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ORIGINAL RESEARCH

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Importance of radiographic tumor regression during radiotherapy in squamous cell versus adenocarcinoma of the uterine cervix as assessed by MRI and cone beam CT

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Abstract

The purpose of this study was to evaluate the kinetics of tumor regression in cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC) using computed tomography (CT) and magnetic resonance imaging (MRI), and to correlate rate of regression and residual tumor with progression and survival. Thirty-two patients with stage IB2-IVA cervical cancer were randomly selected from an institutional database with a 2:1 ratio of SCC to AC. All available on-treatment weekly cone beam CT (CBCT) and pre- and post-external beam MRIs were utilized to generate largest two-dimensional area of tumor and tumor gross tumor volumes (GTV), respectively. Tumor volume regression velocity and percent residual tumor were correlated to 5-year progression-free survival (PFS) and disease-specific survival (DSS) using threshold regression modeling. Kaplan-Meier and Fine-Grey estimators were used for survival and cumulative incidence analysis, respectively. With a median follow-up of 2.9 years, 32 patients were included, 22 (69%) with SCC and 10 (31%) with AC. All received concurrent chemoradiation followed by brachytherapy. The 2-year cumulative incidence (CI) of local progression for both SCC and AC was 10%, and 2-year CI of distant progression was 9% *vs.* 57% (p = 0.02). Deaths occurred in 3/22 (14%) with SCC and 7/10 (70%) with AC, with a 2-year DSS of 90% versus 60%, respectively. Extent and rate of regression on CBCTs were not correlated with progression or survival; however, consistent rates of tumor regression for both SCC and AC. Thresholds of $\geq$20% residual disease on post-external beam pre-brachytherapy MRI and regression velocity $\leq$1.8%/day were associated with worse PFS and DSS. This study showed cervical AC is associated with higher rates of distant progression and worse overall survival than SCC. Cervical AC tends to have a higher initial and residual tumor burden. Our identified thresholds of $\geq$20% residual tumor and tumor regression of $\leq$1.8%/day may help identify cases warranting dose escalation.

Keywords

Cervical cancer; Squamous cell carcinoma; Adenocarcinoma; Tumor regression; Residual tumor; Radiotherapy; Radiation therapy

1. Introduction

The standard of care in the treatment of locally advanced stage IB-IVA cancer of the uterine cervix is definitive external beam chemoradiation to the pelvis followed by dose-escalated radiation (RT) to the primary cervical tumor using brachytherapy. Current treatment guidelines in the USA and Europe do not stratify or adjust recommendations based on whether the cervical cancer is squamous cell carcinoma (SCC; 70% of patients) or adenocarcinoma/adenosquamous carcinoma (AC; 20%), despite the historically worse outcomes in patients with cervical adenocarcinoma or adenosquamous carcinoma [**? ? ?**].

Patients receiving radiation therapy will undergo a multi-modal imaging for diagnostic staging, treatment planning, and guidance during daily treatment delivery. This includes a staging positron emission tomography/computed tomography (PET/CT) prior to the beginning of treatment and 3 months after the completion of brachytherapy, a staging MRI prior to treatment, a cone beam CT for image guidance with each fraction of radiation, and fan-beam CTs for radiation planning and with every fraction of brachytherapy. The addition of a post-external beam, pre-brachytherapy planning MRI for image-guided adaptive brachytherapy (IGABT) has become

an increasingly common practice, replacing historical two-dimensional point-A planning techniques. This large volume of imaging provides a unique opportunity to track tumor growth or regression during the course of treatment.

Cervical cancers are responsive to chemoradiotherapy as demonstrated by physical exam, CT, MRI and PET with an approximate 50% reduction in tumor size after three weeks or 20 Gy of radiation [**? ? ? ? ? ?**]. Several studies have found cervical AC to be less responsive to radiotherapy than SCC with variable findings on specific survival outcomes, though it is generally felt to have poorer outcomes than SCC [**? ? ?**]. Multiple groups have reported on cervical cancer survival outcomes relative to clinical or radiographic tumor regression after external beam radiation or brachytherapy [**? ? ? ? ? ? ? ? ? ?**]. These reports analysed either SCC only or mixed cohorts. Few reports compared the kinetics of tumor regression between cervical SCC versus AC in patients undergoing radiation therapy and the prognostic implications of the extent of the histology-specific response to radiotherapy [**?**]. Prior studies have demonstrated increased risk of local progression and benefit to dose-escalation based on the extent of residual tumor, though given the differential response to radiation in squamous carcinoma versus adenocarcinoma, there may be different residual tumor thresholds based on the specific histology of the cervical cancer, with adenocarcinoma anticipated to have a slower response. Herein we endeavor to evaluate the response of the primary cervical tumor to external beam radiotherapy with concurrent chemotherapy in stage IB2-IVA cervical SCC and AC and evaluate how extent of progression correlates with progression-free survival (PFS) and disease-specific survival (DSS).

2. Materials and methods

2.1 Patient population

Thirty-two patients with biopsy-proven, stage IB2-IVA cervical cancer who received external beam radiotherapy followed by brachytherapy were randomly selected from an institutional database with a roughly 2:1 ratio of squamous cell carcinoma to adenocarcinoma.

2.2 Treatment

All patients were treated at the University of Utah Huntsman Cancer Institute between the years of 2012 and 2020. All patients received staging imaging, including a pretreatment diagnostic CT, PET/CT and MRI scans. All patients received definitive external beam radiotherapy via intensity-modulated radiotherapy (IMRT) to the pelvis using 6 MV photons to a dose of 45 Gy in 1.8 Gy daily fractions with 5–6 cycles of concurrent weekly 40 mg/m^2 cisplatin, with daily cone beam CTs (CBCTs) for image guidance. The full prescription dose was constrained to cover at least 97% of the planning target volume, with no more than 0.03cc to receive $>$110% or $<$93% of prescription dose. Patients with involved lymph node received a simultaneous integrated boost to 55 Gy in 2.2 Gy daily fractions to enlarged or morphologically abnormal lymph nodes, constrained to have 98% of prescription dose covering at least 97% of the boost target. Constraints for organs at risk were derived from the TIME-C and Radiation Therapy Oncology Group (RTOG) 0418 trials [**? ? ?**]. The target fields covered the cervix, uterus, parametria, upper portion of the vagina with additional vagina included if involved, along with obturator, internal iliac, external iliac, common iliac and periaortic lymph nodes, typically with superior field border at L4/L5 vertebral body interface or at aortic bifurcation, or T11/T12 if para-aortic nodes involved.

