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Evaluating the Impact of Dose Escalation and Chemosensitizers in Intensity-Modulated Chemoradiation for Squamous Cell Carcinoma of the Anus: A Single-Institution Study

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ABSTRACT

Intensity-modulated radiation therapy (IMRT) is widely accepted as the preferred approach for managing anal squamous cell carcinoma (SCCA), yet comprehensive data from large cohorts on treatment results and side effects are scarce. This single-institution review retrospectively examines clinical results and adverse events following IMRT combined with chemotherapy for SCCA, assesses whether increasing the radiation dose beyond 54 Gy provides benefits, and contrasts the use of fluoropyrimidine-based regimens paired with either mitomycin or cisplatin as sensitizing agents. The analysis encompassed individuals who underwent IMRT combined with chemotherapy at The University of Texas MD Anderson Cancer Center from 2003 through 2018. Estimates of time to local-regional relapse, need for permanent colostomy, and overall survival were derived via Kaplan-Meier analysis. Four hundred twenty-eight cases were reviewed, with an average follow-up period of 4.4 years. Most patients (334, or 78%) received cisplatin plus a fluoropyrimidine concurrently, while 160 (about 37%) were given radiation doses higher than 54 Gy. At two years and five years post-treatment, rates of freedom from local-regional recurrence stood at 86.5% and 81.2%; avoidance of colostomy at 90.0% and 88.3%; and overall survival at 93.6% and 85.8%. Higher radiation doses or mitomycin-containing chemotherapy did not yield superior tumor control or survival. However, mitomycin regimens correlated with roughly 2.5-fold higher rates of severe (grade 3+) short-term side effects, and doses exceeding 54 Gy linked to approximately 2.6-fold greater long-term severe toxicities. Findings indicate that combining IMRT with cisplatin and a fluoropyrimidine offers an effective and tolerable strategy for SCCA, likely with reduced short-term adverse effects compared to mitomycin alternatives. Benefits from escalating radiation doses remain unproven and warrant additional prospective evaluation.

Keywords: Oxicity, Colostomy, Intensity-modulated radiation therapy, Radiation dose, Cisplatin, Anal squamous cell carcinoma

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Introduction

Though uncommon, the occurrence of anal squamous cell carcinoma (SCCA) has been steadily climbing over the past two decades [1, 2]. Organ-preserving chemoradiotherapy remains the cornerstone of management, backed by strong cure probabilities shown in two key randomized studies: RTOG 9811 and UK ACT II [3, 4]. Cure probabilities were generally strong, yet those with tumors exceeding 5 cm or with involved lymph nodes faced greater chances of locoregional relapse (LRF) [5]. The ACT II study found no meaningful survival distinctions in advanced cases when contrasting cisplatin plus 5-fluorouracil (5FU) against mitomycin C plus 5FU as agents to enhance radiation sensitivity.

Both landmark trials employed 2D or 3D conformal radiotherapy methods, which exposed nearby healthy structures to high radiation levels and led to notable side effects [6, 7]. Adoption of intensity-modulated radiotherapy (IMRT) as the method of choice followed the RTOG 0529 findings, which highlighted fewer short-term toxicities and reduced treatment pauses relative to the older conformal approaches used in RTOG 9811. The

original RTOG 0529 report did not include tumor control data [8], but a smaller retrospective review of 43 cases applying a similar IMRT protocol noted 95% local control at two years, 92% freedom from distant spread, 90% avoidance of colostomy, and 94% overall survival at two years [9].

Reports on IMRT combined with chemotherapy for SCCA tend to involve modest patient cohorts and/or shorter observation periods [10-14]. Typically, these feature radiation doses around 50-54 Gy together with mitomycin-C (MMC) and 5FU concurrently. This work seeks to (1) present figures for locoregional failure (LRF), colostomy needs (CF), overall survival, and side effects among patients managed with IMRT-based chemoradiotherapy at our facility, (2) explore whether raising doses above 54 Gy influences results, and (3) contrast MMC-containing versus cisplatin-containing concurrent chemotherapy approaches in terms of effectiveness and tolerability.

Materials and Methods

This study received institutional review board approval along with a waiver of informed consent. We included all sequential patients managed at our center between January 1, 2003, and December 31, 2018, who underwent definitive chemoradiotherapy (CRT) delivered via intensity-modulated radiation therapy (IMRT) for non-metastatic squamous cell carcinoma of the anus (SCCA).

