Prognostic Impact of Pathological Adverse Features in Surgically Resected Adenocarcinoma of Esophagogastric Junction

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Research

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Abstract

Objective The prognostic value of lymphovascular invasion (LVI), perineural invasion (PNI), and poor differentiation (PD) has been widely studied in different solid tumors. However, it was still controversial in adenocarcinoma of esophagogastric junction (AEG). We investigated the prognostic impact of combining LVI, PNI and PD for predicting the survival in patients with AEG.

Methods We retrospectively investigated the data of patients who performed surgical resection of AEG on Guangdong Provincial Hospital and Guangdong Provincial Hospital of Chinese Medicine from Jan. 2004 to Dec. 2018. According to the status of LVI, PNI and differentiation, pathological adverse features were divided into three groups: 0, 1 or 2 and 3 adverse features, their impact on prognosis was evaluated.

Results Univariate analysis indicated pT, pN, LVI , PNI , PD and pathological adverse features were risk factors for both overall survival (OS) and disease-specific survival (DSS), and multivariate analysis indicated that pathological adverse feature was independent risk factor for both OS and DSS. In subgroup analyses, adverse features were independent risk factor for DSS of stage II AEG but not for stage I or III.

Conclusions The pathological adverse features were independent prognostic factors for AEG patients and they can help for further risk stratification in stage II patients.

Introduction

With the gradual increase in incidence, adenocarcinoma of esophagogastric junction (AEG) has attracted attention worldwide and gradually become a separate entity for treatment and research. Accurately staging not only help for predicting patients' survival and is of great significance for individualized and precise treatment. Up to now, staging system for AEG is still under debate. This study aimed to explore the impact of the pathological factors, including lymphovascular invasion (LVI), perineurial invasion (PNI), and poor differentiation (PD) on the prognosis of surgically resected AEG, investigating whether they could help for better risk stratification.

Methods

Patients

We retrospectively collected data of AEG patients who underwent surgery at Guangdong Provincial Hospital and Guangdong Provincial Hospital of Chinese Medicine from January 2004 to December 2018. Included criteria: (1) The tumor invaded the dentate line, and tumor center was located at the area 5 cm above or below the dentate line; (2) Pathologically diagnosis of adenocarcinoma; (3) No history of other malignant tumors; (4) Radical surgery; (5) Complete clinical and follow-up data. Exclusion criteria: (1) With distant metastasis; (2) Palliative surgery; (3) Incomplete clinical or follow-up data. This study was approved by both the Ethics Committee of Guangdong Provincial Hospital and Guangdong Hospital of Chinese Medicine and was conducted in accordance with ethical standards of the Helsinki Declaration of the World Medical Association.

Data

The clinicopathological data were extracted from the electronic patient management system, including age, sex, Siewert subtype, LVI, PNI, degree of differentiation, pathological T stage, pathological N stage. Tissue slides of each patient were firstly examined by the junior pathologist and the reports were reconfirmed by at least one senior pathologist. The tumors were classified by the Siewert classification, based on the patient's gastroscopy, computed tomography, contrast radiography and postoperative specimens. Pathological T staging and N staging were based on the TNM staging standards of the AJCC and UICC 8th edition. Siewert type I and type II refer to stages of esophageal cancer, and Siewert type III refers to stages of gastric cancer.

LVI, PNI, PD were named as pathological adverse features, each patient was assigned to 0, 1 or 2, or 3 adverse features group based on the pathology reports.

Statistical Analyses

Spss 22.0 was used for data analysis, categorical variables were expressed in percentage or rate; continuous variables were expressed in mean ± SD or median and quartile (Q1, Q3); chi-square test was used for intergroup comparison of categorical variables, student t test was used for comparison of continuous variables. Kaplan-Meier method was used for univariate analysis and Cox regression method was used for multivariate analysis of overall survival and disease-specific survival. A P value of < 0.05 was considered statistically significant.

