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Survival impact of prolonged treatment duration in primary chemoradiation for cervical cancer

Abstract

Objective: Prolonged radiation treatment duration has been negatively associated with treatment outcomes in cervical cancer. We sought to evaluate factors associated with radiation treatment duration and to analyze the impact of prolonged treatment duration on cervical cancer survival outcomes in the era of chemoradiation.

Methods: Data for patients undergoing primary radiation for cervical cancer at 2 affiliated teaching institutions from 1999–2008 were retrospectively reviewed. Clinicopathologic and treatment factors were assessed for an association with treatment duration. The impact of treatment duration on disease frees (DFS) and overall (OS) survival was analyzed.

Results: Median treatment duration for the 129 patients who received external beam radiation therapy (EBRT) and brachytherapy was 72 days. 49 patients (38%) completed treatment within 63 days. In multivariate analysis, extent of EBRT field, timing and type of brachytherapy, treatment site and administrative delays were all predictors of treatment duration. In multivariate analysis, treatment duration greater than 63 days was associated with worse DFS (HR 2.61; 95% CI 1.22–5.56; p=0.013) and OS (HR 7.34; 95% CI 1.68–32.1; p=0.008) in early and locally advanced disease. Mortality increased by 1.3% per day for each day of prolongation of radiation duration.

Conclusion: In this retrospective analysis, completion of primary chemoradiation for cervical cancer within 63 days was associated with improved DFS and OS. By focusing on potentially modifiable factors including initiation of brachytherapy during EBRT and the resolution of administrative barriers, it may be possible to improve treatment duration, which may result in better patient outcomes.

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Malaika W Amneus,[1,2] Susan Park,[1,2] Lejla Delic,[1,2,3] Peter Chung,[4] Marc Botnick,[5] Ilana Cass,[2,6] Christine H Holschneider[1,2]

[1]Department of Obstetrics and Gynecology, Olive View-UCLA Medical Center, USA
[2]David Geffen School of Medicine at UCLA, USA
[3]South Coast Gynecologic Oncology, USA
[4]Department of Medicine, Olive View-UCLA Medical Center, USA
[5]Vantage Oncology, Sherman Oaks, USA
[6]Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, USA

Correspondence: Christine H Holschneider, Olive View-UCLA Medical Center, Department of Obstetrics and Gynecology, 14445 Olive View Drive, Sylmar, CA 91342, Room 6D-116, USA, Tel 818-364-3222, Fax 818-364-3255, Email: CHolschneider@dhs.lacounty.gov

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Introduction

The negative impact of prolongation in radiation treatment time on local tumor control has been investigated in many tumor sites including head and neck, lung, breast and cervical cancers, with most studies revealing that prolonged treatment schedules are associated with inferior local control.[1] In a retrospective study of 1,224 patients with stage IB-III cervical cancer treated with radiation therapy, Perez et al.[2] demonstrated that every day of prolongation of treatment time beyond 30 days resulted in a 0.85% reduction in pelvic tumor control rate.[2] Similarly, Petereit et al.[2] demonstrated in a cohort of 209 cervical cancer patients undergoing primary radiation therapy that each additional day of treatment delay beyond 55 days was associated with a 0.7% loss of pelvic tumor control and a 0.6% reduction in survival.[3] Other retrospective studies report similar findings suggesting an approximately 1% (range 0.3-1.6%) loss of local tumor control for each day of prolongation of primary radiation therapy for cervical cancer.[3] Randomized controlled data are not available to identify the optimal treatment window in the primary treatment of cervical cancer. While one cannot ignore the potential interrelation of radiation treatment duration and confounding factors related to tumor anatomy, tumor biology, and tumor response, it has been well accepted that unnecessary delays and breaks in radiation therapy should be avoided. Based on a review of five large retrospective studies investigating the impact of treatment duration on the efficacy of radiation therapy in cervical cancer, it appears that overall treatment time should be limited to 56 days.[2–7]

