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Journal

Gynecologic Oncology, 167(2)

ISSN

0090-8258

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Publication Date

2022-11-01

DOI

10.1016/j.ygyno.2022.09.018

Peer reviewed

HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2023 October 23.

Published in final edited form as:

Gynecol Oncol. 2022 November ; 167(2): 159–166. doi:10.1016/j.ygyno.2022.09.018.

Time to Completion of Radiation Treatment in Locally Advanced Squamous Cell Carcinoma of the Vulva and the Impact on Survival

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Abstract

Objective: To assess whether radiation completion within a planned timeframe in locally advanced squamous cell vulvar cancer impacts overall survival (OS).

Methods: The National Cancer Database from 2004–2017 was used to identify women ≥ 18 years old with stage II-IVA squamous cell vulvar cancer. We included women who received radiation alone (RT) or concurrent chemoradiation (CRT) for initial vulvar cancer treatment. Primary outcome was overall survival associated with time of delay in radiation completion.

Results: There were 2,378 women identified (n=856 RT and n=1,522 CRT). Median age was 67 (IQR 56–78), majority (88.35%) were white with advanced stage III or IVA (72.29 %) disease. Median radiation dose was 5720 centi-Gray (IQR 5040–6300). Radiation completion with delay ≥ 7 days resulted in reduction in survival compared to delay of < 7 days (unadjusted HR 1.183 [95%CI: 1.066–1.313], p=0.0016). When delays extended to ≥ 14 days compared to < 14 days there was increased hazard of death (unadjusted HR: 1.263 [95%CI:1.126–1.416], p<0.0001). Survival improved for patients with < 7 versus ≥ 7 days delay whether treatment was with RT (median OS: 34.9 months versus 21.6 months, p < 0.01) or CRT (Median OS:58 months versus 41.3 months, p < 0.01). Stage IVA disease was associated with the greatest increase in hazard of death (HR 1.759 [95%CI 1.517–2.039], p<0.0001) compared to stage II.

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Conclusion: Radiation completion with < 7 days delay is associated with improved overall survival, independent of concurrent chemotherapy. This suggest that strategies to minimize delays in radiation are crucial in locally advanced vulvar cancer.

Keywords

vulvar cancer; radiation; chemoradiation; treatment delay

INTRODUCTION:

Vulvar cancer is a rare gynecologic malignancy with an increasing incidence and mortality [1]. It is estimated in the United States that there were approximately 6,120 new cases of vulvar cancer diagnosed and 1,550 vulvar cancer deaths in 2021 [1]. Worldwide, approximately 45,240 vulvar cancer cases and 17,427 vulvar cancer deaths were reported in 2020 [2]. Well known predictors of poor prognosis in vulvar cancer include increasing age and advanced stage of cancer [3,4]. Unfortunately, at least a third of patients are initially diagnosed with locally advanced disease, with squamous cell carcinoma being the most common histology [1,5]. Locally advanced squamous cell vulvar cancers are frequently associated with disease located adjacent to or involving surrounding organs requiring complex treatment strategies [6].

The standard treatment modalities for locally advanced squamous cell vulvar cancers include surgical resection and/or radiation with or without chemotherapy. Given the almost unavoidable morbidity from upfront radical surgeries often required for these advanced cancers, women with nonresectable disease are frequently offered primary treatment with radiation (RT) alone or concurrent chemoradiation (CRT) in lieu of surgery [7]. Evolving evidence has shown that the addition of concurrent chemotherapy to radiation is associated with improved outcomes, thus should be considered over radiation therapy alone in the treatment of these vulvar cancers [7–9]. Despite improvements with chemoradiation, women with locally advanced squamous cell vulvar cancer have poor overall prognosis and treatment schemes continue to explore how to improve non-surgical options [7–10]. Thus, it is essential to optimize approaches to RT and CRT regimens to improve outcomes in these women.

Although vulvar cancer differs from cervical cancer, there are similarities in the disease behavior and treatment approaches for these two malignancies, and treatment strategies for vulvar cancer are often extrapolated from the cervical cancer literature. Similar to vulvar cancer, RT and CRT are primarily used to treat locally advanced squamous cell carcinoma of the cervix [11]. Notably, the completion of RT or CRT within a targeted timeframe is a well-established quality metric strongly linked to improved survival outcomes in locally advanced cervical cancer [12–18]. Vulvar cancers like cervical cancers are fast growing with the potential to repopulate if there is a treatment delay, however benefits associated with time to completion of radiation has not been established in locally advanced vulvar cancer. We hypothesize there may be similar survival improvement in women with vulvar cancer receiving radiation, RT or CRT, within a confined timeframe, yet there is limited evidence to suggest this. Therefore, the objective of this study is to evaluate if the time to completion

of radiation, with or without chemotherapy, in locally advanced squamous cell vulvar cancer impacts survival. Assessing the impacts of survival will provide important foundational understanding in the field of vulvar cancer treatment.

