Journal of Gastrointestinal Surgery (2019) 23:712–719
https://doi.org/10.1007/s11605-018-04068-x

2018 SSAT QUICK SHOT PRESENTATION

The Role of Multiagent Chemoradiation in the Management and Prognosis of Anal Squamous Cell Carcinoma

Paolo Goffredo[1] · Alan F. Utria[1] · Jennifer E. Hrabe[1] · Irena Gribovskaja-Rupp[1] · Muneera R. Kapadia[1] · Imran Hassan[1]

Received: 10 September 2018 / Accepted: 24 November 2018 / Published online: 14 January 2019

Abstract

Introduction The standard treatment for anal squamous cell carcinoma (ASCC) is multiagent chemotherapy with radiation (CRT). This is based on several randomized trials demonstrating lower recurrence and colostomy-free survival rates with multiagent CRT; however, these studies could not confirm an overall survival (OS) benefit. We hypothesized that the lack of improved OS was due to limited sample sizes and follow-up, and that multiagent CRT is associated with higher OS.

Methods The National Cancer Database was queried for patients diagnosed with stages I, II, and II ASCC and received between 45 and 59.4 Gy of radiation between 2004 and 2015. OS of patients receiving multiagent CRT compared to monoagent CRT and radiation alone was analyzed across stages.

Results A total of 10,438 patients received multiagent CRT, 1163 had monoagent CRT and 446 received radiation alone. Compared to the other two groups, patients receiving multiagent CRT were younger, had fewer comorbidities, and more advanced disease (all $p < 0.001$). After adjusting for available confounders, multiagent CRT remained independently associated with higher OS for stages II and III ASCC. A subset analysis of patients ≥ 70 years demonstrated similar survival between monoagent versus multiagent CRT across all stages.

Conclusion Multiagent CRT is associated with an OS benefit compared to monoagent CRT or radiation alone for stages II and III, but not stage I ASCC. Monoagent CRT may represent an adequate treatment for selected patients ≥ 70 years. The benefit of multiagent CRT should be balanced against treatment-related toxicities depending on disease stage and patient physiology.

Keywords Anal squamous cell carcinoma · Chemotherapy · Radiation · Survival

Introduction

Anal squamous cell cancer (ASCC) is a rare type of cancer, with an estimated 8580 new cases and 1160 cancer-related deaths in the USA in 2018.[1] Although ASCC accounts for only 2.7% of all gastrointestinal cancers, its incidence has been steadily increasing over the last four decades in both men and women in the USA.[2]

Abdominoperineal resection (APR) used to be considered the primary treatment modality for ASCC before the development of effective chemoradiation therapy. In the early 1970's, Norman Nigro and colleagues established that ASCC patients treated with low-dose pelvic radiation (30 Gy) plus concurrent 5-flourourcil (5FU) and mitomycin C (MMC) could achieve a complete pathologic response.[3] They subsequently demonstrated that the long-term oncologic outcomes were comparable to those achieved with an APR, but without its adverse consequences.[4] As a result, over the next four decades, several randomized control trials (RCTs) were conducted to determine the optimal radiation dose and strategy as well as chemotherapy regimens that would optimize oncologic outcomes while minimizing short- and long-term treatment-related morbidity. In this context, while multiagent chemoradiation (CRT) was determined to be effective, concerns were raised about the high morbidity due to the synergetic effect of chemotherapy and radiation-related toxicities. Also, several earlier studies evaluating high doses of radiation alone in the treatment of ASCC had shown promising efficacy.[5] Therefore, the question became as to whether chemotherapy was indeed essential in the treatment regimen for ASCC. In order to address this

Presented as a quick shot presentation at the Society for Surgery of the Alimentary Tract, Washington, DC, June 2–5, 2018.