Following the 1999 National Cancer Institute Clinical Alert[8] and based on the results of 5 randomized controlled cervical cancer trials[9–13] showing a 30-50% improvement in the risk of relapse or death for those patients receiving cisplatin (alone or with other agents) with their radiation therapy,[14] concomitant chemotherapy has become the standard of care for patients undergoing primary radiation therapy for cervical cancer. In the current era of chemoradiation, we have limited data on the impact of treatment duration in patients receiving radiation with concurrent chemotherapy for the primary treatment of cervical cancer. We have identified only two studies to date, a secondary analysis of patients treated with weekly cisplatin with radiation therapy on two different Gynecologic Oncology Group protocols (GOG 165 and GOG 120), that explored this relationship, which reported conflicting results.[15,16]

The purpose of our current investigation was to identify clinicopathologic and treatment factors that were associated with treatment duration and to evaluate the impact of treatment duration on disease free (DFS) and overall (OS) in patients undergoing primary radiation therapy for cervical cancer in the era of chemoradiation at two academically affiliated teaching hospitals.

Methods and statistics

Following IRB approval, the records of 180 consecutive patients treated between 1999 and 2008 with primary definitive radiation therapy for cervical cancer at two institutions and their provider networks (one university affiliated public teaching hospital and one private, academically affiliated hospital) were reviewed. We excluded 36 patients who did not have complete treatment records available, 1 patient who received neoadjuvant chemotherapy prior to chemoradiation therapy, 14 patients who did not receive brachytherapy, and 1 patient who did not have disease status documented after completion of treatment, leaving 128 patients available for analysis.

None of the patients included in the study cohort received adjuvant chemotherapy following completion of chemoradiation.

Demographic information, tumor characteristics, treatment related data, administrative factors and survival outcomes were collected from electronic and paper medical records. Treatment duration was defined as the number of days elapsed from the first to the last radiation treatment (including EBRT and brachytherapy). Treatment duration of greater than 63 days (9 weeks) was chosen as the cut-off for prolonged radiation duration based on previously published data suggesting the need to limit radiation duration to 56 days[6] plus one week for potentially acceptable deviations. "Optimal chemotherapy" was defined as having received weekly cisplatin for at least 6 doses or per protocol completion of any of the other generally accepted cisplatin based chemoradiation regimens.[9–13] Of note, in this cohort all patients receiving "optimal chemotherapy" received either weekly cisplatin or concurrent cisplatin and fluorouracil (5-FU).

Overall survival (OS) was calculated from the date of initiation of radiation therapy to the date of death. Patients who were alive were censored at the date of last follow-up. Disease free survival (DFS) was calculated from the date of completion of radiation therapy to the date of clinical or radiologic evidence of recurrence. Patients who were without evidence of disease were censored at the date of last follow-up. For patients diagnosed with persistent or progressive disease at the completion of radiation, the disease free survival was considered to be "zero" days. In order to assess the association of treatment duration with prognosis and minimize the confounding impact of additional therapeutic interventions initiated for persistent disease following primary chemoradiation, disease free survival was reported rather than progression free survival.

The following variables were analyzed for their effect on radiation duration as a continuous variable using the Wilcoxon rank sum test: patient age (≤51 years vs. >51 years), ethnicity (Hispanic vs. Non-Hispanic), stage (IB-IIA vs. IIB-IVA), tumor size (≤5cm vs. >5cm), histology (squamous vs. non-squamous), administrative factors that delayed therapy (ex: awaiting insurance approval)(present vs. absent), radiation field (pelvic vs. extended field), timing of brachytherapy initiation (during EBRT vs. after completion of EBRT), type of brachytherapy (intracavitary vs. interstitial and HDR vs. LDR), treatment site (public vs. private) and "optimal" vs. "suboptimal" chemotherapy. A multivariate analysis using Classification and Regression Tree (CART) Analysis was performed to determine which of the 12 aforementioned factors were simultaneously predictive of radiation duration. This method is highly applicable to clinical data and results in the creation of an easy to interpret classification tree,[17] which, in this case, identifies various subgroups of patients that have different treatment durations.

The Kaplan-Meier method was used to calculate disease free and overall survival curves. For bivariate analysis, the differences in the survival curves were evaluated using the log-rank test. For multivariate analysis, the impact of stage, age, tumor size, histology and chemotherapy status on DFS and OS was simultaneously assessed using a Cox proportional hazard rate regression model. Radiation duration was assessed both in a bivariate manner (≤63 days vs. >63 days) and as a continuous variable.

