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Early Colorectal Adenocarcinoma in Adenomatous Polyp: Clinical Characteristics and Prognostic Factors from 9899 Patients

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Abbreviations:

E-ACAP: Early Colorectal Adenocarcinoma in Adenomatous Polyp; CRC: Colorectal Cancer; APs: Adenomatous Polyps; SEER: Surveillance, Epidemiology and End Results; ICD: International Classification of Disease; PSM: Propensity Score Matching; NLNE: Lymph Nodes Examined; COD: Cause of Death; TNM: Tumor-Node-Metastasis; OS: overall survival; CSS: Cancer-Specific Survival; NOS: Not Specified

1. Abstract

1.1. Background and Aim

About 85%-90% of colorectal cancer (CRC) develops from adenomatous polyps. The aim of this study is to identify the clinical characteristics and prognostic factors of early colorectal adenocarcinoma in adenomatous polyp (E-ACAP).

1.2. Methods

Data of patients with E-ACAP was obtained from the Surveillance, Epidemiology, and End Results database for the years of 2010 and 2015. Multivariate logistic modeling was then performed to assess the impact of treatment methods on the prognosis of patients.

1.3. Results

In total, 9889 E-ACAP patients were included. The mean diagnostic age was 65.25 ± 12.26 years (range: 14-101), including 67.92% of 50-74 years,and 7.84% of less than 49 years which more than half (4.00%) were in 45-49 years. 94.35% (9340/9899) patients received coloproctectomy or colonoscopic local tumor destruction/excision, with 5.46% (540/9899) not receiving any treatment. 4.05% (401/9899) patients died of their E-ACAP, in comparison with the 72.38% (7165/9899) patients who survived or died of other causes. The effect on E-ACAP prognosis was multifactorial, including age, gender, race, healthcare, marital status, tumor grade and size, and treatment. Multivariate logistic modeling showed that patients who received coloproctectomyor colonoscopic local tumor destruction/excision had significant improved survival, compared with those who did not receive such treatment (overall survival [OS], $P < 0.001$; cancer-specific survival [CSS], $P < 0.001$).

1.4. Conclusion

E-ACAP has good prognosis. However, benefits of coloproctectomy are dissimilar among different age groups and attention needs to be paid to CRC screening of patients aged 45-49-years-old.

2. Introduction

Colorectal cancer (CRC), also termed large intestine cancer, is the third most common cause of cancer deaths in the United States [1]. Most of the CRCs (95%) are adenocarcinomas [2], and about 85%-90% of CRCs develop from adenomatous polyps (APs), following the adenoma-carcinoma sequence [2,3]. APs themselves are the most common neoplasm, according to histologic findings of biopsies from colonoscopy screening for CRC. Moreover, evidences

show that detection and removal of these cancer precursor lesions may prevent many cancers and reduce mortality [4]. CRC progression from a precancerous lesion to cancer generally takes 5-10 years, which provides an important time window for early diagnosis and clinical intervention; thus, screening programs for CRC are important among the general population [5]. Because of the aged condition itself and other coexisting conditions the occur more frequently with age, more and more CRC-diagnosed elderly patients cannot tolerate surgical treatment and suffer greater from related complications. Attributable to the widespread use of colonoscopic procedures, malignant lesions confined to the submucosa can be removed. However, colonoscopic local resection cannot solve the problem of lymph node metastasis nor distant metastasis. Different from lymph node metastasis with other tumor types, lymph node metastasis in CRC can occur in the very early stage. The choice of optimized interventions for such patients remains a practical concern of clinical management. In addition, in the United States, CRC incidence rates have been increasing among people less than 50 years of age, since 1990 [6,7], highlighting the importance of answering the question of what is the most reasonable age for starting CRC screening. This study was based upon a large sample of clinical and pathological data from patients with early colorectal adenocarcinoma in adenomatous polyp (E-ACAP) from the Surveillance, Epidemiology and End Results (SEER) database and was designed to analyze the essential situation of diagnosis and treatment of E-ACAP. The findings were expected to provide a clinical basis for the diagnosis, treatment and prevention of early CRC.

3. Materials and Methods

3.1. Patient Database

The data source was the SEER database of the National Cancer Institute (https://seer.cancer.gov/), which documents information on morbidity, mortality, and prevalence of millions of malignancies in the United States. We obtained all research data used in this study *via* the SEER-Stat software (SEER*Stat 8.3.6), which facilitates download of SEER cancer records and generates statistical data for the study of influence of a cancer of interest on a population. According to the third edition of the International Classification of Disease for Oncology (ICD-0-3), which was used in the SEER database, the diagnosis code of large intestine adenocarcinoma in ACAP is 8210/3. We collected SEER data for ACAP patients diagnosed between 2010 and 2015' these data originated from 18 registries linked to the County Attributes - Time Dependent (1990-2017) Income/Rurality, 1969-2018 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2020 and based on the November 2019 submission. Only patients with early-stage cancers, according to the American Joint Committee on Cancer 7th edition, were included for the current study. In addition, we took into account age, sex, race, marital status at diagnosis, as well as insurance recode, tumor site and size, number of *in situ*/malignant tumors, number of lymph nodes examined (NLNE), site-specific surgery, chemotherapy, radiation, cause of death (COD), specific death classification, and survival months for each patient.