Treatment details

Every patient was treated with definitive CRT employing an IMRT approach previously detailed in the literature [13]. Radiation dose and fractionation were tailored according to primary tumor size: T1 lesions received 50 Gy in 25 fractions, T2 lesions 54 Gy in 27 fractions, and T3/T4 lesions 58 Gy in 29 fractions. Most patients were given concurrent weekly cisplatin (20 mg/m² intravenously each week) combined with continuous-infusion 5-fluorouracil (5-FU; 300 mg/m²/day on radiation treatment days), as described earlier [15]. A smaller proportion received mitomycin-C (MMC; 10 mg/m² on days 1 and 29). In some cases, oral capecitabine (825 mg/m² twice daily on radiation days) was substituted for infusional 5-FU. Although our multidisciplinary team favored cisplatin plus 5-FU as the standard concurrent regimen, MMC was frequently selected for individuals with preexisting renal impairment, notable neuropathy, or hearing deficits. Furthermore, patients treated at certain regional network sites—where care was shared between our institution's radiation oncologists and external medical oncologists—were more likely to receive MMC-based chemotherapy.

Patients were evaluated weekly during therapy for adverse effects, with routine laboratory studies including complete blood counts with differential. Acute side effects were graded each week by the treating physician using Common Terminology Criteria for Adverse Events version 4 (CTCAEv4) and documented in the electronic health record. Follow-up visits occurred every 3–6 months for the first 5 years after therapy. Adverse events occurring within 6 weeks of completing CRT were classified as acute, while those arising later were categorized as chronic or late.

Statistical analysis

Key oncologic outcomes were calculated as follows: time to locoregional failure (LRF), measured from the start of radiation to either disease recurrence in the anal canal or pelvic nodes following a complete clinical response, or to biopsy-confirmed residual disease ≥6 months after finishing CRT; time to colostomy, measured from the start of radiation to colostomy placement for progression or treatment-related complications; and overall survival (OS), measured from the start of radiation to death from any cause. Patients without events or lost to follow-up were censored. Kaplan–Meier estimates were used to calculate median time-to-event outcomes. Univariate comparisons employed log-rank tests and Cox proportional hazards models. Multivariate Cox regression, with stepwise variable selection guided by the Bayesian Information Criterion, was performed to identify factors independently associated with oncologic endpoints. Toxicity outcomes were analyzed using multivariate logistic regression with similar variable selection. Radiation doses ≤54 Gy were categorized as standard, whereas >54 Gy were considered escalated. Statistical significance was set at $P < .05$. Analyses were conducted using R software version 4.0.5.

Results and Discussion

Patient demographics

The cohort comprised 428 patients. Median follow-up [interquartile range (IQR)] from the initiation of CRT was 4.4 [2.73–7.09] years. Baseline patient characteristics stratified by T-stage are summarized in **Table 1.**

Table 1. Tumor, patient, and treatment characteristics by T-stage.

Characteristic	T1 N = 80 (18.7%)	T2 N = 192 (44.9%)	T3 N = 105 (24.5%)	T4 N = 51 (11.9%)	Total N = 428 (%)	P value *a*
Sex						
Female	66 (82.5%)	146 (76.0%)	72 (68.6%)	34 (66.7%)	318 (74.3%)	.090
Male	14 (17.5%)	46 (24.0%)	33 (31.4%)	17 (33.3%)	110 (25.7%)	
Age						
Median [IQR]	60 years [53–67]	61 years [52–67]	59 years [52–68]	59 years [52–66]	60 years [52–67]	
≤65 years	58 (72.5%)	135 (70.3%)	74 (70.5%)	38 (74.5%)	305 (71.3%)	.932
>65 years	22 (27.5%)	57 (29.7%)	31 (29.5%)	13 (25.5%)	123 (28.7%)	
Smoking history						
Never	48 (60.0%)	103 (53.6%)	47 (44.8%)	16 (31.4%)	213 (49.8%)	<.001
Former	26 (32.5%)	68 (35.4%)	31 (29.5%)	23 (45.1%)	148 (34.6%)	
Current	6 (7.5%)	21 (10.9%)	27 (25.7%)	12 (23.5%)	66 (15.4%)	
HIV status *b*						
Positive	2 (2.5%)	10 (5.2%)	6 (5.7%)	2 (3.9%)	20 (4.7%)	
Negative	78 (97.5%)	182 (94.8%)	99 (94.3%)	49 (96.1%)	408 (95.3%)	.731
N-stage						
N0	60 (75.0%)	107 (55.7%)	32 (30.5%)	11 (21.6%)	210 (49.1%)	<.001
N1	20 (25.0%)	85 (44.3%)	73 (69.5%)	40 (78.4%)	218 (50.9%)	
Excisional biopsy before RT						
Yes	44 (55.0%)	50 (26.0%)	14 (13.3%)	2 (3.9%)	110 (25.7%)	
No	36 (45.0%)	142 (74.0%)	91 (86.7%)	49 (96.1%)	318 (74.3%)	<.001
Radiation dose						
Median [IQR]	50 Gy [50–50]	54 Gy [54–54]	58 Gy [58–58]	58 Gy [58–58]	54 Gy [54–58]	
>54 Gy	1 (1.2%)	17 (8.9%)	95 (90.5%)	47 (92.2%)	160 (37.4%)	
≤54 Gy	79 (98.8%)	175 (91.1%)	10 (9.5%)	4 (7.8%)	268 (62.6%)	<.001
Time from diagnosis to RT						
Median [IQR]	53 days [40–66]	48 days [36–62]	41 days [32–53]	46 days [29–85]	47 days [34–62]	
≤42 days	27 (33.8%)	76 (39.6%)	60 (57.1%)	22 (43.1%)	185 (43.2%)*	.007
>42 days	53 (66.3%)	116 (60.4%)	45 (42.9%)	29 (56.9%)	243 (56.8%)*	
Concurrent chemotherapy						
MMC-based	13 (16.3%)	30 (15.6%)	23 (21.9%)	7 (13.7%)	73 (17.1%)	

