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A Population-Based and Propensity Score-Matched Investigation of the Occurrence, Management, and Prognosis of Anal Mucinous Adenocarcinoma Patients

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Keywords

Anal mucinous adenocarcinoma · Anal squamous cell carcinoma · Anal adenocarcinoma · Incidence · Surgery · Radiation therapy · Prognosis

Abstract

Introduction: Anal mucinous adenocarcinoma (AMAC) is an extremely rare form of anal cancer. Our objective was to examine the incidence, management, and prognostic factors of AMAC. ***Methods:*** We analyzed age-adjusted incidence (AAI) rates over time and compared the prognosis of AMAC with anal squamous cell carcinoma (ASCC) and adenocarcinoma (AAC) using propensity score matching and Kaplan-Meier analysis. Patients were classified based on summary stage and treatments to determine cancer-specific survival. ***Results:*** AAI of AMAC fluctuated within a narrow range (0.082–0.237 per million person-years) from 2000 to 2018. AMAC had a slight non-significant trend of worse prognosis than ASCC ($p = 0.348$) and a better prognosis than AAC ($p < 0.01$). Females made up a larger proportion of patients diagnosed with the distant disease ($p < 0.05$) and unmarried ($p < 0.05$) and somewhat less probably to need surgical removal ($p < 0.01$) and radiotherapy ($p < 0.01$). Elderly patients have lower rates of survival ($p < 0.05$). Localized stage was associated with better prognosis ($p < 0.05$). Surgery was associated with a tendency toward better survival ($p = 0.095$). ***Conclusions:*** AMAC exhibits a low incidence yet favorable prognosis compared to typical AAC and slightly worse compared to ASCC. Elderly age is associated with poorer prognosis, while localized stage indicates better prognosis. Surgery demonstrates a trend toward improved survival.

Introduction

Anal cancer is very uncommon, accounting for just around 1–3% of all malignancies that occur in the digestive system [1, 2]. Anal squamous cell cancer (ASCC) is the most prevalent type from a pathology point of view and accounts for approximately 85–90% of all cases; the second most common subtype is anal adenocarcinoma (AAC), which accounts for approximately 5–10%; anal mucinous adenocarcinoma (AMAC) is even rarer, accounting for less than 3% of all cases. AMAC, also known as mucinous adenocarcinoma of the anus, is a rare subtype of anal cancer that originates in the mucous-producing glands of the anal canal. These glands are responsible for lubricating the anal canal and aiding in the passage of stool. Histologically, mucinous adenocarcinoma is characterized by the presence

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of malignant cells that produce significant amounts of mucin, a gelatinous substance found in mucus. This mucin production distinguishes it from other types of anal cancer [2–4]. The rarity of AMAC and the limited data available from case reports and short case series have led to a lack of understanding regarding its clinical features and prognosis.

Owing to the limited availability of evidence derived from case reports and short case series, the clinical progression of AMAC in comparison to typical ASCC and AAC remains a topic of debate [3, 5, 6]. With inadequate population-level data and inconsistent information on survival rates, our study aimed to address the following research questions using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program: (1) estimation of AMAC prevalence across different age-groups; (2) identification of the common clinical features of AMAC; (3) comparison of the prognosis of AMAC with typical ASCC and AAC; and (4) determination of the factors that impact AMAC cancer-specific survival (CSS).

Patients and Methods

Study Population

The National Cancer Institute's SEER database (SEER Research Plus Data, 18 Registries, Nov 2020 sub [2000–2018]) was utilized throughout this analysis. The SEER program is typical of the USA in terms of demographics, tumor, diagnostic as well as therapeutic features since it is composed of 18 population-based cancer registries and comprises roughly 26% of the sample population. The International Classification of Disease for Oncology-3rd edition (ICD-O-3) was utilized to identify AMAC patients (code: 8480/3), typical AAC (code: 8140/3), and typical ASCC (code: 8070/3). Patients having these malignant sequence digits, designated "one primary only," were chosen from the group of patients identified between 2000 and 2018 with histologic verification via biopsy or surgical pathology. Additionally, we excluded the patients without survival information.