After completing all 25 fractions of external beam radiotherapy, all patients received 3–5 high dose rate (HDR) brachytherapy treatments with a Fletcher-style tandem and ovoid device. All patients received MRI-guided volume-based planning brachytherapy with a post-external beam radiotherapy limited T2-weighted pelvic MRI to aid tumor delineation for the high risk clinical target volume (HR-CTV). Patients did not receive contrast-enhanced or diffusion-weight sequences, which has been a long-standing institutional practice to permit acquisition of imaging expeditiously for treatment planning. The HR-CTV was defined as all radiographically visible tumor on T2-weighted MRI at the time of brachytherapy, any tumor palpable on clinical exam, and the entire cervix. The HR-CTV was prescribed either 30 Gy in 5 fractions, 28 Gy in 4 fractions, or 27 Gy in 3 fractions, with a goal of 90% of the HR-CTV receiving a combined 2 Gy biologic equivalent dose (EQD2) of $>$85 Gy to the cervix in 2 Gy equivalents.

2.3 Image analysis

Twenty-four patients had both pre-treatment MRI (MRI_1) and post-external beam brachytherapy-planning MRI (MRI_2) and were included for imaging analysis. T_2-weighted axial and sagittal sequences were imported into Medical Image Merge (MIM) software (version 5.1, MIM Software, Cleveland, OH, USA). The tumor was identified on both axial and sagittal sequences and cervical gross tumor volumes (GTVs) were generated. GTV volumes were then extracted *via* 3-D volumetry from the MIM software.

The CBCTs used for daily imaging guidance from days 1, 7, 13, 19 and 25 were selected for each patient ($CBCT_1$–$CBCT_{25}$) and imported into MIM. These correspond to doses received at the time of CBCT of 0, 10.8, 21.6, 32.4, and 43.2 Gy, respectively. Due to the limited resolution of cone beam imaging, the axial plane with the largest two-dimensional tumor size was selected and measured along the lateral and anterior-posterior axis. The measurements were then multiplied together to generate the two-dimensional product of diameters.

Timing of imaging during the treatment course is illustrated in Fig. **??**.

For proportional volume measurements, the GTV volume measured on MRI_1 is defined as 100% for MRI analyses. Volume regression over time curves were generated, with the slope of the resulting line (% volume/time) representing the tumor shrinkage velocity during treatment. All imaging-defined data was then extracted for analysis, including pre-treatment tumor volume, residual tumor volume, and rates of regression.

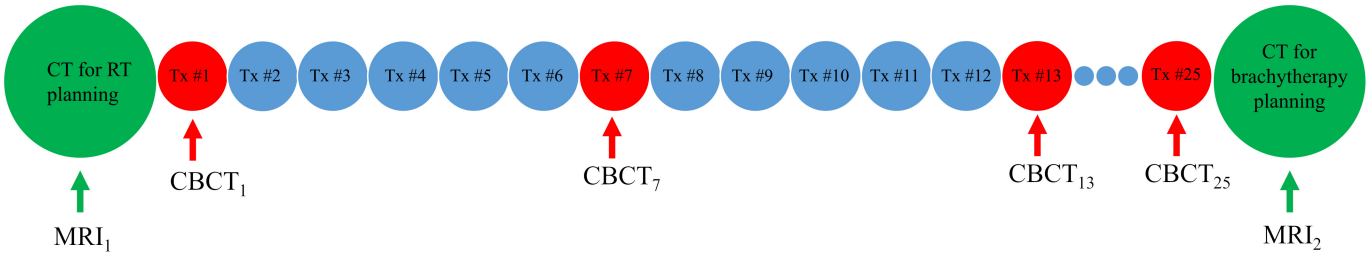

FIGURE 1. Schematic delineating the timing of MRI_1, MRI_2, $CBCT_1$, $CBCT_7$, $CBCT_{13}$, $CBCT_{19}$, and $CBCT_{25}$. All imaging is completed prior to the initiation of HDR brachytherapy. CT, computed tomography, MRI; magnetic resonance imaging; RT: radiation; CBCT: cone beam CT.

TABLE 1. Patient characteristics.

	All patients	SCC	AC
	(n = 32)	(n = 22)	(n = 10)
	No. (%)	No. (%)	No. (%)
Age, median	49	50	47
Stage			
IB	4 (13)	1 (5)	3 (30)
IIA-IIB	13 (40)	11 (50)	2 (20)
IIIA-IVA	15 (47)	10 (45)	5 (50)
Nodal involvement	12 (38)	7 (32)	5 (50)
Chemotherapy	32 (100)	22 (100)	10 (100)
Dose reductions	3 (9)	3 (14)	0 (0)
Human Papilloma Virus positive	29 (91)	22 (100)	7 (70)
Smoking history	13 (41)	9 (41)	4 (40)
Brachy fxns, median	5	5	4
HR-CTV D90% EQD2			
Median	85.8	86.8	83.6
IQR	81.7–88.1	82.8–88.8	81.8–87.0
Total treatment time			
≤8 weeks	32 (100)	22 (100)	10 (100)
≤7 weeks	19 (59)	13 (59)	6 (60)
Progression	11 (34)	4 (18)	7 (70)
Local	3 (9)	2 (9)	1 (10)
Distant	8 (25)	2 (9)	6 (60)
Death	10 (31)	3 (14)	7 (70)

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma; Brachy, brachytherapy; fxns, fractions; HR-CTV, high-risk clinical target volume; D90%, dose covering 90% of the target volume; EQD2, equivalent dose in 2 Gy fractions after external beam and brachytherapy; IQR, interquartile range.