✉ Imran Hassan
ihassan1995@yahoo.com

Paolo Goffredo
paolo-goffredo@uiowa.edu

1 Department of Surgery, University of Iowa Hospitals & Clinics, 200 Hawkins Drive, 1516 JCP, Iowa City, IA 52242, USA

issue, several RCTs investigating the need and type of chemotherapy were designed.[6,7]

The United Kingdom Coordinating Committee on Cancer Research Anal Cancer Trial I (UKCCCR ACT I) and the European Organization for Research and Treatment of Cancer (EORTC) trials confirmed the benefit of multiagent CRT (5FU and MMC) over radiation alone by demonstrating lower local failure rates.[6,7] Although the ACT I and EORTC trials established the benefit of chemotherapy with radiation, they did not determine whether multiagent CRT was necessary as both studies used MMC and 5FU. Hence, the Radiation Therapy Oncology Group (RTOG) 87-04 trial[8] was conducted to compare multiagent versus monoagent CRT regimens and found a higher rate of disease-free (DFS) and colostomy-free (CFS) survival in the multiagent group. While the above three trials demonstrated significantly lower locoregional failure rates and higher DFS in patients who received multiagent CRT, they failed to demonstrate an overall survival (OS) benefit with this regimen. Also, the toxicity rates were significantly higher in the patients receiving MMC across all the trials. Furthermore, the aforementioned trials excluded older patients and those with low performance status and did not include or had a small number of patients with stage I disease, thus limiting their external validity to the general ASCC population.

We hypothesized that the lack of evidence for benefit in OS in the above RCTs was due to limited sample sizes or length of follow-up and that multiagent CRT is in fact associated with a more favorable OS as compared to monoagent CRT or radiation alone. We also hypothesized that stage I disease and older patients may not experience an OS benefit from the addition of a second chemotherapeutic agent to their CRT regimen. The primary aim of the current study was therefore to investigate differences in OS rates among different CRT strategies based on stage and age at presentation. The secondary aim was to identify patient, disease, and treatment factors associated with receiving multiagent CRT.

Patients and Methods

Data Sources and Study Subjects

The National Cancer Database (NCDB) is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society.[9] It is a nationwide oncology outcomes database that collects data for approximately 70% of all newly diagnosed cancers in the USA. Data elements are collected and submitted to the NCDB from CoC-accredited cancer program registries using nationally standardized data item and coding definitions.

The NCDB Participant User File was used to identify all patients diagnosed with ASCC from 2004 to 2015. This database utilizes the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) for histology coding (SCC: code 8070-8078).[10] Patients aged < 18 years were excluded from this study. The analyses were further restricted to those patients who had known data regarding staging and treatment. Standard radiation dose was defined per NCCN guidelines as receiving between 45 and 59.4 Gy.[11]

Demographic variables of interest were patient gender, age at diagnosis, race, insurance status, annual income, education level, institution type, and facility volume (defined as high if > upper quartile = 4 cases/year). Clinical variables included Charlson/Deyo score to evaluate comorbidity, radiation dose, undergoing salvage APR, and type of chemotherapy (multiagent versus monoagent). Radiation dose was binary treated as low (45–54) vs high (54.1–59.4 Gy). Pathologic variables were tumor size, lymph node and metastatic status, and AJCC stage. Tumors > 200 mm were excluded from our size analyses due to the possibility of coding errors.

Statistical Analyses

Demographic, clinical, and pathologic data were analyzed using summary statistics; chi-square and Student's *t* test were used to compare categorical and continuous variables, respectively. A stepwise binary logistic regression was employed to identify factors associated with receiving multiagent chemotherapy.

The Kaplan-Meier method was used to analyze the overall survival, and the log-rank test to calculate statistical significance of comparisons of survival. The Cox proportional hazards regression was employed for the multivariable models; hazard ratios and 95% confidence intervals were calculated for the strength of association between each variable and survival. A subset analysis similar to the one performed on the entire cohort was performed in patients older than 70 years of age.

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 23.0; SPSS Inc., Chicago, IL); all tests were two-sided, and a p value of < 0.05 was set for statistical significance. The NCDB database is publicly available, and all patient information is de-identified; hence, this study was deemed exempt from our institutional review board approval.

