International Journal of Colorectal Disease (2019) 34:607–612
https://doi.org/10.1007/s00384-018-03232-8

ORIGINAL ARTICLE

# Surgery and chemotherapy are associated with improved overall survival in anal adenocarcinoma: results of a national cohort study

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Accepted: 27 December 2018 / Published online: 11 January 2019


## Abstract

**Purpose** Anal adenocarcinoma (AAC) is a rare disease with treatment protocols that mimic both that of rectal adenocarcinoma (RAC) and anal squamous cell carcinoma (ASCC). Due to its rarity, data regarding outcomes are lacking. We sought to determine outcomes of patients with AAC compared to RAC and ASCC and to evaluate risk factors for mortality in AAC.

**Methods** The United States' National Cancer Database was queried for all adult patients presenting with nonmetastatic AAC, RAC, or ASCC from 2003 to 2011. The primary outcome was overall survival. Intergroup univariate comparisons, unadjusted Kaplan-Meier, and multivariable Cox proportional hazards modeling were used to compare outcomes between AAC, RAC, and ASCC and to identify factors associated with survival within AAC.

**Results** The query identified 129,153 patients ($N = 2117$ AAC, 19,427 ASC, 107,609 RAC). AAC patients were less likely than RAC patients to have surgery (72.5 vs. 87.1%), and also less likely to receive chemotherapy (54.7% vs. 96.1%) and radiation (58.2% vs. 74.1%) than patients with ASCC (all $p < 0.001$). Overall median survival in AAC was 65 months compared to 109 months for RAC and > 120 months for ASCC. On multivariable analysis, independent treatment-related predictors of decreased mortality hazard in AAC included proctectomy (hazard ratio [HR], 0.66) and chemotherapy (HR, 0.60) (both $p < 0.001$).

**Conclusion** AAC tumors have worse prognosis than either RAC or ASCC. Within patients with AAC, nonsurgical management was independently associated with increased mortality hazard. Patients with AAC should be evaluated in a multidisciplinary setting and referred for surgery.

**Keywords** Anal cancer · Adenocarcinoma · Outcomes

## Introduction

Anal canal cancers are rare malignancies and projected to account for only 2.5% (8580 cases) of new gastrointestinal cancer diagnoses in 2018 [1]. Compounding this rarity is that anal canal cancer can present with different histologic types, including squamous and glandular, while anal adenocarcinoma (AAC) accounts for only 10% of anal cancer cases, whereas squamous cell carcinomas constitute approximately 80% [2].

Owing to its rarity, treatment for AAC is not well established, particularly when compared to the defined treatment regimens that exist for both ASCC [3] and rectal adenocarcinoma (RAC) [4]. Currently, AAC is predominantly treated similar to advanced RAC with neoadjuvant chemoradiation followed by surgical resection and adjuvant chemotherapy. However, this approach is largely based on reports from single institutions with low numbers of AAC cases [5–7]. Additionally, survival of AAC relative to that of ASCC or RAC is unknown, as is the impact of different treatment regimens on AAC survival.

Utilizing the multi-institutional nature of the National Cancer Center Database (NCDB) to evaluate the largest sample of patients with AAC to date, we sought to compare survival between patients treated for AAC, ASCC, or RAC and to determine how the receipt of various treatment modalities impacted survival in patients with AAC.

This work was presented at the International Society of Surgery 47th World Congress of Surgery Kitajima Prize Session from August 13-17, 2017 in Basel, Switzerland.

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## Materials and methods

This is a retrospective cohort study of the National Cancer Data Base (NCDB) participant user files (PUF) from 2003 to 2011 for all adult patients presenting with nonmetastatic AAC, ASCC, or RAC. Our institutional review board exempts from review studies utilizing the NCDB. The data source itself includes over 30 million individual cancer case records collected by over 1500 Commission on Cancer facilities in all regions of the USA [8, 9].

For this analysis, a PUF issued in 2014 was used with follow-up information available through the end of 2012. This PUF was queried for rectal and anal cancer patients diagnosed between 2003 and 2011 ($N = 384{,}933$). Patients in whom this was not the first cancer diagnosis of their life ($N = 54{,}882$), those receiving care at a site other than the reporting center ($N = 14{,}336$), those receiving palliative treatment ($N = 106{,}104$), and patients lost to follow-up ($N = 21{,}287$) were excluded. The remaining patients were then queried for a diagnosis of either rectal or anal carcinoma using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography (anal, C21.0–C21.8; rectal, C20.9) and histology (adenocarcinoma, 8140–8144, 8210, 8211, 8260–8263, 8440, 8480, 8481, and 8490; squamous carcinoma, 8070–8078) codes (included $N = 188{,}104$). Patients with missing data on survival ($N = 25{,}505$), clinically metastatic disease ($N = 18{,}407$), or unknown stage ($N = 15{,}039$) were then excluded. Surgical treatment was identified by surgery of primary site codes, and administration of chemotherapy and/or radiation was similarly identified. Patients without information on the administration of nonsurgical therapy were flagged with an indicator variable.

