Conditional Survival After Surgical Resection of Appendiceal Tumors: a Population-based Study

Shutao Zhao
The Second Hospital of Jilin University
Chang Lu
The Second Hospital of Jilin University
Junan Li
The Second Hospital of Jilin University
Chao Zhang
The Second Hospital of Jilin University
Xudong Wang (wangxud@jlu.edu.cn)
The Second Hospital of Jilin University

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Abstract

Background: This study aimed to evaluate the conditional survival (CS) of appendiceal tumors (ATs) after surgery.

Methods: A total of 3,031 patients with ATs who underwent surgery were included in the Surveillance Epidemiology and End Results (SEER) database from 2004 to 2016. A multivariate Cox regression model was used to analyze the prognostic factors affecting overall survival (OS) and cancer-specific survival (CSS). CS was used to calculate the probability of survival for another 3 years after the patient had survived x years. The formulas were COS3 = OS (x + 3) /OS (x), and CCS3 = CSS (x + 3)/CSS (x).

Results: The 1-year, 3-year, and 5-year OSs for all patients were 95.6%, 83.3%, and 73.9%, respectively, while the 1-year, 3-year, and 5-year CSSs were 97.0%, 87.1%, and 79.9%, respectively. Age, grade, histology, N stage, carcinoembryonic antigen (CEA), and radiation were independent prognostic factors for OS and CSS. For patients that survived for 1 year, 3 years, and 5 years, their COS3s were 81.7%, 83.9%, and 87.0%, respectively. The CCS3s were 85.5%, 88.3%, and 92.0% respectively. In patients with poor clinicopathological factors, COS3 and CCS3 increased significantly, and the survival gap between OS and COS3, CSS and CCS3 was more obvious.

Conclusions: CS for appendiceal tumors were dynamic and increased over time, especially in patients with poor prognosis.

Introduction

Appendiceal tumors (ATs) are very rare, accounting for only about 1% of gastrointestinal tumors [1]. Merling first reported AT cases in 1838 [2]. Primary malignant ATs are divided into epithelial and non-epithelial tumors, and epithelial tumors mainly include appendiceal mucinous adenocarcinoma, non-mucous adenocarcinoma, and signet-ring cell carcinoma, among others. Non-epithelial tumors mainly include neuroendocrine tumors, leiomyosarcoma, and malignant lymphoma. Primary malignant tumors of the appendix lack specific clinical symptoms, and the initial manifestations mostly include appendicitis symptoms, which are typically found during operation. Previously, this disease was mostly diagnosed as mucinous carcinoma of the ovary, however, with the increase in people's cognition of the disease, it is believed to originate from the appendix, with some patients having secondary involvement in the ovary [3]. The prognosis of ATs is primarily related to their histological types and stages, and the 5-year disease-free survival rate is between 10% and 93%. Due to the lack of obvious clinical symptoms and late detection, prognosis is typically worse than that of colorectal cancer. Due to the low incidence of ATs, there are few studies on the relevant clinicopathological factors affecting prognosis, and our understanding of such factors is also limited [4]. At present, surgery is the only treatment for primary malignant AT s. In addition to surgical treatment, the treatment of malignant ATs also includes systemic chemotherapy and symptomatic support treatment.

The survival rate obtained from the survival curve refers to the OS or CSS at a fixed time point. For most patients with long-term survival of tumors, the risk of death changes with time. Thus, approaches of only studying survival rates at specific time points have their limitations. Conditional survival (CS) is a concept used to describe dynamic survival probabilities by considering changes in survival risk caused by prolonged survival periods [5–7]. Because it fully takes into account changes in the risk of death with survival time, it can provide more accurate prognostic information and follow-up strategies for long-term survival patients. CS has also been confirmed in a variety of digestive tract tumors [8–10]. To our knowledge, there have been no studies on the CS of ATs after surgery.

The purpose of this study was to identify the clinicopathological factors that influenced the OS and CSS in patients with postoperative appendiceal tumors using data from a large sample from the SEER database, and to further evaluate the postoperative changes in survival in patients with ATs using CS.

Materials And Methods

Patient population

SEER*Stat (version 8.3.6) software was used to identify patients with ATs diagnosed between 2004–2016. The inclusion criteria were: (1) pathologically confirmed ATs (ICD-O-3: 18.1), (2) no neoadjuvant radiotherapy, (3) surgical operation, (4) no distant metastasis (5) complete follow-up and survival data. The included variables were: age, sex, race, marital status, grade, surgery, histology, N stage, carcinoembryonic antigen (CEA), tumor deposits, radiotherapy and chemotherapy information, and survival information. We did not include T-staging as the criteria are different for appendiceal adenocarcinoma and carcinoid carcinoma. The T-staging criteria for appendiceal adenocarcinoma were based on the depth of tumor invasion, and the T-staging criteria for carcinoid carcinoma were based on the size of tumor. If the details of the above variables were unknown, they were excluded.

Statistical analysis

OS was defined as the time from postoperative onset to death (for any reason). CSS was defined as the time from the beginning of surgery to death due to ATs [11]. The Kaplan-Meier method was used for survival analyses, the log-rank was used to test differences between survival curves, and the Cox proportional hazard regression model was used to analyze the correlation between different clinicopathological factors and OS and CSS. $P < 0.05$ (bilateral) was considered statistically significant.

The 3-year CS calculated the possibility of survival for another 3 years after the patient had survived for x years. The formula was, CS3 = S (x + 3)/S, where S was OS or CSS at a specific time point [12]. In this study, COS3 and CCS3 were used instead of CS3 to calculate the survival rate of patients in the xth year. The 3-year CS was calculated as: COS3 = OS (x + 3)/OS(x), and CCS3 = CSS (x + 3)/CSS(x), respectively. Differences in CS between groups was calculated using a standardized differences (d) method [13], where d = (P2 - P1)/$\sqrt{}$ [P (1 - P)]. A $|d| < 0.1$ indicated no differences between groups; $0.1 \leq |d| < 0.3$ indicated small differences between the groups; $0.3 \leq |d| < 0.5$ indicated moderate differences between groups; and $|d| \geq 0.5$ indicated significant differences between groups. R software 4.0.0 and SPSS 21.0 were used for the analyses. $P < 0.05$ was considered to be statistically significant.