Cisplatin-based	63 (78.8%)	152 (79.2%)	78 (74.3%)	41 (80.4%)	334 (78.0%)	.846
Other *c*	4 (5.0%)	10 (5.2%)	4 (3.8%)	3 (5.9%)	21 (4.9%)	
Radiation treatment break						
Yes	7 (8.7%)	25 (13.0%)	12 (11.4%)	5 (9.8%)	49 (11.4%)	
No	73 (91.3%)	167 (87.0%)	93 (88.6%)	46 (90.2%)	379 (88.6%)	.758

Pearson chi-square test.

Only 3 HIV+ patients had a CD4 count <200 at the time of treatment initiation.

Other chemotherapy included capecitabine monotherapy, 5-fluorouracil monotherapy or capecitabine + oxaliplatin.

Abbreviations: Gy, gray; Cis, cisplatin; IQR, interquartile range; HIV, human immunodeficiency virus; RT, radiation therapy; MMC, mitomycin C.

Locoregional recurrence

Among the cohort, 396 individuals (92.5%) attained a complete clinical remission (cCR), with the median interval to achieving this response being 2.8 months (IQR 1.8–4.2). A total of 57 patients (13.3%) developed either residual disease or subsequent locoregional relapse. The projected rates of remaining free from locoregional recurrence at 2 and 5 years were 85.7% (95% CI 82.5%–90.1%) and 79.7% (95% CI 75.7%–83.9%), respectively. Findings from the single-variable analysis are displayed in **Table 2.** In the adjusted multivariable analysis, variables independently linked to elevated risk of locoregional recurrence included HIV positivity (hazard ratio 3.146, 95% CI 1.501–6.595; P = .008), ongoing tobacco use (hazard ratio 2.206, 95% CI 1.272–3.825; P = .02), and administration of radiation doses exceeding 54 Gy (hazard ratio 3.348, 95% CI 2.076–5.399; P < .001).

Table 2. Univariate analysis of factors associated with colostomy failure, locoregional failure, and overall survival.

Characteristic	N (%)	Overall Survival HR (95% CI)	P-value	Colostomy Failure HR (95% CI)	P-value	Locoregional Failure HR (95% CI)	P-value
Sex							
Male	110 (25.7%)	1.707 (1.013–2.878)	0.045	1.068 (0.553–2.062)	0.845	1.248 (0.768–2.029)	0.371
Female	318 (74.3%)	Reference		Reference		Reference	
Age							
>65 years	123 (28.7%)	1.219 (0.715–2.079)	0.467	0.528 (0.246–1.131)	0.101	0.785 (0.469–1.316)	0.358
≤65 years	305 (71.3%)	Reference		Reference		Reference	
Smoking status							
Never smoker	213 (49.8%)	Reference		Reference		Reference	
Former smoker	148 (34.6%)	0.864 (0.473–1.578)	0.634	1.163 (0.598–2.265)	0.656	1.155 (0.676–1.973)	0.599
Current smoker	66 (15.4%)	1.981 (1.072–3.659)	0.029	1.703 (0.792–3.664)	0.173	2.750 (1.600–4.725)	<0.001
HIV status							
Positive*	20 (4.7%)	3.237 (1.471–7.122)	0.004	2.831 (1.118–7.168)	0.028	3.000 (1.443–6.238)	0.003
Negative	408 (95.3%)	Reference		Reference		Reference	
T-stage							
T1	80 (18.7%)	Reference		Reference		Reference	
T2	192 (44.9%)	1.450 (0.588–3.581)	0.420	1.581 (0.525–4.764)	0.416	1.581 (0.688–3.632)	0.280