MATERIALS AND METHODS:

Data source:

This is a retrospective cohort study using the National Cancer Database (NCDB). The NCDB is a national outcomes database that is a joint project of the Commission on Cancer of the American College of Surgeons and American Cancer Society. The NCDB encompasses standardized collection of cancer data from over 1500 hospitals accredited by the Commission on Cancer [19]. As a result, the NCDB captures approximately 70% of newly diagnosed cancer patients in the United States [19]. Data within the NCDB is de-identified of all patient and cancer treatment hospital data. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methods used or conclusions drawn by the investigators of this study. The analysis of the NCDB data was determined to be not human subjects research by the University of California Davis Institutional Review Board and was exempt from institutional board review.

Cohort Selection:

Patients 18 years or older with locally advanced vulvar cancer, defined as International Federation of Gynecology and Obstetrics (FIGO) stage II to IVA vulva cancer, were identified from the NCDB from 2004–2017. We included patients who received external beam radiation as part of their initial vulvar cancer treatment course. Patients who had concurrent chemotherapy with radiation were defined as those in whom chemotherapy was given within 4 weeks from the initiation of radiation therapy. Given known differences in clinical behavior by vulvar cancer histology types [20], we included only patients with squamous cell carcinoma histology confirmed by pathology and were identified by assigned International Classification of Disease for Oncology (ICD-O) codes: 8052, 8070–8084 and 8560. We excluded patients who received systemic therapies including chemotherapy alone, any hormonal therapy or immunotherapy as the primary cancer treatment. Patients who received less than 20 fractions of radiation or greater than 45 fractions of radiation were assumed to have received radiation doses markedly outside of standard recommended radiation doses for the intent of curative primary vulvar cancer treatment [7], therefore were excluded. The small number of patients who received brachytherapy as part of the radiation treatment plan were excluded given that details of how brachytherapy was incorporated in the primary treatment plan was not available in the database. We also excluded patients with multiple primary cancer diagnosis receiving cancer treatment, those who did not receive cancer treatment at the facility of cancer diagnosis, and those with missing data regarding complete cancer staging, treatment details or vital status.

Variables:

Patient demographic characteristics included patient age, race and Charlson-Deyo Comorbidity Score, which is an index used to measure the baseline patient comorbidity

summary provided in the NCDB [22]. We assessed patient clinical characteristics including the year of cancer diagnosis, tumor grade, tumor size, lymph node status, type of external beam radiation used and total radiation treatment dose in centi-Gray (cGy). American Joint Committee on Cancer staging provided in the NCDB was converted to the corresponding 6th or 7th edition FIGO staging, based on year of vulvar cancer diagnosis.

The primary outcome was overall survival (OS), defined as the time interval in months from the date of initial cancer diagnosis to the date of last contact or death. Based on literature supporting worse oncologic outcomes associated with noncompliance and delays in planned radiation treatment [21], we assessed the association of OS with time to radiation completion based on extent of delay in radiation therapy completion. The time to radiation completion was defined as the number of days from the initiation to completion of radiation. The delay of radiation completion was calculated as the difference between the actual time to radiation completion and the predicted duration of radiation based on patients receiving standard 5 fractions of radiation each week. Thus, if more fractions of radiation were prescribed for a patient, the extra time to receive the radiation was accounted for in the predicted time to completion. The OS was determined for each cohort based on the duration of delay of radiation treatment completion with a cut off of < 7 days versus ≥ 7 days delay. To assess the effects on OS when the duration of delay in radiation completion was further extended, the cut off was extended to < 14 days versus ≥ 14 days. To account for potential confounding effects on survival from the use of concurrent chemotherapy with radiation compared to those who had radiation alone, types of radiation treatment (RT or CRT) were grouped based on the delay of radiation completion, < 7 days versus ≥ 7 days and further expanded to < 14 days versus ≥ 14 days delay.

Statistical Methods:

Chi-square or Fisher's exact test were used for dichotomous variables including lymph node status, external beam technique, vital status as well as categorical data including race, tumor size, FIGO stage, tumor grade, and Charlson-Deyo Comorbidity Score. ANOVA or Kruskal-Wallis tests were used for numeric variables including age, external beam radiation dose and median time to follow up. Kaplan-Meier curves with log-rank tests were fit for univariate time-to-event analysis. Multivariable Cox proportional hazard models were fit to assess effects after controlling for confounders included in the model with age, FIGO stage, Charlson-Deyo Comorbidity score and total radiation dose of treatment.