Patients were categorized among three age groups using two methods, one as follows: less than 49-years-old, 50- to 64-years-old, and over 65-years-old [1]; other as follows: less than 49-years-old, 50- to 74-years-old, and over 75-years-old. Race-based classification included White, Black, other (American Indian/Alaska native, Asian/Pacific Islander), and unknown. Tumors were classified in two categories, according to their size: above 2 cm, and below 2 cm. The selection of cut-offs for continuous variables was based on the existing ACAP-related literature [3,8]. Patients with no available information on the considered clinical characteristics or survival information were excluded from analysis; this resulted in a final dataset of 9899 patients. The protocol of our study was approved by the Ethics Review Committee of the Shanghai Fifth People's Hospital affiliated to Fudan University. Due to the nature of the retrospective study, informed consent was not required.

3.2. Multivariate Logistic Modeling and Propensity Score Matching (PSM)

A multivariate logistic model was constructed with clinical factors including age, race, sex, marital status, registry, tumor stage, tumor size, NLNE, tumor location and chemotherapy to calculate the probability that a patient will undergo surgery. PSM was applied to reduce the effect of selection bias. All factors included in the aforementioned model were considered for PSM. Propensity score values are between 0 and 1, and patients with similar propensity scores from the treatment group and control group were matched until all patients in the smaller group were matched [8]. These clinicopathological characteristics, including sex, age, NLNE, pathological tumor-node-metastasis (TNM) stage, tumor location, marital status, race, and tumor size were identified as independent prognostic factors for CRC. Therefore, we selected variables based on their clinical significance in the univariate and multivariate analyses. The multivariate logistic model of the matched population was then used to develop a nomogram to predict the survival probability of patients with E-ACAP at 2, 4, 6 and 8 years post-diagnosis. The "MatchIt" package in R software was applied for this analysis, and the algorithm of 1:1 nearest neighbor matching was used in the model.

3.3. Statistical Analysis

All data were analyzed using the SPSS statistical software package, version 18 (IBM Corp., Armonk, NY, United States) and R version 3.5.2 (https://www.R-project.org/). The $\chi 2$ test was used, before and after PSM, to analyze the clinicopathological characteristics of patients undergoing lesion resection. Survival curves were plotted by the Kaplan-Meier method and compared using the log rank test. Univariate and multivariate Cox regression model analyses were performed with the R packages of "survminer" and "survival". The 2-, 4-, 6- and 8-year overall survival (OS) rates and cancer-specific survival (CSS) rates served as endpoints in the nomogram for multi-

variate Cox proportional hazards modeling. All statistical tests were 2-sided and a value of $P < 0.05$ was considered to indicate statistical significance.

4. Results

4.1. Clinical Characteristics of the Study Cohort

The clinical characteristics of the 9899 E-ACAP patients diagnosed between 2010 and 2015 and obtained for this study from the SEER database are shown in Table 1. On an annual basis, 1597 (16.13%), 1683 (17.00%), 1737 (17.55%), 1595 (16.11%), 1647 (16.64%) and 1640 (16.57%) E-ACAP cases had been diagnosed in 2010, 2011, 2012, 2014 and 2015, respectively. Considering the study population as a whole, the median survival time was 39 months (range: 0–83 months). A total of 401 (4.05%) of the patients died of E-ACAP by the end of follow-up.

Table 1: Clinical characteristics of patients with early colorectal adenocarcinoma in adenomatous polyp in the study cohort

Characteristics	**Cases, *n***	**Percent**
Total	9899	100.00
Age at diagnosis in year		
49	776	7.84
50 to 64	3920	39.60
≥ 65	5203	52.56
Sex		
Female	4411	44.56
Male	5488	55.44
Race		
White	7627	77.05
Black	1090	11.01
Other*	997	10.07
Unknown	185	1.87
Marital status at diagnosis		
Single (Never married)	1321	13.34
Married (including common law)	5525	55.81
Divorced	916	9.25
Widowed	1097	11.08
Unknown	1025	10.35
Insurance recode		
Insured**	9156	92.49
Uninsured	177	1.79
Unknown	566	5.72
Location		
Appendix	13	0.13
Colon	7245	73.19
Rectum	2641	26.68
Tumor size		
< 2 cm	3806	38.45
≥ 2 cm	1615	16.31
Unknown	4478	45.24
Number of *in situ*/malignant tumors		
1	6721	67.90
≥ 2	3178	32.10
NLNE		
< 15	6970	70.41

≥ 15	2929	29.59
Surgery		
Surgery-	540	5.46
Surgery+		
Local tumor destruction/excision	3281	33.14
Coloproctectomy	6078	61.40
Chemotherapy		
Chemotherapy-	9090	91.83
Chemotherapy+	809	8.17
Radiation Radiation-	9695	97.94
Radiation+	204	2.06
Death classification Alive or dead of other cause	7165	72.38
Dead: Attributable to this cancer	401	4.05
Dead: Missing/unknown cause of death	20	0.20
Not first tumor	2313	23.37

*Other indicates American Indian/Alaska native and Asian/Pacific Islander; **Insured indicates Insured+ Insured/no specifics +any Medicaid. NLNE: Number of lymph nodes examined.

4.2. Age

4.2.1. Age at Diagnosis and Year of Birth: For the entire population of 9899 E-ACAP patients, the age of diagnosis ranged from 14-years-old to 101-years-old, with a mean of 62.25 ± 12.27 years. The number of E-ACAP patients by age in years is shown in Figure 1. The majority of patients were born in the decade of 1940 to 1949, represented by a total of 2847 cases (28.76%). This was followed by 2488 (25.13%) cases born in 1950-1959, 2009 (20.29%) born in 1930-1939 and 1364 (13.80%) born in 1960-1969. The greatest portion of patients (6981/9899, 70.52%) were born after 1940, having an age of diagnosis less than 75-years-old. Six patients were born in the decade of 1990-1999 (0.06%) (Figure 2), having the youngest age at diagnosis of 14 years old.