Results

Study Population Characteristics

Totally 223 surgical resected AEG patients were included in the study. There were 170 (76.2%) males and 53 (23.8%) females. Mean age was 63.8 ± 9.3 years old, ranging from 30 to 86. Siewert type I, II, III were accounted for 6 (2.7%), 133 (59.6%), 84 (37.7%) respectively. Transthoracic surgery was performed in 70 (31.4%) patients while 153(68.6%) patients underwent transabdominal surgery. 23 (10.3%) patients had preoperative treatment and 101(45.3%) received postoperative treatment (Table 1).

Table 1
Patients' Clinicopathological Characteristics

		Number of patients(%)
Age	65	125(56.1)
	≥ 65	98(43.9)
Sex	Male	170(76.2)
	Female	53(23.8)
Siewert Classification	I + II	139(62.3)
	III	84(37.7)
Surgical Approach	Transthoracic	70(31.4)
	Transabdominal	153(68.6)
pT	T1-2	40(17.9)
	T3-4	183(82.1)
pN	N0-1	114(51.1)
	N2-3	109(48.9)
Preoperative therapy	Yes	23(10.3)
	No	200(89.7)
Postoperative therapy	Yes	101(45.3)
	No	122(54.7)
PNI	Yes	138(61.9)
	No	85(38.1)
LVI	YES	106(47.5)
	No	117(52.5)
Differentiation	PD	103(46.2)
	NPD	120(53.8)
Pathological Adverse Features	0	48(23.1)
	1 or 2	123(54.2)
	3	52(22.7)

Abbreviations: PNI = Perineural invasion. LVI = Lymphovascular invasion. PD = Poor differentiation; NPD = Non poor differentiation.

Pathological Data

The relation between tumor invasion (pT), lymphatic node metastasis (pN), LVI, PNI, and degree of differentiation were shown in Table 2. LVI, PNI and PD were all significantly correlated with higher pT stage and pN stage. Patients with LVI significantly had higher percentage of PNI or poor differentiation, vice versa.

Table 2
Clinicopathological data in relation to PNI, LVI and Differentiation.

		PNI(+)	PNI(-)	P	LVI(+)	LVI(-)	p	PD	NPD	P
Age		61.31 ± 9.3	65.24 ± 8.8	< 0.01	61.83 ± 8.2	63.69 ± 10.0	0.13	62.17 ± 9.6	63.36 ± 9.0	0.34
Sex	Male	102(53.8)	68(46.2)	0.30	81(47.6)	89(52.4)	0.95	71(41.8)	99(58.2)	0.018
	Female	36(67.9)	17(32.1)		25(47.2)	28(52.8)		32(60.4)	21(39.6)	
Siewert Classification	I/II	76(54.7)	63(45.3)	< 0.01	56(40.3)	83(59.7)	< 0.01	62(44.6)	77(55.4)	0.542
	III	62(73.8)	22(26.2)		50(59.5)	34(40.5)		41(48.8)	43(51.2)	
pT	T1-2	4(10)	36(90)	0.01	9(22.5)	31(77.5)	< 0.01	13(32.5)	27(67.5)	0.094
	T3-4	134(73.2)	49(26.8)		97(53)	86(47)		90(49.2)	93(50.8)	
pN	N0-1	50(43.9)	64(56.1)	0.01	28(24.6)	86(75.4)	0.01	40(35.1)	74(64.9)	<0.01
	N2-3	88(80.7)	21(19.3)		78(71.6)	31(28.4)		63(57.8)	46(42.2)	
Preoperative Therapy	Yes	15(65.2)	8(34.8)	0.728	10(43.5)	13(56.5)	0.68	12(52.2)	11(47.8)	0.543
	No	123(61.5)	77(38.5)		96(48)	104(52)		91(45.5)	109(54.5)	
PNI(+)		NA	NA		NA	NA		NA	NA	
PNI(-)										
LVI(+)		89(84)	17(16)	0.01	NA	NA		NA	NA	
LVI (-)		49(41.9)	68(58.1)							
PD		76(73.8)	27(26.2)	0.01	60(58.3)	43(41.7)	< 0.01	NA	NA	
NPD		62(51.7)	58(48.3)		46(38.3)	74(61.7)				

Abbreviations: PNI = Perineural invasion. LVI = Lymphovascular invasion. PD = Poor differentiation; NPD = Non poor differentiation.