Results

Patient Characteristics

A total of 12,047 patients were identified: 86.6% underwent treatment with multiagent CRT, 9.7% had monoagent CRT, and 3.7% received radiation only (Table 1). Patient who received multiagent chemotherapy were younger, healthier, and

Table 1 Demographic, clinical, and pathologic characteristics of patients with ASCC who received multiagent CRT, monoagent CRT, and radiation alone, NCDB 2004–2015 (All patients received radiation dose between 45 and 59.4 Gy)

	Patient characteristics	ASCC			*p* value
		Multiagent *n* = 10,438, %	Monoagent *n* = 1163, %	No chemo *n* = 446, %	
Demographic	Gender				0.077
	Female	68.1	66.2	63.7	
	Age at diagnosis, years (mean ± SD)	58.8 ± 11.1	62.4 ± 14.2	63.2 ± 15.0	< 0.001
	Race	*n* = 10,378	*n* = 1154	*n* = 439	0.351
	White	88.2	87.6	86.3	
	Black	10.0	10.3	12.5	
	Others	1.8	2.1	1.1	
	Primary payer	*n* = 10,312	*n* = 1151	*n* = 440	< 0.001
	Not insured	5.6	4.4	5.9	
	Private	48.8	39.8	36.6	
	Government	45.5	55.8	57.5	
	Income	*n* = 10,116	*n* = 1122	*n* = 423	0.352
	Low	32.8	34.0	35.7	
	Education level	*n* = 10,116	n = 1122	n = 423	0.133
	Low	36.5	33.9	33.8	
	Institution	*n* = 10,086	*n* = 1119	*n* = 433	0.803
	Academic	34.7	36.0	34.9	
	Comprehensive	55.5	53.9	54.3	
	Community	9.8	10.1	10.9	
	Facility Volume	*n* = 10,093	*n* = 1114	*n* = 437	0.924
	High	25.6	25.5	24.7	
Clinical	Salvage APR				0.177
	Yes	1.8	1.5	*	
	Radiation dose, Gy				0.231
	High (54–59.4)	11.4	10.0	12.6	
	Median	50.4	50.4	50.0	
	Charlson/Deyo score				0.010
	0	81.2	79.2	77.6	
	1	12.1	11.8	13.0	
	≥ 2	6.7	9.0	9.4	
Pathologic	AJCC T stage	*n* = 9878	*n* = 1073	*n* = 376	< 0.001
	T1, ≤ 20	17.9	20.8	29.8	
	T2, 21–50	53.8	50.7	44.9	
	T3, > 50(− 200)	21.6	20.9	19.1	
	T4, spread to nearby organs	6.8	7.6	6.1	
	Lymph node involvement	*n* = 9973	*n* = 1084	*n* = 390	< 0.001
	N+	36.9	33.8	21.0	
	Metastases	*n* = 10,120	*n* = 1114	*n* = 439	0.039
	M+	3.3	4.5	*	
	AJCC stage (A-SCC)				< 0.001
	I	33.6	17.9	16.3	
	II	41.9	44.0	42.8	
	III	36.7	31.6	21.5	
	IV	4.0	4.8	*	

Percentages have been rounded and may not add up to 100%

APR, abdominoperineal resection; *CRT*, chemoradiation

*Per NCDB policy, the exact number of cells < 10 cannot be reported

had a higher stage at presentation. No significant difference was observed in race and socioeconomic distributions.

After adjustment for available confounders, factors associated with receiving multiagent chemotherapy were female gender, younger age, Charlson/Deyo score < 2, and advanced disease at presentation (Table 2). Race, social-economic status, and being uninsured and treated at a community-based hospital were not associated with monoagent CRT or radiation alone.

Survival Analyses

The unadjusted 5-year OS was consistently higher for patients receiving multiagent CRT as compared to monoagent CRT or radiation alone (Fig. 1). Five-year OS for stage I was 86, 80, and 77%, respectively ($p = 0.004$); stage II was 77, 70, and 55% ($p < 0.001$); and stage III was 67, 57, and 40% ($p < 0.001$).

After stratifying by stage and adjusting for available confounders, male gender, older age, private insurance, higher number of comorbidities, undergoing salvage APR, and receiving radiation alone were associated with lower OS across all three stages. Monoagent CRT was associated with lower OS only in patients with stages II and III disease (Table 3). Higher doses of radiation did not improve OS (Table 3).