Results

Clinicopathological characteristics

A total of 3,031 patients who met the inclusion criteria were included in this study (Fig. 1). The median survival time was 48 months (0–155 months). The median age of the patients was 58 years; 65.8% were < 65-years-old, 50.1% were men, and the incidence in white men was higher (82.2%). A total of 67.7% of individuals were married, 23.7% had a tumor size < 2 cm, 66.6% had high and moderate differentiation, and 40.4% of patients underwent local resection. The histological type was adenocarcinoma in 36.2% of cases, N stage accounted for 79.3% of cases, and CEA was less than 5 ng/ml ratio was 17.9%. The proportion of patients who received postoperative radiotherapy and chemotherapy was 2.6% and 29.5, respectively (Supplementary file, Table S1).

Actual OS and CSS

By the end of the last follow-up, the median follow-up time was 64.0 months. A total of 841 patients (27.7%) died, 593 of whom (19.6%) died from cancer-specific causes. The 1-year, 3-year, and 5-year OSs were 95.6%, 83.3%, and 73.9%, respectively (Fig. 2A), and the 1-year, 3-year, and 5-year CSSs were 97.0%, 87.1%, and 79.9%, respectively (Fig. 2C). Univariate analysis showed that age, marital status, size, grade, history, N stage, CEA, tumor deposits, radiation, and chemotherapy were related to OS, and those factors were also related to CSS (Supplementary file, Table S2). Furthermore, age, marital status, grade, histology, N stage, CEA, and radiation were independent prognostic factors of OS. Similarly, age, size, grade, histology, N stage, CEA, radiation and chemotherapy were also independent prognostic factors of CSS (all $P < 0.05$; Table 1).

Table 1
The multivariate analyses of factors associated with overall survival and cancer-specific survival

Variable	OS-multivariate Cox regression		CSS-multivariate Cox regression	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (year)				
< 65				
≥ 65	2.125(1.840–2.454)	< 0.001	1.696(1.432–2.009)	< 0.001
Sex				
Male				
Female				
Race				
White				
Black				
API				
Other				
Marital status				
Married				
Unmarried	1.270(1.049–1.538)	0.014		
Unknown	1.208(1.002–1.455)	0.048		
Size				
< 2cm				
≥ 2cm			1.512(1.147–1.993)	0.003
Unknown			1.563(1.173–2.083)	0.002
Grade				
Well/moderately				
Poorly/undifferentiated	1.627(1.360–1.946)	< 0.001	1.725(1.404–2.121)	< 0.001
Unknown	1.178(0.959–1.446)	0.119	1.127(0.873–1.455)	0.358
Surgery				
Partial				
Total				
Surgery, NOS				
Histology				
Adenocarcinoma				
neuroendocrine carcinoma	0.285(0.176–0.461)	< 0.001	0.138(0.056–0.340)	< 0.001
Adenocarcinoid tumor	0.688(0.528–0.897)	0.006	0.669(0.486–0.922)	0.014
Mucinous	0.944(0.807–1.104)	0.470	0.993(0.825–1.195)	0.941
Signet ring cell carcinoma	1.050(0.809–1.363)	0.715	0.974(0.718–1.320)	0.864

CEA, carcinoembryonic antigen; API, Asian/Pacific Islander; OS, overall survival; CSS, cancer-specific survival

Variable	OS-multivariate Cox regression		CSS-multivariate Cox regression	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Other	0.690(0.341–1.397)	0.303	0.514(0.190–1.390)	0.190
N stage				
N0				
N+	2.326(1.998–2.709)	< 0.001	2.651(2.189–3.209)	< 0.001
Unknown	2.143(1.203–3.817)	0.010	3.186(1.686–6.018)	< 0.001
CEA (ng/ml)				
≤ 5				
> 5	2.020(1.576–2.587)	< 0.001	2.079(1.570–2.752)	< 0.001
Unknown	1.222(1.015–1.471)	0.035	1.178(0.950–1.460)	0.135
Tumor deposits				
Negative				
Positive				
Unknown				
Radiation				
No				
Yes	1.833(1.342–2.504)	< 0.001	1.847 (1.310–2.604)	< 0.001
Chemotherapy				
No				
Yes			1.324(1.095-1.600)	0.004
CEA, carcinoembryonic antigen; API, Asian/Pacific Islander; OS, overall survival; CSS, cancer-specific survival				

COS and comparisons to actual OS

By analyzing the mortality rate of disease progression over time, we found that the overall risk of death in patients remained at a low level with increasing time, while the risk of death from ATs decreased to the lowest level in the 10th year (Fig. 2B). However, the risk of death from ATs gradually increased after 10 years (Fig. 2D). The 3-year postoperative survival rate and 3-year COS are shown in Fig. 3A. We found that the COS3 of postoperative patients began to increase year over year from the third year, while the actual OS decreased year over year. In the first year, the COS3 decreased by 1.6 (81.7%), and in the third and fifth years, the COS3 increased by 0.6 (83.9%) and 3.7 (87.0%), respectively. The corresponding actual OSs decreased by 5.2 (78.1%), 13.4 (69.9%) and 19.0 (64.3%), respectively, in years 4, 6, and 8.

Table 2 gives detailed CS rates for patients who survived to a specific point in time. For example, if the patient survived at 1, 2, 3 and 4 years after surgery, the probability of survival at 5 years was 77.3%, 82.8%, 88.7%, and 94.6%, respectively.

Table 2
The probability that patients with appendiceal tumors after surgical resection will remain alive at a specific time point given that they have already survived for a certain amount of time

Total overall survival time, y	If the patient has survived, %							
	1y	2y	3y	4y	5y	6y	7y	8y
1	100							
2	93.4	100						
3	87.1	93.3	100					
4	81.7	87.5	93.8	100				
5	77.3	82.8	88.7	94.6	100			
6	73.1	78.3	83.9	89.5	94.6	100		
7	70.0	74.9	80.3	85.7	90.5	95.7	100	
8	67.2	72.0	77.2	82.3	87.0	92.0	96.1	100
y, year								