T3	105 (24.5%)	2.699 (1.089–6.693)	0.032	3.004 (0.997–9.055)	0.051	3.348 (1.466–7.645)	0.004
T4	51 (11.9%)	3.305 (1.248–8.755)	0.016	5.384 (1.736–16.702)	0.004	4.055 (1.668–9.862)	0.002
Prior excision before radiotherapy							
Yes	110 (25.7%)	0.312 (0.134–0.726)	0.007	0.503 (0.225–1.126)	0.095	0.362 (0.181–0.726)	0.004
No	318 (74.3%)	Reference		Reference		Reference	
Radiotherapy dose							
>54 Gy	160 (37.4%)	2.780 (1.664–4.695)	<0.001	3.082 (1.693–5.610)	<0.001	3.578 (2.247–5.698)	<0.001
≤54 Gy	268 (62.6%)	Reference		Reference		Reference	
N-stage							
N0	210 (49.1%)	Reference		Reference		Reference	
N1	218 (50.9%)	1.573 (0.941–2.630)	0.084	1.972 (1.045–3.517)	0.036	1.940 (1.223–3.076)	0.005
Time from diagnosis to radiotherapy							
Median [IQR]	47 days [34–62]						
>42 days	160 (42.0%)	2.795 (1.664–4.695)	<0.001	3.082 (1.693–5.610)	<0.001	3.579 (2.247–5.698)	<0.001
≤42 days	268 (58.0%)	Reference		Reference		Reference	
Concurrent chemotherapy							
Mitomycin-C (MMC)	73 (17.1%)	1.641 (0.894–3.011)	0.110	0.621 (0.244–1.578)	0.317	0.945 (0.508–1.756)	0.858
Cisplatin	334 (78.0%)	Reference		Reference		Reference	
Other**	21 (4.9%)	1.944 (0.821–4.603)	0.131	1.330 (0.410–4.318)	0.635	1.889 (0.862–4.140)	0.112
Radiotherapy interruption							
Yes	49 (11.4%)	2.451 (1.340–4.464)	0.004	1.344 (0.570–3.175)	0.499	1.337 (0.688–2.597)	0.392
No	379 (88.6%)	Reference		Reference		Reference	

Among the HIV-positive patients, only three individuals had a CD4 count below 200 cells/μL at the start of treatment.

The "other" concurrent chemotherapy regimens consisted of single-agent 5-fluorouracil, single-agent capecitabine, or the combination of capecitabine and oxaliplatin.

Abbreviations: Cis, cisplatin; CI, confidence interval; HIV, human immunodeficiency virus; Gy, gray; IQR, interquartile range; HR, hazard ratio; Ref, reference; MMC, mitomycin C; RT, radiation therapy.

Colostomy failure

Prior to beginning therapy, seven patients needed a diverting colostomy because of complications such as fistula, bowel obstruction, or intractable pain. By the time of last follow-up, a total of 47 patients (11.0%) had received a colostomy—39 cases due to persistent or relapsed cancer and 8 cases to address late toxicity from radiotherapy. The estimated rates of remaining colostomy-free at 2 and 5 years were 90.0% and 88.3%, respectively. Results from the univariate analysis appear in **Table 2**. On multivariable analysis, the sole independent predictor of higher

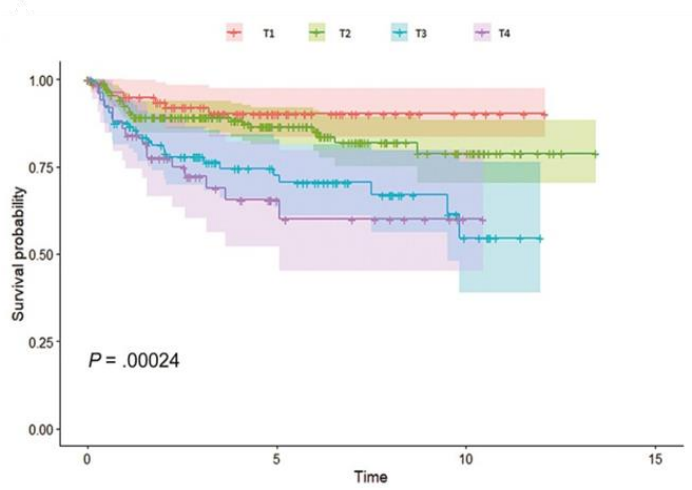
colostomy failure risk was delivery of a radiotherapy dose exceeding 54 Gy (HR 3.082, 95% CI 1.693–5.610; P < .001).