In a subset analysis of patients ≥ 70 years, male gender, older age, higher Charlson/Deyo score, and undergoing salvage, APR remained independently associated with lower OS (Table 4). Within this subset, patients with stage I disease had similar OS regardless of the treatment strategy employed. In stages II and III, there was no significant difference in OS between multiagent and monoagent chemotherapy, while receiving radiation alone was associated with worse OS.

Discussion

The current study analyzes a large hospital-based cohort of patients diagnosed with ASCC between 2004 and 2015. We found that multiagent CRT therapy was independently associated with higher OS as compared to monoagent CRT in stages II and III ASCC, but was not associated with improved OS in stage I patients. In a subset of patients older than 70 years, receiving monoagent CRT did not impact the overall prognosis across all stages and had similar OS to patients receiving multiagent CRT. Factors associated with receiving standard multiagent chemotherapy were younger age, having fewer comorbidities, and advanced tumor stage; however, race, socioeconomic status, being uninsured, or treatment at a community-based hospital were not associated with receiving monoagent CRT or radiation alone.

Table 2 Multivariable analysis for factors associated with receiving multiagent chemoradiation

Characteristics	ASCC		
	OR	95% CI	*p* value
Gender, male	0.89	0.79–1.00	0.050
Age, years	0.97	0.97–0.98	< 0.001
Insurance			
Government		Reference	
None	0.89	0.68–1.17	0.420
Private	1.14	1.00–1.30	0.047
Institution type			
Academic		Reference	
Comprehensive	1.16	1.03–1.32	0.013
Community	1.07	0.88–1.30	0.506
Charlson/Deyo score			
0		Reference	
1	1.10	0.93–1.30	0.285
≥ 2	0.75	0.61–0.92	0.007
AJCC staging			
I		Reference	
II	1.48	1.28–1.70	< 0.001
III	1.74	1.49–2.04	< 0.001

OR indicates odds ratio; *CI*, confidence interval

Multiagent chemotherapy with radiation is considered to be the first-line treatment for non-metastatic ASCC.[2] This recommendation has been based upon empiric evidence from several randomized trials that were designed to determine the optimal chemotherapy regimen to treat ASCC patients. The ACT 1 trial was the first study to provide definitive evidence of better oncologic outcomes with radiation plus 5FU and MMC versus radiation alone.[7] A total of 585 patients of all ages with stage I–IV ASCC were randomized to the two arms (stage IV patients were included as the primary outcome measure was locoregional disease control). The study demonstrated a reduction in the risk of local failure and improved DFS in patients receiving CRT but no difference in OS. This study however excluded patients with stage I ASCC that were amenable to local excision and only had 12% patients with stage I disease. The long-term follow-up analysis of the ACT I trial showed similar results to the initial report, but still no significant improvement in OS for the CRT arm (HR 0.70–1.04).[12] The benefit of multiagent CRT was confirmed in the EORTC-22861 trial, which randomized 110 patients with stages II and III disease, ECOG performance status of 0 or 1, and age < 76 years between multiagent CRT and radiation alone. This trial also found that the combination of radiation plus 5FU and MMC was associated with better locoregional control and progression-free survival but could not establish a difference in OS. Finally, in order to determine the benefit of multiagent versus monoagent chemotherapy, the RTOG 87-04 randomized 291 patients with Karnofsky performance status of > 60 and a median age of 60 years (only 15% patients of the study had stage I disease). The patients receiving MMC had a better DFS and CFS, but did not experience a statistically significant increase in OS. Moreover, most of the benefit in oncologic outcomes was seen in larger primary tumors (T3/T4) as compared to small primary tumors (T1/T2). While all the above-discussed trials established the benefit of 5FU and MMC in improving DFS and CFS, they could not show a difference in OS. Our data, likely due to the larger number of patients and longer follow-up, indicate that multiagent chemotherapy with appropriate radiation doses is in fact associated with an OS benefit in patients with stages II and III disease compared to monoagent chemotherapy or radiation alone. However, we were unable to observe an OS benefit for multiagent CRT in stage I cancers, suggesting that monoagent CRT could be considered an appropriate treatment in stage I ASCC patients.