Propensity score weighted comparison analysis was performed. Comparisons were assessed based on delays < 7 days versus ≥ 7 days in radiation completion for the entire cohort including RT and CRT. Additional subcategory comparisons of effects in the RT alone or CRT groups were performed. We calculated inverse probability of treatment weighting (IPTW) using propensity scores that were calculated based on multivariable logistic regression using age, FIGO stage, Charlson-Deyo Comorbidity score, and total radiation dose. Weights greater than 10 were trimmed to 10. The adjusted Kaplan-Meier curves and Cox proportional hazard models were fit using these weights. All data analysis was performed using SAS® software for Windows® version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS:

There were 66,543 patients age 18 years or older with a diagnosis of vulvar cancer identified in the NCDB from 2004–2017. Of those, 13,139 patients underwent radiation therapy for initial vulvar cancer treatment. After applying additional study criteria, n=2,378 patients were identified for final cohort analysis, n=856 in RT group and n=1522 in the CRT group, (Figure 1). Delay of treatment of at least 7 days or more were observed in 51.64% and 43.34% in the CRT and RT groups, respectively. The median age of the cohort was 67 (IQR 56–78) years old. Most patients were white race (88.35%) with advanced FIGO stage III or IVA (72.29 %) disease. Many patients (44.66%) had tumor size larger than 4 cm at the time of initial cancer diagnosis. The median dose of total external beam radiation treatment used was 5720 cGy (IQR 5040–6300) with higher doses observed in the ≥ 7 days versus < 7 days delay group, ($p<0.0001$). The median follow-up of the cohort was 27.2 months (IQR 11.8–57.9), (Table 1).

For the total cohort, including both RT and CRT, there was a reduction in survival observed when delay in time to radiation completion was ≥ 7 days versus < 7 days delay, (unadjusted HR 1.183 [95%CI: 1.066–1.313], p=0.0016), (Table 2). The corresponding median overall survival was (median OS 32.95 months versus 43.66 months, p=0.002), respectively for patients with ≥ 7 days versus < 7 days delay in radiation completion, as shown in (Figure 2A). When the delay in radiation completion was extended to ≥ 14 days versus < 14 days, survival was further reduced (median OS: 28.19 months vs 42.81 months, $p<0.0001$) respectively, and is shown in (Figure 2B). Further analysis of the radiation groups, RT or CRT, were performed to take into account potential survival differences with the addition of concurrent chemotherapy to radiation compared to those who received radiation alone. For both radiation groups, completion of radiation treatment with delay of equal to or more than 7 days delay sustained a worse overall survival compared to those with less than 7 days delay in radiation treatment, with RT group (unadjusted HR 1.254 [1.067–1.473]), $p<0.0001$) and CRT group (unadjusted HR 1.197 [95% CI: 1.043–1.373], $p<0.0001$), (Table 2). Median overall survival amongst the radiation groups associated with < 7 days versus ≥ 7 days delay in radiation completion were: RT group (Median OS 34.9 months versus 21.6 months, $p < 0.0001$) and CRT group (Median OS 58 months versus 41.3 months, $p < 0.0001$), (Figure 2C). When excluding time of radiation delays, the addition of concurrent chemotherapy to radiation was associated with improved survival (unadjusted HR 0.742 [95% CI:0.668–0.825], $p<0.0001$) compared to radiation alone.

On multivariable analysis, controlling for confounders including age, FIGO stage, comorbidities, and total radiation treatment dose, the observed decrease in survival persisted when radiation completion was delayed ≥ 7 days versus < 7 days in the total cohort, (adjusted HR:1.183 [95% CI 1.065–1.314], p=0.0017), (Table 3). Similar survival trends were seen in the two radiation group analyses with the CRT group (adjusted HR 1.158 [95% CI 1.009–1.329], p=0.0132) and RT group (adjusted HR 1.229 [95% CI:1.045–1.445], p=0.0132). There was no significant difference between radiation groups when there were similar treatment delays in RT compared to CRT with equal to or more than 7 days delay, (adjusted HR 1.075 [95% CI:0.921–1.254], p=0.3587). Extended delay in treatment to ≥ 14 days versus < 14 days was associated with a persistence of worse survival, (Table 3). On

further analysis, the hazard ratio for survival was associated with an increase of 0.8% for any given additional day of delay in the time of radiation completion from the predicted time to treatment plan completion.