Variable Definitions

The patients' demographic variables (age at diagnosis, sex, race, as well as marital status), tumor grade (well, moderately, poorly, undifferentiated, and unknown), SEER summary stage (localized, regional, distant, as well as unknown), altogether with treatment modality were the covariates of concern that were extracted for each case (surgery, radiation therapy [RT], and chemotherapy).

Statistical Analyses

SEER*Stat Software version 8.4.0.1 was used for the purpose of conducting an analysis of age-adjusted incidence (AAI) rates (Surveillance Research Program, National Cancer Institute, seer.cancer.gov/seerstat). AAI was carried out in accordance with the US Standard Population from the year 2000. The student's t test was used in order to compare the ongoing data, meanwhile the χ^2 test was utilized in order to analyze the categorical data. It was determined that using a propensity score matching (PSM) analysis was the most effective method for removing selection bias from the AMAC, AAC, as well as ASCC patient populations. The PSM was carried out as a 1:1 ratio matching with the caliper width set to 0.01, and it was based on the closest neighbor matching approach with no replacement. The PSM model took into account the patient's age, race, marital status, the grade of their malignancy, as well as the SEER summary stage. The Kaplan-Meier technique was used in order to estimate survival probability, and the log-rank test was utilized in order to analyze whether or not there were any significant differences in CSS when stratified by each covariate. Analyses of the relationships between patient characteristics and treatment modalities and patient survival were conducted with the help of Cox proportional hazards models. Only those factors considered for inclusion in the multivariate Cox analysis that was shown to have a significant association with survival in the univariate Cox analysis. Both univariate and multivariate approaches were used in order to estimate the hazards ratios (HRs) and confidence intervals (CIs) for 95%. The SPSS Statistical Package version 26.0 was used to conduct the statistical analysis (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was regarded to be statistically significant.

Results

Incidence

As shown in Figure 1, in the year 2018, the AAI of AMAC is approximately 10% that of AAC and 100% that of ASCC. The AAI of AMAC fluctuated within a very narrow range from 0.082/1,000,000 person-years to 0.237/1,000,000 person-years during the study period from 2000 to 2018, with a slope (±standard error [SE]) of −0.002 ± 0.002 ($p = 0.222$, $R^2 = 0.086$); similarly, the AAI of AAC fluctuated within a very narrow range from 0.608/1,000,000 person-years to 0.989/1,000,000 person-years during the study period from 2000 to 2018, with a slope (±SE) of −0.004 ± 0.004 ($p = 0.434$, $R^2 = 0.036$); however, the AAI of ASCC significantly steadily increased during the study period from 4.9482/1,000,000 person-years in 2000 to 9.353/1,000,000 person-years in 2018, with a slope (±SE) of 0.254 ± 0.012 ($p < 0.0001$, $R^2 = 0.963$).

Patient Characteristics

Demographic data for AMAC patients are shown in Table 1. The mean age at diagnosis was 64.72 ± 14.71 years. The majority of patients (68.56%) were white. Almost half of the subjects (46.72%) were married. Almost one-third of patients (32.31%) had moderately differentiated tumors. A small minority of cases (15.05%) were categorized as distant stages. Most of the patients were undergoing surgery (74.67%), RT (62.88%), and chemotherapy (63.32%).

There were no statistically significant variations in terms of age, racial background, or tumor grade among AMAC patients when the data were broken down and analyzed according to the summary stage (Table 2). Patients who presented with a distant form of the disease were significantly more likely to be female ($p = 0.018$), less likely to be married ($p = 0.014$), and significantly less likely to have undergone surgical resection ($p = 0.004$) or radiotherapy ($p = 0.001$). Patients who came with a disease