Survival Analyses

Univariate analysis indicated pT, pN, LVI, PNI, PD, pathological adverse features were risk factors for both overall survival (OS) and disease-specific survival (DSS), while multivariate analysis indicated pathological adverse features were independent risk factor for both OS and DSS (Table 3). The median OS age was 88(53.8-122.2), 59(40.1–77.9), 24(10.9–37.1) months for 0, 1 or 2, 3 adverse features and 5-year OS rate was 73.5%, 46.0% and 25.6%, respectively (Fig. 1). The median DSS age was not reach in 0 and 1–2 adverse features, while 41(20.4–61.6) months for 3 adverse features group. The 5-year DSS rate was 87.7%, 58.6% and 31.2% respectively (Fig. 2).

Table 3
Univariate and Multivariate Analysis of Patients' Characteristics for DSS and OS.

Characteristics	DSS		OS	
	univariate p value	multivariate p value	univariate p value	multivariate p value
Sex (male vs female)	0.788	-	0.86	-
Age (< 65 vs ≥ 65)	0.968	-	0.94	-
Siewert Classification (I + II vs III)	0.632	-	0.354	-
Surgical Approach (Transthoracic vs Transabdominal)	0.215	-	0.185	-
pT (T1-2 vs T3-4)	< 0.01	0.091	0.02	0.47
pN (N0-1 vs N2-3)	< 0.01	0.083	< 0.01	0.033
Preoperative therapy	0.798	-	0.851	-
Postoperative therapy	0.798	-	0.212	-
LVI	< 0.01	0.68	< 0.01	0.706
PNI	< 0.01	0.8	< 0.01	0.748
PD	< 0.01	0.692	< 0.01	0.456
PAF				
0 vs 1/2	< 0.01	< 0.01 (0)	0.011	0.012 (0)
0 vs 3	< 0.01	0.04 (1/2)	< 0.01	0.072 (1/2)
1/2 vs 3	< 0.01	< 0.01 (3)	< 0.01	< 0.01 (3)

Abbreviations: PNI = Perineural invasion. LVI = Lymphovascular invasion. PD = Poor differentiation; PAF = Pathological adverse features.

In subgroup analysis, pathological adverse features were independent risk factor of DSS in stage II AEG. The median DSS age were not reach in 0 and 1–2 adverse features, and 19(13.0–25.0) months in 3 adverse features group. The 5-year DSS rate was 81.3%, 65%, 16.7%, respectively (Fig. 3).

Discussion

Due to the special anatomical site, controversies exist in many aspects of adenocarcinoma of esophagogastric junction (AEG), such as the pathogenesis, the origin of tumor cells, and surgical strategy[1–3]. Siewert et al.[4] defined AEG as adenocarcinoma invading the dentate line within 5cm crossing the gastroesophageal junction, which played an important role guiding clinical treatment and research.

Conflicts

still exist on how to stage AEG more accurately. The 8th edition AJCC/UICC considered Siewert III AEG as gastric cancer and Siewert I and II remain to esophageal cancer entity, changing from previous edition that all three subtypes staging as esophageal cancer. Better risk stratification and more accurate assessment of prognosis would be of great importance for individualized and precise management of AEG. Our research aims to investigate the impact of pathological risk factors on AEG prognosis and whether they could help for better risk stratification.

LVI, PNI, and PD were priori of malignant biological behavior of many solid tumors, indicating worse prognosis[5–9]. NCCN guidelines had also pointed out that patients with early stage esophageal or gastric cancer receiving endoscopic treatment, when

pathological risk factors exist, more comprehensive systemic treatment and careful follow-up should be considered[10, 11]. In terms of AEG, conflicts still existed on whether the pathological adverse features would independently impact prognosis[12–14] like esophageal cancer or gastric cancer[15–17].