Propensity score comparisons of the entire study cohort, regardless of RT or CRT, by delay of < 7 days versus ≥ 7 days delay showed the groups were well matched. Adjusting for age, FIGO stage and Charlson-Deyo comorbidity score, delay in treatment equal or greater than 7 days was associated a 15% increased risk in all-cause mortality (HR 1.152 [95% CI: 1.070–1.240], p=0.0002). Additional comparison analysis was performed for the four subcategory cohorts based on radiation alone or concurrent chemotherapy and delay in treatment. Propensity score comparisons amongst the RT alone and CRT cohorts with treatment delay of < 7 days versus ≥ 7 days showed comparability between the groups. A similar trend of increased risk of all-cause mortality with 7 days or greater delay persisted, regardless of if patients were treated with RT or CRT, (Table 4).

DISCUSSION:

Radiation alone or concurrent chemoradiation is a standard of care treatment option for locally advanced squamous cell vulvar cancer. To our knowledge, our cohort study using the National Cancer Database is the first to demonstrate that a delay in time to completion of radiation treatment in locally advanced stage squamous cell vulvar cancer impacts overall survival. We observed an improved overall survival associated with minimal delays in time to radiation completion. To account for the potential influence of the role of concurrent chemotherapy with radiation, survival analysis was further grouped based on use of chemoradiation versus radiation alone which showed that survival was worse when there was an increased delay in time of radiation completion regardless of the use of concurrent chemotherapy with radiation. However, the impact of overall survival difference was most prominent in the radiation alone compared to chemoradiation, Median OS 34.9 versus 21.6 months, p < 0.0001. This suggests that the role of chemotherapy partially mitigated the adverse effects on survival associated with a delay in radiation completion. This is consistent with findings from Rao et al [8], that showed an improved survival when concurrent chemotherapy radiation compared to radiation alone was used for definitive treatment of squamous cell carcinoma of the vulva.

Previous studies exhibited that a delay in completion of radiation treatment in locally advanced cervical cancer to be associated with poor clinical outcomes [12–18], however there is limited evidence to date to suggest similar outcomes in locally advanced vulvar cancer. A recent study using the NCDB assessed overall treatment time from surgery to completion of post-operative adjuvant radiation in node positive squamous cell vulvar cancer [23]. The study was limited to exclusively completely resected node positive patients treated with adjuvant radiation, and reported overall treatment time (OTT) which included the summation of both the time from initial surgery to initiation of radiation plus the interval time of completion of radiation. The study reported worse survival in patients who had an OTT of 105 days or more compared to OTT of 104 days or less [23]. This study differs from our study cohort which focused on survival effects from the duration of time for radiation completion in locally advanced staged vulvar cancers, FIGO stage

II-IVA, and included nonresectable disease and those who received definitive radiation treatment. However, the prior study does corroborate with our study findings that time to radiation treatment completion is an associated risk factor for vulvar cancer survival [23]. Similarly, this survival determinant has been observed in other HPV dependent squamous cell carcinomas, such as in cervical as well as head and neck cancers [16–18, 24].

Potential reasons for delay in radiation treatment completion are most likely multifactorial. Delayed treatment completion may be related to logistics of coordination of weekly radiation treatment, financial or insurance impediments, transportation and housing needs or other unforeseen psychosocial needs during treatments that has been observed in cervical cancer radiation treatment [25,26]. Additionally, treatment breaks related to side effects, complications or other patient factors may contribute to prolonged time to completion of radiation treatment. Approximately half of patients in the CRT group had delays in radiation completion which may be attributed to logistics of adding weekly chemotherapy to planned radiation treatments or delays from adverse effects of chemotherapy, both potentially impacting delay in treatment. Thus, it is important to take into consideration the appropriate patient selection for concurrent chemotherapy to radiation that may contribute to delays in treatment and survival. Our study did not investigate the etiologies contributing to delay in treatment which merits further investigation to help mitigate possible disparities in radiation treatment approaches for vulvar cancers.

The recommended completion time of radiation treatment for vulvar cancer has not been established in treatment guidelines, which differs from the clear guidelines for cervical cancer [7,11]. Given the non-standardized treatment duration for vulvar cancer, we did not use concrete interval times as a proxy for survival outcomes. Instead, we focused on standard radiation doses patients received for treatment [7], calculated the expected time frame to deliver this dose, and demonstrated the impact of delays of completion of the prescribed radiation prescription. We excluded patients who were treated with shorter palliative regimens or hyper-fractionated regimens requiring twice daily treatments. On multivariate analysis, we observed that radiation dose was not associated with overall survival ($p=0.2333$). Thus, when radiation was prescribed at an acceptable and recommended dose range, the total radiation dose level did not influence outcomes but rather the delays in time to completion was a predictor of survival outcomes. Other independent patient risk factors associated with poor survival included older age, more advanced stage at diagnosis, and the presence of co-morbidities.