A subgroup analysis was performed based on independent prognostic factors associated with OS to further assess the effect of clinicopathological features on OS and COS3 (Figs. 4 and 5). OS decreased over time in each subgroup, while the value of COS3 increased gradually after surgery. In addition, COS3 values exceeded the OS values for each prognostic factor. Moreover, the difference between OS and COS3 was more significant in patients with clinicopathological features indicating an initially poor prognosis. On the contrary, the difference between them was relatively small in patients with clinical pathological features that indicated a good initial prognosis. For example, the 8-year OS of patients with grade 3/4 was 44.9%, and the 5-year COS3 was 79.8% (34.9%), while the 8-year OS of patients with grade 1/2 was 68.0%, and 5-year COS3 was 88.0% (20.0%). In patients with initially-poor clinicopathological prognostic features, the gap between COS3 was more significant. For example, the COS3 of grade 3/4 patients increased by 12.0% (67.1%-79.1%) within 5 years after surgery, while the COS3 of grade 1/2 patients only increased by 3.9%(84.1–88.0%) within 5 years after surgery. The d values (except for radiation and CEA) among all subgroups decreased with time. For example, the $|d|$ value between N0 and N1 dropped from 0.60 off the baseline to 0.30 for 3 years and then to 0.08 for 5 years (Table 3).

Table 3
Three-year conditional survival rates of patients with appendiceal tumors after surgical resection in relation to prognostic factors

Variable	COS3, %						CCSS3, %					
	Years since diagnosis						Years since diagnosis					
	Basline	1y	2y	3y	4y	5y	Basline	1y	2y	3y	4y	5y
Overall	83.3	81.7	82.8	83.9	85.7	87.0	87.1	85.5	86.8	88.3	90.3	92.0
Age (year)	0.37	0.39	0.38	0.37	0.35	0.34	0.34	0.35	0.34	0.32	0.30	0.27
< 65	88.0	86.3	86.6	86.9	88.7	89.7	89.7	87.9	88.6	89.5	91.2	92.1
≥ 65	74.0	72.2	74.2	76.9	78.4	80.6	81.9	80.3	82.8	85.6	88.3	91.9
d(< 65 vs. ≥65)	0.38	0.36	0.33	0.27	0.29	0.27	0.21	0.22	0.17	0.12	0.09	0.01
Marital status												
Married	84.1	81.7	82.1	84.2	86.0	87.5						
Unmarried	84.4	84.1	85.7	84.1	85.7	87.7						
Unknown	77.5	78.7	82.2	81.7	82.9	83.8						
d(Married vs. Unmarried)	-0.01	-0.06	-0.09	0.0	0.01	-0.01						
d(Married vs. Unknown)	0.17	0.08	-0.0	0.07	0.08	0.10						
Size												
< 2cm							93.9	92.2	92.4	93.2	95.4	97.8
≥ 2cm							83.7	81.6	83.7	85.8	88.1	89.9
Unknown							87.2	86.4	87.1	88.6	90.3	91.4
d(< 2cm vs. ≥2cm)							0.30	0.30	0.26	0.23	0.24	0.29
d(< 2cm vs. Unknown)							0.20	0.17	0.16	0.14	0.17	0.24
Grade												
Well/moderately	85.8	84.1	84.6	85.7	87.3	88.0	89.8	87.8	88.4	89.4	91.2	92.3
Poorly/undifferentiated	69.0	67.1	71.4	72.9	77.0	79.8	73.1	71.2	76.3	78.4	82.2	84.3
Unknown	86.2	84.2	84.6	85.0	85.9	88.2	89.1	88.4	89.0	90.7	92.2	94.8
d(Well/moderately vs. Poorly/undifferentiated)	0.45	0.44	0.35	0.35	0.29	0.24	0.49	0.47	0.36	0.34	0.30	0.30
d(Well/moderately vs. Unknown)	-0.01	-0.0	0.0	0.02	0.04	-0.01	0.02	-0.02	-0.02	-0.04	-0.03	-0.09
Histology												
Adenocarcinoma	79.3	77.4	79.5	82.7	86.6	88.0	84.3	82.3	84.2	87.4	90.7	93.0
Neuroendocrine carcinoma	96.5	97.3	98.4	95.9	96.5	91.1	98.9	99.6	100.0	100.0	100.0	100.0
Adenocarcinoid tumor	88.9	88.1	86.9	84.8	86.4	89.2	91.7	91.1	90.8	90.0	90.8	92.8
Mucinous	83.7	81.6	82.5	82.7	84.0	85.6	86.8	84.8	86.3	86.6	88.8	89.9
Signet ring cell carcinoma	71.0	69.1	72.5	80	76.4	79.7	75.4	71.8	75.9	85.0	86.4	89.9
Other	88.8	86.5	82.4	88.1	95.2	100.0	94.3	96.8	92.2	95.2	95.2	100.0

CEA, carcinoembryonic antigen; API, Asian/Pacific Islander; COS3, 3-year conditional overall survival; CCSS3, 3-year conditional cancer-specific survival; y, year; d, standardized difference

Variable	COS3, %						CCSS3, %					
d(Adenocarcinoma vs. Neuroendocrine carcinoma)	-0.46	-0.51	-0.50	-0.36	-0.28	-0.09	-0.43	-0.49	-0.46	-0.39	-0.31	-0.26
d(Adenocarcinoma vs. Adenocarcinoid tumor)	-0.26	-0.27	-0.19	-0.06	0.01	-0.04	-0.22	-0.25	-0.19	-0.08	0.00	0.01
d(Adenocarcinoma vs. Mucinous)	-0.12	-0.11	-0.08	0.00	0.07	0.07	-0.07	-0.07	-0.06	0.03	0.06	0.11
d(Adenocarcinoma vs. Signet ring cell carcinoma)	0.22	0.21	0.18	0.07	0.29	0.24	0.26	0.30	0.24	0.08	0.14	0.11
d(Adenocarcinoma vs. Other)	-0.26	-0.23	-0.08	-0.15	-0.25	-0.35	-0.29	-0.41	-0.24	-0.24	-0.15	-0.26
N stage												
N0	87.8	85.7	85.7	85.6	86.9	87.4	91.8	89.6	90.0	90.1	91.7	92.8
N+	65.6	64.7	68.4	74.4	78.7	84.8	68.9	68.0	71.8	78.1	81.8	86.9
Unknown	69.2	73.8	82.2	81.8	81.8	90.0	69.2	73.8	82.2	90.9	90.9	100.0
d(N0 vs. N+)	0.60	0.54	0.46	0.30	0.23	0.08	0.67	0.62	0.54	0.38	0.33	0.22
d(N0 vs. Unknown)	0.50	0.31	0.09	0.11	0.15	-0.08	0.66	0.45	0.23	-0.03	0.03	-0.27
CEA (ng/ml)												
≤ 5	83.6	80.0	83.4	86.4	88.6	88.9	86.0	83.2	86.7	89.7	91.5	91.4
> 5	69.4	69.3	68.5	71.5	73.2	79.6	72.1	73.6	76.4	80.4	83.7	88.0
Unknown	84.7	83.4	84.0	84.4	86.1	87.3	89.0	87.3	87.9	88.8	90.7	92.6
d(≤ 5 vs. >5)	0.38	0.27	0.39	0.40	0.44	0.27	0.41	0.27	0.32	0.29	0.26	0.13
d(≤ 5 vs. Unknown)	-0.03	-0.09	-0.02	0.05	0.08	0.05	-0.09	-0.12	-0.04	0.03	0.03	-0.04
Radiation												
No	83.7	82.4	83.6	84.5	86.0	87.3	87.6	86.2	87.7	88.9	90.9	92.3
Yes	68.3	59.7	56.2	63.8	71.8	81.7	71.5	61.6	58.7	65.6	73.7	81.8
d(No vs. Yes)	0.42	0.58	0.72	0.56	0.41	0.16	0.47	0.70	0.85	0.73	0.57	0.39
Chemotherapy												
No							90.9	90.1	90.6	91.1	92.4	93.4
Yes							78.3	75.1	77.6	81.4	85.1	88.3
d(No vs. Yes)							0.37	0.43	0.38	0.30	0.24	0.19