2.4 Outcome analysis

All patients were followed at 3–6 month intervals for the first 5 years, followed by annual examinations thereafter. Local progression was defined as tumor growth in the cervix, uterus or treated lymph nodes in the pelvis after treatment completion. Distant progression was defined as tumor growth outside of the treated pelvis. Patient characteristics and imaging-defined tumor characteristics were analyzed using multivariable logistic regression to identify factors associated with progression or death. Threshold regression modeling was used to identify residual tumor volume and tumor kinetics predictive of progression or death. Five-year PFS and DSS were selected as discrete endpoints for threshold regression modeling. Kaplan-Meier estimators were used for survival analyses. Fine-grey analyses were used to estimate cumulative incidence (CI) of progression using a competing risk of death. All statistical analysis performed in Stata18 (Stata Corporation, College Station TX, USA).

3. Results

3.1 Overall cohort

With a median follow-up of 2.9 years, 11 of the 32 patients experienced progression, and 10 had died, 9 of whom from progression of disease. All patients received five or six cycles of concurrent weekly cisplatin with external beam radiotherapy, with majority receiving six cycles (84%), and all received intracavitary brachytherapy after external beam radiation. None of the patients received interstitial needles during brachytherapy for disease coverage. The majority (59%) of patients received five HDR brachytherapy treatments. All completed their external beam and brachytherapy treatments within eight weeks of commencing radiation, and the majority completed within seven weeks (59%). None of the patients received adjuvant chemotherapy after brachytherapy by institutional practice. Patient characteristics are shown in Table **??**.

Two patients with SCC (9%) and one with AC (10%) experienced local progression after treatment. One SCC patient and one AC patient each developed pelvic masses involving the cervix and uterus, while one SCC patient had pelvic and paraaortic nodal failures, all within external beam radiation fields. The 2-year cumulative incidence (CI) of local progression with competing risk of death for SCC and AC was 10% at for both groups (p = 0.81 and p = 0.86, respectively). CI of local progression for SCC and AC is shown in Fig. **??**.

Distant progression was higher in patients with AC, as six (60%) experienced a distant failure compared to two (9%) patients with SCC. The SCC failures were in lung alone for one patient and liver and rib the other patient, well outside of the external beam radiation field. Four of the AC patients had failures in the lung and two in bone. Two of the AC patients with lung metastases also had retroperitoneal and paraesophageal lymph node failures, respectively, outside of the pelvic radiation field. The 1- and 2-year CI of distant progression with competing risk for SCC versus AC were 9% versus 43% (p = 0.01) and 9% versus 57% (p = 0.02), respectively. CI of distant progression for SCC and AC is shown in Fig. **??**.

Disease-specific survival was shorter in patients with AC compared to SCC. The 1- and 2-year DSS for SCC versus AC was 100% versus 60% ($p < 0.01$) and 90% versus 51% ($p < 0.01$), respectively. DSS by for SCC and AC is shown in Fig. **??**.

On multivariable analysis of the entire cohort, patients who did not complete treatment within 7 weeks had a higher risk of progression (odds ratio (OR) 3.1, $p = 0.05$) and death (OR 1.6, $p = 0.03$), while AC histology was associated with a higher risk of any progression (OR 2.6, $p = 0.02$) and death (OR 2.4, $p = 0.03$). No other factors were found to be significant.

3.2 Imaging analysis

Twenty-four patients within our study population had both MRI_1 and MRI_2 available for analysis. This cohort comprised of 17 patients with SCC and 7 with AC. All 24 had 5 CBCTs available for analysis.

The median two-dimensional product of diameters measured on the $CBCT_1$ was 31.4 cm^2 (range 17.9–59.1 cm^2) and 18.4 cm2 (range 9.5–36.0 cm^2) on $CBCT_5$. All patients showed measurable response to therapy during the course of external beam radiotherapy.

Tumor regression velocity during external beam radiotherapy as measured by CBCT and MRI is shown in Fig. **??**.

Similarly, all patients showed significant measurable response to external beam therapy between MRI_1 and MRI_2, as shown in Fig. **??**. Four SCC patients (24%) had complete radiographic resolution of tumor on MRI_2; no AC patient had a complete radiographic response. Tumor characteristics and kinetics as measured by MRI are shown in Table **??**.

Threshold regression analysis was utilized to identify tumor response characteristics on the CBCTs and MRIs correlated with 5-year DSS and PFS. Using the CBCT data, no statistically significant thresholds were identified that correlated with DSS or PFS. Using the MRI data, analysis demonstrated worse 5-year DSS and 5-year PFS with a residual tumor volume threshold of $\geq$20%. The 5-year PFS for patients with $<$20% residual tumor versus $\geq$20% was 90.9% versus 50.0% (p = 0.024) and the 5-year DSS for $<$20% versus $>$20% residual was 81.8% versus 51.3% (p = 0.045). When SCC and AC were analyzed separately for thresholds associated with worse 5-year PFS, a threshold of $\geq$16% for SCC and $\geq$55% for AC trended toward significance (p = 0.052 and p = 0.10, respectively), while a 5-year DFS threshold of $\geq$45% trended toward significance for AC (p = 0.12)

A threshold of $\leq$1.8% per day average volume reduction in gross tumor volume was also found to be associated with worse 5-year PFS and DSS. The 5-year PFS for patients with $\leq$1.8%/day of tumor regression versus $>$1.8%/day was 46.2% versus 100% (p = 0.011), respectively, with 5-year DSS of 47.0% versus 90.0% (p = 0.048), respectively.

The association between DSS and PFS and residual tumor volume and regression velocity are shown in Fig. **??**A–D.