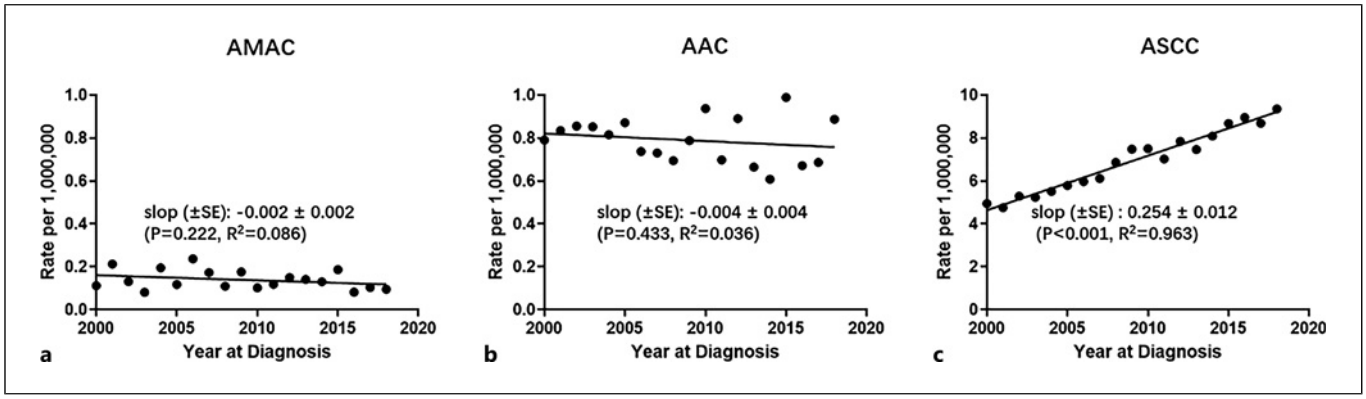

Fig. 1. AAI rates of AMAC (**a**), AAC (**b**), and ASCC (**c**). The AAI has been performed according to the 2000 US Standard Population. The lines represent the results from linear regression analysis. SE, standard error; R^2, R squared, the goodness of fit.

Table 1. AMAC patient demographics and clinical characteristics (n = 229)

Characteristics	Level	*N* (%)
Age at diagnosis	Mean±SD	64.72±14.71
	Median (range)	65 (27~97)
Sex, *n* (%)	Male	147 (64.19)
	Female	82 (35.81)
Race, *n* (%)	White	157 (68.56)
	Black	52 (22.71)
	Asian or Pacific Islander	16 (6.99)
	Others/unknown	4 (1.75)
Marital status, *n* (%)	Married	107 (46.72)
	Unmarried/unknown	122 (53.28)
Tumor grade, *n* (%)	Well differentiated	40 (17.47)
	Moderately differentiated	74 (32.31)
	Poorly differentiated	36 (15.72)
	Undifferentiated	2 (0.87)
	Unknown	77 (33.62)
Summary stage, *n* (%)	Localized	80 (34.93)
	Regional	87 (37.99)
	Distant	45 (15.05)
	Unknown	17 (5.69)
Surgery, *n* (%)	Yes	171 (74.67)
	None/unknown	58 (25.33)
RT, *n* (%)	Yes	144 (62.88)
	RT prior to surgery	53 (36.81)
	RT after surgery	57 (24.89)
	No cancer-directed surgery	34 (14.85)
	None/unknown	85 (37.12)
Chemotherapy, *n* (%)	Yes	145 (63.32)
	No/unknown	84 (36.68)

RT, radiation therapy.

that was confined had a significantly lower likelihood of using chemotherapy (p = 0.02) There were no statistically significant differences seen between AMAC patients in terms of age, gender, race, marital status, RT, or chemotherapy when the patients were stratified due to the surgical treatment they received (Table 3).

Patient Survival

From 2000 to 2018, all patients labeled with one primary tumor of AMAC (n = 229), AAC (n = 1,228), and ASCC (n = 11,188) were included in Kaplan-Meier analyses for CSS (Fig. 2a), which demonstrated that AMAC had a worse prognosis than ASCC (p < 0.001), as well as a

Table 2. AMAC patient characteristics by SEER summary stage (n = 212)