4.2.2. Incidence by age group: The incidence of each age group is shown in Figure 3A. In detail, 52.56% were ≥ 65-years-old (Figure 4B) and 67.92% were 50-74-years-old at age of onset (Figure 4C). After 75 years of age, the number of patients with E-ACAP onset gradually declined in parallel with increasing age. Among the 776 (7.84% of the total) E-ACAP patients who were less than 49-years-old (mean: 43.12 ± 5.70 years) at age of onset, more than half (396/9899, 4.00%) were concentrated in the 45-49 years age range (Figure 3B); the E-ACAP incidence rates among that 45-49 years age group is shown in Figure 3C.

4. 3. Sex Disparities

The incidence of E-ACAP was higher among men (5488/9899, 55.44%) than among women (4411/9899, 44.56%). Among patients younger than 49 years of age, the incidence of E-ACAP was slightly higher for women (8.5%) than for men (7.3%), and the incidence of E-ACAP was higher for men aged 50-74 years compared to their female counterparts. After 65 years of age, especially after 75 years of age, the incidence of E-ACAP was higher for women (Figure 4B and 4C, respectively). Incidence of E-ACAP was also higher among married men than among married women, but higher among divorced and widowed women than among their male counterparts (Figure 4D).

4.4. Racial/Ethnic Disparities

The incidence among various races is shown in Figure 5A-C. Correspondingly, the medical insurance ratio was lower in the other-race group than that among either Whites or Blacks. Looking within races, we noted that White women (7628/9899, 42.92%) had a higher incidence of E-ACAP than White men (3378/9899, 34.12%).

4.5. Pathological Characteristics

The data for location, pathology and stage of E-ACAP are shown in Table 2. Grade II, moderately differentiated was the most common pathological grade (5917/9899, 59.77%). Among the total E-ACAP patients, 10.1% (1009/9899) had lymph node metastasis and 2.51% (248/9899) had distant metastasis.

4.6. Treatment and Factors Affecting Prognosis

Details regarding receipt of surgery, chemotherapy and radiotherapy and the various types (methods) of each treatment are shown in Table 3. Multivariate logical modeling analyses (including age at diagnosis, sex, race, health care, marital status, tumor grade and size, and treatment) compared the effects of different treatments on prognosis and the results are shown in Figure 6. The multivariate logistic

modeling analysis showed the CSS and OS of the untreated group to be significantly lower than those of the groups that received coloproctectomy or colonoscopic local tumor destruction/excision ($P < 0.001$) (Figure 6A and 6B, respectively). In order to compare the effects of the different methods of lesion resection on prognosis, PSM was used. All cases were screened before application of PSM for removal of cases involving the appendix ($n = 13$), of dead missing/unknown COD ($n = 20$), and of not-first tumor ($n = 2313$). After PSM, analysis showed that the CSS and OS of the coloproctectomy group were higher than those of the colonoscopic local tumor destruction/excision group ($P < 0.001$) (Figure 6C and 6D, respectively).

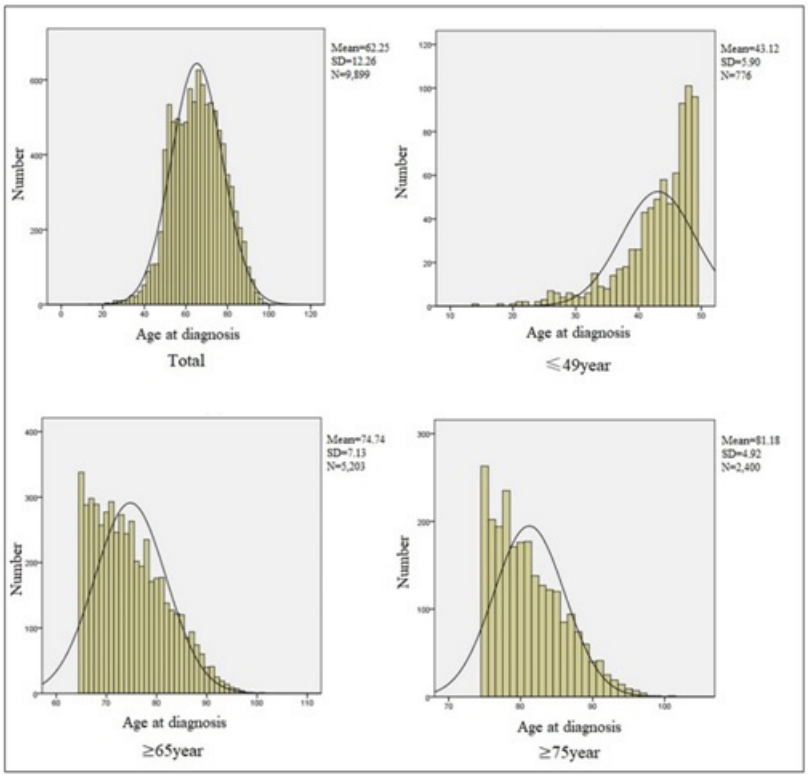

Figure 1: Early colorectal adenocarcinoma in adenomatous polyp patients classified by age at diagnosis**.** A: Entire study population; B: Under 49 years of age; C: Over 65 years of age; D: Over 75 years of age. E-ACAP: Early colorectal adenocarcinoma in adenomatous polyp.