4. Discussion

The prognostic impact of the initial clinically-measured volume of tumor on local progression and survival in cervical

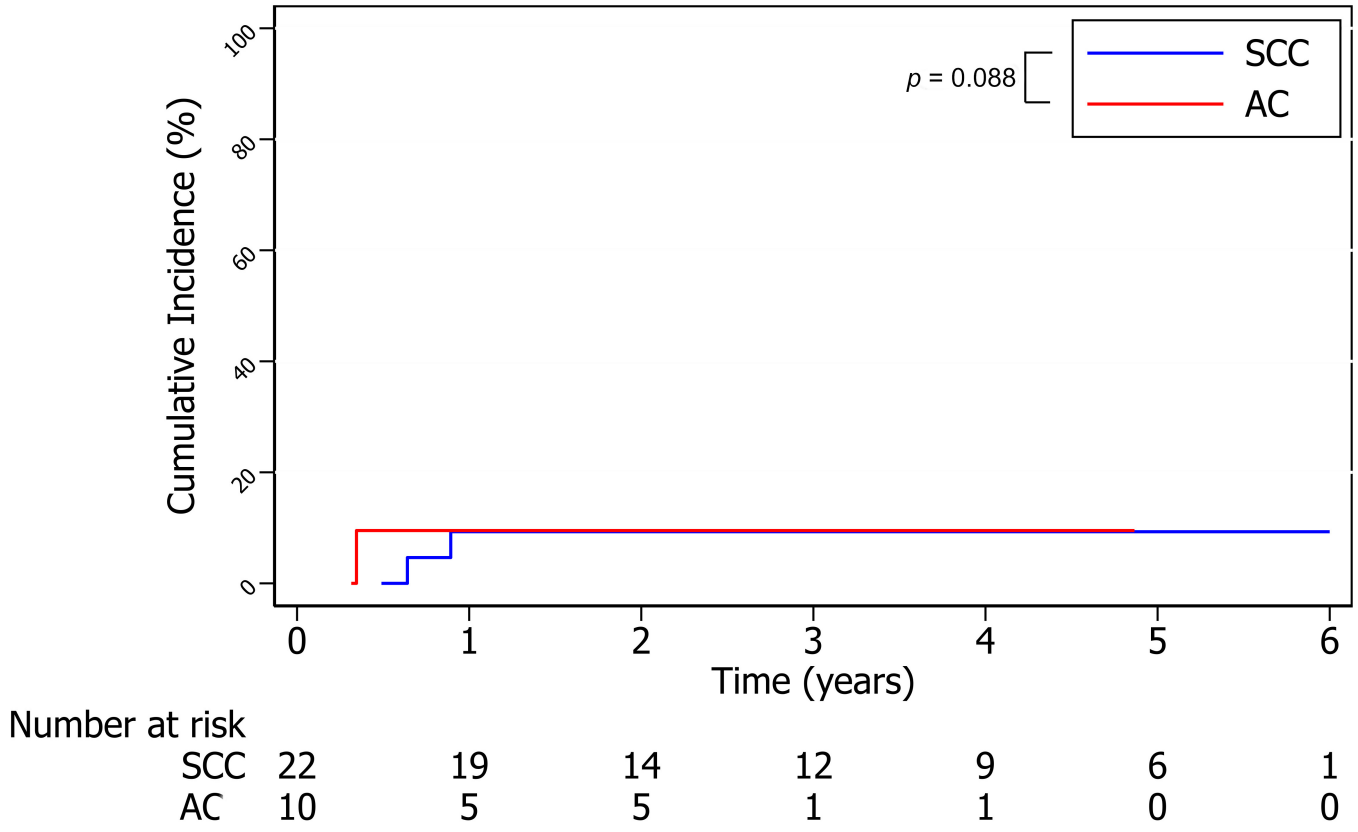

FIGURE 2. Cumulative incidence of local progression with competing risk of death for cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC). The CI was 10% for both SCC and ACC at all time points from one year post-treatment onward.