CEA, carcinoembryonic antigen; API, Asian/Pacific Islander; COS3, 3-year conditional overall survival; CCSS3, 3-year conditional cancer-specific survival; y, year; d, standardized difference

CCS and comparisons to actual CSS

The actual CSS and CCS3 are shown in Fig. 3B. We found that postoperative CCS3 began to increase year over year in the third year, while the actual CSS decreased year over year. The 1-year CCS3 decreased by 1.6 (85.5%), and the 3-year and 5-year CCS3 increased by

+ 1.2 (88.3%) and + 4.9 (92.0%), respectively, while the corresponding actual CSS decreased by 4.2 (82.9%), 10.2 (76.9%), and 13.6 (73.5%), respectively in years 4, 6 and 8.

The detailed CCS3 of patients who survived to a specific point in time are shown in Table S3 (Supplementary file). For example, if the patient survived 1, 2, 3, and 4 years after surgery, the probability of not dying of appendiceal tumor-related diseases at 5 years was 82.4%, 86.8%, 91.7%, and 96.4%, respectively.

A subgroup analysis was performed based on independent prognostic factors associated with CSS to further assess the effect of clinicopathological factors on CSS and CCS3 (Supplementary file, Figure S1,2). CSS decreased over time in each subgroup, while postoperative CCS3 values increased gradually. In addition, CCS3 values exceeded the CSS values for each prognostic factor. Moreover, the difference between CSS and CCS3 was more obvious in patients with initially poor prognostic clinicopathological characteristics. In contrast, the difference was relatively small in patients with good initial prognoses based on clinicopathological features. For example, the 8-year CSS for patients with grade 3/4 was 52.8%, and the 5-year CCS3 was 84.3% (31.5%), the 8-year CSS for patients with Grade 1/2 was 76.7%, and the 5-year CCS3 was 92.3% (15.6%). Moreover, the difference between CCS3 was more significant in patients with initially poor prognostic clinicopathological characteristics. For example, the 5-year postoperative CCS3 in patients with grade 3/4 increased 11.2% (73.1–84.3%), while the 5-year postoperative CCS3 in patients with grade 1/2 only increased 4.5% (87.8% – 92.3%). The *d* value (except for the radiation group) among all subgroups decreased over time. For example, the |*d*| value between N0 and N1 dropped from 0.67 at baseline to 0.38 in year 3 and 0.22 in year 5 (Table 3).

Discussion

Among the appendix specimens removed during appendectomies in foreign countries, approximately 1% had ATs [14, 15]. The 5-year OS of primary ATs reached 46.2%, and the prognosis largely depended on the histological subtypes [16]. However, due to its low incidence, most studies detailing AT prognosis have been retrospective studies with small sample sizes. Additionally, the prognostic factors for AT remain controversial. For example, Kabbani et al. [17] showed that mucinous adenocarcinoma had a better prognosis than non-mucinous adenocarcinoma, while Ito et al. [18] suggested that mucinous adenocarcinoma had a worse prognosis than non-mucinous adenocarcinoma. Therefore, it is important to analyze the prognostic factors in large samples of patients with primary ATs as the traditional assessment of survival at a specific time point cannot accurately assess patient prognosis.

Our study found that age, marital status, grade, history, N stage, CEA, and radiation were independent prognostic factors of OS and CSS (all $P < 0.05$). Asare et al. [19] found that regardless of whether an adenocarcinoma was mucinous (HR = 1.03; 95% CI: 1.03–1.04; $P < 0.001$) or non-mucinous (HR = 1.03;95% CI: 1.0–1.04; $P < 0.001$), old age was a poor prognostic factor. Our study also found that patients aged ≥ 65 had a poor prognosis, which may be related to the decreased perception and reaction ability of elderly patients, and the high incidence of postoperative complications.

Our study found that the prognosis of unmarried patients was poor, which may be due to their low enthusiasm and unwillingness to obtain treatment [20]. Our study found that the prognosis of poorly differentiated and undifferentiated ATs was worse. Previous studies found that the 5-year OS of well-differentiated and undifferentiated ATs was 56.7%, while that of undifferentiated tumors was only 11.3% [19]. Overman et al. [21] also found that the 5-year CSS of well differentiated ATs was 48%, while that of poorly differentiated ATs was only 5%, which was consistent with our research results.