Characteristics	Level	Summary stage			p value
		localized (n = 80)	regional (n = 87)	distant (n = 45)	
Age at diagnosis	Mean±SD	65.43±14.04	62.77±13.94	64.67±16.92	
	Median (range)	67 (32–95)	62 (32–94)	67 (27–97)	
	≤60	28 (35)	34 (39.08)	17 (37.78)	0.859
	>60	52 (65)	53 (60.92)	28 (62.22)	
Sex, n (%)	Male	50 (62.50)	64 (73.56)	22 (48.89)	0.018
	Female	30 (37.5)	23 (26.44)	23 (51.11)	
Race, n (%)	White	53 (66.25)	64 (73.56)	29 (64.44)	0.82
	Black	18 (22.50)	18 (20.69)	10 (22.22)	
	Asian or Pacific Islander	7 (8.75)	4 (4.60)	5 (11.11)	
	Others/unknown	2 (2.5)	1 (1.15)	1 (2.22)	
Marital status, n (%)	Married	46 (57.5)	42 (48.28)	14 (31.11)	0.014
	Unmarried	24 (30.00)	35 (40.23)	28 (62.22)	
	Unknown	10 (12.50)	10 (11.49)	3 (6.67)	
Tumor grade, n (%)	Low	42 (52.50)	47 (54.02)	20 (44.44)	0.705
	High	11 (13.75)	15 (17.24)	10 (22.22)	
	Unknown	27 (33.75)	25 (28.74)	15 (33.33)	
Surgery, n (%)	Yes	63 (78.75)	76 (87.36)	28 (62.22)	0.004
	None/unknown	17 (21.25)	11 (12.64)	17 (37.78)	
RT, n (%)	Yes	36 (45.00)	64 (73.56)	26 (57.78)	0.001
	None/unknown	44 (55.00)	23 (26.44)	19 (42.22)	
Chemotherapy, n (%)	Yes	44 (55.00)	65 (74.71)	32 (71.11)	0.02
	No/unknown	36 (45.00)	22 (25.29)	13 (28.89)	

Seventeen patients with the unknown stage were excluded from this analysis. The p value was calculated by the χ^2 test for categorical covariates. Low tumor grade, well and moderately differentiated tumor grade; high, poorly differentiated and undifferentiated tumor grade.

Table 3. AMAC patient characteristics by surgery treatment (n = 229)

Characteristics	Level	Surgery (n = 171)	Non-surgery/unknown (n = 58)	p value
Age	Mean±SD	63.89±14.57	67.16±14.97	
	Median (range)	64 (27–97)	68 (32–95)	
	≤60	64 (37.43)	19 (32.76)	0.523
	>60	107 (62.57)	37 (67.24)	
Sex, n (%)	Male	109 (63.74)	38 (65.52)	0.808
	Female	62 (36.26)	20 (34.48)	
Race, n (%)	White	112 (65.50)	45 (77.59)	0.06
	Black	40 (23.39)	12 (20.69)	
	Asian or Pacific Islander	15 (8.77)	1 (1.72)	
	Others/unknown	4 (2.34)	0 (0.00)	
Marital status, n (%)	Married	84 (49.12)	23 (39.66)	0.457
	Unmarried	69 (40.35)	28 (48.28)	
	Unknown	18 (10.53)	7 (12.07)	
Tumor grade, n (%)	Low	88 (51.46)	26 (44.83)	0.006
	High	34 (19.88)	4 (6.90)	
	Unknown	49 (28.65)	28 (48.28)	
RT, n (%)	Yes	109 (63.74)	35 (60.34)	0.643
	None/unknown	62 (36.26)	23 (39.66)	
Chemotherapy, n (%)	Yes	112 (65.50)	33 (56.90)	0.24
	No/unknown	59 (34.50)	25 (43.10)	

The p value was calculated by the χ^2 test for categorical covariates. Low tumor grade, well and moderately differentiated tumor grade; high tumor grade, poorly and undifferentiated tumor grade.