The toxicity profile of MMC includes myelosuppression resulting in dose limiting thrombocytopenia and leukopenia,

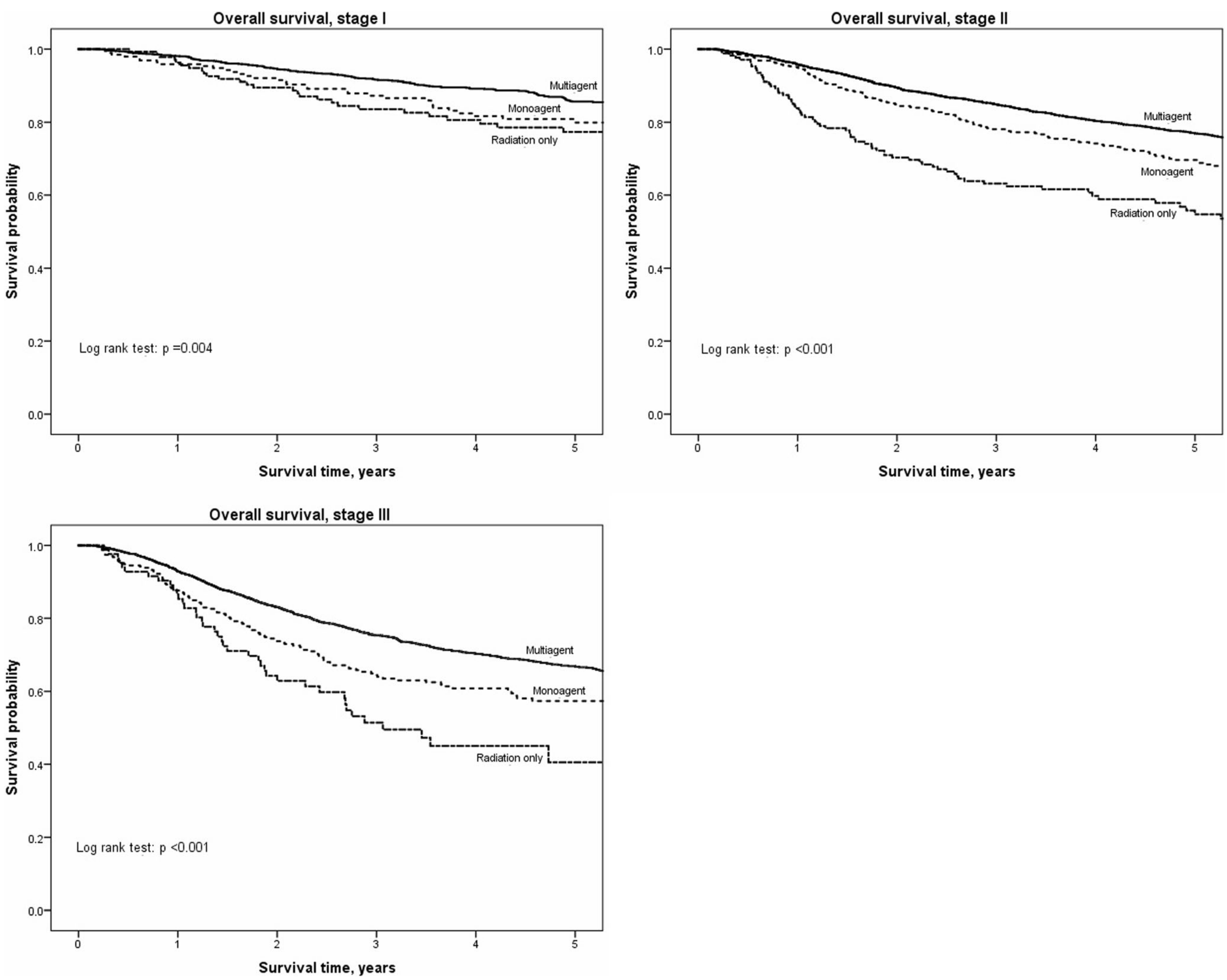

Fig. 1 Overall survival based on treatment by stage, NCDB 2004–2015

pulmonary toxicity, nephrotoxicity, and hemolytic uremic syndrome.[13] Grade 3+ toxicities have been reported in approximately 80% of patients undergoing multiagent CRT and are primarily driven by MMC.[14,15] Due to its toxicities, other agents such as Cisplatin have been evaluated and compared to MMC in the RTOG 98-11, ACT II, and ACCORD-03 trials.[16–18] However, MMC-based regimens were still found to be superior to the cisplatin-based regimens. Therefore, while the benefit of MMC has been well established in the treatment of ASCC, its positive impact on oncologic outcomes has to be balanced against its toxicities. Because of its significant morbidity, Buckstein et al. have recently analyzed the outcomes of chemoradiation versus radiation alone in a population-based study from the Surveillance, Epidemiology and End Results registry linked to Medicare between 1996 and 2011. They analyzed 200 patients with stage I ASCC older than 65 years[19] and observed similar OS, DFS, and CFS between the two groups. They concluded that the exclusion of chemotherapy might not adversely impact oncologic outcomes in the subset of the elderly population with early stage anal cancers. Furthermore, they observed that addition of chemotherapy was associated with an increased risk of toxicity. Nevertheless, the authors did not differentiate between monoagent and multiagent CRT regimens and did not report the radiation doses or compliance with therapy due to limitations of their database. In our analyses, we found that there was no difference in OS between older patients receiving multiagent and monoagent chemotherapy and appropriate radiation across