Appendiceal carcinoid is a neuroendocrine tumor with low incidence, mostly young women. It is a low grade malignant tumor and consists of intestinal silver cells. Carcinoid tumors are primarily located in the submucosa of the head or middle portion of the appendix, with slow growth. Most carcinoid tumors have biological characteristics of benign tumors; there are few manifestations of carcinoid syndrome, when the syndrome appears, the tumor has extensive metastasis, most of which have low metastasis rate and good prognosis [22–23]. Adenocarcinoma accounts for 67% of ATs, and its biological behavior is similar to that of colon cancer. Adenocarcinoma has a high degree of malignancy in appendiceal malignant tumors, and most of which exhibit metastases at the time of surgery [24, 25]. Modlin et al. [16] found that the 5-year OS of ATs was 47.9%, while that of neuroendocrine tumors was 83.3%, that of signet-ring cell carcinomas was 20.3%, and that of lymphomas was 1.7%. Our study also showed that the prognosis of neuroendocrine tumors was better than that of adenocarcinoma.

The presence of lymph node metastasis means that the stage is late, the scope of surgical resection and dissection must be increased, and the prognosis is poor. Our study found that the prognosis of patients with lymph node metastases was poor. However, some studies have found that lymph node metastasis is not an independent prognostic factor for OS ($P = 0.22$), which may be due to the small number

of cases and selection bias [21]. Due to the lack of specific clinical manifestations in patients with ATs, early diagnosis is difficult, and most of the patients are already in the advanced stage when they are identified. Therefore, early serum markers are urgently needed to diagnose and implement treatment measures.

CEA is an independent prognostic factor for patients with colorectal cancer. Our study found that CEA was also an independent prognostic factor for patients with appendiceal tumors, and was conducive to the early prognosis of patients and the implementation of reasonable treatment programs to improve prognosis [26, 27]. For appendiceal adenocarcinoma, the chemotherapy regimen for colorectal cancer is often implemented. Studies have shown that a FOLFOX or XELOX regimen can improve the prognosis of patients with adenocarcinoma [28, 29]. Appendiceal neuroendocrine tumors are not sensitive to radiotherapy, and chemotherapy only has a temporary effect; thus, conventional radiotherapy and chemotherapy are not used for neuroendocrine tumors. A CHOP regimen can improve the OS of patients with lymphoma. Our study found that chemotherapy failed to improve the overall prognosis of patients, and that the adverse effects of radiotherapy outweighed the benefits. Complete surgical resection achieved a better prognosis. Therefore, we do not recommend that patients with appendiceal tumor receive radiotherapy or chemotherapy after surgery, while patients with lymphoma or adenocarcinoma should consider chemotherapy. However, some studies have shown that surgery combined with intraperitoneal chemotherapy can effectively reduce recurrence and prolong the survival time of patients with appendiceal tumors with peritoneal metastasis [1, 30, 31]. Immune and targeted therapy may be the focus of future research [32, 33].

Survival statistics are significant for monitoring the prognosis of patients. The traditional prognostic evaluation methods for patients with primary appendiceal tumors are based on histological type, and cumulative survival rates (OS, CSS). However, this traditional survival assessment method only provides a static risk assessment and does not take into account changes in the risk of death based on the time of survival after surgery. Notably, the risk of death after diagnosis changes with extensions in patients' survival periods [34]. Compared with the traditional evaluation methods, the CS has the advantage of reflecting the survival probability over time, which may be more useful for postoperative monitoring.

In this study, we draw several conclusions. First, in contrast to traditional OS assessments, CSS showed a downward trend over time, while COS3 and CCS3 showed an initial downward trend followed by an increase over time. CCS3 reached more than 90% after 4 years of survival, indicating that those patients had a high expectation of cancer-free survival. With the extension of survival time, COS3 and CCS3 were higher than the actual survival at each time point. In addition, the difference between the actual survival rate and the estimated values of COS3 and CCS3 was larger in patients who were initially diagnosed with clinicopathological features with poor prognosis. Moreover, the COS3 and CCS3 of those patients showed a more significant growth trend over time. This suggests that the impact of those clinicopathological features with poor prognosis on patients may decrease over time. We found that with the exception of radiation and CEA, the d values between prognostic factors gradually decreased as time progressed. Those data indicated that with the progression of time, the prognosis of patients with high risk factors was similar to that of patients with low risk factors. Those findings can reduce the anxiety of patients with adverse prognostic pathological factors in the early stage and have important guiding significance for their long-term survival [35].

Our study also had some guiding significance for follow-up strategies. As time progressed, the risk of death decreased and CS may reach a critical point. For example, the COS3 of N0 patients reached 89.6% in the first year, while that of N + patients only reached 86.9% in the fifth year. Thus, the 5-year follow-up may be insufficient for patients with poor prognosis, but it may be too long for patients with good prognosis. This conclusion helps clinicians formulate individual follow-up strategies, reduce unnecessary follow-up, reduce medical expenses, and reduce the anxiety of patients caused by tumor recurrence; thereby improving their quality of life.

Our study also had some limitations. First, this was a retrospective study, and inevitably there was selection bias. There was a lack of information on neoadjuvant therapy in the study and it is undeniable that neoadjuvant therapy can change the postoperative recurrence pattern of patients, which may also be an important research direction for this disease in the future. Our results lacked validation from patient data from Asia and Europe. Our study is the first to dynamically evaluate the prognosis of patients with large sample data and fully incorporate various clinicopathological factors that may affect patients' OS and CSS.

Conclusions

Our study showed that age, grade, histology, N stage, CEA, and radiation were independent prognostic factors for OS and CSS in patients with postoperative appendiceal tumors. The CS after primary appendiceal tumor surgery was dynamic and decreased briefly before increasing over time. CS increased more significantly in patients with poor prognostic clinicopathological characteristics. Therefore, CS can provide more valuable and accurate long-term prognoses in patients with appendiceal tumors after surgery.

Declarations

AUTHORS' CONTRIBUTIONS

XDW designed the research. STZ took part in designing the research, CL collected the data, JAL analyzed the date and wrote the manuscript. CZ collected the data, analyzed the date. All authors reviewed the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

All data used in this study is available at www.seer.cancer.gov.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was based on publicly available data from the SEER database, and did not involve interaction with human subjects or the use of personally identifiable information. The study did not require informed consent for SEER registration cases, and the author obtained a "limited use data agreement" from SEER. No trial registration was required.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

There is no competing interest regarding the publication of this paper.