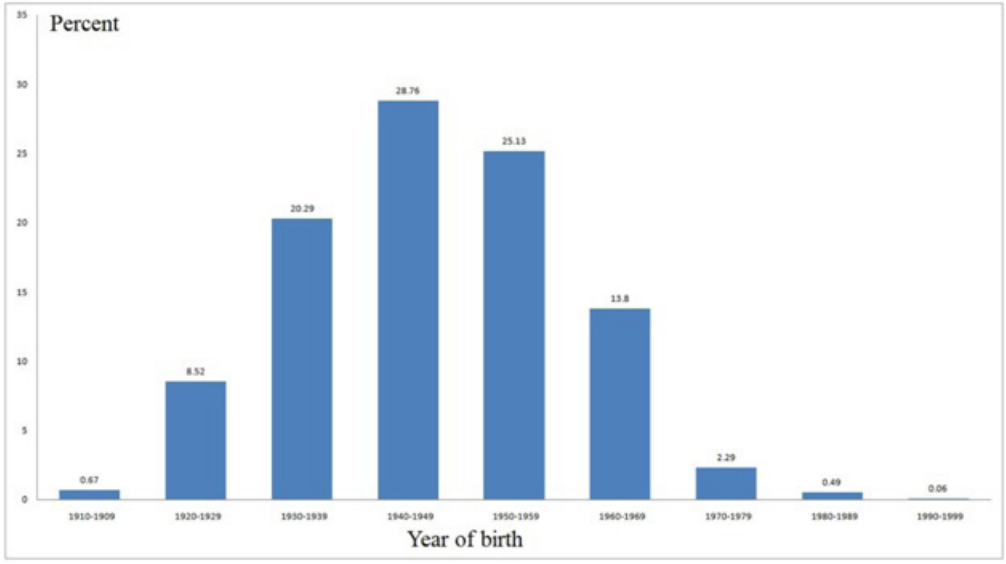

Figure 2: Early colorectal adenocarcinoma in adenomatous polyp patients classified by year of birth

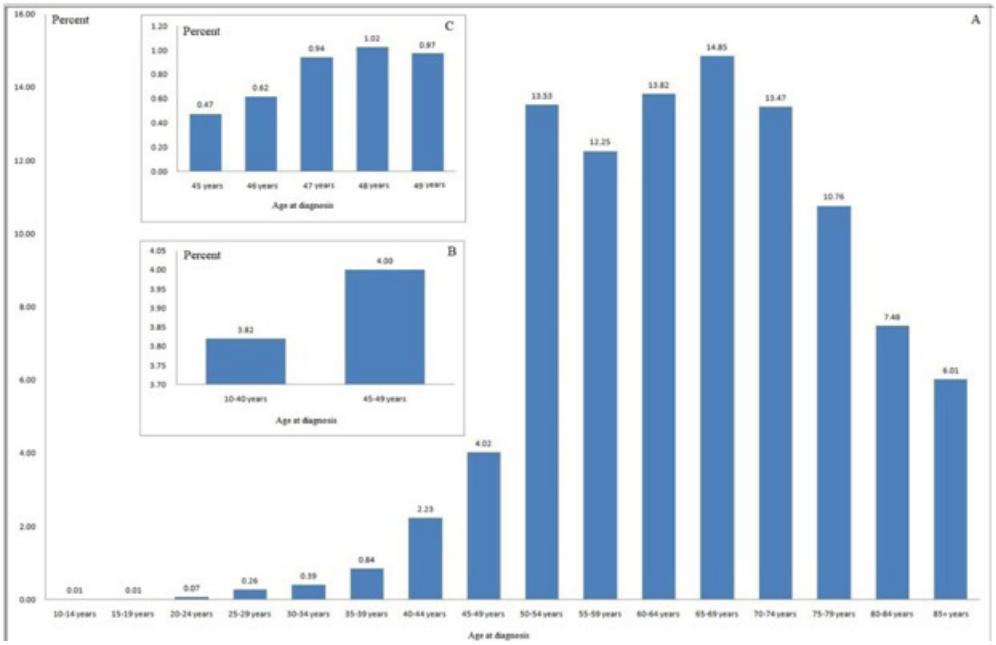

Figure 3: Incidence of age-specific early colorectal adenocarcinoma in adenomatous polyp classified by age. A: Ages 10 to > 84 years, subgrouped by 5-year intervals; B: Ages 10-40 years and 45-49; C: Individual ages between 45-49 years.