Results

Patient and treatment characteristics

Patient and treatment characteristics are detailed in Table 1. Median patient age was 51 years. 17% of patients had stage I disease, 50% had stage II disease, 30% had stage III disease, and 2% had stage IV disease. The median tumor size was 5cm. 84% had squamous cell carcinoma histology, 9% adenocarcinoma, 5% adenosquamous, and histology was undocumented in 1%. 59% were Hispanic, 21% Caucasian, 9% Black, 8% Asian and 3% unknown. The median total dose of EBRT was 5040 cGy and the median brachytherapy dose was 3000 cGy. Chemotherapy was given during radiation therapy to 120 patients (94%), with 116 patients (97% of those receiving chemotherapy) receiving a platinum agent. Sixty-one patients (48%) received "optimal chemotherapy". No patient received adjuvant chemotherapy following completion of chemoradiation. The median radiation treatment duration was 72 days, with 49 patients (38%) completing treatment within 63 days, and 79 patients (62%) completing treatment in greater than 63 days.

Table 1 Patient and treatment characteristics (n=128)

	Median (Range)	N (Percent)
Age	51 years	(25-90)
Stage		
IB		22 (17.2%)
IIA		19 (14.8%)
IIB		45 (35.2%)
IIIA		3 (2.3%)
IIIB		36(28.1%)
IVA		3 (2.3%)
Tumor Size	5cm (microscopic-10cm)	
Histology		
Squamous		107 (83.6%)
Adeno		12 (9.4%)
Adenosquamous		7 (5.5%)
Undocumented		2 (1.6%)
Ethnicity		
Hispanic		75 (58.6%)
Caucasian		27 (21.1%)
Black		12(9.4%)
Asian		10 (7.8%)
Unknown		4 (3.1%)
EBRT		
Dose	5040 cGy	(4000-6075 cGy)
Brachytherapy		
Dose	3000 cGy	(600-4271 cGy)
Fractions	5 (1-10)	
Chemotherapy		
Received Chemotherapy		120 (93.8%)
Platinum agent		116 (96.7%)
No platinum agent		4 (3.3%)
No chemotherapy	6 (0-10)	8 (6.7%)
Number of cycles		61 (47.7%)
Optimal chemotherapy1		67 (52.3%)
Suboptimal chemotherapy		

Citation: Amneus MW, Park S, Delic L, et al. Survival impact of prolonged treatment duration in primary chemoradiation for cervical cancer. *Obstet Gynecol Int J.* 2015;3(3):314–321. DOI: 10.15406/ogij.2015.03.00081

Table Continues...

	Median (Range)	N (Percent)
Radiation treatment duration		
£ 63 days	72 days (37-207)	49 (38.3%)
>63 days		79 (61.7%)

1Optimal chemotherapy was defined as having received weekly cisplatin for at least 6 doses or per protocol completion of another generally accepted cisplatin based chemoradiation regimen

Factors associated with radiation duration

In univariate analysis, brachytherapy initiation during EBRT, use of intracavitary brachytherapy, treatment at the public treatment site, lack of administrative problems that delayed XRT, and the delivery of optimal chemotherapy were associated with shorter radiation duration (Table 2). The median radiation duration was 58.8 days for patients who initiated brachytherapy during EBRT and 81 days for those who initiated brachytherapy after completion of EBRT ($p<0.0001$). Patients receiving intracavitary brachytherapy completed radiation at a median of 70 days, while those receiving interstitial brachytherapy completed radiation at a median of 86 days $p=0.002$). Patient treated at the public site completed radiation at a median of 65 days, compared to 78 days at the private institution ($p=0.0029$) Patients who experienced administrative delays in care completed treatment at a median of 86 days, compared to 70 days in those without administrative delays in care ($p=0.0038$). Patient who received optimal chemotherapy completed treatment at a median of 69 days, compared to 76 days in those who received suboptimal chemotherapy (0.047). Patient age, ethnicity, stage, tumor size, histologic subtype, XRT field, and HDR vs. LDR brachytherapy were not significantly associated with radiation duration in univariate analysis.