Overall survival

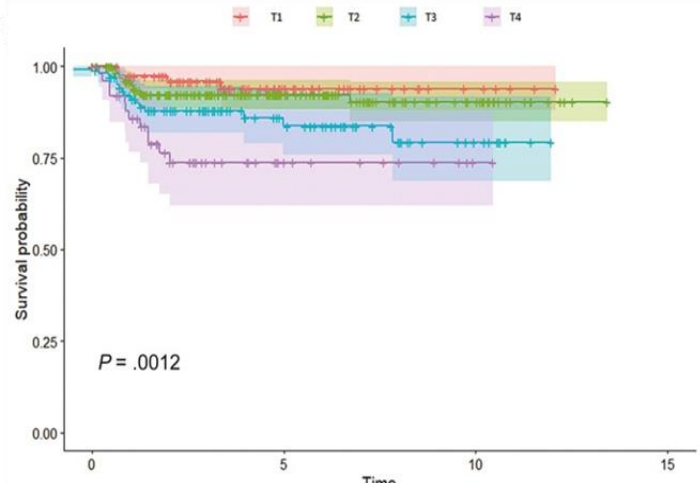
At last follow-up, 364 patients (85.0%) remained alive. The projected overall survival rates at 2 and 5 years were 93.6% and 85.8%, respectively. Univariate findings are detailed in **Table 2.** Multivariable analysis identified several independent predictors of reduced survival: HIV-positive status (HR 2.884, 95% CI 1.295–6.419; P = .022), radiotherapy dose >54 Gy (HR 2.411, 95% CI 1.474–4.978; P < .001), and unplanned interruptions during treatment (HR 2.709, 95% CI 1.474–4.978; P = .003). Conversely, patients who underwent local tumor excision before chemoradiotherapy demonstrated significantly better survival (HR 0.358, 95% CI 0.149–0.859; P = .010).

Influence of tumor stage on treatment outcomes

In a separate multivariable model that excluded radiation dose as a variable, advancing T-stage (treated as a continuous ordinal variable) emerged as a strong independent predictor of poorer outcomes: increased locoregional recurrence risk per stage increment (HR 1.698, 95% CI 1.361–2.120; P < .001), greater likelihood of colostomy failure per stage (HR 1.668, 95% CI 1.248–2.231; P < .001), and diminished overall survival per stage (HR 1.567, 95% CI 1.204–2.040; P < .001). Survival curves illustrating locoregional control, colostomy-free survival, and overall survival according to T1–T4 categories are shown in **Figures 1a-1c**, respectively.



a)



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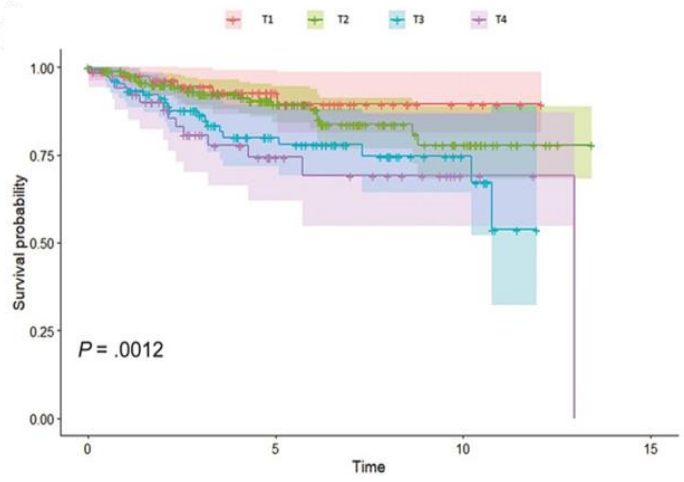

c)

Figure 1. Kaplan-Meier curves depicting freedom from locoregional recurrence (Panel a), colostomy-free survival (Panel b), and overall survival (Panel c) in patients with anal squamous cell carcinoma treated with intensity-modulated radiotherapy (IMRT)-based chemoradiotherapy, stratified according to T-stage.