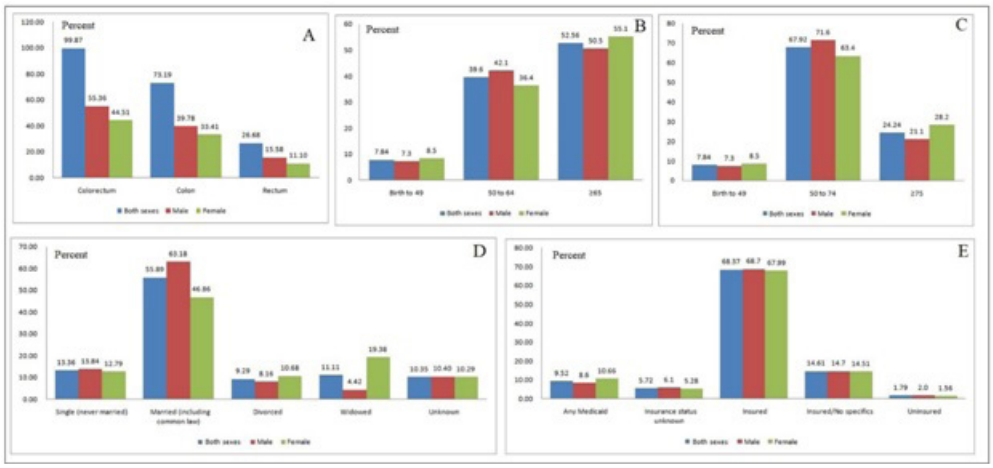

Figure 4: Subgroup incidences of early colorectal adenocarcinoma in adenomatous polyp. A: Tumor subsite; B: Age at diagnosis (less than 49-years-old, 50- to 64-years-old, and over 65-years-old); C: Age at diagnosis (less than 49-years-old, 50- to 74-years-old, and over 75-years-old);D: Marital status; E: Health care.

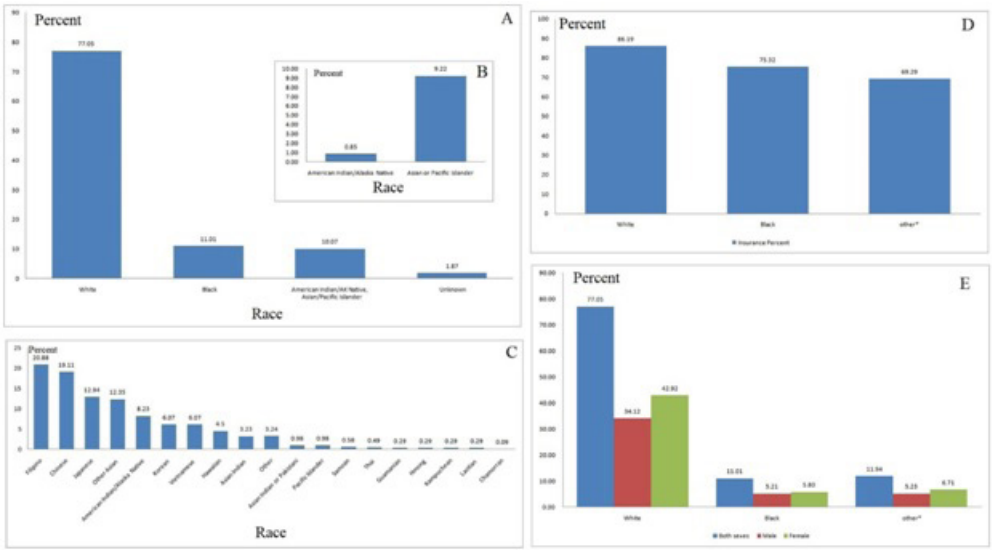

Figure 5: Incidence of early colorectal adenocarcinoma in adenomatous polyp patients classified by race. A: Race/ethnicity; B: Outline of race/ethnicity of American Indian/Alaska native and Asian/Pacific Islander; C: Detailed race/ethnicity of American Indian/Alaska native and Asian/Pacific Islander; D: Race/ethnicity and health care; (E) Race/ethnicity and sex.

Table 2: Pathological features of patients with early colorectal adenocarcinoma in adenomatous polyp in the study cohort

Features	Cases, *n*	Percent
Total	9899	100.00
Site Appendix	13	0.13
Cecum	776	7.84
Ascending colon	1183	11.95
Hepaticflexure	277	2.80
Transverse colon	758	7.66
Splenicflexure	153	1.55
Descending colon	599	6.05
Sigmoidcolon	3394	34.29
Rectosigmoidjunction	626	6.32
Rectum	2015	20.36
Large intestine,NOS	105	1.06
Site classification Distant	248	2.51
Localized	9031	91.23
Regional	620	6.26
Grade* Grade I	1609	16.25
GradeII	5917	59.77
GradeIII	548	5.54
GradeIV	79	0.80
Unknown	1746	17.64
N N0	8890	89.81
N1a	368	3.72
N1b	161	1.63
N1c	19	0.19
N1NOS	56	0.57
N2	1	0.01
N2a	56	0.57
N2b	18	0.18
N2NOS	2	0.02
NX	328	3.31
M M0	9651	97.49
M1a	152	1.54
M1b	86	0.87
M1NOS	10	0.10

*Grade: I denotes well differentiated; II denotes moderately differentiated; III denotes poorly differentiated; IV denotes nondifferentiated (anaplastic). M: Metastasis; N: Node; NOS: Not specified.

Table 3: Treatment of patients with early colorectal adenocarcinoma in adenomatous polyp in the study cohort

Treatment	Cases, *n*	Percent
Total Surgery	9899	100.00
Yes	9340	94.35
No		
Not performed, patient died prior to recommended surgery	3	0.03
Not recommended	392	3.96
Not recommended, contraindicated due to other condition; autopsy only	29	0.29
Recommended but not performed, patient refused	51	0.52
Recommended but not performed, unknown reason	50	0.51
Recommended ,unknown if performed	15	0.15
Death certificate; or autopsyonly	19	0.19
Chemotherapy No	9090	91.83
Yes	809	8.17
Radiation No	9695	97.94
Yes		
After surgery	124	1.25
Before and after surgery	7	0.07
Prior to surgery	66	0.67
Sequence unknown but both were given	1	0.01
Surgery both before and after radiation	6	0.06
Radiation No		
None/unknown	9608	97.06
Refused	19	0.19
Recommended, unknown if administered	16	0.16
Yes		
Beam radiation	246	2.49
Combination of beam with implants or isotopes	2	0.02
Radiation ,NOS method or sourcenot specified	6	0.06
Radioactive implants, includes brachytherapy	1	0.01
Radioisotopes	1	0.01

NOS: Not specified.