For univariate intergroup comparisons, categorical variables were examined with Pearson's chi-square test. Survival analysis was performed using the method of Kaplan-Meier and time from diagnosis to death or censor. The log-rank test was used for comparison of survival estimates. The multivariable survival model that included all histologies adjusted for tumor subtype, age, Charlson-Deyo score, node status, tumor grade, receipt of chemotherapy, receipt of radiation, and type of operation. The multivariable model for survival within AAC used the same variables as above as well as margin status, but it did not contain tumor histologic subtype. A $p$ value $< 0.05$ was considered statistically significant for all comparisons. Missing data were handled with indicator variables of "missing." Statistical analysis was performed with R version 3.2.4 ("Very Secure Dishes"—R Foundation for Statistical Computing—Vienna, Austria www.r-project.org).

## Results

The query identified 129,153 patients ($N = 2117$ AAC, 19,427 ASCC, 107,609 RAC). A greater proportion of patients with AAC were over 65 years old (AAC, 50%; RAC, 45%; ASCC, 25%) and African American (AAC, 14%; RAC, 9%; ASCC, 12%) than patients with RAC or ASCC (all $p < 0.001$), but patients with ASCC had greater comorbidity burden (Charlson-Deyo score of 2 or greater) than those with AAC (7% vs. 5%; $p < 0.001$).

With respect to tumor biology, RAC tumors were most often high grade (86.0%) followed closely by AAC (75.8% high grade), with ASCC (22.4%) much less often high grade. Margin status showed the opposite trend with ASCC most frequently having positive margins (39%) followed by AAC (16%) and RAC (6%). Treatment choices also varied widely with patients with AAC treated with surgery at a much higher rate than those ASCC (73% vs. 44%), but at a lower rate than patients with RAC (87%). Operative choice for treatment of AAC differed by stage; over 70% of patients who were stage 0 or I underwent local excision, whereas nearly 80% of patients who were stage II or III underwent proctectomy (Fig. 1). The proportion of patients treated with radiation was similar for adenocarcinoma regardless of anal or rectal anatomic site

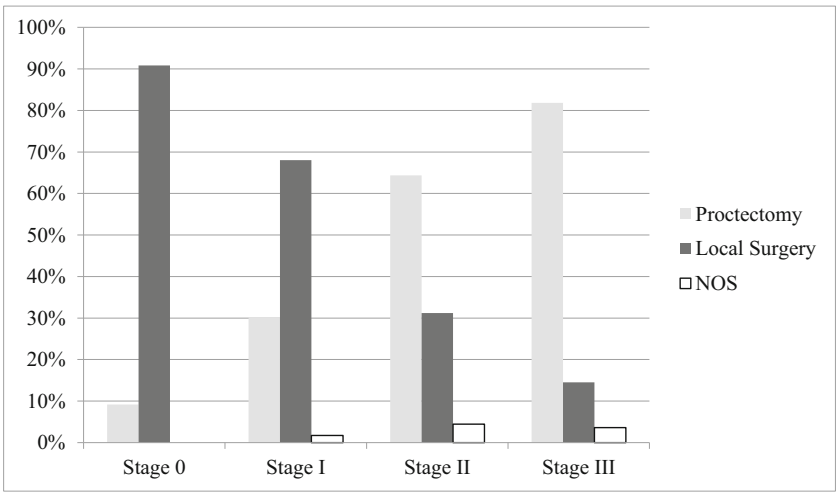


**Fig. 1** Operation variation for AAC by stage; NOS, not otherwise specified

(AAC, 58%; RACL, 58%), and both proportions were significantly lower than the proportion of anal squamous cancer patients treated with radiation (74%). Chemotherapy rates for adenocarcinoma were also similar regardless of anatomic site (AAC, 55%; RAC, 58%), and significantly lower than the rate of chemotherapy treatment in patients with anal squamous cancer (96%) (Table 1).

Regardless of treatment received and anatomic site, patients with adenocarcinoma had decreased unadjusted univariate survival outcomes compared to those with ASCC. AAC patients had the shortest median overall survival (65 months), whereas patients with ASCC experienced the longest median overall survival (> 120 months) (Table 1, Fig. 2).