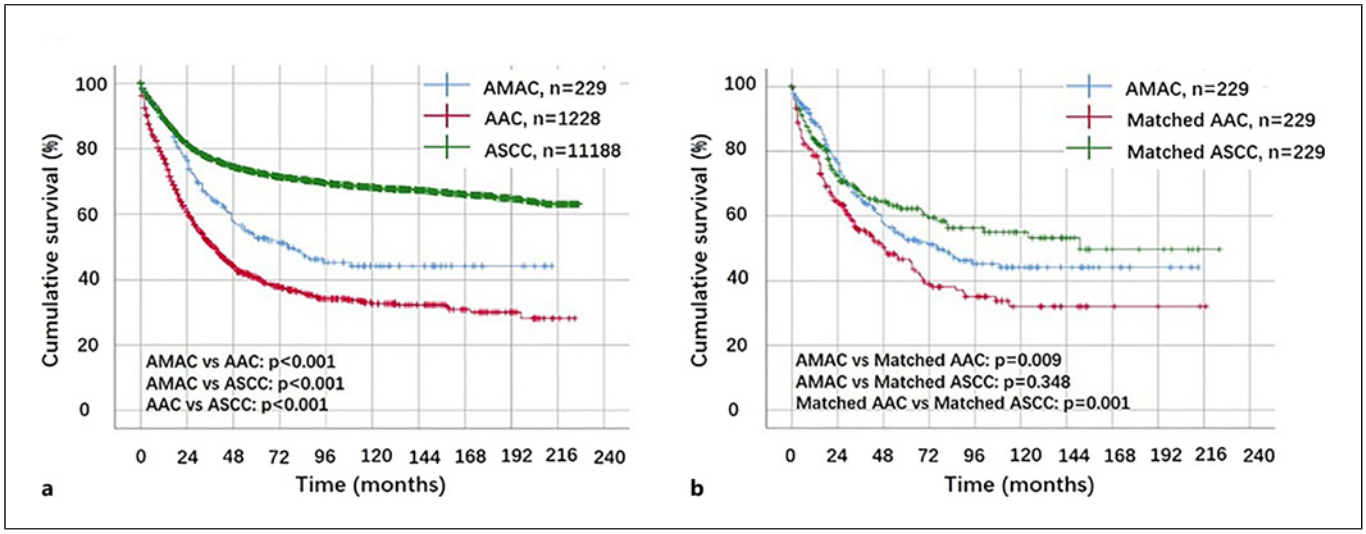

Fig. 2. a From 2000 to 2018, all patients labeled with one primary tumor of AMAC (n = 229), AAC (n = 1,228), or ASCC (n = 11,188) were included in Kaplan-Meier analyses. Kaplan-Meier estimated CSS for the AMAC, AAC, and ASCC patients (AMAC vs. AC: p < 0.001; AMAC vs. ASCC: p < 0.001; AAC vs. ASCC: p < 0.001). **b** From 2000 to 2018, all patients labeled with one primary tumor of AMAC (n = 229) and the matched AAC (n = 229) and ASCC (n = 229) were included in Kaplan-Meier analyses. Kaplan-Meier estimated CSS for AMAC, AAC, and ASCC patients (AMAC vs. AC: p = 0.009; AMAC vs. ASCC: p = 0.348; AAC vs. ASCC: p = 0.001).

more sophisticated prognosis than AAC (p < 0.001). Furthermore, from 2000 to 2018, all patients labeled with one primary tumor of AMAC (n = 229) and the matched AAC (n = 229) and ASCC (n = 229) were included in Kaplan-Meier analyses for CSS (Fig. 2b), which demonstrated that AMAC had a more sophisticated prognosis than AAC (p = 0.001) and had a slightly worse prognosis than ASCC without statistical significance (p = 0.348).

Kaplan-Meier estimated CSS for localized and regional AMAC patients (localized vs. regional: p = 0.034) (Fig. 3a); Kaplan-Meier estimated CSS for AMAC patients with and without surgery (p = 0.095) (Fig. 3b); Kaplan-Meier estimated CSS for AMAC patients with and without radiation (p = 0.296) (Fig. 3c); Kaplan-Meier estimated CSS for AMAC patients with and without chemotherapy (p = 0.781) (Fig. 3d). Univariate and multivariate Cox proportional hazards analyses were used to investigate factors that might possibly affect CSS (Table 4); elderly patients (multivariate HR = 2.173, 95% CI 1.158–3.854; p = 0.012), the regional stage (multivariate HR = 1.795, 95% CI 1.055–3.054; p < 0.031) demonstrated worse chances of survival overall.

Discussion

AAI Was Extremely Low and Stable

Anal canal malignancies are rare tumors that represent approximately 1–3% of all digestive tract cancers [1, 2]. The most common pathologic type is ASCC, which accounts for approximately 85–90% of all cases; and the second common pathologic type is AAC (about 5–10%) [2–4]. In most countries, the incidence of AAC is far lower than that of ASCC; the exceptions to this rule include Japan, Singapore, and a few other nations, while the incidence of AAC and SCC is similar, or even the incidence of AAC and SCC is slightly higher [7, 8]. On the other hand, in Japan and Singapore, where a significant number of instances of anal cancer are overlapping tumors of the rectum as well as the anus, it is possible that some patients' cancer diagnoses were incorrectly classified as those of rectal cancer [7].