Table 2 Univariate analysis of factors associated with radiation treatment duration (n=128)

Variable	N	XRT duration (median days)	P value
Brachytherapy Initiation*			
During EBRT	50	58.5	<0.0001
After EBRT	76	81	
Type of Brachytherapy**			
Intracavitary	108	70	0.002
Interstitial	19	86	
Treatment Site			
Public	79	65	0.0029
Private	49	78	
Administrative Delays			
Absent	116	70	0.0038
Present	12	86	
Chemotherapy			
Optimal1	61	69	0.047
Suboptimal	67	76	
Ethnicity***			
Hispanic	75	70	0.12
Non-hispanic	49	77	

Table Continues...

Variable	N	XRT duration (median days)	P value
Age			
≤51 years	65	72	0.41
>51 years	63	73	
Stage			
I-IIA	41	69	0.18
IIB-IVA	87	76	
Tumor Size***			
≤5cm	62	71.5	0.46
>5cm	51	76	
Histology***			
Squamous	107	70	0.35
Non-squamous	19	75	
Radiation Field***			
Pelvic Field	90	70.5	0.36
Extended Field	37	73	
Dose Rate of Brachytherapy**			
HDR	108	71.5	0.61
LDR	19	75	

*Date of first brachytherapy unknown for 2 patients (excluded from analysis)

**1 patient received both HDR intracavitary and LDR interstitial brachytherapy (excluded from analysis)

***Missing data accounts for < 128 data points

1Optimal chemotherapy was defined as having received weekly cisplatin for at least 6 doses or per protocol completion of another generally accepted cisplatin based chemoradiation regimen

Classification and Regression Tree (CART) analysis was performed to identify factors associated with variations in treatment time in a multivariate fashion. The resulting model accounted for 40% of the variation in radiation duration and identified 6 subgroups of patients with significantly different treatment times (Figure 1). The strongest factor was the timing of brachytherapy initiation, which accounted for 18.6% of the overall variation in treatment duration. Treatment site was also a significant factor within the subset of patients who initiated brachytherapy during EBRT, accounting for an additional 7.5% of the overall variation. For patients who initiated brachytherapy after completion of EBRT, type of brachytherapy (intracavitary vs. interstitial), EBRT field (pelvic vs. extended) and administrative delays (present vs. absent), were significantly associated with radiation duration, accounting for 7.5%, 5.1%, 4.6% and 3.5% of the overall variation in radiation duration respectively.

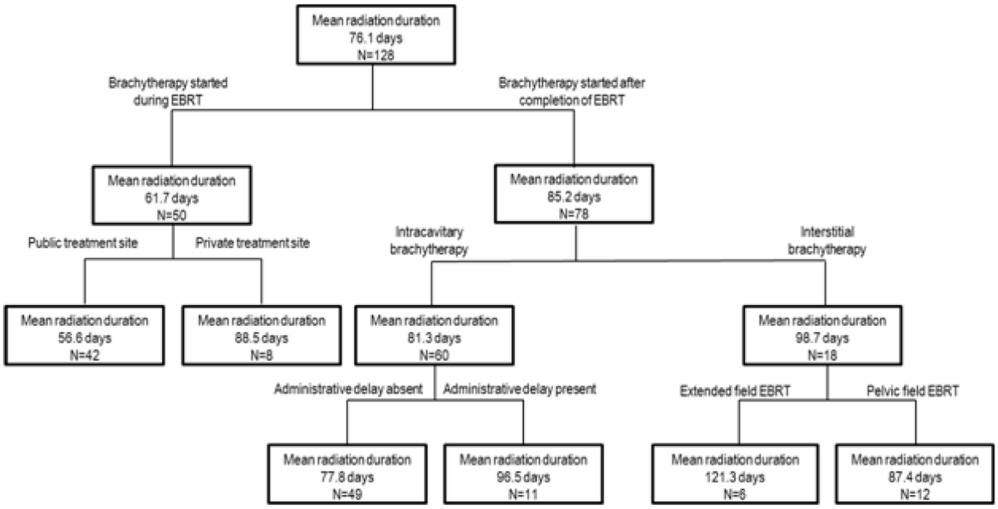

Figure 1 Multivariate CART analysis of factors associated with variation in radiation treatment duration.