Our study strengths include the large cohort size for a rare malignancy and access to a detailed national database. However, we recognize that our study conveys many limitations, including the inherent limitation to retrospective studies which is susceptible to selection bias and often cannot verify clinical outcomes data. The use of a national database relies exclusively on selective recorded data entered into the database, which could have limited access to all treatment records as well as a possibility for miscoding of clinical and treatments outcomes or other data errors. Although many radiation treatment parameters regarding dosage and type of radiation used were available, there were limited information on the radiation field used and the exact radiation plan prescribed. Similarly, the type of chemotherapy used and compliance to chemotherapy in the CRT group was not available.

The Charlson-Deyo Comorbidity score was used as an index of patient comorbidity [22], limiting the ability to control for the effects of individual comorbidities on radiation treatment delay and survival in this study. Importantly, the NCDB also lacks information on recurrence or disease and cause-specific survival data, therefore it is possible that death could be from other causes not related to vulvar cancer. The NCDB does not provide descriptive variables that would allow us to investigate the details for the cause for delay of radiation time to treatment completion, which would be important to apply to our study findings and to future strategies to address these delays.

In conclusion, our study is the first to demonstrate that a delay in the time to radiation treatment completion in locally advanced squamous cell vulvar cancers affects survival. Completion of radiation with or without concurrent chemotherapy with less than 7 days delay is associated with improved overall survival. These findings highlight the significance of considering future strategies to minimize treatment delays when radiation is used for the treatment of women with locally advanced vulvar cancer. Furthermore, identifying patient and clinical characteristics, and obstacles in care delivery associated with delays of radiation treatment in locally advanced vulvar cancer should be a next step to this strategy of optimizing treatment plans for these patients.

Conflicts of interest statement:

Rebecca A. Brooks disclosures include Speaker's bureaus for Astra Zeneca, Advisory board for Merck, Tempus, and GlaxoSmithKline, Evidence panel for American College of Obstetrics Gynecology and Society of Gynecologic Oncology. Mathew Ponzini and Machelle Wilson disclose that they were supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Nancy T. Nguyen, Xiao Zhao and Gary Leiserowitz have nothing to disclose.

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Highlights:

- Increased delay of radiation completion in locally advanced squamous cell vulvar cancer is associated with decreased overall survival
- Survival decreases with radiation completion delays regardless of concurrent chemotherapy use with radiation
- Minimizing delays in radiation treatment is important in treatment of locally advanced squamous cell vulvar cancer.

