–IVa vulvar cancer who did not undergo surgery has indicated that definitive chemoradiation improves OS compared with radiation therapy alone.[22] However, patients with stage IVb vulvar cancer were excluded, and patients in different periods were not described separately because of confounding factors, which may have led to imprecise conclusions. Our study described the overall and matched cohorts and focused only on patients with metastatic vulvar cancer with unfavorable prognoses. A nationwide survey by the Japanese Gynecologic Oncology Group has indicated that concurrent chemoradiotherapy yields improved outcomes compared with radiotherapy alone in terms of OS.[7] A retrospective study using the National Cancer Database (NCDB) reported that chemoradiotherapy is associated with improved outcomes compared with those associated with radiotherapy in patients with stage III–IV vulvar cancer when diagnosed at <75 years of age.[18] Although these studies did not focus specifically on distant-stage diseases, their results remain meaningful.

Interestingly, although most patients with metastatic vulvar cancer had not undergone surgery, our findings identified surgery at the primary site as a protective factor and support the recommendation that surgery that removes or destroys tissue at the primary site should be considered if tolerated by the patient. The National Comprehensive Cancer Network (NCCN) and FIGO guidelines differ in terms of their recommendations for surgery in patients with advanced vulvar cancers. The NCCN guidelines

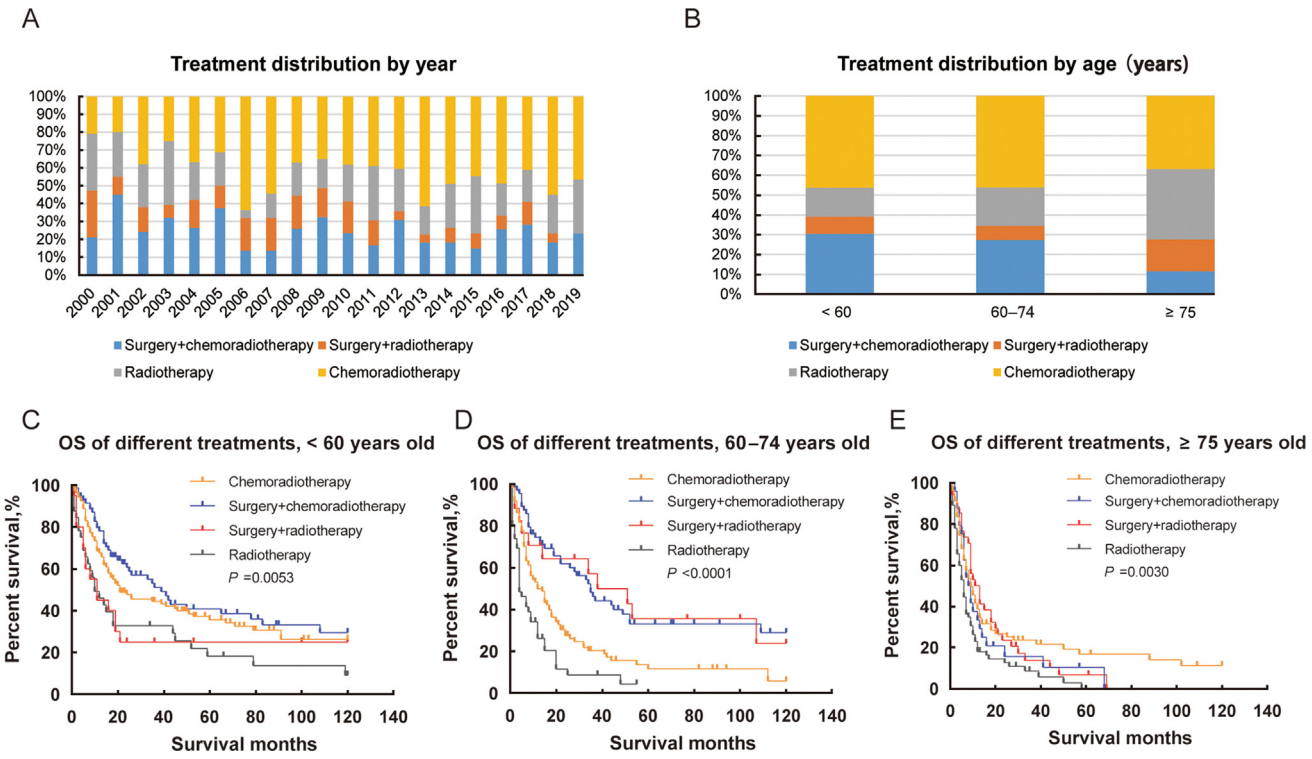

Figure 5. Frequency distribution and Kaplan–Meier survival curves of combinations of treatment in patients with metastatic vulvar cancer per age group. (A) Frequency distribution of different treatment combinations from 2000 to 2019; (B) Distribution of different treatment combinations per age group; (C) OS in patients aged <60 years; (D) OS in patients aged 60–74 years; and (E) OS in patients aged ≥75 years. OS: Overall survival.