all three stages. In the absence of prospective randomized clinical trials, large retrospective databases offer the unique opportunity to explore potential oncologic outcomes of non-standard treatments. Additionally, even though this database does not collect data on recurrence and colostomy rates, these findings bring attention to the importance of individualized

Table 3 Multivariable analysis for factor associated with overall survival by stage, NCDB 2004–2015

Risk factor	Stage I, $n = 1761$		Stage II, $n = 4553$		Stage III, $n = 3502$	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender, male	1.40 (1.08–1.81)	0.012	1.50 (1.33–1.69)	< 0.001	1.65 (1.45–1.88)	< 0.001
Age, years	1.04 (1.03–1.06)	< 0.001	1.03 (1.02–1.03)	< 0.001	1.02 (1.01–1.02)	< 0.001
Institution						
Academic	Reference					
Comprehensive	N/A		1.23 (1.07–1.41)	0.003	N/A	
Community	N/A		1.43 (1.18–1.75)	< 0.001	N/A	
Insurance						
Medicare	Reference					
Private	0.60 (0.45–0.81)	0.001	0.66 (0.57–0.76)	< 0.001	0.65 (0.56–0.75)	< 0.001
None	1.08 (0.60–1.94)	0.800	0.97 (0.72–1.30)	0.826	1.05 (0.84–1.32)	0.656
Comorbidities						
None	Reference					
1	1.25 (0.89–1.78)	0.201	1.37 (1.17–1.61)	< 0.001	1.20 (1.01–1.43)	0.048
≥ 2	2.08 (1.39–3.11)	0.001	2.07 (1.72–2.50)	< 0.001	1.69 (1.37–2.07)	< 0.001
Radiation, high dose	N/A		N/A		1.20 (1.02–1.41)	0.029
Chemotherapy						
Multiagent	Reference					
Monoagent	1.14 (0.81–1.60)	0.462	1.27 (1.07–1.51)	0.008	1.31 (1.08–1.58)	0.006
Radiation alone	1.54 (1.07–2.22)	0.020	2.10 (1.65–2.68)	< 0.001	1.87 (1.35–2.58)	< 0.001
Surgery						
None	Reference					
Salvage APR	4.58 (2.09–10.03)	< 0.001	3.37 (2.50–4.55)	< 0.001	2.66 (1.96–3.61)	< 0.001

Race and social-economic factors were not significant

HR indicates hazard ratio; *CI*, confidence interval

medicine with older individuals potentially not needing aggressive chemotherapy regimens.