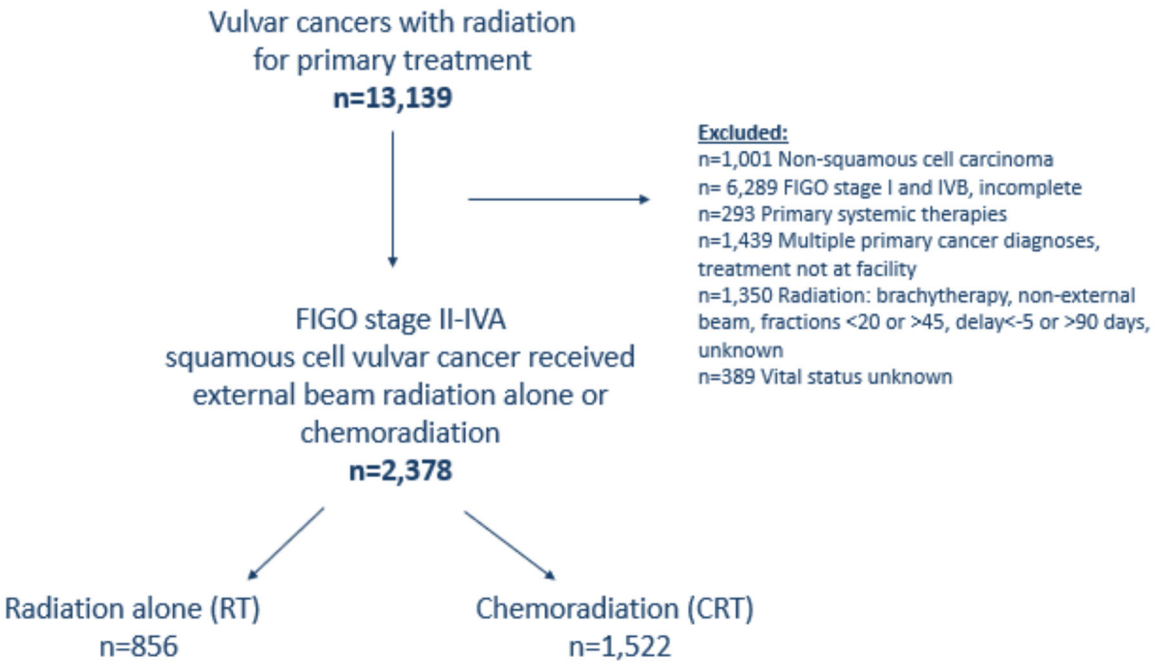
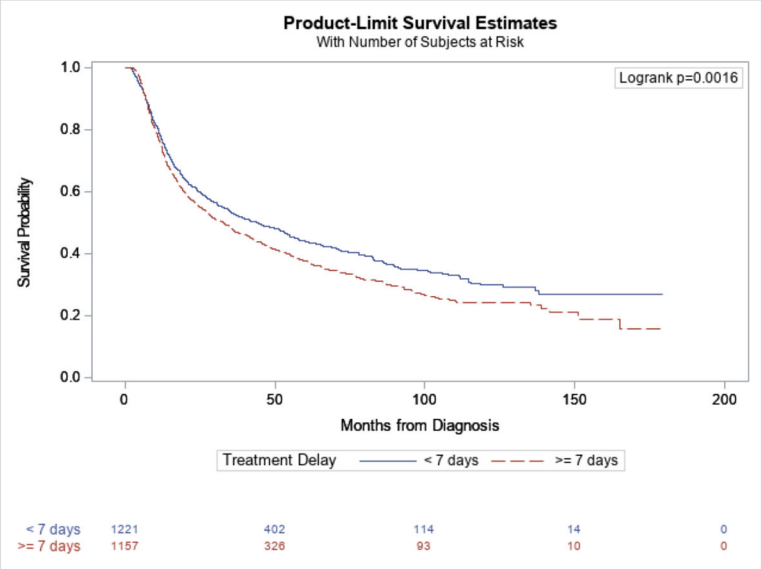
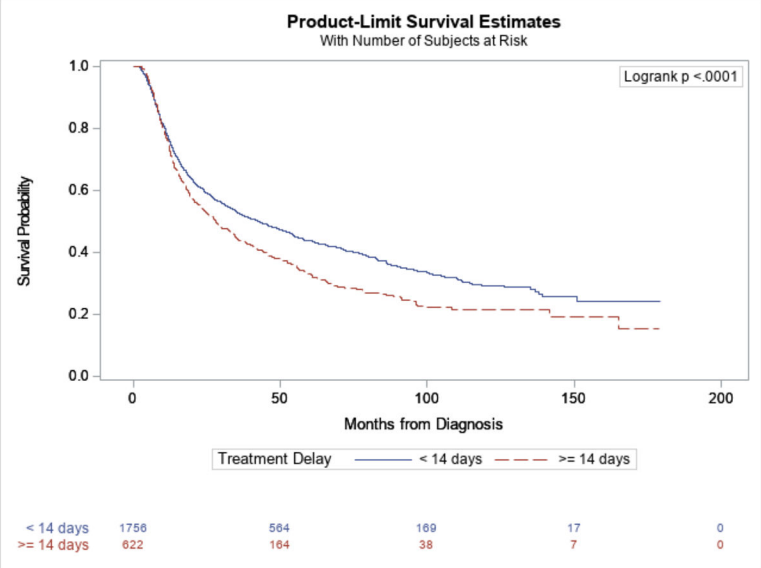


Figure 1.
Schema of cohort selection

A) Overall cohort with ≥ 7 day vs < 7 day delay



B) Overall cohort with ≥ 14 day vs < 14 day delay



C) Radiation groups, RT or CRT with ≥ 7 day vs < 7 day delay

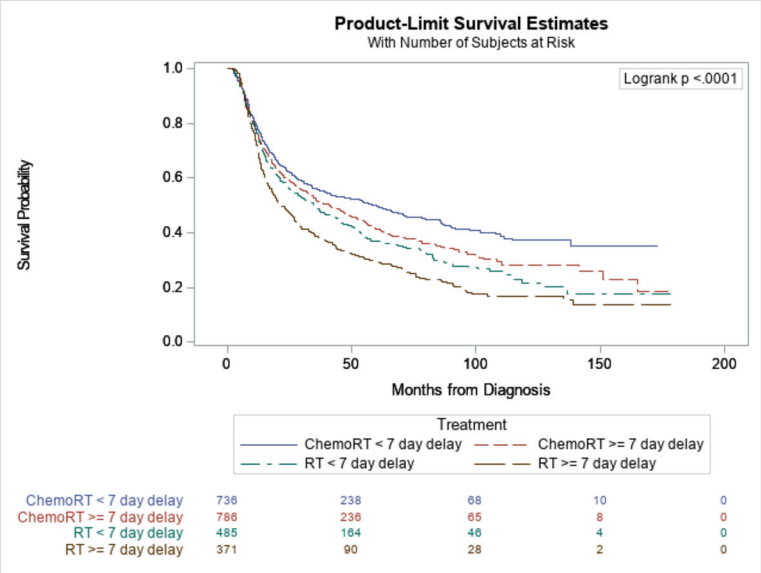


FIGURE 2.
Overall survival curves

Table 1.