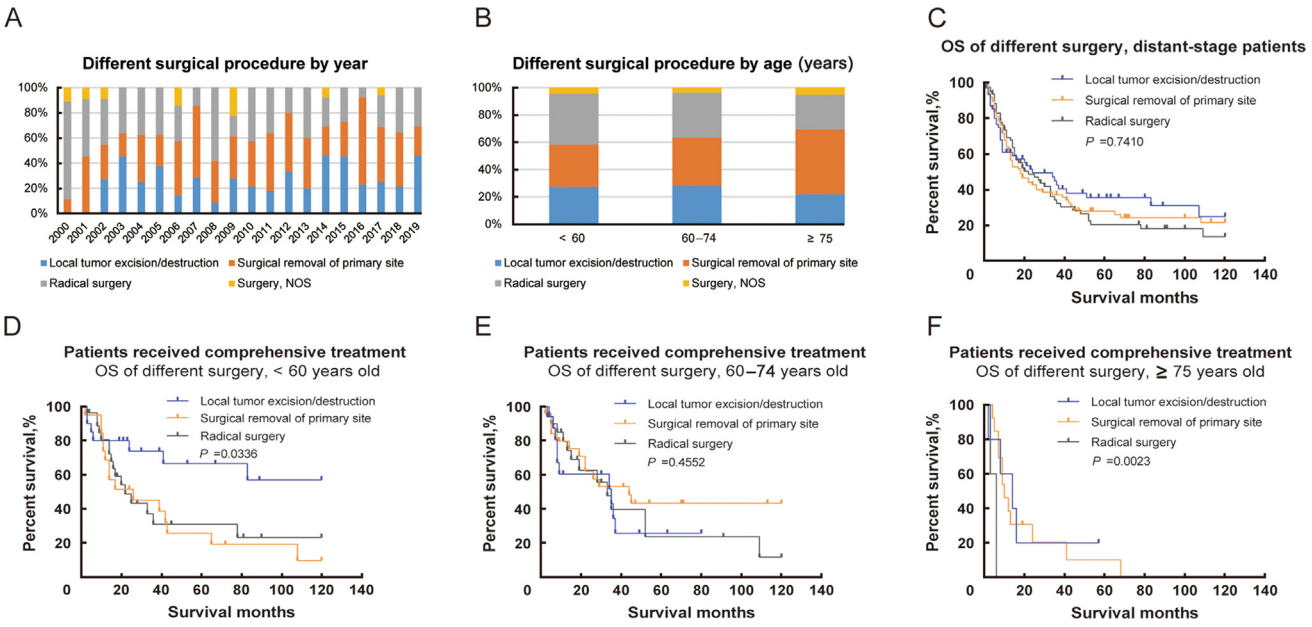

Figure 6. Frequency distribution and Kaplan–Meier survival curves of surgical procedures in patients with metastatic vulvar cancer who had undergone comprehensive treatment (surgery + chemoradiotherapy) per age group. (A) Frequency distribution of surgical procedures from 2000 to 2019; (B) Distribution of surgical procedures per age group; (C) OS in the overall cohort; (D) OS in patients aged <60 years; (E) OS in patients aged 60–74 years; and (F) OS in patients aged ≥75 years. OS: Overall survival.

indicate that surgery cannot completely remove lesions. Therefore, concurrent chemoradiotherapy and systemic therapy are preferred.[24] However, the FIGO guidelines recommend surgery as the preferred option, which can be combined with radiotherapy and systemic therapy.[1] Our findings support the FIGO recommendations. Several studies have suggested that surgery remains the cornerstone of treatment for most patients with vulvar cancer, and many studies have encouraged adjuvant chemoradiotherapy or radiotherapy before surgery because preoperative radiation or chemotherapy can make initially inoperable patients suitable for surgery and improve the postoperative survival rate.[14–16,25,26] An NCDB study has found that adjuvant chemoradiotherapy significantly improves OS rates compared with radiotherapy alone in patients with

lymph node metastasis (stage III–IVa) who had undergone surgery, and adjuvant chemotherapy is recommended in high-risk groups, which is similar to our findings.[27] In contrast, surgery may be effective but may lead to serious postoperative complications. Vulvar cancer frequently occurs in the elderly, and many patients may not be able to tolerate surgical treatment. Therefore, radiotherapy or chemotherapy is recommended as an alternative approach.[9,28,29] A phase II study of 52 patients with locally advanced vulvar cancer (mainly T2/T3) has shown that chemoradiation results in considerable locoregional control with acceptable survival rates and manageable acute and late toxicity, and is thus a feasible alternative to extensive surgery in locally advanced vulvar cancer.[9] However, a recent study has reported that surgery without radiotherapy is associated with a higher OS,[25] which contradicts our findings. Our study focused on a different population; we concentrated on patients with metastatic cancer with unfavorable prognoses that require more treatment options to improve OS rates.