The secondary aim of our analysis was to evaluate factors associated with receiving multiagent CRT. In a previous study from the NCDB, Geltzeiler et al.[20] demonstrated that several patient- and treatment-related factors influenced the receipt of CRT in the USA. They analyzed 12,801 patients with stages II and III ASCC treated from 2003 to 2010 of which 88% patients received CRT. They found that CRT was less likely to be administered to males, Black patients, and those with multiple comorbidities. While we identified similar discrepancies in treatment for males and patients with higher Charlson/Deyo score, we did not observe racial (and socioeconomic) disparities. This is likely due to a selection bias in our subset of patients as we included in the study only those who had a therapeutic dose of radiation and therefore had already access to healthcare.

The limitations of the current study include those inherent to an analysis of the NCDB, including coding errors and lack of data on potentially informative variables, such as local and regional recurrence rates, colostomy-free survival, dose and type of chemotherapeutic agents administered, treatment compliance, and treatment-related complications and toxicities. Another limitation is related to the potential for selection bias due to the relatively smaller number of patients who may have been too frail to tolerate the standard multiagent chemoradiation treatment or opted for palliative treatment. Therefore, given the retrospective nature of this series, our results may not be completely generalizable due to non-random selection and unmeasurable differences in patient populations. Information regarding the HIV status, human papillomavirus infection, and other known risk factors are either not included or reliably reported in the database. Finally, even though the NCDB is a national database that captures most newly diagnosed cancers in the USA, all participating hospitals are CoC accredited, thus limiting the generalizability of these findings to patients treated at non-CoC accredited facilities. Regardless of these limitations, the NCDB has been well validated for oncologic studies.[21,22]

In conclusion, our data suggest that multiagent chemotherapy with radiation is associated with a definite overall survival benefit compared to monoagent chemotherapy or radiation alone in patients with stages II and III but not stage I ASCC. Therefore, the potential oncologic benefits associated with

Table 4 Multivariable analysis for factor associated with overall survival by stage in patient over the age of 70 years, NCDB 2004–2015

Risk factor	Stage I, $n = 355$		Stage II, $n = 1018$		Stage III, $n = 583$	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Gender, male	N/A		1.43 (1.15–1.77)	0.001	1.70 (1.29–2.24)	< 0.001
Age, years	1.08 (1.04–1.12)	< 0.001	1.07 (1.05–1.09)	< 0.001	1.06 (1.04–1.08)	< 0.001
Institution						
Academic	Reference					
Comprehensive	N/A		1.11 (0.86–1.41)	0.428	N/A	
Community	N/A		1.49 (1.06–2.09)	0.021	N/A	
Comorbidities						
None	Reference					
1	1.43 (0.85–2.38)	0.177	1.49 (1.17–1.90)	0.001	1.18 (0.86–1.62)	0.302
≥ 2	2.30 (1.15–4.60)	0.018	1.59 (1.15–2.21)	0.006	1.84 (1.10–3.07)	0.020
Chemotherapy						
Multiagent	Reference					
Monoagent	1.07 (0.66–1.72)	0.798	0.98 (0.75–1.28)	0.883	1.32 (0.93–1.86)	0.121
Radiation alone	1.62 (0.94–2.77)	0.081	1.56 (1.10–2.20)	0.012	1.81 (1.07–3.05)	0.026
Surgery						
None	Reference					
Salvage APR	N/A		3.41 (1.95–5.98)	< 0.001	4.80 (2.10–11.00)	< 0.001

Race and high-radiation dose were not significant

HR indicates hazard ratio; *CI*, confidence interval

multiagent chemotherapy should be balanced against its toxicities in the management of ASCC patients, particularly for stage I cancers. Conversely, given the lack of improvement in OS among the elderly population with the addition of a second chemotherapeutic agent, healthcare providers might consider a less aggressive management strategy for older patients who may have a limited physiologic reserve and/or functional capacity.

Acknowledgments We would like to thank Timothy Ginader from the University of Iowa Biostatistics Core Alliance for his statistical support.