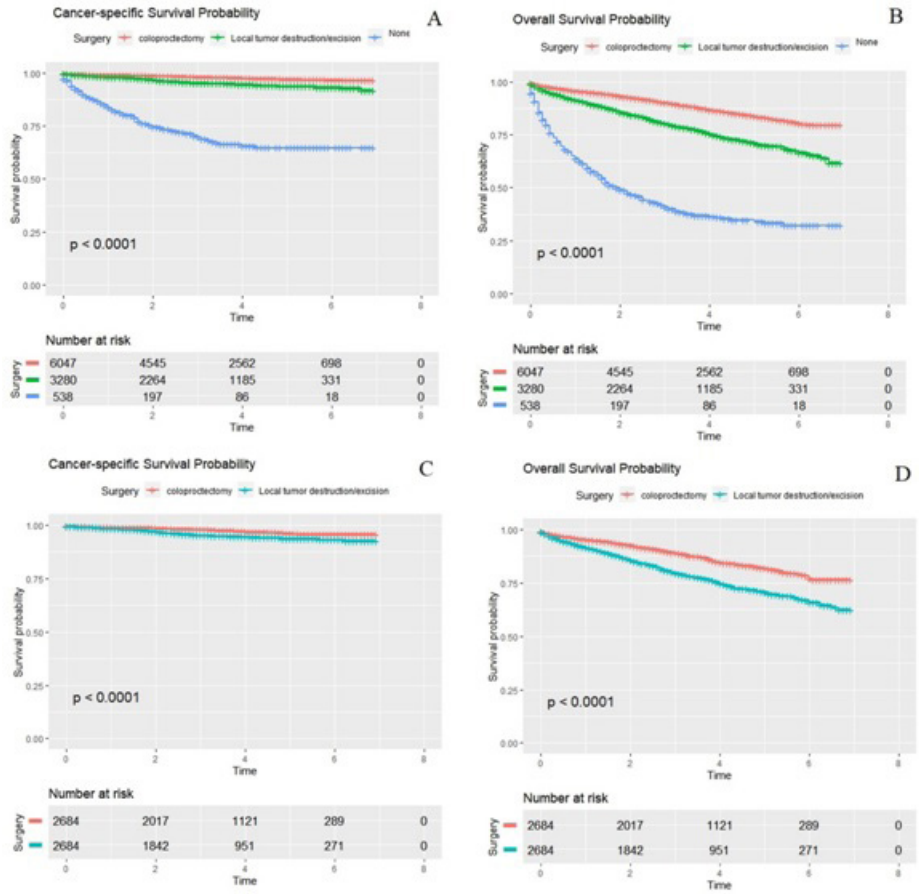

Figure 6: Multivariate logistic modeling. A-B: Overall survival (OS) (A) and cancer-specific survival (CSS) (B) analyses showed that early colorectal adenocarcinoma in adenomatous polyp (E-ACAP) patients who received coloproctectomy or colonoscopic local tumor destruction/excision had significantly improved survival, compared with those who did not receive such treatment (OS, $P < 0.001$; CSS, $P < 0.001$); C-D: OS (C) and CSS (D) analyses showed that E-ACAP patients who underwent coloproctectomy had better prognosis than those only received colonoscopic local tumor destruction/excision after propensity score matching (OS, $P < 0.001$; CSS, $P < 0.001$).

Table 4: Clinical characteristics of the study cohort before and after propensity score matching

	Before PSM			**After PSM**		
	Coloproctectomy	**Local tumor destruction/ excision**	***P*-value**	**Coloproctectomy**	**Local tumor destruction/ excision**	***P*-value**
Number	6047	3280		2684	2684	
Age in year			<0.001			0.725
≤49	513 (8.5)	221 (6.7)		194 (7.2)	191 (7.1)	
50-74	4240 (70.1)	2186 (66.6)		1787 (66.6)	1814 (67.6)	
≥75	1294 (21.4)	873 (26.6)		703 (26.2)	679 (25.3)	
Race			<0.001			0.948
Black	642 (10.6)	361 (11.0)		305 (11.4)	297 (11.1)	
Other*	610 (10.1)	349 (10.6)		275 (10.2)	279 (10.4)	
Unknown	37 (0.6)	116 (3.5)		33 (1.2)	37 (1.4)	
White	4758 (78.7)	2454 (74.8)		2071 (77.2)	2071 (77.2)	
Maritalstatus			<0.001			0.911
Married	3656 (60.5)	1634 (49.8)		1481 (55.2)	1494 (55.7)	
Unmarried	2013 (33.3)	1106 (33.7)		919 (34.2)	904 (33.7)	
Unknown	378 (6.3)	540 (16.5)		284 (10.6)	286 (10.7)	