Our results showed that as an adjunctive therapy or definitive chemoradiotherapy, radiotherapy plus chemotherapy can improve OS rates for patients with metastatic vulvar cancer. Therefore, compared with radiotherapy alone, we recommend chemoradiotherapy as the preferred treatment regimen. Additionally, our results indicated that surgery is a key factor in improving OS rates. Therefore, we suggest appropriate surgical treatment for patients with metastatic vulvar cancer who can tolerate surgery because undertreatment of vulvar cancer may lead to disease progression and further complications.

Limitations and strengths

Our study has some limitations: (1) Information on chemoradiotherapy was missing, such as dose and volume of radiotherapy, sequential *vs.* concurrent chemoradiotherapy, number of cycles, treatment toxicity, complications, disease-free survival, and recurrence rate, which limited the inclusion of covariates and comorbidities; (2) The sample size was limited due to the rarity of vulvar cancer; (3) The SEER database contains limited data; therefore, comprehensive risk adjustments could not be made. Information about patients' physical condition, palliative care intentions, extent of surgical resection, or presence of lymphatic vascular infiltration was not available. These factors may significantly affect prognosis; (4) Further analysis of the mortality factors in patients with metastatic vulvar cancer is necessary, which may help guide individualized and comprehensive treatment. Nonetheless, propensity score matching was designed to address these limitations; therefore, our results are still relevant.

Our study's strength is related to the advantages that large databases offer for studying rare diseases for which treatments are controversial, whereas small cohort research often yields inconsistent conclusions. The SEER database allows the study of the treatment and prognosis of rare malignancies in large cohorts.

Implications for practice and future research

Reports focusing on advanced diseases are limited. Although metastatic vulvar cancer is rare, poor survival and controversial treatment modalities justify studies comparing the prognoses associated with different treatment options. Thus, in this study, we reanalyzed existing data to compare the outcomes of chemoradiotherapy and radiotherapy in patients in a large cohort and further explored surgical treatment, which may provide helpful insights for the clinical treatment of vulvar cancer.

Based on the molecular and virological similarities of squamous cell carcinoma of the external genitalia and that of skin/cervical origin, immunotherapy appears to be the most promising alternative treatment strategy for patients with advanced or metastatic vulvar cancer.[30–32] Previous studies have proposed that immune cells highly infiltrate vulvar tumor tissue, and clinical trials and case reports have confirmed the efficacy of immunotherapy in recurrent or metastatic vulvar cancer.[31,33–37] Therefore, personalized immunotherapy combined with radiotherapy or chemotherapy may be a promising treatment strategy for women with advanced vulvar cancer in the future. Vulvar malignant melanoma has unique characteristics, with different staging and treatment options than squamous carcinoma. Surgery and immunotherapy are essential for treating vulvar melanomas. Due to the low incidence of vulvar melanoma in our study population and the lack of immunotherapy information in the SEER database, we did not analyze melanoma separately.

Conclusions

Metastatic vulvar cancer is rare in older women and is associated with poor survival rates. In this population, chemoradiotherapy was associated with higher OS rates compared with radiotherapy alone. Surgical treatment is recommended if patients can tolerate it, and adjuvant therapy should be encouraged to improve the prognoses in high-risk populations. In future studies, immunotherapy and targeted therapy for vulvar melanoma should be explored, and further analysis of treatment and prognosis in patients with stage IVb vulvar cancer using larger cohorts should be undertaken.

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Authors contributions

Xiaolin Meng: Conceptualization, Software, Writing–Original draft preparation; Shuaiqingying Guo: Data curation, Methodology; Xue Feng: Visualization, Investigation; Jihui Ai: Validation, Supervision, Writing–Reviewing and Editing; Jie Yang: Validation, Supervision, Writing–Reviewing and Editing. All the authors have read and approved the manuscript.

Ethics statement

Due to the National Cancer Institute's SEER database as an open-access resource, approval from the ethics committee was not required for this study.

Data availability statement

The datasets generated and/or analyzed in the current study are publicly available in the [SEER* STAT version 8.4.01] repository [https://seer.cancer.gov/seerstat/releasenotes.html].

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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