Multivariable analysis demonstrated persistently increased mortality hazard for AAC compared to ASCC (hazard ratio [HR], 1.54; $p < 0.001$). Independent tumor and treatment-related predictors of increased mortality hazard included positive lymph nodes (N1 HR, 1.69; N2 HR, 2.76, both $p < 0.001$) nonsurgical management (proctectomy HR, 0.49; $p < 0.001$) and nonreceipt of chemotherapy (chemotherapy HR, 0.74; $p < 0.001$) (Fig. 3).

Examining survival amongst only patients with AAC, undergoing an operation (proctectomy HR, 0.66; $p = 0.03$; local surgery HR, 0.42; $p < 0.001$) and receiving chemotherapy (HR, 0.60; $p < 0.001$) were both independently associated with decreased mortality, while receipt of radiotherapy did not have an effect (HR, 1.08; $p = 0.51$). Other risk factors for mortality included increased tumor grade, positive margins at surgery, and having nodal involvement (Fig. 4).

## Discussion

While the management of both RAC and ASCC are well established, the optimal treatment of AAC is not. Utilizing the NCDB to accrue the largest sample of AAC patients to date, we have shown that AAC has a worse prognosis than either RAC or ASCC. Additionally, patients with AAC are less likely to undergo surgery than patients with RAC, and this lack of surgery is an independent risk factor for mortality. Given the worse survival of AAC, there is a clear need for an established treatment algorithm. Based on these findings, it should consist of surgical resection and the consideration of chemotherapy.

The median overall survival of patients presenting with AAC of 65 months is better than the majority of previously published studies. The next largest study of AAC used the Surveillance, Epidemiology, and End Results (SEER) 18 database and median overall survival was only 33 months. This difference is likely secondary to their inclusion of patients

**Table 1** Demographics, cancer characteristics, and treatment

| | AAC, $n = 2117$ | RAC, $n = 107{,}609$ | ASCC, $n = 19{,}427$ | $p$ value |
|---|---|---|---|---|
| Age 65+ | 50.0% | 45.0% | 25.4% | $< 0.001^a$; $< 0.001^b$ |
| Female | 47.9% | 45.0% | 60.4% | $< 0.001^a$; $< 0.001^b$ |
| African American | 14.4% | 8.5% | 12.2% | $< 0.001^a$; $< 0.001^b$ |
| CDS 2+ | 4.9% | 4.8% | 7.1% | $0.09^a$; $< 0.001^b$ |
| Stage | | | | $< 0.001^a$; $< 0.001^b$ |
| 0 | 7.7% | 8.5% | 13.8% | |
| I | 24.5% | 34.2% | 20.3% | |
| II | 38.5% | 26.5% | 38.5% | |
| III | 29.3% | 30.7% | 29.3% | |
| High grade | 75.8% | 86.0% | 22.4% | $< 0.001^a$; $< 0.001^b$ |
| Positive margins | 16.3% | 6.1% | 39.1% | $< 0.001^a$; $< 0.001^b$ |
| Treatment modality | | | | |
| Surgery | 72.5% | 87.1% | 44.3% | $< 0.001^a$; $< 0.001^b$ |
| Radiation | 58.2% | 57.8% | 74.1% | $0.91^a$; $< 0.001^b$ |
| Chemotherapy | 54.7% | 57.8% | 96.1% | $0.002^a$; $< 0.001^b$ |
| Median overall survival, months (95% CI) | | | | |
| All | 65.2 (61.1–70.4) | 109.2 (107.4–110.3) | > 120 | |
| Surgery alone | 86.4 (75.2–NR) | 118.9 (117.0–121.0) | > 120 | |
| Chemo/radiation | 36.3 (32.6–44.1) | 39.4 (37.7–40.8) | > 120 | |
| Surgery+chemoradiation | 74.3 (67.5–93.0) | 117.4 (115.1–120.0) | > 120 | |