Owing to its low incidence compared with ASCC and AAC, reports regarding AMAC have been insufficient over the last several decades; some existing articles mainly focus on case reports with small samples. In this research, we investigated the occurrence of AMAC as well as the variables that influence its prognosis by making use of the large sample size offered by the SEER database. To our knowledge, this is the largest sample size of the AMAC study to date. In this study, the AAI of AMAC and AAC is stable over time. The results of previous investigations were consistent with the occurrence of this phenomenon [7, 9, 10]. However, the AAI of ASCC has been steadily increasing over time, which is consistent with the finding of the previous reports [7, 9–12]. Although the causes of the elevation in the frequency of ASCC are unclear, one of the contributing reasons is probably an increase in the prevalence of variables that may promote the incidence and persistence of anal HPV infection, such as cervical HPV infection among women [9, 13]. In addition, HIV seems to be a significant risk factor throughout the development of ASCC. The growing incidence of ASCC is

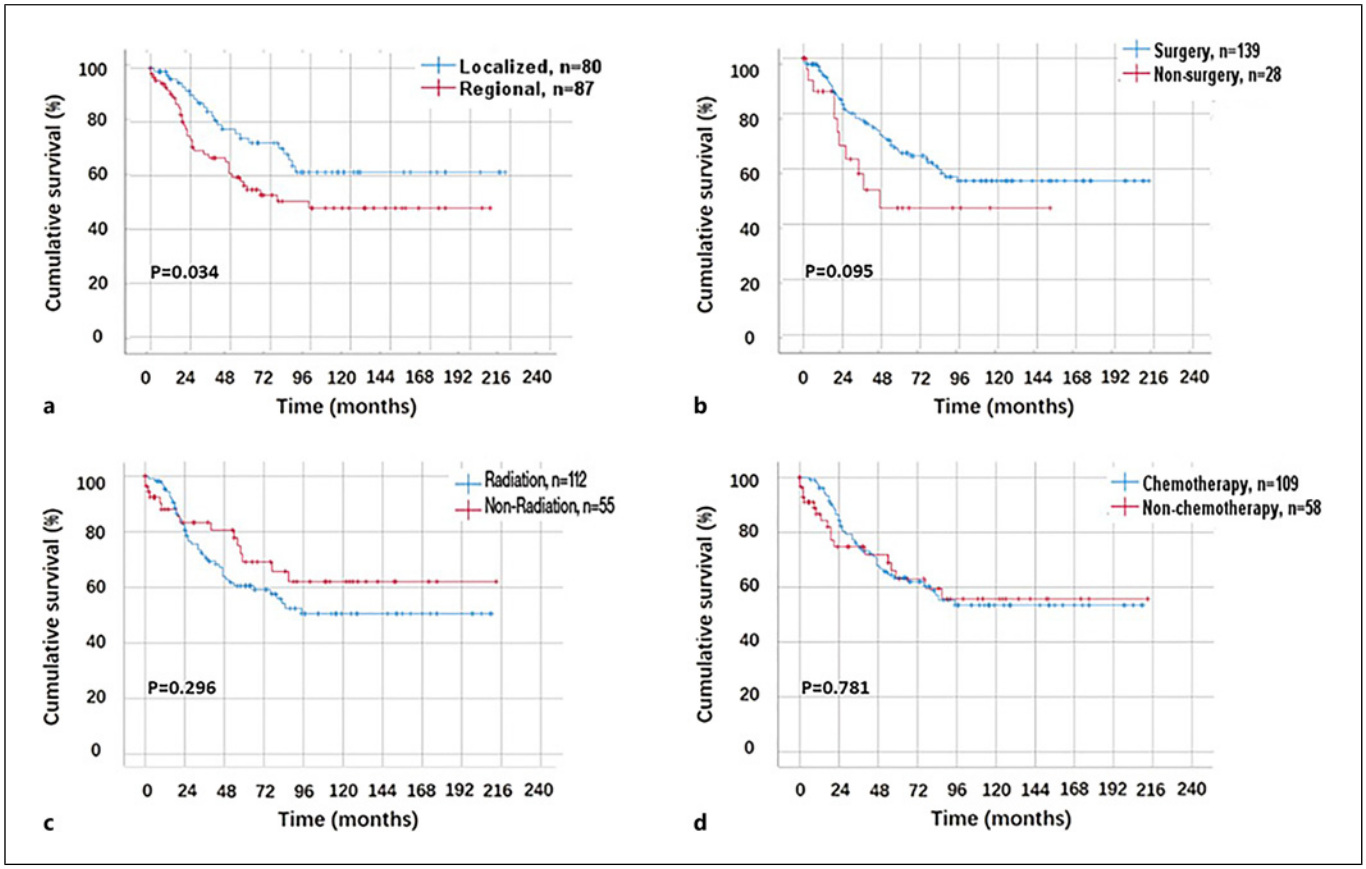

Fig. 3. a Kaplan-Meier estimated CSS for localized and regional AMAC patients (localized vs. regional: $p = 0.034$). **b** Kaplan-Meier estimated CSS for AMAC patients with and without surgery ($p = 0.095$). **c** Kaplan-Meier estimated CSS for AMAC patients with and without radiation ($p = 0.296$). **d** Kaplan-Meier estimated CSS for AMAC patients with and without chemotherapy ($p = 0.781$).

related to the higher count of individuals living with HIV in developed countries, where, throughout the era of highly active antiretroviral therapy, people living with HIV are capable of achieving a life expectancy that is near normal and go on to develop long-term sequelae of HIV infection. The increasing incidence of ASCC is related to the higher number of people living with HIV [14].

AMAC Showed a Better Prognosis than Typical ACC

Several previous studies have reported that patients with rectal MAC are associated with a poorer prognosis than rectal AC [15–17]; patients with rectal AC are worse prognosis than rectal SCC [2, 18]; patients with AAC has a worse prognosis than ASCC [2, 4, 19]. However, previous studies lacked survival data comparing AMAC with ASCC and AAC. This is the only research that we are aware of that compares the prognostic data of AMAC with