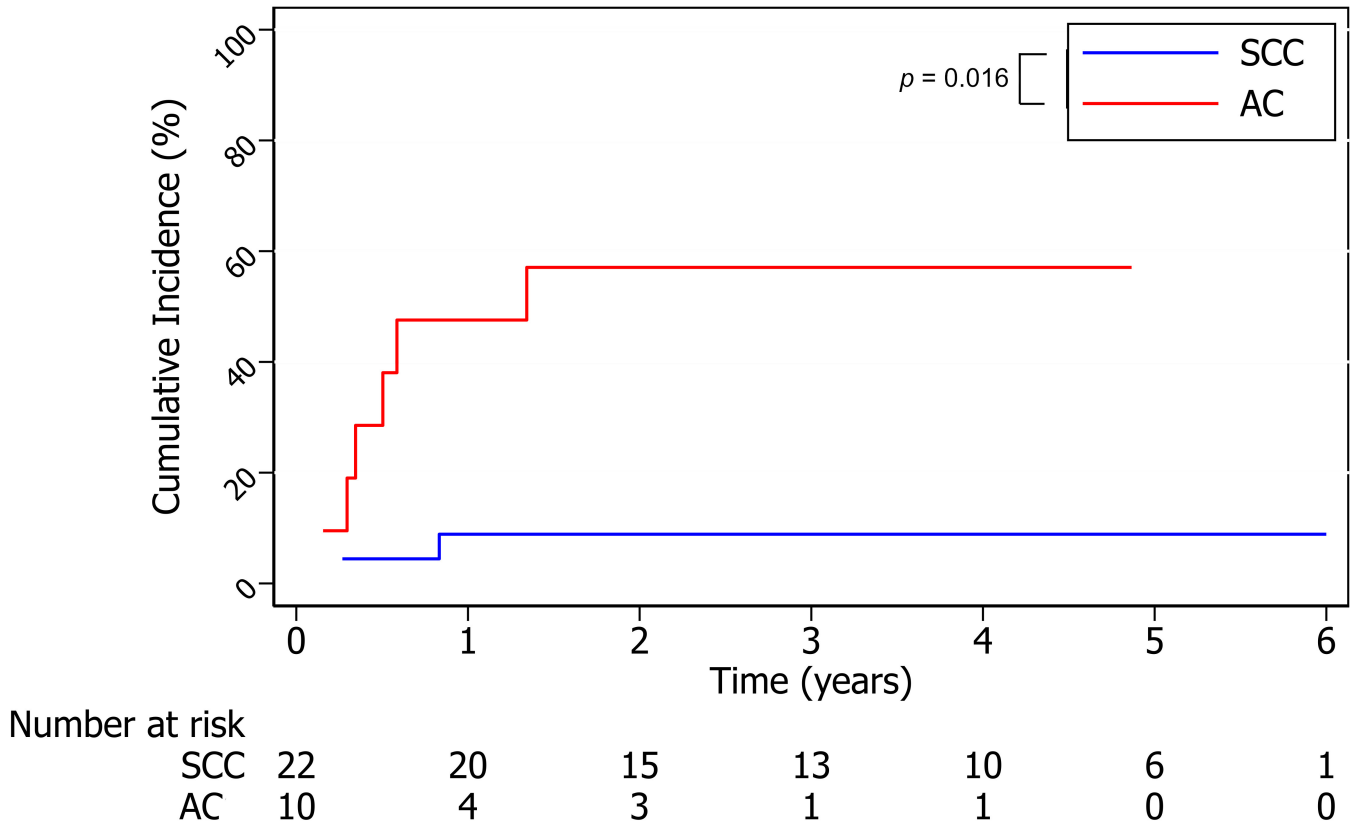

FIGURE 3. Cumulative incidence of distant progression with competing risk of death for cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC).

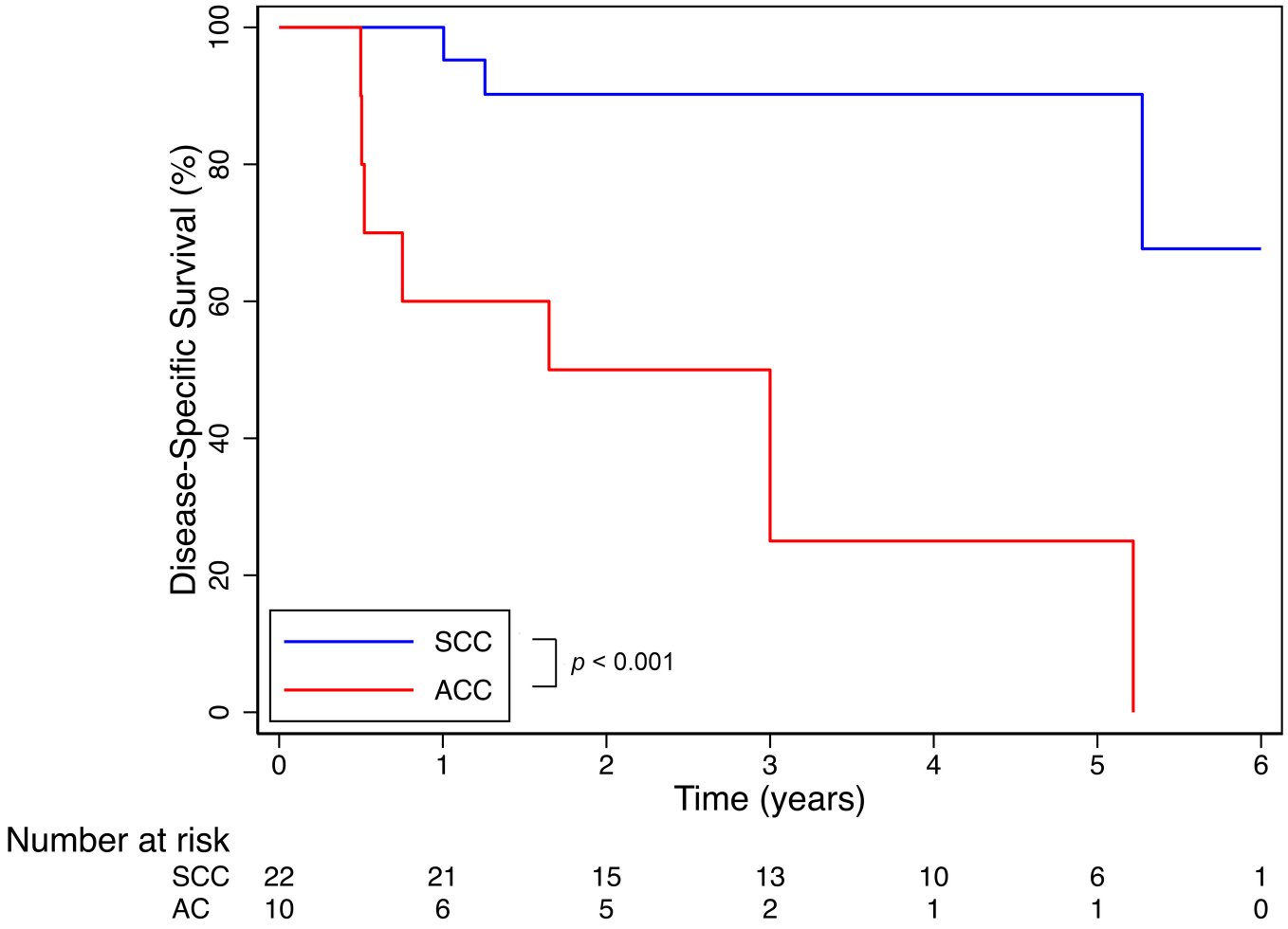

FIGURE 4. Disease-specific survival for cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC).