Demographic and clinical characteristics

Characteristic	Overall (N = 2378)	RT, delay <7days (N = 485)	RT, delay ≥ 7days (N =371)	CRT, delay <7days (N = 736)	CRT, delay≥ 7days (N = 786)	*p*-value
Age, median [IQR]	67 [56–78]	74 [61–83]	75 [61–84]	63 [53–73]	64 [53–75]	<0.0001
Year of Diagnosis (%)						
2004–2009	36.54	43.92	44.47	29.62	34.73	<0.0001
2010–2014	43.48	39.59	41.51	44.16	46.18	
2015–2017	19.97	16.49	14.02	26.22	19.08	
Race (%)						
White	88.35	91.55	82.41	86.68	87.91	0.0184
Black or African American	9.29	5.57	10.51	10.46	9.92	
Asian	0.97	1.65	0	01.09	0.89	
Other	0.34	0	0	0.68	0.38	
Unknown	1.05	1.24	1.08	1.09	0.89	
Tumor Size (%)						
≤ 2cm	8.41	9.90	9.43	9.10	6.36	<0.0001
2.1–4cm	25.90	32.16	31.27	22.28	22.90	
> 4cm	44.66	44.74	37.47	48.10	44.78	
Unknown	21.03	13.20	21.83	20.52	25.95	
FIGO Stage (%)						
II	27.71	35.88	32.35	24.73	23.28	<0.0001
III	49.16	47.63	47.98	50.14	49.75	
IVA	23.13	16.49	19.68	25.14	26.97	
Grade (%)						
1	16.65	16.08	14.56	16.85	17.81	0.0002
2	44.28	50.10	43.94	44.29	40.84	
3	19.60	21.65	21.02	20.38	16.92	
4	0.63	0.62	0.54	0.82	0.51	
Unknown	18.84	11.55	19.95	17.66	23.92	
Lymph Nodes status (%)						
Positive	34.69	50.72	37.47	33.42	24.68	<0.0001
Negative	10.13	12.78	10.78	10.05	8.27	
Unknown	55.17	36.49	51.75	56.52	67.05	
Charlson-Deyo Score (%)						
0	73.55	70.31	66.85	76.63	75.83	0.0114
1	18.97	21.65	22.91	16.85	17.43	
2	4.75	4.33	5.93	4.62	4.58	
3	2.73	3.71	4.31	1.90	2.16	
Vital Status (%)						
Alive	40.24	34.23	25.61	50.14	41.61	<0.0001

Characteristic	Overall (N = 2378)	RT, delay <7days (N = 485)	RT, delay ≥ 7days (N =371)	CRT, delay <7days (N = 736)	CRT, delay≥ 7days (N = 786)	*p*-value
External Beam Technique						
3D-CRT	9.38	10.72	12.40	6.93	9.41	0.0004
IMRT	35.49	33.81	27.49	40.76	35.37	
Unknown	55.13	55.46	60.11	52.31	55.22	
External Beam Total Dose (cGy) median [IQR]	5720 [5040–6300]	5044.5 [5000–5940]	5760 [5040–6300]	5760 [5040–6300]	5940 [5040–6480]	<0.0001
Median follow up months [IQR]	27.2 [11.8–57.9]	28.42 [11.60–61.57]	20.21 [10.91–49.74]	29.80 [12.73–60.22]	28.32 [12.25–57.10]	0.0245

Abbreviations: IQR, interquartile range; cGy, centi-gray; FIGO, International Federation of Gynecology and Oncology; RT, radiation therapy; CRT, chemoradiation therapy; IMRT, intensity-modulated radiation therapy; 3D-CRT, three-dimensional conformal radiation therapy.

Table 2.

Univariate analysis of all-cause mortality.