Treatment-related toxicity

Unplanned interruptions in radiotherapy lasting at least one day occurred in 49 patients (11.4%), with a median break duration of 3 days (interquartile range 2–7 days). Additionally, 63 patients (14.7%) required hospitalization during the course of treatment.

Acute grade 3 or higher (G3+) toxicity involving gastrointestinal, genitourinary, or dermatologic systems was observed in 139 patients (32.5%), comprising 56 gastrointestinal, 11 genitourinary, and 90 dermatologic events. Six patients experienced grade 4 acute toxicity, and one patient suffered fatal (grade 5) acute gastrointestinal toxicity.

On multivariable analysis, the use of concurrent mitomycin-C (MMC) was independently associated with a higher risk of acute G3+ gastrointestinal, genitourinary, or dermatologic toxicity (odds ratio 2.484, 95% CI 1.480–4.175; P < .001); **(Table 3).** Patients treated with MMC-based chemotherapy also had a significantly higher rate of grade 3+ neutropenia compared with those receiving other regimens (30.9% versus 3.5%; P < .001); **(Table 4).**

Chronic grade 3 or higher toxicity affecting at least one organ system developed in 39 patients (9.1%), including 32 gastrointestinal, 39 genitourinary, and 1 dermatologic event. The majority were grade 3, although nine patients experienced grade 4 late gastrointestinal toxicity and two patients had grade 4 late genitourinary toxicity.

In multivariable analysis, administration of a radiation dose exceeding 54 Gy was the only factor independently linked to an elevated risk of late severe toxicity (odds ratio 2.644, 95% CI 1.361–5.257; P = .005); **(Table 3).**

Table 3. presents the univariate analysis of clinical and treatment-related factors associated with the development of acute and late grade 3 or higher toxicities involving the gastrointestinal, genitourinary, and dermatologic systems.

Factor	Category	Total (N)	Late Toxicity (N=39)	OR (95% CI)	P-value	Acute Toxicity (N=139)	OR (95% CI)	P-value
Sex	Female	318 (74.3%)	25 (7.9%)	Reference	–	98 (30.8%)	Reference	–
	Male	110 (25.7%)	14 (12.7%)	1.707 (0.787–3.574)	.129	41 (37.3%)	1.333 (0.822–2.147)	.238
Age	≤65 years	305 (71.3%)	26 (8.5%)	Reference	–	92 (30.2%)	Reference	–
	>65 years	123 (28.7%)	13 (10.6%)	1.267 (0.576–2.667)	.101	77 (62.6%)	1.431 (0.899–2.267)	.118

Smoking	Never	213 (49.8%)	15 (7.0%)	Reference	–	59 (27.7%)	Reference	–
	Former	148 (34.6%)	16 (10.8%)	1.598 (0.713–3.601)	.252	56 (37.8%)	1.587 (0.990–2.547)	.051
	Current	66 (15.4%)	7 (10.6%)	1.563 (0.514–4.310)	.432	24 (36.4%)	1.489 (0.790–2.771)	.217
HIV Status	Negative	408 (95.3%)	37 (9.1%)	Reference	–	134 (32.8%)	Reference	–
	Positive[a]	20 (4.7%)	2 (10.0%)	2.831 (1.118–7.168)	**.028**	5 (25.0%)	0.682 (0.190–2.028)	.626
T-stage	T1	80 (18.7%)	6 (7.5%)	Reference	–	19 (23.8%)	Reference	–
	T2	192 (44.9%)	10 (5.5%)	0.679 (0.214–2.358)	.572	60 (31.3%)	1.457 (0.777–2.819)	.243
	T3	105 (24.5%)	11 (10.5%)	1.440 (0.463–4.975)	.610	39 (37.1%)	1.891 (0.949–3.861)	.057
	T4	51 (11.9%)	12 (23.5%)	3.754 (1.194–13.18)	**.017**	21 (41.2%)	2.233 (0.980–5.144)	.051
Excision Before RT	No	318 (74.3%)	31 (9.7%)	Reference	–	113 (35.5%)	Reference	–
	Yes	110 (25.7%)	8 (7.3%)	0.727 (0.279–1.684)	.565	26 (23.6%)	0.562 (0.328–0.942)	**.025**
RT Dose	≤54 Gy	268 (62.6%)	16 (6.0%)	Reference	–	78 (29.1%)	Reference	–
	>54 Gy	160 (37.4%)	23 (14.4%)	2.638 (1.285–5.537)	**.005**	61 (38.1%)	1.499 (0.970–2.316)	.056
N-stage	N0	210 (49.1%)	20 (9.5%)	Reference	–	67 (31.9%)	Reference	–
	N1	218 (50.9%)	19 (8.7%)	0.907 (0.443–1.853)	.867	72 (33.0%)	1.052 (0.688–1.611)	.837
Time to RT	≤42 days	268 (58.0%)	21 (7.8%)	Reference	–	57 (21.3%)	Reference	–
	>42 days	160 (42.0%)	18 (11.3%)	0.626 (0.304–1.277)	.177	82 (51.3%)	3.579 (2.247–5.698)	**<.001**