ACC based on the findings of a large population-based investigation, to the best of our knowledge. Our study highly indicates that AMAC had a better prognosis than typical ACC; and AMAC might have a slight trend of worse prognosis than ASCC. Clarifying the reason behind why AMAC had a better prognosis than AAC is still a problem, and more research is required to fully understand the disease's pathophysiology and prognosis in order to do so.

Older Age at Diagnosis Was Associated with Poor Survival

Median age at diagnosis of AMAC in our study was 65 years; according to the findings of Malakhov et al. [20], the median age of patients with AAC is 66 years old, which is much older than the median age of patients with SCC, which is 59 years old. An older age (age >65 years) was related with a bad prognosis in our study, which is in line with the findings of earlier studies of typical ASCC and ACC cases [19–21]. Our findings could make a difference in the ability to forecast the outcome of treatment for this unusual histological subtype of anal cancer. It is possible that the low Karnofsky Performance Status (KPS) score in older patients, who often are unable to withstand intense therapy, is to blame for the poorer prognosis in these patients as they become older.

Table 4. Univariate and multivariate analyses for CSS of localized and regional AMAC patients

Variables	Level	Univariate		Multivariate	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	≤60 years	1		1	
	>60 years	2.131 (1.213–3.743)	0.009	2.137 (1.185–3.854)	0.012
Sex	Male	1		/	/
	Female	1.004 (0.583–1.730)	0.988	/	/
Race	White	1		/	/
	Black	1.319 (0.731–2.379)	0.358	/	/
	Asian or Pacific Islander	0.610 (0.189–1.969)	0.408	/	/
	Others/unknown	0.000 (0.000–0.000)	0.976	/	/
Marital status	Married	1		1	
	Unmarried	1.705 (1.003–2.898)	0.049	1.291 (0.741–2.249)	0.367
	Unknown	1.096 (0.422–2.849)	0.850	0.820 (0.309–2.177)	0.691
Tumor grade	Low	1		/	/
	High	1.403 (0.722–2.726)	0.318	/	/
	Unknown	0.944 (0.518–1.722)	0.852	/	/
Summary stage	Localized	1		1	
	Regional	1.744 (1.035–2.939)	0.037	1.795 (1.055–3.054)	0.031
Surgery	Yes	1		1	
	None/unknown	1.736 (0.899–3.353)	0.100	/	/
RT	Yes	1		/	/
	None/unknown	0.734 (0.409–1.317)	0.299	/	/
Chemotherapy	Yes	1		/	/
	No/unknown	1.082 (0.622–1.880)	0.782	/	/

CSS, cancer-specific survival; HR, hazard ratio; low tumor grade, well and moderately differentiated tumor grade; high tumor grade, poorly and undifferentiated tumor grade; RT, radiation therapy.