Explanatory Variable	Univariate Hazard Ratio (95% CI)	Univariate *p*-value
All cohort ≥ 7 day delay vs < 7 day delay	1.183 (1.066–1.313)	0.0016
All cohort > 14 day delay vs < 14 day delay	1.263 (1.126–1.416)	<0.0001
CRT vs RT	0.742 (0.668–0.825)	<0.0001
Radiation Treatment Group		
RT delay ≥ 7 days vs < 7 days	1.254 (1.067–1.473)	<0.0001
CRT delay ≥ 7 days vs < 7 days	1.197 (1.043–1.373)	
Radiation Treatment Group		
RT delay ≥ 14 days < 14 days	1.379 (1.149–1.655)	<0.0001
CRT delay ≥ 14 days vs < 14 days	1.244 (1.074–1.441)	
Age	1.041 (1.037–1.045)	<0.0001
Radiation dose > 57cGy vs ≤ 57cGy	0.970 (0.874–1.077)	0.5722
FIGO Stage		
II	[Reference]	
III	1.177 (1.035–1.338)	0.0127
IVA	1.517 (1.310–1.756)	<0.0001
Comorbidities, Charlson-Deyo Score		
0	[Reference]	
1	1.286 (1.130–1.464)	0.0001
2	1.284 (1.015–1.624)	0.0368
3	1.313 (0.964–1.788)	0.0843

Abbreviations: cGy, centi-gray; FIGO, International Federation of Gynecology and Oncology; CI, confidence interval; RT, radiation therapy; CRT, chemoradiation therapy.

Table 3.

Multivariable analysis of all-cause mortality.

	All cohort		Delay by Treatment	
Explanatory Variable	**Multivariable Hazard Ratio (95% CI)**	**Multivariable *p*-value**	**Multivariable Hazard Ratio (95% CI)**	**Multivariable *p*-value**
	Using a 7-day cutoff in delay of treatment			
All cohort ≥ 7 day delay vs < 7 day delay	1.183 (1.065–1.314)	0.0017	-	-
Radiation Treatment Group				
RT delay ≥ 7 days vs < 7 days	-	-	1.229 (1.045–1.445)	0.0132
CRT delay ≥ 7 days vs < 7 days			1.158 (1.009–1.329)	
Age	1.042 (1.038–1.047)	<0.0001	1.042 (1.038–1.046)	<0.0001
Radiation dose > 57cGy vs ≤ 57cGy	0.937 (0.843–1.043)	0.2333	0.941 (0.845–1.047)	0.2662
FIGO Stage				
II	[Reference]	<0.0001	[Reference]	<0.0001
III	1.221 (1.073–1.388)		1.225 (1.077–1.394)	
IVA	1.759 (1.517–2.039)		1.769 (1.524–2.053)	
Comorbidities, Charlson-Deyo Score				
0	[Reference]	0.0040	[Reference]	0.0047
1	1.234 (1.083–1.405)		1.230 (1.080–1.401)	
2	1.264 (1.000–1.599)		1.265 (1.000–1.600)	
3	1.225 (0.899–1.669)		1.215 (0.892–1.656)	
	Using a 14-day cutoff in delay of treatment			
All cohort ≥ 14 day delay vs < 14 day delay	1.262 (1.124–1.417)	<0.0001	-	-
Radiation Treatment Group				
RT delay ≥ 14 days vs < 14 days	-	-	1.310 (1.091–1.575)	0.0010
CRT delay ≥ 14 days vs < 14 days			1.235 (1.065–1.432)	
Age	1.042 (1.038–1.047)	<0.0001	1.042 (1.038–1.046)	<0.0001
Radiation dose > 57cGy vs ≤ 57cGy	0.935 (0.841–1.040)	0.2159	0.938 (0.843–1.044)	0.2443
FIGO Stage				
II	[Reference]	<0.0001	[Reference]	<0.0001
III	1.207 (1.061–1.373)		1.212 (1.065–1.379)	
IVA	1.747 (1.506–2.026)		1.756 (1.513–2.038)	
Comorbidities, Charlson-Deyo Score				
0	[Reference]	0.0030	[Reference]	0.0034
1	1.242 (1.091–1.415)		1.240 (1.088–1.412)	
2	1.264 (1.000–1.599)		1.264 (1.000–1.599)	

	All cohort		Delay by Treatment	
Explanatory Variable	**Multivariable Hazard Ratio (95% CI)**	**Multivariable *p*-value**	**Multivariable Hazard Ratio (95% CI)**	**Multivariable *p*-value**
3	1.225 (0.899–1.668)		1.216 (0.892–1.658)	

Abbreviations: cGy, centi-gray; FIGO, International Federation of Gynecology and Oncology; CI, confidence interval; RT, radiation therapy; CRT, chemoradiation therapy.

Table 4.

Propensity score analysis of all-cause mortality.

Variable	Hazard Ratio (95% CI)	*p*-value
All cohort ≥ 7 day delay vs < 7 day delay	1.152 (1.070–1.240)	0.0002
Radiation Treatment Group		<0.0001
RT delay ≥ 7 days vs < 7 days	1.122 (1.042–1.207)	
CRT delay ≥ 7 days vs < 7 days	1.127 (1.045–1.216)	

Abbreviations: CI, confidence interval; RT, radiation therapy; CRT, chemoradiation therapy