Only three HIV-positive patients had CD4 counts below 200 when they began treatment.
Additional chemotherapy regimens included 5-fluorouracil alone, capecitabine alone, or a combination of capecitabine and oxaliplatin.
Abbreviations: Cis, cisplatin; CI, confidence interval; HIV, human immunodeficiency virus; Gy, gray; IQR, interquartile range; RT, radiation therapy; HR, hazard ratio; Ref, reference; MMC, mitomycin C.

Table 4. Treatment-related toxicity per concurrent chemotherapy regimen and radiation dose.

Toxicity (N, %)	**Total (N=428)**	**Radiation Dose**		**P-value**	**Concurrent Chemotherapy Regimen**			**P-value**
		≤54 Gy (N=268)	>54 Gy (N=160)		Cisplatin-based (N=334)	MMC-based (N=73)	Othera (N=21)	

Acute Grade ≥3 Gastrointestinal (GI), Genitourinary (GU), or Skin Toxicity								
Yes	139 (32.5%)	83 (31.0%)	56 (35.0%)		94 (28.1%)	36 (49.3%)	9 (42.9%)	
No	289 (67.5%)	185 (69.0%)	104 (65.0%)	0.389	240 (71.9%)	37 (50.7%)	12 (57.1%)	0.001
Acute Grade ≥3 Neutropeniac								
Yes	28 (7.0%)	13 (5.2%)	15 (10.0%)		11 (3.5%)	17 (30.9%)	0 (0%)	
No	373 (93.0%)	238 (94.8%)	135 (90.0%)	0.067	317 (96.5%)	38 (69.1%)	18 (100%)	<0.001
Hospitalization During Treatment								
Yes	63 (14.7%)	40 (15.0%)	23 (14.4%)		39 (11.7%)	21 (29.2%)	3 (14.3%)	
No	364 (85.3%)	227 (85.0%)	137 (85.6%)	0.864	295 (88.3%)	51 (70.8%)	18 (85.7%)	<0.001
Unplanned Radiation Therapy Interruption								
Yes	49 (11.4%)	25 (9.3%)	24 (15.0%)		30 (9.0%)	15 (20.6%)	4 (19.1%)	0.010
No	379 (88.6%)	243 (90.7%)	136 (85.0%)	0.075	304 (91.0%)	58 (79.5%)	17 (80.9%)	
Late Grade ≥3 GI, GU, or Skin Toxicity								
Yes	39 (9.1%)	26 (9.7%)	13 (8.1%)		31 (9.3%)	6 (8.2%)	2 (9.5%)	
No	389 (90.9%)	242 (90.3%)	147 (91.9%)	0.584	303 (90.7%)	67 (91.8%)	19 (90.5%)	0.958

Additional chemotherapy regimens consisted of 5-fluorouracil alone, capecitabine alone, or a combination of capecitabine and oxaliplatin. Analyses were performed using the Pearson chi-square test.
Laboratory data were available for 401 patients.
Abbreviations: GU, genitourinary; GI, gastrointestinal; MMC, mitomycin C; Gy, gray.

In this retrospective review of 428 consecutive patients with SCCA who received IMRT-based chemoradiation (CRT), more than 90% achieved a complete clinical response (cCR) following CRT. At 5 years, the rates of freedom from local-regional failure (LRF), freedom from colostomy, and overall survival (OS) were 80%, 88%, and 86%, respectively. These outcomes compare favorably with cooperative group studies from the 3D radiation era. For instance, in RTOG 9811, the 5-year disease-free survival (DFS) was 68% in the MMC/5FU arm versus 58% in the cisplatin/5FU arm, with 5-year OS of 78% and 71%, respectively [4]. Similarly, in the UK ACT II trial, approximately 90% of patients achieved cCR at 26 weeks, and the 3-year progression-free survival (PFS) was around 74% [3]. Although MMC/5FU remains the established standard of care [16], our institution primarily employs weekly low-dose cisplatin with daily 5FU during radiation [15]. While retrospective data cannot substitute for randomized trial evidence, our favorable results align with several smaller IMRT-based studies [10–14].