Survival analysis

The median follow-up time for analyzed patients was 26 months. There were 12 patients with persistent or progressive disease (9%) and 33 patients who developed recurrent disease (26%). There were 26 recorded deaths (20%). The 12-month estimated survival is 92% (standard error 2.6%) and the 36 month estimated survival is 77.7% (standard error 4.4%).

In univariate analysis, radiation duration >63 days (HR 3.32; 95% CI 1.66–6.66; p=0.0007) and suboptimal chemotherapy status (HR 1.92; 95% CI 1.07–3.45; p=0.026) were significantly associated with worse DFS, while stage and tumor size were of borderline significance. In multivariate analysis, radiation duration remained the only factor significantly associated with DFS (HR 2.61; 95% CI 1.22–5.56; p=0.013); tumor size and chemotherapy status were of borderline significance (Table 3).

In univariate analysis, only radiation duration > 63 days was significantly associated with worse OS (HR 6.72; 95% CI 2.01–22.48; p=0.002). Stage and chemotherapy status were of borderline significance. In multivariate analysis, radiation duration >63 days remained significantly associated with worse OS (HR 7.34; 95% CI 1.68–32.1; p=0.008) and stage was of borderline statistical significance (Table 4).

The significant association between radiation duration >63 days and poor outcome was consistent in both early (I-IIA) and locally advanced (IIB-IVA) disease (Figure 2). For stage I-IIA disease, the hazard ratio for DFS was 5.22 (95% CI 1.14-24.0; p=0.016) and the hazard ratio for OS was not calculable due to the fact that there were no deaths in the group of patients treated within 63 days (p=0.0148). For stage IIB-IVA disease, the hazard ratio for DFS was 2.61 (95% CI 1.19-5.7; p=0.0119) and the hazard ratio for OS was 4.03 (95% CI 1.18-13.75; p=0.0159).

Table 3 Factors associated with disease free survival: univariate and multivariate analysis (n=128)

	Univariate analysis			**Multivariate analysis**		
Prognostic Factor	**Hazard ratio**	**95% CI**	**P value**	**Hazard ratio**	**95% CI**	**P value**
Radiation Duration						
≤63 days	Referent		0.0007	Referent		0.013
>63 days	3.32	1.66-6.66		2.61	1.22-5.56	
Chemotherapy						
Optimal1	Referent		0.026	Referent		0.103
Suboptimal	1.92	1.07-3.45		1.71	0.90-3.25	
Age						
≤51	Referent		0.5	Referent		0.951
>51	1.21	0.69-2.11		1.02	0.51-2.06	
Stage						
I-IIA	Referent		0.073	Referent		0.445
IIB-IVA	1.81	0.95-3.48		1.34	0.63-2.83	
Tumor Size						
≤5cm	Referent		0.102	Referent		0.154
>5cm	1.65	0.90-3.02		1.61	0.84-3.09	

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Table Continues...

	Univariate analysis			Multivariate analysis		
Prognostic Factor	**Hazard ratio**	**95% CI**	**P value**	**Hazard ratio**	**95% CI**	**P value**
Histology						
Squamous	Referent		0.792	Referent		0.721
Non-Squamous	1.09	0.59-2.00		1.12	0.59-2.12	

1Optimal chemotherapy was defined as having received weekly cisplatin for at least 6 doses or per protocol completion of another generally accepted cisplatin based chemoradiation regimen

Table 4 Factors associated with overall survival: univariate and multivariate analysis (n=128)