Medicare			<0.001			0.136
Insured	5837 (96.5)	2861 (87.2)		2517 (93.8)	2483 (92.5)	
Uninsured	91 (1.5)	67 (2.0)		58 (2.2)	62 (2.3)	
Unknown	119 (2.0)	352 (10.7)		109 (4.1)	139 (5.2)	
Location			<0.001			0.645
Colon	4929 (81.5)	1943 (59.2)		1772 (66.0)	1755 (65.4)	
Rectum	1118 (18.5)	1337 (40.8)		912 (34.0)	929 (34.6)	
Site classification			<0.001			0.275
Distant	42 (0.7)	77 (2.3)		39 (1.5)	54 (2.0)	
Localized	5410 (89.5)	3189 (97.2)		2629 (98.0)	2616 (97.5)	
Regional	595 (9.8)	14 (0.4)		16 (0.6)	14 (0.5)	
Grade			<0.001			0.808
I-II	4797 (79.3)	2391 (72.9)		1979 (73.7)	1995 (74.3)	
III-IV	414 (6.8)	178 (5.4)		153 (5.7)	156 (5.8)	
Unknown	836 (13.8)	711 (21.7)		552 (20.6)	533 (19.9)	
Size			<0.001			0.772
＜2 cm	2636 (43.6)	1122 (34.2)		974 (36.3)	999 (37.2)	
≥2 cm	1035 (17.1)	345 (10.5)		336 (12.5)	334 (12.4)	
Unknown	2376 (39.3)	1813 (55.3)		1374 (51.2)	1351 (50.3)	
Radiotherapy			0.059			0.414
No						
Yes	119 (2.0)	85 (2.6)		57 (2.1)	67 (2.5)	
Chemotherapy			<0.001			0.228
No	5518 (91.3)	3130 (95.4)		2577 (96.0)	2558 (95.7)	
Yes	529 (8.7)	150 (4.6)		107 (4.0)	126 (4.7)	

Values are presented as *n* (%). *Other indicates American Indian/Alaska native and Asian/Pacific Islander. NLNE: Number of lymph nodes examined; PSM: Propensity score matching.

5. Discussion

CRC mortality rates are associated with tumor pathological types and stages. The majority of CRCs arise from APs, and, histologically-speaking, ACAP (in ICD-0-3) is the most common pathological type of CRC. Through this cohort study of 9889 E-ACAP patients diagnosed between 2010 and 2015 in the United States, we were able to describe E-ACAP characteristics from the sex-based perspective of age at diagnosis, year of birth, sex disparities, racial/ethnic disparities, pathological characteristics, and treatment. In particular, we compared the effects of different methods of treatment on the prognosis of E-ACAP and those patients who survived or died of other causes by using multivariate logistic modeling; we found that patients who underwent coloproctectomy had both high OS and high CSS. However, the multivariate logistic modeling analysis in our study also showed that the effect on E-ACAP prognosis was related to multiple factors; for example, the benefits of coloproctectomy were not the same in patients of different ages and, as such, the choice of treatment methods should be based on the age and condition of the patients. The reported 5-year relative survival rate of stage I CRC is 90%, while that of stage IV CRC with distant metastasis is only 14% [1]. The current study showed that the death rate (only 4.05%) in the E-ACAP group is significantly lower than that in the group of E-ACAP concurrent with other tumors (23.37%), and that in the group of patients who were still alive or who died of other causes (72.38%). In short, our study's findings suggest that E-ACAP has a better prognosis and lower mortality in general, highlighting the importance of diagnosis of T1 stage to reduce the mortality of CRC. The incidence and death rates for CRC in the United States have shown a declining trend in recent years since CRC screening was established for the general population [1]. The median age of diagnosis has dropped from 72 years during 2001-2002 to 66 years during 2015-2016 [9]. Interestingly, in this study, the incidence of E-ACAP in elderly patients was high and the maximum age was 101-years-old. More than half (52.56%) of patients with E-ACAP were diagnosed at ages ≥ 65 years, with 67.92% of the patients in this group being between the ages of 50-74-years-old. E-ACAP has a good prognosis and age of diagnosis is high in general, which may have provided an explanation for the death of a considerable number of patients in this study from other diseases or coexistent tumors of other types.