T stage is a well-recognized prognostic factor for LRF and DFS [5, 6, 17]. Interestingly, in our analysis, radiation doses exceeding 54 Gy were even more strongly associated with worse LRF, colostomy-free survival (CF), and OS than T stage. In this cohort, radiation dose correlated with T stage because our institutional protocol prescribes 50 Gy for T1, 54 Gy for T2, and 58 Gy for T3–T4 tumors. When radiation dose was excluded from the multivariate model, T stage became significantly predictive of poorer outcomes. The stronger correlation of higher dose with adverse outcomes likely reflects residual confounding, as dose selection varied by individual patient factors. For instance, larger T2 lesions with adverse features could receive >54 Gy, whereas small, favorable T3/T4 tumors might be treated with ≤54 Gy. Additionally, patients who underwent partial excision may have received doses based on initial T stage rather than post-excision assessment.

Although higher radiation doses (>54 Gy) were not directly linked to worse outcomes, our findings suggest no improvement in LRF, CF, or OS with dose escalation. This aligns with prior studies showing no clear benefit of higher doses in advanced disease [11, 18]. Our data therefore cannot define an advantage of dose escalation, and further evidence from prospective trials—such as PLATO ACT5, which is comparing escalated doses (61.6 or 58.5 Gy) versus 53.2 Gy in advanced cases [19]—is awaited. Similarly, the ECOG EA2165 trial is exploring adjuvant nivolumab following CRT as a therapeutic intensification strategy in advanced disease [20].

We observed that current smoking, HIV positivity, and unplanned CRT interruptions were associated with inferior oncologic outcomes. Previous studies have also linked smoking to poorer LRF and OS [21]. Although earlier pre-antiretroviral-era studies reported worse outcomes in patients living with HIV [22], more recent evidence shows comparable survival between HIV-positive and HIV-negative groups [23]. The proportion of HIV-positive patients in our cohort was small (<5%), which may limit these findings. Existing database analyses also indicate that prolonged CRT is associated with reduced survival [24, 25]. The apparent association between pre-CRT excision and improved OS in our study likely reflects underlying early-stage disease rather than the surgical procedure itself, given that over 85% of those who underwent excision had T1–T2 tumors. The controversy regarding the role of local excision in early SCCA management remains acknowledged [26].

The RTOG 0529 trial showed significantly lower rates of grade ≥3 (G3+) acute genitourinary (2%), dermatologic (23%), and gastrointestinal (21%) toxicities in patients treated with IMRT compared with those receiving 3D conformal radiation in RTOG 9811. In our cohort, the rates were similar for GU (2.6%) and dermatologic (21.3%) toxicities, while G3+ gastrointestinal toxicity was lower (13%). MMC-based chemotherapy was linked to higher rates of acute G3+ non-hematologic toxicities, G3+ neutropenia, unplanned treatment interruptions, and hospitalizations. The only significant predictor of increased late G3+ non-hematologic toxicity was receiving a radiation dose above 54 Gy. Nevertheless, prospective collection of patient-reported outcomes will be needed for a more accurate understanding of toxicity. Ongoing cooperative trials are assessing treatment de-escalation via reduced radiation dose or field size to mitigate toxicity [19, 27].

This study's limitations include the retrospective design, lack of prospectively gathered toxicity data, and absence of patient-reported outcomes. Additionally, patient selection bias—common at tertiary care centers—may have contributed to better outcomes. Despite these constraints, this analysis provides valuable evidence as one of the largest modern IMRT-based CRT datasets for definitive treatment of SCCA. Importantly, unlike many earlier studies, the majority of patients in our cohort were treated with cisplatin/5FU without compromising efficacy.

Conclusion

In summary, patients treated with IMRT combined with weekly low-dose cisplatin and daily 5FU experienced comparable disease control to those treated with MMC/5FU but with fewer acute toxicities, hospitalizations, and radiation interruptions. These promising findings warrant prospective validation. Dose escalation beyond 54 Gy did not enhance outcomes and was associated with increased late toxicity. Further research should explore whether selective dose escalation could benefit patients at elevated risk of local recurrence.

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