[a] Comparison between AAC and RAC

[b] Comparison between AAC and ASCC; CDS, Charlson-Deyo score

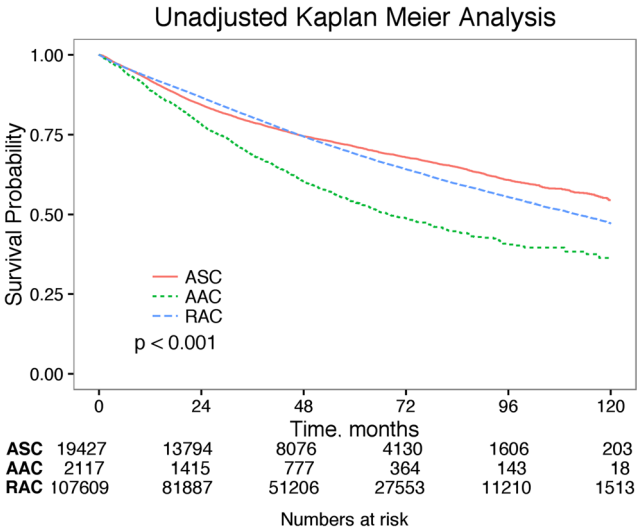


**Fig. 2** Unadjusted Kaplan-Meier Survival by tumor histology

with distant disease, which made up 21% of their sample and was the greatest risk factor for mortality in their study [10]. Additionally, an earlier SEER study included only patients with nonmetastatic AAC and found a 5-year survival rate of over 50% for those undergoing abdominal perineal resection (APR) lending credence to this theory [11]. Other smaller single-center and multi-institutional studies have reported both similar [5, 12–14] and dissimilar 5-year survivals to our results [6, 7, 15], but the majority either have a small number of patients, encompass cases from as far back as the 1970s, or suffer from both these limitations.

Despite the apparent improvement in overall survival with AAC compared to prior studies, survival is still worse than that of both RAC and ASCC. This is likely secondary to the lack of guidelines on whether to treat AAC as either a RAC or an ASCC. The data reflect this, as patients with AAC are simultaneously both less likely to undergo surgery than those with RAC and less likely to receive chemotherapy or radiation than those with an ASCC.

From a surgical perspective, both proctectomy and local excision were associated with decreased mortality hazard ratios on multivariable analysis. This is in line with the study using SEER 18 data where no difference in overall survival was observed between local excision and radical resection [10]. Local excision had been previously associated with decreased recurrence-free and overall survival compared to radical surgery. However, 10 of the 13 patients treated by local excision in that study had stage II or greater disease [5]. Local excision is likely a reasonable strategy for small AACs detected early similar to the criteria for local excision for T0 and T1 RAC. Local excision would still allow for salvage by APR in the case of a local recurrence as previously demonstrated [6]. Appropriate selection of candidates for local excision for cure of AAC may decrease the rate of positive margins observed and bring this rate closer to the rate seen in RAC. In the current study, over 20% of patients with stage II or III disease underwent local excision though these tumors are likely T2 or greater and if it was RAC, they would not typically be candidates for local excision for cure [4]. This is particularly important since positive margin status was an independent risk factor for mortality in AAC.

While national data favors surgical resection [10, 11], a number of institutional studies advocate for chemoradiation over radical resection [12, 14–16]. In a series of 82 patients, Belkacemi et al. demonstrated an unadjusted increased overall survival with chemoradiation compared to radiation plus