In our study, 47.5%, 61.9%, 46.2% patients had LVI, PNI and PD respectively. When patients had LVI, there were higher proportion of these patients developed PNI or PD, vice versa. The overall median survival time was 88, 61 and 31 for 0, 1 or 2, 3 adverse features respectively, and 5 years overall survival rate was 73.5%, 46.0% and 25.6%, respectively. Univariate analysis suggests that LVI, PNI, and PD were all risk factors for overall survival and disease-specific survival. However, only integrating all three factors, which divided into 0, 1 or 2, and 3 pathological adverse features, had significant prognostic impact on multivariate analysis, indicating when these factors combined, they could more accurately predict patients' survival comparing with either single factor. Although some research indicated that difference existed between Siewert subtypes in tumor behavior like histological subtype, pathological characters[18, 19]. However, recent studies have suggested that from molecular and genomic point of view, AEG tend to be uniform in different Siewert subtype[20, 21]. Our study found that pathological adverse features had impact across three Siewert subtypes, coming up as a practical way to integrate different subtypes.

In the subgroup analysis, pathological adverse features had significant prognostic impact on stage II AEG, but not stage I and III. 17 stage I patients had no adverse features and no disease-related death occur, while 12 patients had 1 or 2 features and there were 2 patients died due to tumor recurrence. All these patients had not receive adjuvant therapy. Whether early-stage patients with adverse feature would benefit from systemic therapy and whether adverse features would be the remark for metastatic potential for these patients need further investigation. As for stage III patients, all patients died within 5 years even though they did not have adverse features. It is hypothesis that these locally advanced tumor already had great potential for systemic metastasis no matter adverse feature present or not. For stage II patients, 5-year DSS was 81.3%, 65.0%, 16.7% for three groups respectively. Adverse features could further stratify disease-related survival, it might due to the heterogenicity of these patients. Although TNM system had divided Stage II into IIA and IIB for both esophageal and gastric cancer. Warneke et al. considered this strategy more mathematical calculation where the addition of the value of T and N equal to the sum in each subgroup based on 5-year overall survival rather reflecting the biological behavior[22]. Lee et al. also found that T2N1 gastric cancer patients had better survival benefit from adjuvant chemotherapy compared to T3N0 or T1N2[23], indicating the patients within same group still had different biological behavior. Based on our study, pathological adverse features could further distinguish stage II AEG into three different risk group, further refining the survival of patients within same stage.

As preoperative chemoradiotherapy or chemotherapy has become the standard procedure for advanced AEG[24, 25], recent study showed that when AEG has more pathological adverse features, they had worse response to neoadjuvant therapy but benefit more in postoperative treatment[26, 27]. However, as D2 gastrectomy followed by adjuvant chemotherapy was the standard procedure for gastric cancer in Asia, most of the patients in earlier year did not receive preoperative treatment in our study. Whether pathological adverse features could predict the tumor response to neoadjuvant therapy in patients needed further investigation.

Our study had some limitations. It contained patients only from two institute. Since neural invasion was not standardize including in the pathology report until 2008 in our center, we exclude the patients without neural invasion record. Thus this retrospective study with few cases and a selection bias. Because of the uneven distribution of cases, subgroup analysis for different stage patients may have been affected by the small number of cases in some subgroups.

In summary, pathological adverse features were independent prognostic risk factor for AEG. In stage II AEG, it helped to further stratify the disease-specific survival rate. Pathological adverse features can help for better risk stratification across different subtypes of AEG.

Declarations

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Competing interests The authors declare that they have no competing interests.

Availability of data and materials The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions Guarantor of the article: Li Yong. Conceptualization: Li Yong and Wang Wei; Study design: LQ, WJ and ZJ; Acquisition of data: Xiong Wenjun, Hu Xu, Zheng Chengbin, Deng Zhenru, Feng Huolun; Methodology: Liao Qianchao and Zheng Jiabin; Formal analysis and interpretation: Liao Qianchao, Xiong Wenjun, Zheng Jiabin; Writing—original draft preparation: Liao Qianchao, Zheng Jiabin; Writing—review and editing: Li Yong and Wang Wei; Statistical analysis: Liao Qianchao, Zheng Jiabin. Study supervision: Li Yong and Wang Wei. All authors read and approved the final manuscript.