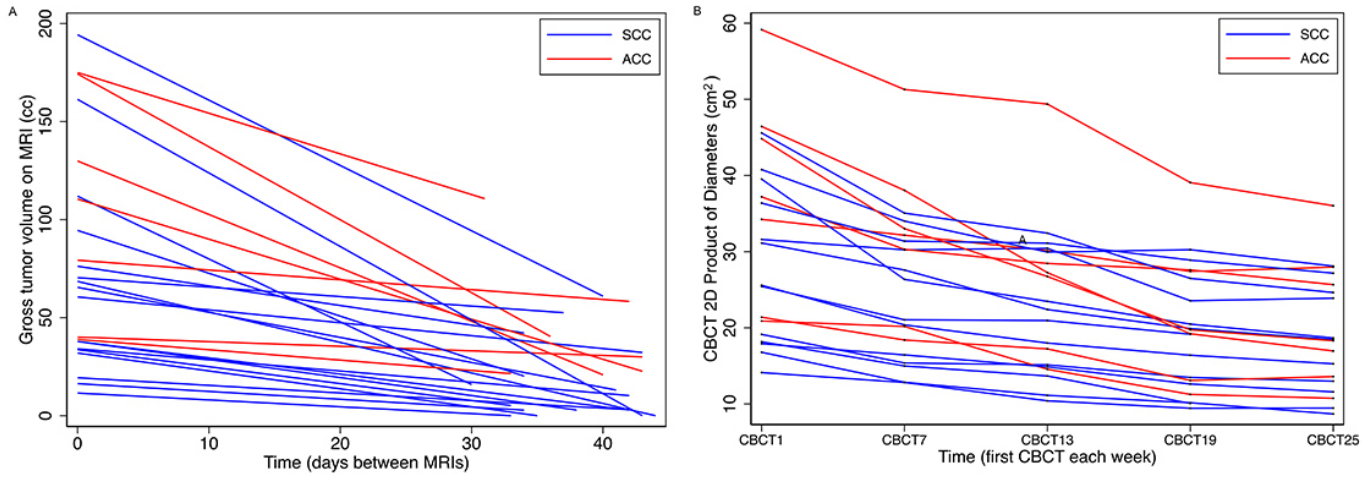

FIGURE 5. Tumor regression over time as evaluated in MRI and cone beam CT. (A) Plot of gross tumor volume for squamous cell carcinoma (SCC) and adenocarcinoma (AC) between MRI_1 and MRI_2. Both modalities demonstrate tumor response during radiotherapy. (B) Plot of two-dimensional product of diameters for cervical squamous cell carcinoma SCC and AC as delineated on cone beam CTs performed for image guidance during external beam radiotherapy. MRI, magnetic resonance imaging; CBCT: cone beam computed tomography.

squamous cell carcinoma was established more than three decades ago [**? ?**]. However, clinical measurements, which by design assume spherical or ellipsoid tumor shape, have been shown to be notoriously imprecise for infiltrating, irregular tumors like cervical cancer when compared to modern imaging techniques like MRI [**? ?**]. The adoption of MRI evaluation for both staging and, at some centers, brachytherapy planning has become increasing common and has allowed for substan-