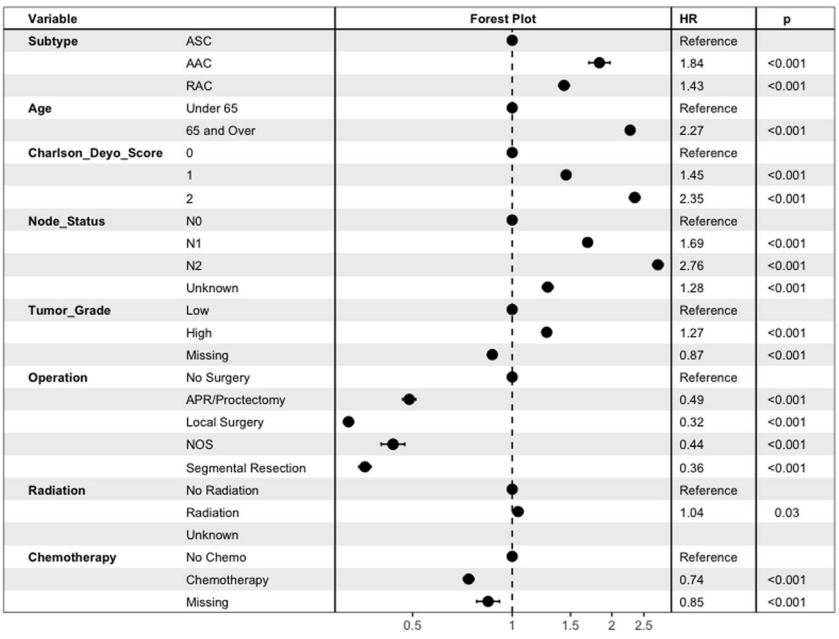


**Fig. 3** Adjusted survival analysis for all histologies

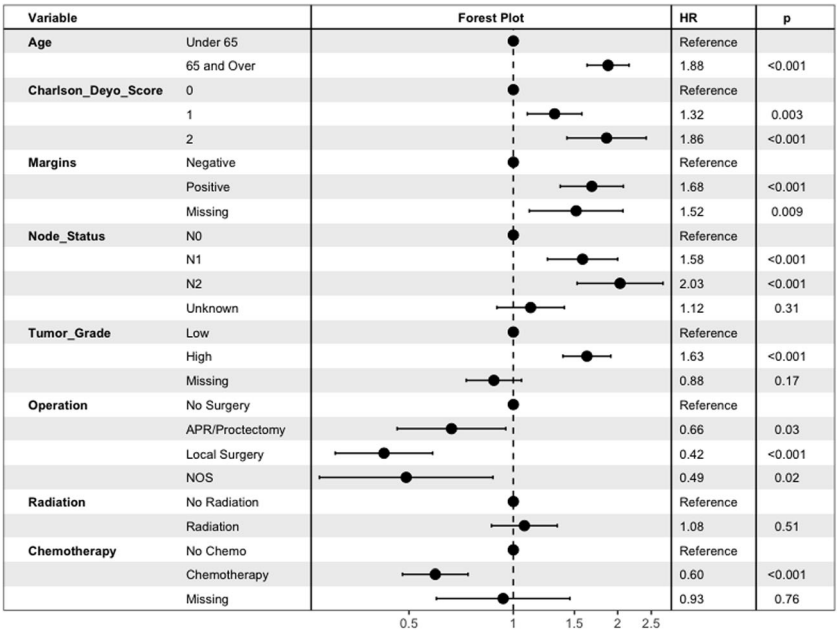


**Fig. 4** Adjusted survival analysis for AAC only

surgery or surgery alone. On multivariable analysis, chemoradiation was an independent protective factor for both disease-free and overall survival compared to radiation plus surgery. However, the addition of radiation to surgery did not increase survival when compared to having surgery alone [15]. More recently, Kounalakis et al. also found no difference in overall survival between patients treated with APR plus radiation or APR alone. However, they found a significantly worse overall survival in those treated with radiation alone [11]. Similarly, Franklin et al. showed no improvement in survival with the use of radiation therapy [10]. Based on these data and the data within this report, it seems that radiation does not improve outcomes in AAC.

It remains unknown whether chemotherapy has a role in the treatment of AAC due to SEER not having chemotherapy data and institutional studies being underpowered. We have shown that receipt of chemotherapy is a protective factor for overall survival in AAC. Therefore, it is important to decide whether the chemotherapy regimen utilized should be FOLFOX based as in the treatment of RAC or 5-fluorouracil (5-FU)/mitomycin based as in ASCC treatment. Where chemotherapy regimens have been reported, regimens have largely been in the form of radiosensitizing chemotherapy with 5-FU infusion or capecitabine [5, 6, 15], but one study reported the use of adjuvant 5-FU with or without oxaliplatin or irinotecan [7]. No comparisons between the regimens have been published and no study has examined the role of FOLFOX directly. Since there is a lack of benefit with radiation therapy and given histologic similarities between rectal adenocarcinoma and anal adenocarcinoma, it is logical that FOLFOX-based chemotherapy regimens would be more effective in treating AAC. Results from clinical practice are necessary to confirm this assumption.

Other disease specific risk factors associated with poorer survival in the patients with AAC included higher tumor grade and positive lymph nodes. These are consistent with identified risk factors for decreased survival across other studies of AAC that are adequately powered [10, 11, 15]. As AAC is known to be more aggressive than its anatomic counterpart ASCC, early detection and the use of either neoadjuvant or adjuvant chemotherapy will be critical if survival is to approach that of RAC or ASCC.

Our study is limited by its retrospective and nonrandomized nature. Additionally, our inability to fully understand treatment decisions limits the strength of the conclusions that can be drawn. This is an important source of unmeasured confounding. Finally, cancer-specific survival and recurrence data are unavailable in the NCDB, which prevents us from assessing these cancer-specific outcomes.

## Conclusions

In the largest study of the multidisciplinary management of AAC, AAC was found to be a tumor with a prognosis worse than both RAC and ASCC. Nonsurgical management was independently associated with increased mortality hazard. Patients presenting with AAC should be seen by a surgical specialist and considered for multidisciplinary management.

**Acknowledgments** The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in the study are derived from a de-identified NCDB participant user file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methods or the conclusions drawn from these data by the investigators.

**Grant support** This work has been supported indirectly by the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery and by the Mayo School of Graduate Medical Education Clinician Investigator program. No specific grant number is associated with the work.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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