Author Contribution Each Author meets the International Committee of Medical Journal Editors (ICMJE), including:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
- Drafting the work or revising it critically for important intellectual content;
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Disclosure None to report. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

References

1. NIH. Cancer Stat Facts: Anal Cancer. https://seer.cancer.gov/statfacts/html/anus.html. Accessed 1 August 1st 2018.
2. Benson AB, 3rd, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK et al. Anal Carcinoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network : JNCCN. 2018;16(7):852–71. doi:https://doi.org/10.6004/jnccn.2018.0060.
3. Nigro ND, Vaitkevicius VK, Considine B, Jr. Combined therapy for cancer of the anal canal: a preliminary report. Diseases of the colon and rectum. 1974;17(3):354–6.
4. Leichman L, Nigro N, Vaitkevicius VK, Considine B, Buroker T, Bradley G et al. Cancer of the anal canal. Model for preoperative adjuvant combined modality therapy. The American journal of medicine. 1985;78(2):211–5.
5. Shridhar R, Shibata D, Chan E, Thomas CR. Anal cancer: current standards in care and recent changes in practice. CA: a cancer journal for clinicians. 2015;65(2):139–62. doi:https://doi.org/10.3322/caac.21259.
6. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997;15(5):2040–9. doi:https://doi.org/10.1200/jco.1997.15.5.2040.

7. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet. 1996;348(9034):1049–54.
8. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1996;14(9):2527–39. doi:https://doi.org/10.1200/jco.1996.14.9.2527.
9. National Cancer Database ncdbpuf.facs.org. 2018. Accessed March 2018.
10. Fritz ACP, A Jack, K Shanmugarathnam, L Sobin, DM Parkin, S Whelan. International Classification of Disease for Oncology. 3rd ed. Geneva: World Health Organization; 2000.
11. National Comprehensive Cancer Network 2017. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed May 2017.
12. Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). British journal of cancer. 2010;102(7):1123–8. doi:https://doi.org/10.1038/sj.bjc.6605605.
13. Ludmir EB, Kachnic LA, Czito BG. Evolution and Management of Treatment-Related Toxicity in Anal Cancer. Surgical oncology clinics of North America. 2017;26(1):91–113. doi:https://doi.org/10.1016/j.soc.2016.07.004.
14. Yeung R, McConnell Y, Roxin G, Banerjee R, Urgoiti GB, MacLean AR et al. One compared with two cycles of mitomycin C in chemoradiotherapy for anal cancer: analysis of outcomes and toxicity. Current oncology (Toronto, Ont). 2014;21(3):e449–56. doi:https://doi.org/10.3747/co.21.1903.
15. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. International journal of radiation oncology, biology, physics. 2013;86(1):27–33. doi:https://doi.org/10.1016/j.ijrobp.2012.09.023.
16. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB, 3rd et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(35):4344–51. doi:https://doi.org/10.1200/jco.2012.43.8085.
17. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 x 2 factorial trial. The Lancet Oncology. 2013;14(6):516–24. doi:https://doi.org/10.1016/s1470-2045(13)70086-x.
18. Peiffert D, Tournier-Rangeard L, Gerard JP, Lemanski C, Francois E, Giovannini M et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(16):1941–8. doi:https://doi.org/10.1200/jco.2011.35.4837.
19. Buckstein M, Arens Y, Wisnivesky J, Gaisa M, Goldstone S, Sigel K. A Population-Based Cohort Analysis of Chemoradiation Versus Radiation Alone for Definitive Treatment of Stage I Anal Cancer in Older Patients. Diseases of the colon and rectum. 2018;61(7):787–94. doi:https://doi.org/10.1097/dcr.0000000000001103.
20. Geltzeiler CB, Tsikitis VL, Kim JS, Thomas CR, Jr., Herzig DO, Lu KC. Variation in the Use of Chemoradiotherapy for Stage II and III Anal Cancer: Analysis of the National Cancer Data Base. Annals of surgical oncology. 2016;23(12):3934–40. doi:https://doi.org/10.1245/s10434-016-5431-9.
21. Winchester DP, Stewart AK, Phillips JL, Ward EE. The national cancer data base: past, present, and future. Annals of surgical oncology. 2010;17(1):4–7. doi:https://doi.org/10.1245/s10434-009-0771-3.
22. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Annals of surgical oncology. 2008;15(3):683–90. doi:https://doi.org/10.1245/s10434-007-9747-3.