	Univariate analysis			Multivariate analysis		
Prognostic factor	**Hazard ratio**	**95% CI**	**P value**	**Hazard ratio**	**95% CI**	**P value**
Radiation Duration						
≤63 days	Referent			Referent		
>63 days	6.72	2.01-22.48	0.002	7.34	1.68-32.1	0.0082
Chemotherapy						
Optimal1	Referent			Referent		
Suboptimal	1.81	0.83-4.00	0.139	1.4	0.59-3.33	0.444
Age						
≤51	Referent			Referent		
>51	1.12	0.52-2.43	0.766	0.66	0.25-1.74	0.395
Stage						
I-IIA	Referent			Referent		
IIB-IVA	2.63	0.98-7.04	0.539	2.44	0.77-7.72	0.129
Tumor size						
≤5cm	Referent			Referent		
>5cm	1.26	0.56-2.86	0.579	1.01	0.39-2.57	0.99
Histology						
Squamous	Referent			Referent		
Non-Squamous	0.95	0.38-2.38	0.917	1.16	0.41-3.24	0.781

1Optimal chemotherapy was defined as having received weekly cisplatin for at least 6 doses or per protocol completion of another generally accepted cisplatin based chemo radiation regimen

Highlights:

1. Completion of chemoradiation for cervical cancer within 63 days is associated with improved DFS and OS.
2. Each day prolongation in chemoradiation was associated with a 1.3% increase in mortality.
3. Attention to potentially modifiable factors such as initiation of brachytherapy during EBRT and elimination of administrative delays in treatment may improve treatment outcomes.

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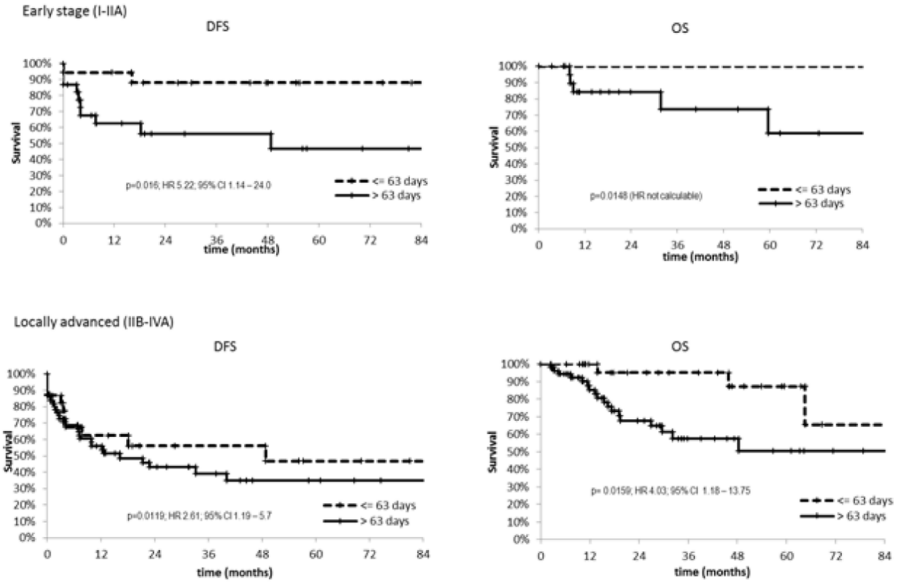

Figure 2 Disease free and overall survival curves for early stage (I-IIA) and locally advanced (IIB-IVA) cervical cancer stratified by radiation treatment duration.

When radiation duration is analyzed as a continuous variable, there is a significant association between prolonged radiation duration and decreased overall survival with a 1.3% per day increase in mortality (HR 1.013; 95% CI 1.002 – 1.024; p=0.016) for each day prolongation in radiation duration in both advanced and early stage patients. A similar trend was seen for disease free survival, but did not reach statistical significance (HR 1.006; 95% CI 0.998–1.014; p=0.16).