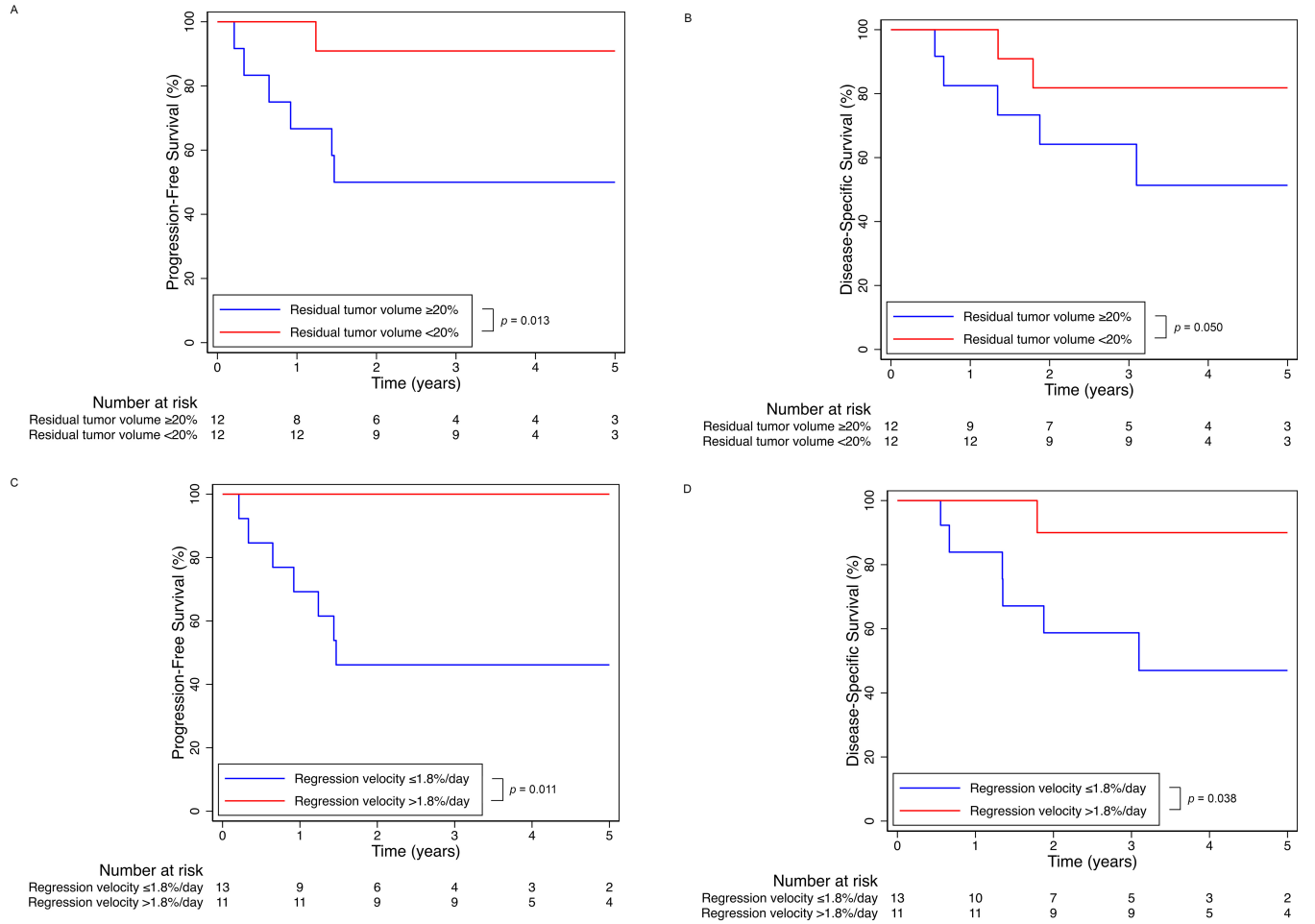

FIGURE 6. Progression-free survival and disease-specific survival by residual tumor volume and gross tumor regression velocity. (A) Progression-free survival in patients with combined histologies stratified by residual tumor volume of ≥20% versus <20%. The 5-year PFS for patients with <20% residual tumor versus ≥20% was 90.9% versus 50.0% ($p = 0.024$). (B) Disease-specific survival in patients with combined histologies stratified by residual tumor volume of ≥20% versus <20%. The 5-year DSS for patients with <20% residual tumor versus ≥20% was 81.8% versus 51.3% ($p = 0.045$). (C) Progression-free survival in patients with combined histologies stratified by tumor regression velocity of ≤1.8%/day versus >1.8%/day. The 5-year PFS for patients with ≤1.8%/day of tumor regression versus >1.8%/day was 46.2% versus 100% ($p = 0.011$), respectively. (D) Disease-specific survival in patients with combined histologies stratified by tumor regression velocity of ≤1.8%/day versus >1.8%/day. The 5-year DSS for patients with ≤1.8%/day of tumor regression versus >1.8%/day was 47.0% versus 90% ($p = 0.048$), respectively.

tially more accurate evaluation of three-dimensional tumor volume. Larger radiographic pre-treatment tumor volume has been correlated with worse PFS in cervical cancer [**?**]. Multiple prior studies have taken advantage of the tissue resolution on MRI and demonstrated the correlation between the radiographic residual cervical primary tumor volume after external beam radiation and increased risk of local progression or death [**? ? ? ? ? ? ? ? ? ? ? ? ?**]. Extent of residual disease after brachytherapy on MRI has additional been shown to correlate with increased risk of treatment failure [**?**].

The findings that residual disease was correlated with worse oncologic outcomes has resulted in numerous feasibility studies evaluating the benefit of dose-escalating the standard of care post-external beam brachytherapy [**?**]. The Magnetic Resonance Imaging-Guided Brachytherpy in Locally Advanced Cervical Cancer (EMBRACE) I trial demonstrated that IGABT with MRI-guided brachytherapy after concurrent chemoradiation to an EQD2 of 90 Gy resulted in very limited severe toxicity [**?**]. Following that, the EMBRACE II trial is focusing on utilizing improvements in IGABT to increase HR-CTV dose coverage to 90–95 Gy using MRI to delineate patients with larger tumor volumes who would benefit from the receipt of combined intracavity and interstitial brachytherapy to achieve better target coverage while still meeting organ at risk constraints, effectively using interstitial treatment as a soft dose escalation [**?**]. Multiple trials of dose escalation using carbon ion therapy alone to 74.4 Cobalt Gray Equivalents (CGE) without brachytherapy has been shown to be safe and effective for locally advanced cervical cancer, and adenocarcinoma-specific results are promising, though access to carbon ion treatment centers are very geographically limited, and prospective comparative trials to standard of care concurrent photon chemoradiation with brachytherapy are still pending [**? ? ? ? ? ? ? ?**]. The use of adjuvant chemotherapy for treatment escalation following chemoradiation and brachytherapy for intact cervix

TABLE 2. Tumor characteristics on MRI_1 and MRI_2, and associated tumor regression kinetics during external beam radiotherapy.

	All patients	SCC	AC
Pretreatment tumor volume on MRI_1			
Median (cc)	67.0	65.4	79.3
Range (cc)	11.5–194.3	11.5–194.3	38.9–175.0
Residual tumor volume on MRI_2			
Median (cc)	18.0	10.3	30.0
Range (cc)	0–110.7	0–61.0	5–110.7
Median (% of initial)	21.4%	17.3%	58.3%
Range (% of initial)	0–74.9%	0–73.1%	11.9–74.9%
Complete radiographic response	4	4	0
Regression velocity			
Median (cc/day)	1.1	1.3	0.99
Range (cc/day)	0.2–4.0	0.5–4.0	0.3–2.1
Median (%/day)	1.6%	2.3%	1.2%
Range (%/day)	0.5–4.0%	0.7–4.0%	0.5–2.2%

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma; cc, cubic centimeters.

patients has been of particular interest in the last two decades given the propensity for adenocarcinoma in particular to fail distantly, though initial results from the OUTBACK trial did not show a survival benefit with adjuvant carboplatin and paclitaxel, and ongoing trials incorporating immunotherapy have yet to be published [**?**].

To date, all of the published reports linking radiographic post-external beam residual tumor to oncologic outcomes have focused either solely on SCC of the cervix, or did not report or analyze by specific histology. The histology warrants consideration, since the two cell types can behave differently. Cervical adenocarcinomas or adenosquamous carcinomas originate from endocervical cells within the canal, and tend to create more expansile barrel-shaped tumors, resulting in large tumors without definitive parametrial invasion. Indeed in our patient cohort, AC patients were more likely to be grade IB despite having larger median pretreatment tumor volume. Cervical AC are also more likely to be human papillomavirus-negative/independent, which has been correlated with increased occult nodal involvement in early stage patients, higher rates of distant metastases, and worse overall survival compared to human papillomavirus-positive disease [**? ?**]. A review of 1671 patients treated on the Gynecologic Oncology Group (GOG) trials demonstrated that the patients with cervical AC treated with radiation alone had statistically worse survival than SCC, however the survival detriment was erased with the addition of concurrent chemotherapy [**?**]. This suggests both that patients with cervical AC may benefit more from dose-escalation, and that distant disease control during primary treatment is a concern in AC. Other comparisons of outcomes between AC and SCC were more definitive, with multiple reports demonstrating worse overall survival and disease-free survival in stage IB-IVA AC patients, even with the addition of concurrent chemoradiation [**? ?**].