Surgery Was Associated with a Tendency toward Better Survival

Because AMAC is so uncommon, there has never been a clinical study conducted to investigate potential treatments for the condition. For the most common subtype of anal cancer, ASCC, the primary therapy is chemoradiotherapy; survival rates comparable to those achieved with surgical treatment are offered, and sphincter function is maintained [11, 22–24]. However, for the second common type of anal cancer, AAC, several studies have reported that combined modality including surgery with neoadjuvant or adjuvant chemoradiation can significantly improve survival [21, 25]. Consensus on treatment protocols has not been reached due to the low number of causes and lack of clinical trials. According to the findings of our research, surgery, which is the primary therapeutic option for AMAC patients, has a beneficial function in extending life. The Kaplan-Meier curves analysis and the Cox proportional hazards analysis both proved that not getting surgery was related to a tendency toward bad prognosis in CSS for non-metastatic AMAC patients. However, although both RT and chemotherapy have been used for most AMAC patients, both the Kaplan-Meier curves analysis and univariate Cox proportional hazards analysis demonstrated that receiving RT and chemotherapy was not associated with better survival. However, the SEER database lacks local control information, and the role of RT and chemotherapy in local control needs to be further studied. Therefore, this population-based study confirms the importance of surgery in the treatment of AMAC, which can prolong patient survival to some extent. Future efforts might investigate how to identify the early stage and how to most efficiently schedule these patients for surgical treatment.

Limitation

Our research, like previous studies that have used the SEER database as a data source, has limitations that require careful interpretation of the findings. These limitations are similar to those that have been found in other studies. First, although the SEER data include information regarding the use of surgery, RT, and chemotherapy, the specifics of these treatments (i.e., surgical margins, radiation dose, chemotherapy regimen, and chemotherapy sequence) are not recorded in the database. This is the case even though the data include information regarding the use of these treatments. Second, the SEER database is missing certain

essential clinical information that might be relevant to the patient's prognosis, such as tumor markers. This is a significant limitation. Third, the SEER database does not have the information on local control that is required to conduct an analysis of the association between local control and CSS. Such an analysis might assist us in better comprehending the effect that local control has on survival. In conclusion, even though this research looked at one of the biggest groups of AMAC patients, the total number of patients is still quite small.

Conclusions

In this research, even though AMAC is highly uncommon, we took use of the enormous sample size of the SEER database in order to examine the incidence and prognostic variables of AMAC. As a result of our investigation, we acquired the following insights:(1) AAI of AMAC was extremely low and relatively stable; (2) AMAC showed a better prognosis than typical AAC and had a slight trend of worse prognosis than ASCC without statistical significance; (3) a worse prognosis was related with older age at the time of diagnosis; (4) localized stage was associated with better prognosis; (5) surgery showed a trend toward improved survival of AMAC.

Acknowledgment

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Statement of Ethics

An ethics statement was not required for this study type as it is based exclusively on data extracted from SEER database. The study was based on a secondary analysis of the previously collected, publicly available, and de-identified data. The SEER database holds no identifying patient information. All data are anonymous. Written informed consent was not needed for this study. This investigation was conducted in accordance with ethical standards according to the Declaration of Helsinki and national and international guidelines and the Institutional Review Board of our hospital approved this study.

Conflict of Interest Statement

The authors declare that they have no competing interests, and all authors confirm accuracy.

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Author Contributions

Conceptualization: Guorong Yao, Ziyang Zhou, Feng Zhao, and Senxiang Yan; data curation and formal analysis: Guorong Yao, Ziyang Zhou, Yiqi Wang, Yanting Jiang, and Jili Wang; supervision and writing – review and editing: Feng Zhao and Senxiang Yan; and writing – original draft: Guorong Yao, Ziyang Zhou, and Yanting Jiang. The authors read and approved the final manuscript.

Data Availability Statement

The datasets for this study are publicly available from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute at https://seer.cancer.gov/.

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