Discussion

During the early to mid-1990s, several studies were published which demonstrated an association between prolonged treatment duration and poor outcomes in patients treated with primary radiation therapy for cervical cancer.[2–5,7] These studies highlighted the importance of avoiding unnecessary delays in definitive radiation treatment of cervical cancer as illustrated in the study by Perez et al.[2] who found in 1,224 patients that prolongation of radiation duration decreased pelvic control by 0.85% per day.[2] However, a major shift in treatment guidelines for cervical cancer occurred in 1999 after the publication of several clinical trials showed improved outcomes with the addition of cisplatin based chemotherapy to radiation therapy.[9–13] Whether timely completion of radiation therapy is still critical in the current era of chemoradiation remained unclear. To this date, there is little data available to inform this question. Monk et al.[16] performed a reanalysis of the weekly cisplatin arms of GOG 120 and 165, with mixed results. While they showed that there was an association between PFS (HR 1.98; 95% CI 1.16-3.38; p=0.012) and OS (HR 1.88, 95% CI 1.08-3.26; p=0.024) in patients treated on GOG 165, no such relationship was found in patients treated on GOG 120.[16] Additionally, a recent retrospective study by Song et al.[15] which included 113 patients treated with chemoradiation for IB2-IIIB cervical cancer, showed that completion of brachytherapy treatment in greater than 56 days was associated with worse pelvic control, however this did not translate into a significant difference in disease specific survival.[15] Our study adds to the literature regarding the importance of timely completion of radiation therapy for cervical cancer in the era of concurrent chemotherapy administration. Additionally, our CART analysis uniquely provides an exploratory analysis regarding how various factors (some of which may be alterable) impact radiation treatment time. This information may prove useful in the development of approaches and programs to improve the treatment received by patients with cervical cancer.

Our study demonstrates that prolongation of radiation duration beyond 63 days is associated with significantly worse disease free and overall survival of patients treated with primary chemoradiation for early and locally advanced-stage cervical cancer. These results are similar to those obtain by Monk et al.[16] in the analysis of patients treated on GOG 165, but are contrary to those found in analysis patients treated on GOG 120. In general, the patient population and practice patterns for delivery of chemoradiation at the facilities included in our study are more in line with the characteristics in GOG 165 than GOG 120. For example, surgical staging was optional in GOG 165 and mandatory in GOG 120.[12,18] Surgical staging was not required for inclusion in our study and only 44/128 patients (34%) were surgically staged. Of note, contrary to the GOG protocols, patients with pathologically involved or radiographically suspicious paraaortic lymph nodes were not excluded from our analysis. In GOG 120, there was a scheduled 1-3 week delay between EBRT and brachytherapy initiation and interstitial and HDR brachytherapy were not allowed.[12] In GOG 165, HDR was allowed and brachytherapy was planned to start in during the 4th week of EBRT.[18] At neither site included in our study is a planned treatment break between EBRT and brachytherapy standard practice, but the timing of initiation of brachytherapy was highly variable.

Our data strongly support that the addition of concurrent chemotherapy to radiation therapy in the treatment of cervical cancer does not obviate the negative impact of prolonged radiation duration and demonstrate that this is a relevant concern in the treatment of both early and locally advanced disease. Past studies on the impact of treatment duration on cervical cancer outcomes using data from patients treated with radiation only found a clear, progressive negative correlation between treatment duration, locoregional control and survival. The largest of these was a study of 1,224 patients with stage IB-III cervical cancer.[2] In this study, 46% of patients completed treatment in <7 weeks, 44% between 7 and 9 weeks, and 37% in greater than 9 weeks. Prolonged radiation treatment duration was found to have a significant negative impact on pelvic tumor control

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with an overall decrease in pelvic tumor control of 0.85% per day. Similarly, Lanciano et al.[7] in a study of 837 patients with stage I to stage III cervical cancer, showed that prolongation of radiation duration was associated with an increase in infield recurrence at 4 years (5.4% for duration <6 weeks; 11.3% for 6-7.9 weeks; 14.8% for 8-9.9 weeks; 19.9% for >10 weeks; p=0.0001) and decrease in survival at 4 years (81.8% for duration <6 weeks; 74.5% for 6-7.9 weeks; 74.1% for 8-9.9 weeks; 66.4% for >10 weeks; p=0.0001).[7] In our study of patients treated in the era of chemoradiation, we found similar significant negative impact of prolonged treatment duration on overall survival with an increase in mortality of 1.3% per day for each day of prolongation of radiation duration. Using 9 weeks (63 days) as a cut off for prolonged radiation treatment time, we found prolonged treatment to be associated with worse disease free and overall survival outcomes of patients undergoing primary chemoradiation for both, early or locoregionally advanced-stage cervical cancer. We were unable to investigate the question of whether completion of chemoradiation within even shorter treatment times further improves survival outcomes, as there were too few patients in our cohort completing their chemoradiation in less than 8 weeks for any meaningful analysis.