As CRC screening has become widespread in the United States, inci-

dence among older age groups has declined, coinciding with an increased incidence in younger individuals without CRC screening; this also explains why the CRC patient population as a whole is rapidly shifting towards younger age [10]. Incidence rates for individuals younger than 50-years-old have been increasing since the mid-1990s [10,11]. In this study, 7.84% of the patients with E-ACAP were not more than 49-years-old. The youngest was 14 and 6 patients were born in the decade of 1990-1999. Previous literatures suggest APs are rare under the age of 30 years, but their prevalence increases with increasing age. APs were undoubtedly detected less frequently 40 to 50 years ago than they are in present times [2]. It cannot be excluded that changes in diet and lifestyle, such as a diet high in animal fat and low in fruits and vegetables, smoking, vitamin D deficiency, obesity, and diabetes, might be responsible for this increased prevalence [12,13]. However, it is more likely that the more common observation of these lesions should be attributed to the widespread use of colonoscopy and even more so, in general, to the progressively increasing "medicalization" of Western society [2]. In 2018, the incorporation of these revised CRC incidence rates into microsimulation models led the American Cancer Society to issue a qualified recommendation to initiate CRC screening at age 45 instead of 50 [14,15]. A recent study (2004-2018) on CRC in patients aged 18-49 years, which included 23,977,025 unique individuals, showed that ages 45–49 accounted for 17% of the cohort [6]. In the current study (presented herein), more than half of the E-ACAP patients under 49-years-old received diagnosis at 45-49 years of age. The findings from our study also support the criticality of lowering the CRC screening age to 45 (from 50), especially in the presence of known risk factors. A recent study by others showed that, although the lifetime risk of CRC is similar in men (4.4%) and women (4.1%), because women have a longer life expectancy, the incidence rate is actually 31% higher in men [1]. In our study, the incidence of E-ACAP was also higher in men than in women. However, in our study, the incidence of female E-ACAP increased with age, especially after 75-years-old. In general, the reasons for higher rates in older men are not completely understood but believed to partly reflect differences in cumulative exposure to risk factors, and probably sex hormones, as well as complex interactions between these influencing factors [16,17]. CRC incidence and mortality rates also vary substantially by race and ethnicity. The burden of CRC also varies greatly within the broadly defined racial/ethnic groups in the United States. The reasons for racial disparities in CRC are complex but largely reflect differences in risk factor prevalence and health care access driven by disproportionately low socioeconomic status among Black individuals in the United States [18]. For example, although CRC incidence among Asian/Pacific Island men overall is 25% lower than among non-Hispanic Black men, rates in Japanese males are 23% higher [19]. CRC incidence has been rising by an annual rate of 3%-4% in China over the past nearly 30 years [20]. The Shanghai government established a "community-based CRC screening program" of the major public health services in from 2012 and CRC ranked second among all new cancer cases in Shanghai in 2015 [21,22]. These information serve to illustrate how the ratio of occurrence of CRC among Asians is also higher at present. Indeed, people with the lowest socioeconomic status, measured by self-reported education and census-tract socioeconomic deprivation are reportedly 40% more likely to be diagnosed with CRC than those with the highest socioeconomic status [23]. A similar proportion would be most likely due to historical differences in CRC screening uptake [24]. In our study, the E-ACAP incidence for White, Black and other races were 77.05%, 11.1% and 11.95%, respectively. The entire study population had received their E-ACAP diagnoses in the years between 2010 and 2015, and the proportion of health care for Blacks (75.32%) was higher than that for other races (69.62%), only below that for Whites (85.19%). This finding indicates the advantage of focusing on CRC screening strategies in the Black community. The low proportion of health insurance for people of other races, such as Indian/Alaska native and Asian/Pacific Islander, may have had a certain impact on the discovery of E-ACAP. Appendiceal cancer represents a special form of tumor. However, accumulating data have suggested that these rare malignancies are distinct from CRC in their histology, molecular profile, and clinical characteristics, including response to treatment. The incidence rate was reported as 1.3 per 100,000 person-years during 2012-2016 [25-27]. In 2010, the American Joint Committee on Cancer classified appendiceal carcinomas as separate from CRC for the first time and a new classification was added for appendiceal carcinoid tumors [28,29]. There were 19 appendiceal E-ACAP cases in this study, suggesting that some of the appendiceal cancers originated in polys. However, the specific pathogenesis of appendiceal cancer, the ratio of appendiceal ACAP, prognosis and so on remain unclear, and need further study. In this study, most of the E-ACAP patients had lesions limited to the colon or rectum, but still 10.1% had lymph node metastasis and 2.51% had distant metastasis. Multivariate analysis showed that resection of lesions (surgical and local resection) provided a better prognosis than non-resection. Compared with local resection, the prognosis of surgical patients is better in general. Due to the progress of colonoscopic surgery, more and more early CRC patients are able to have their lesions removed by colonoscopy. However, colonoscopy cannot solve the problem of lymph node metastasis and distant metastasis, so the prognosis of patients undergoing surgical resection is better. Although the prognosis of E-ACAP patients is better, 5.06% of the patients did not receive surgical treatment or colonoscopic local resection. This may be related to the majority of patients in this group having been of older age, either not active in treatment or having associated diseases. Elderly patients who cannot tolerate surgery, local resection under colonoscopy is an option that can improve prognosis. The multivariate logistic modeling analysis applied in our study also showed that the effect on E-ACAP prognosis was multifactorial. The impact of lesion resection method on prognosis of patients with E-ACAP is also relevant to patient age, race, marital status, Medicare, tumor location, tumor size, pathology grade, chemotherapy, and radiothera-

py. The choice of treatment methods should be based on the age and condition of the patients. Although the design and analysis of our study is rigorous, it still has several limitations. First, data on CRC diagnosis stages based on population of the United States were uniquely provided by SEER progrom, which may reflect the impact of the United States' programs and interventions on the prognosis of CRC. Second, the data from the study represent E-ACAP patients diagnosed between 2010 and 2015, and studies with long-term follow-up are recommended to verify our conclusions. In conclusion, E-ACAP mainly occurs in older patients. Patients under 49 years of age are the most common in the 45-49 age group and attention needs to be paid to the CRC screening of patients in this period. Fortunately, E-ACAP has a good prognosis and low mortality. Multiple factors influence E-ACAP prognosis, including age at diagnosis, sex, race, health care, marital status, tumor grade, tumor size and treatment. Although the prognosis of E-ACAP patients who receive coloproctectomy treatment is good, the benefits of coloproctectomy are not exactly the same for patients of different ages. The choice of treatment methods should be based on the age at diagnosis as well as condition of the patients. Coloproctectomy is a first recommended treatment strategy for young E-ACAP patients. For elderly patients, colonoscopic local tumor destruction/excision also has high OS and CSS in patients with E-ACAP and is also an option, especially for those with multiple combined diseases that cannot tolerate surgical treatment.

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