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Figures

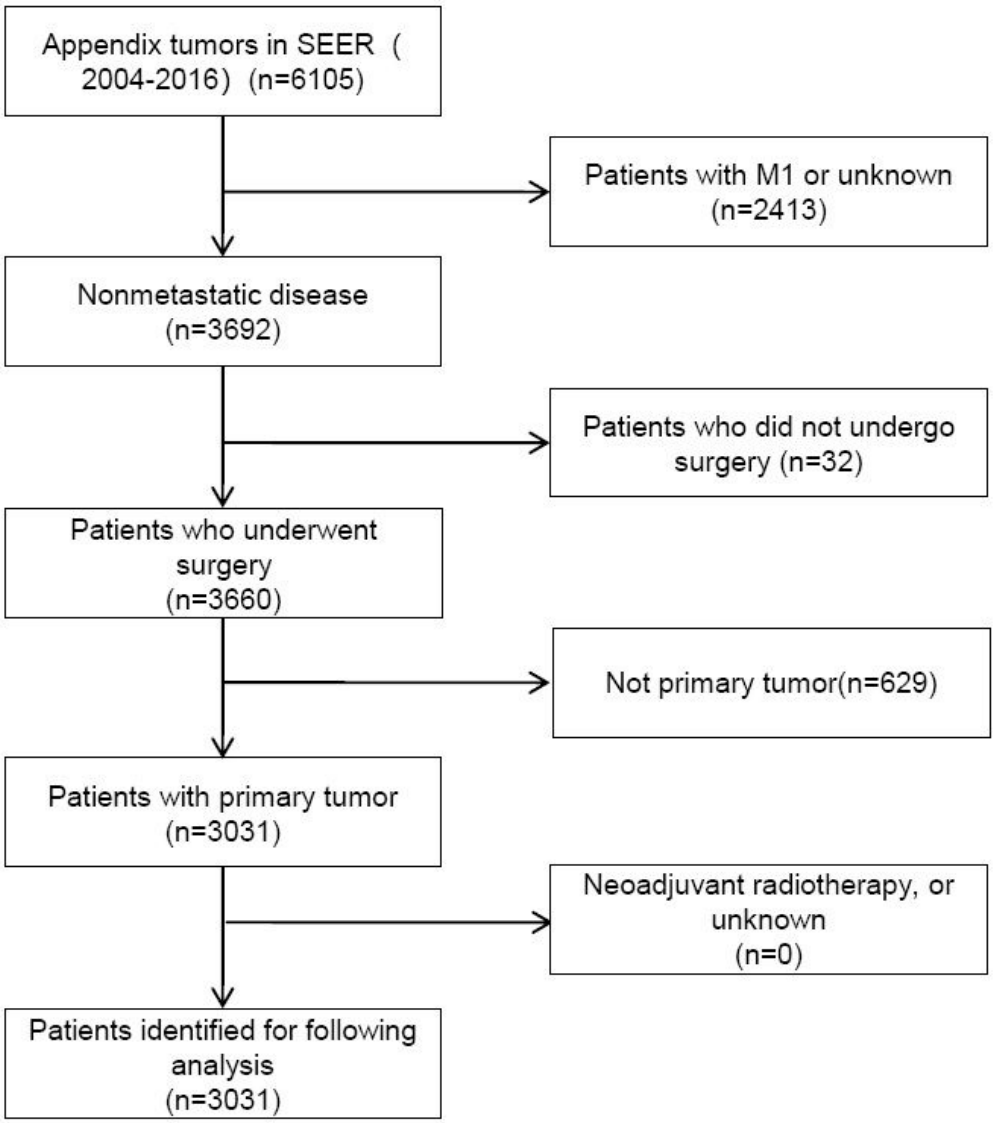

Figure 1

Flowchart of the selection process of included patients

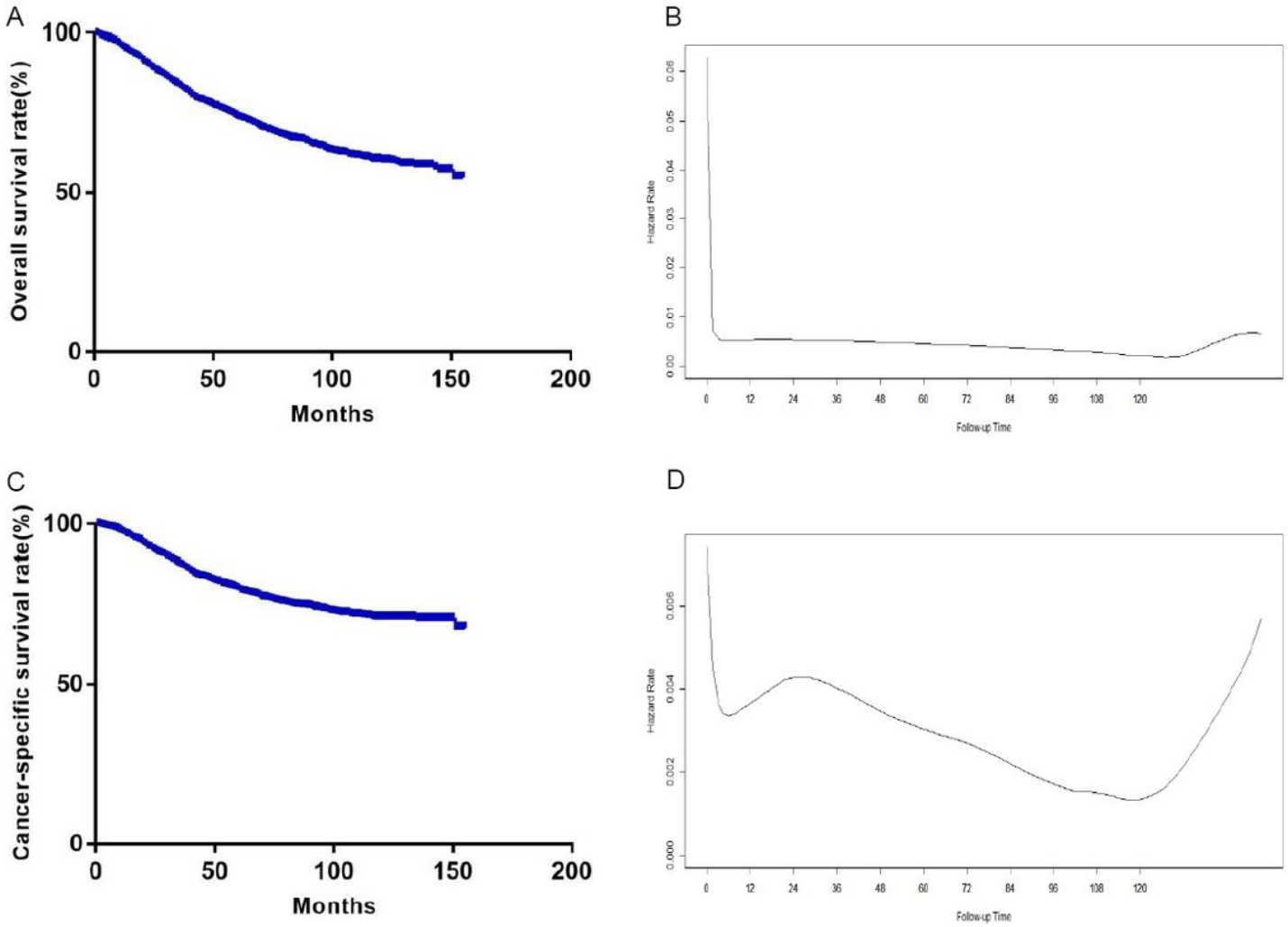

Figure 2

Kaplan-Meier survival curve of overall survival (A) and cancer-specific survival (C); hazard