In our multivariate analysis, the timing of brachytherapy initiation (during vs. after EBRT), treatment site (public vs. private hospital), type of brachytherapy (intracavitary vs. interstitial), administrative problems that delayed radiation therapy (absent vs. present), and radiation field (pelvic vs. extended) were associated with radiation duration. Most significantly, our results indicate that initiation of brachytherapy during EBRT may be of critical importance in allowing patients to complete treatment in a timely manner. In the bivariate analysis, this factor was associated with the largest variation in treatment duration between groups (median of 58.5 days for those initiating brachytherapy during EBRT and 81 days for those initiating brachytherapy after completion of EBRT, for a difference of 22.5 days). If minimizing treatment duration is a goal, then whenever feasible, strong efforts should be made to initiate brachytherapy during the course of EBRT. While some of the other factors, such as radiation field and the need for interstitial therapy are largely dictated by the patient's disease, there were other potentially modifiable factors associated with prolonged treatment duration in our patient cohort. This included administrative factors that led to delays and treatment site, possibly indicating that factors relating to infrastructure and practice patterns at varying institutions may negatively impact radiation treatment duration. We have since initiated a cervical cancer case management and navigation program to prospectively assess our ability to impact treatment duration throughout one of our health systems.

It is notable that our tree model was able to account for only 40% of the variation in radiation duration. We were not able to reliably account for several factors that potentially impact treatment duration, in this retrospective, multi-site study, including patient factors such as compliance, socioeconomic issues, lack of transportation or childcare, and medical factors, such as comorbidities and complications of the cervical cancer or its therapy. For example, it was not reliably documented when patients missed radiation appointments due patient compliance or treatment morbidity.

It is unknown how much of the difference in outcome that is seen in studies such as ours is due to radiation treatment duration itself as opposed to prolonged radiation treatment duration being a marker for other poor prognostic factors that are unable to be accounted for. In the current analysis, prolonged radiation duration was not associated with the non-modifiable variables of stage, histology, age, ethnicity, or tumor size. Factors that could potentially lead to a prolonged treatment course, such as differences in tumor response based on histology, tumor size, or stage, or any differences in patient tolerance to treatment based on extent of disease, age or ethnicity, did not prove to be significant in the current study. Inclusion of an extended radiation field, which can be associated with additional treatment related toxicity, and utilization of HDR brachytherapy (which required inpatient admission and therefore additional care coordination), as opposed to LDR brachytherapy (delivered as an outpatient), also was not shown to impact treatment duration on univariate analysis. However, other potentially important factors that may impact treatment duration and outcome, such as performance status and treatment toxicities, were unable to be included in the analysis. Similarly, lymph node status was not controlled for given that only a minority of the patients (33%) underwent lymphadenectomy.

The retrospective nature of this study should lead to the usual degree of caution in interpreting the results. However, the fact that such a strong and consistent impact of radiation duration was found overall and within the subgroups of both early and locally advanced disease strengthens the supposition that radiation duration remains of prognostic importance in the era of chemoradiation.

Conclusion

In a retrospective analysis of patients treated for cervical cancer in the era of chemoradiation, the completion of primary radiation therapy within 63 days was associated with improved DFS and OS in the entire patient cohort, as well as in subanalysis of early stage (stage I-IIA) and locoregionally advanced (stage IIB-IVA) disease. Multivariate analysis using CART analysis identified initiation of brachytherapy during EBRT, treatment at the public site, use of intracavitary brachytherapy, absence of administrative delays, and a pelvic EBRT field (as opposed to extended field) as predictors of radiation duration. By focusing on potentially modifiable factors including efforts to initiate brachytherapy during EBRT, streamlining processes in order to avoid administrative delays in treatment, and improving patient compliance, it may be possible to improve radiation treatment duration, which may lead to better treatment outcomes.

Acknowledgments

None.

Conflicts of interest

The authors declare there is no conflict of interests.

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