The differences between the AC and SCC patients in our cohort was stark, on multiple levels. While the treatment that each patient received was largely identical with exception to the number of brachytherapy treatments, AC patients were much more likely to be stage I (30% versus 5%), less likely to have parametrial involvement (20% versus 50%), and yet had significantly worse outcomes. While AC and SCC had equivalent/equal rates of local progression cervical (10% for both histologies), AC had a much higher propensity for distant failure (60%) compared to SCC (10%).Similarly, cervical AC had very high rates of death, with an actuarial rate of 70% compared to 14% for SCC, despite the relatively short median follow-up time of 2.9 years.

While both SCC and AC demonstrated consistent regression during external beam radiation, SCC had predictably more regression, with a per day volume regression velocity nearly double that of AC, likely owing to SCC being more radiation sensitive than AC, consistent with similar comparisons in other disease sites like lung or esophagus [**? ? ?**]. Prior studies have reported tumor regression velocities measured clinically or radiographically between 1–2.5%/day; in our cohort, median regression for AC sat on the low end of that range while SCC was toward the higher end [**? ? ? ?**]. While AC tumors were larger pre-treatment, with a median tumor volume roughly 20% larger than SCC, they notably had a 300% larger median residual tumor volume than SCC after external beam. Knowing that larger initial tumor volume and extent of residual tumor are both poor prognostic factors, it can be hard to separate whether the differences in clinical outcomes are due to AC tumor volume or inherent differences in disease behavior. The AC patients had a median residual volume of 30 cc, which is the cutoff identified in EMBRACE I where it became more common to have HR-CTV EQD2 coverage of <85 Gy, and was associated with worse outcomes; EMBRACE II is encouraging the increased utilization of interstitial brachytherapy where appropriate to

increase HR-CTV coverage above 90 Gy, effectively dose escalating large tumors [**?** **?**]. Our median EQD2 for AC patients was <85 Gy likely due to dose limitations to meet organ at risk constraints, and could have contributed to worse overall outcomes, as seen on EMBRACE I. Needless to say, further evaluation of adenocarcinoma-specific residual tumor thresholds is warranted to better characterize which patients would benefit from dose-escalation in the IGABT era, as they may deviate from those identified in cervical SCC patients.

There was marked reduction in tumor size by CBCTs as measured weekly; however there was no correlation between two-dimensional tumor measurements with risk of progression or risk of death. Although daily radiation guidance imaging to monitor the primary tumor during treatment was available, the spatial resolution and likelihood of significant artifact in CBCT imaging compared to diagnostic fan-beam CT resulted in 3D tumor volumes that we felt were unreliable and non-generalizable, particularly owing to the difficulty visualizing the superior-inferior extent of tumors on sagittal reconstructions. To compensate for this, the products of largest orthogonal two-dimensional measurements in axial plane were utilized, which may not have been a reliable estimator of true tumor extent with such ill-defined and irregular tumors, even if the signal over time appeared consistent with expectation. However, the lack of correlation of CBCT data with outcomes could suggest that intratreatment CT monitoring of cervical tumors may not be a reliable representation of intratreatment tumor response, or that intratreatment MRI guidance may be a more accurate and reliable tool in adaptive treatment and dose-escalation studies in the future.

It is worth noting that, even with low patient numbers which limited statistical power, longer total length of treatment time was correlated with increased risk of progression and increased risk of death. Prior reports have demonstrated that every day past 8 weeks is associated with a 1% increased risk of local failure, and while all patients in our cohort completed treatment within 8 weeks, treatment completion requiring longer than 7 weeks was associated with both risk of progression and death [**?**]. Treatment acceleration is a matter ongoing study, with trials like EMBRACE II including schedules for treatment completion within 6 weeks [**?**]. Although not the focus of this study, this continues to be an important metric even in the concurrent chemoradiotherapy era.

A key strength to this study is the differentiation between cervical SCC and AC, as most historical studies either exclude AC or analyze all histologies together. Current treatment guidelines do not distinguish between the two in management recommendations, and current ongoing prospective dose-escalation and de-escalation trials do not stratify by histology. This study adds further evidence to add to the growing body of literature suggesting that there may be benefit to considering histology when evaluating a patient's response to external beam radiotherapy and individualizing a patient's post-external beam treatments. The primary limitation of this study is limited number of patients, which limited the scope of the statistical analysis, particularly in analyzing SCC and AC patients independently. Additionally, the retrospective nature of the patient selection and analysis can introduce selection bias that could be limited in a randomized, prospective analysis. More prospective analysis, particularly in cervical adenocarcinoma and adenosquamous carcinoma, is warranted.

5. Conclusions

This study demonstrates that both squamous cell and adenocarcinoma demonstrate good volumetric response to external beam radiotherapy, with slower, less complete response in adenocarcinoma. While larger patient cohorts would be required to establish meaningful thresholds for adenocarcinoma alone, the differences in kinetics suggest that the residual tumor threshold for adenocarcinoma that correlates with worse outcomes is likely different than squamous cell carcinoma. Further investigation is warranted to inform future dose-escalation studies that may benefit from stratifying by squamous cell carcinoma versus adenocarcinoma.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

CRW, YJH, KG and DKG—designed the research study. CRW, FH, KG and DKG—performed the research and data collection. YJH and ZH—provided help in imaging processing and analysis. CRW, RDK and FH—analyzed the data. CRW, RDK and FH—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Study review was performed by the Huntsman Cancer Institute Project Review & Monitoring Committee, who approved ethics review (approval number: 00144216) and granted waiver of consent.

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CONFLICT OF INTEREST

DKG is the co-chair of the Gynecologic committee of NRG Oncology, PI of the NCI-LAPS grant to the Huntsman Cancer Institute, the PI of an Elekta-funded brachytherapy trial, and the chair of the Data and Safety Monitoring Committee for a phase III industry-funded cervical cancer trial. GS is on the board of the Radiation Oncology Institute.

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