estimates of death from any reason (B) or appendiceal tumors (D) are illustrated for all patients in the cohort

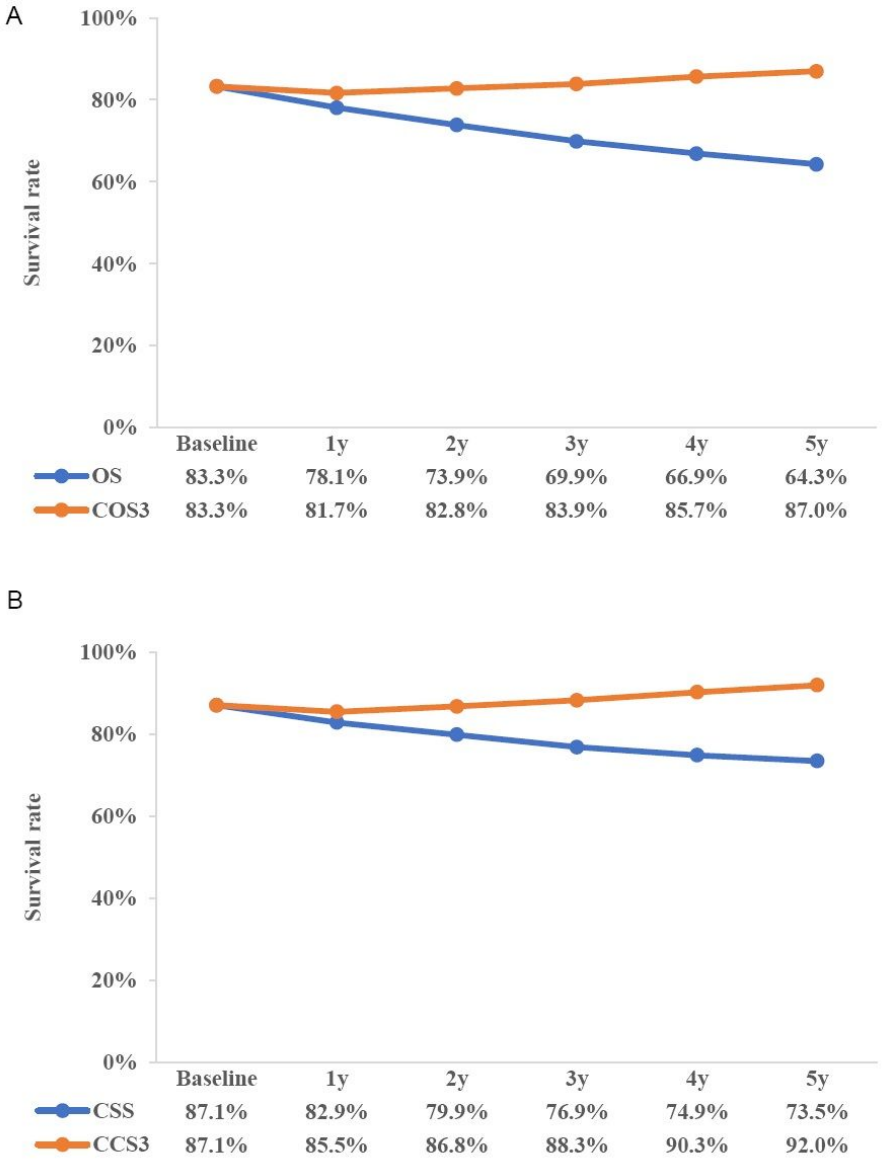

Figure 3

(A) Conditional overall survival relative to actual overall survival; (B) Conditional cancer-specific survival relative to actual cancer-specific survival

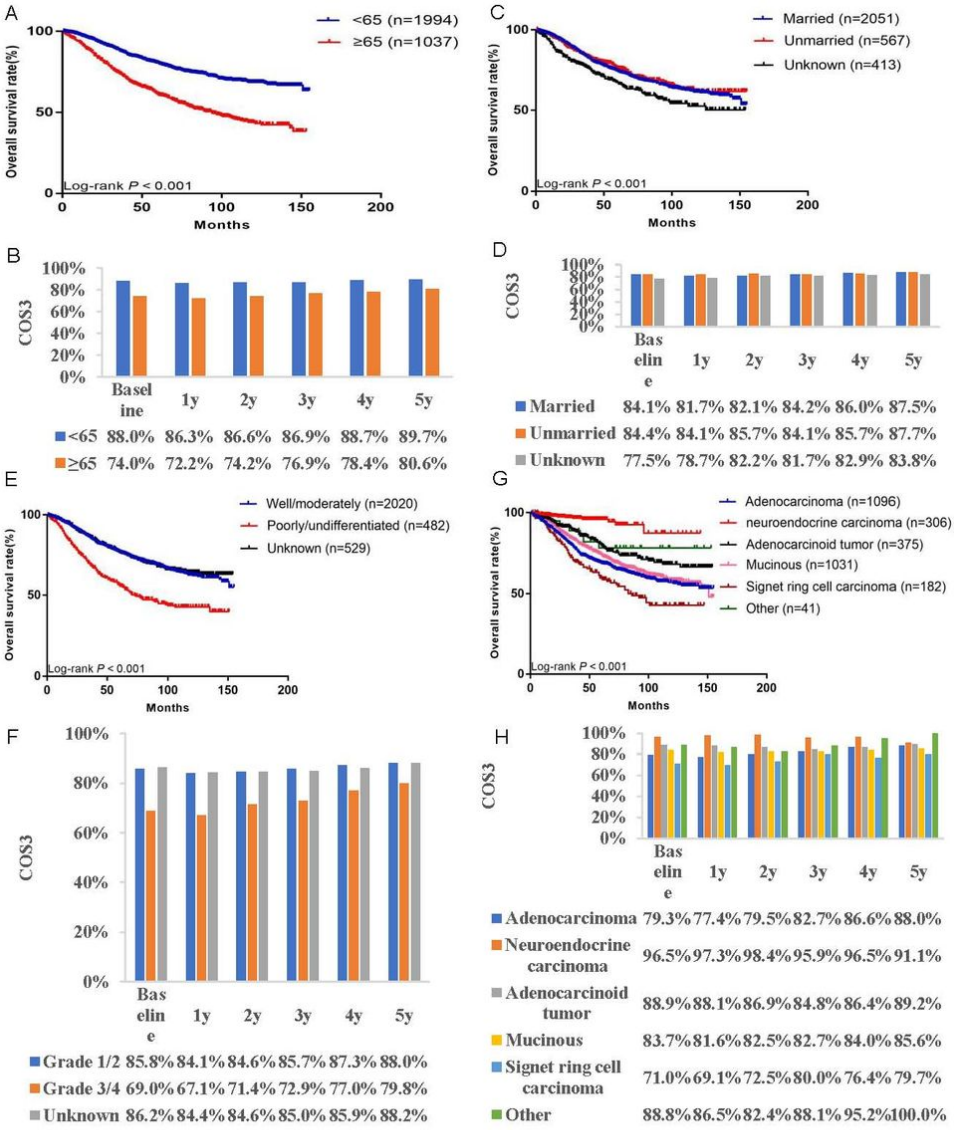

Figure 4

Actual overall survival stratified by: (A) age, (C) marital status, (E) grade, and (G) histology vs conditional overall survival relative to actual survival stratified by: (B) age, (D) marital status, (F) grade, and (H) histology

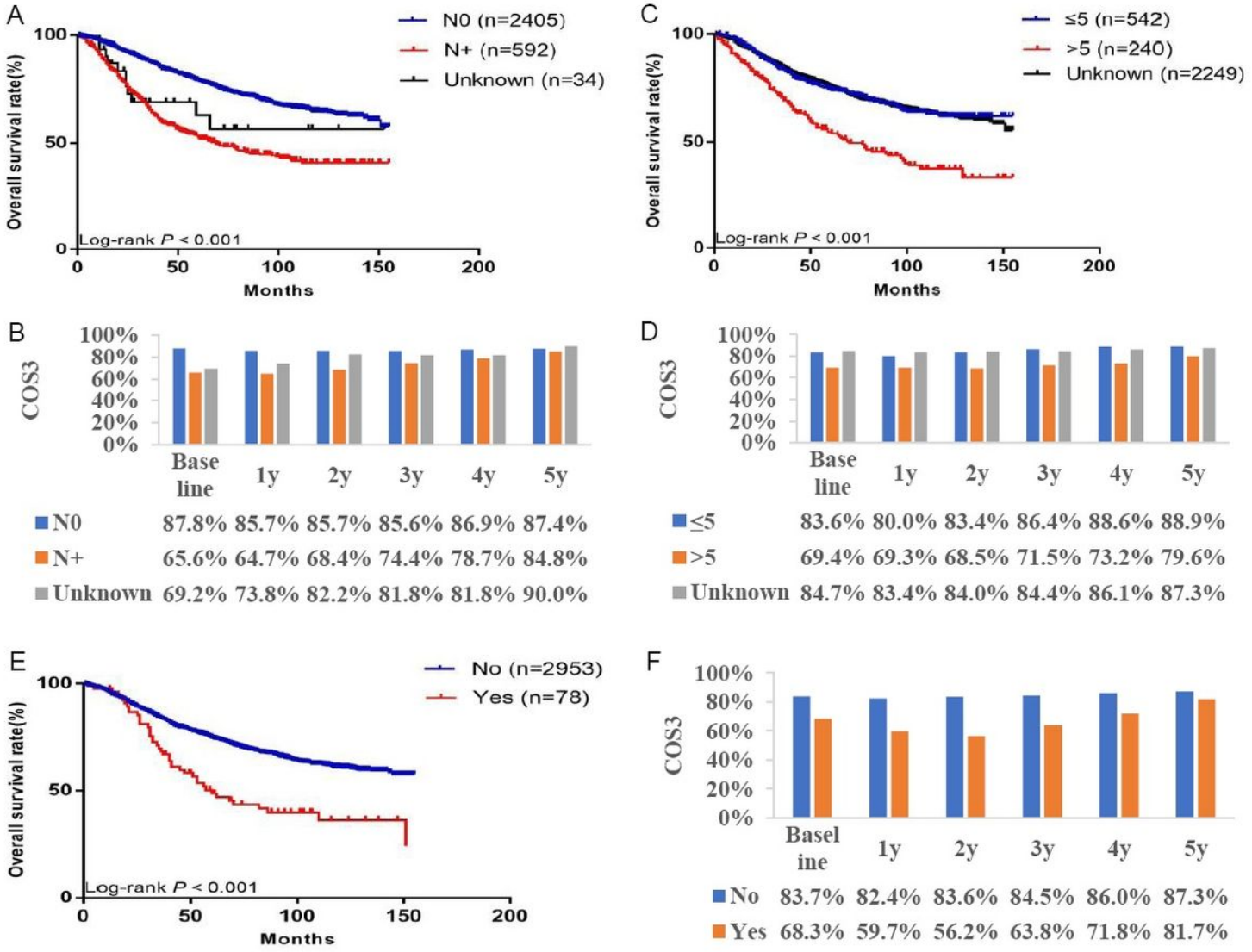

Figure 5

Actual overall survival stratified by: (A) N stage, (C) CEA, and (E) radiation vs conditional overall survival relative to actual survival stratified by: (B) N stage, (D) CEA, and (F) radiation

Supplementary Files

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