Ethical approval and consent to participate The study was approved by both the research ethics committee of Guangdong Provincial People's Hospital and Guangdong Provincial Hospital of Chinese Medicine and was performed in accordance with the standards of the Declaration of Helsinki. Patients admitted to the hospital have signed informed consent forms stating that clinical data during hospitalization can be used for anonymous retrospective studies, and it has been approved by the hospital ethics committee.

Consent for publication Written informed consent for publication was obtained from all participants.

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Figures

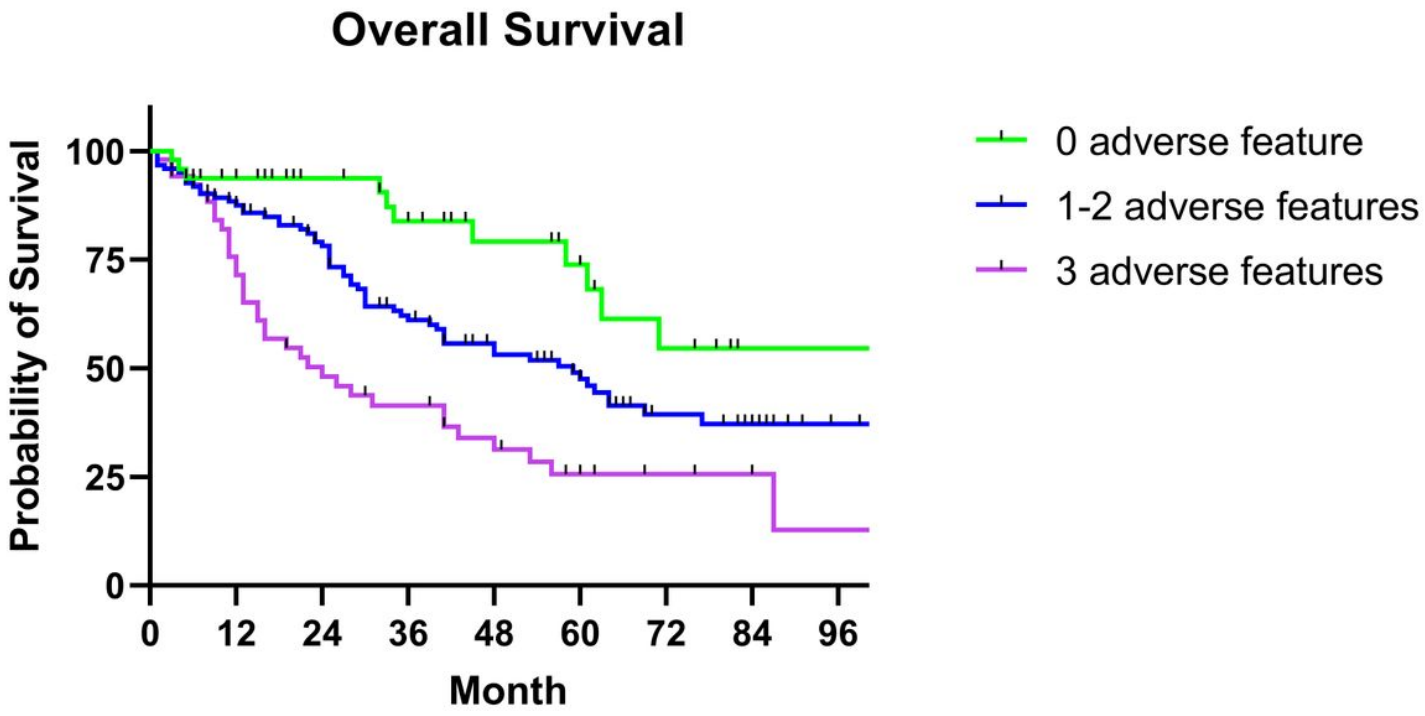

Figure 1. Overall survival in patients with AEG after radical resection.

Figure 1

Overall survival in patients with AEG after radical resection. Green line: Patients with no pathological adverse feature Blue line: Patients with 1 or 2 pathological adverse features Purple line: Patients with 3 pathological adverse features Black dot in each line: Censored cases

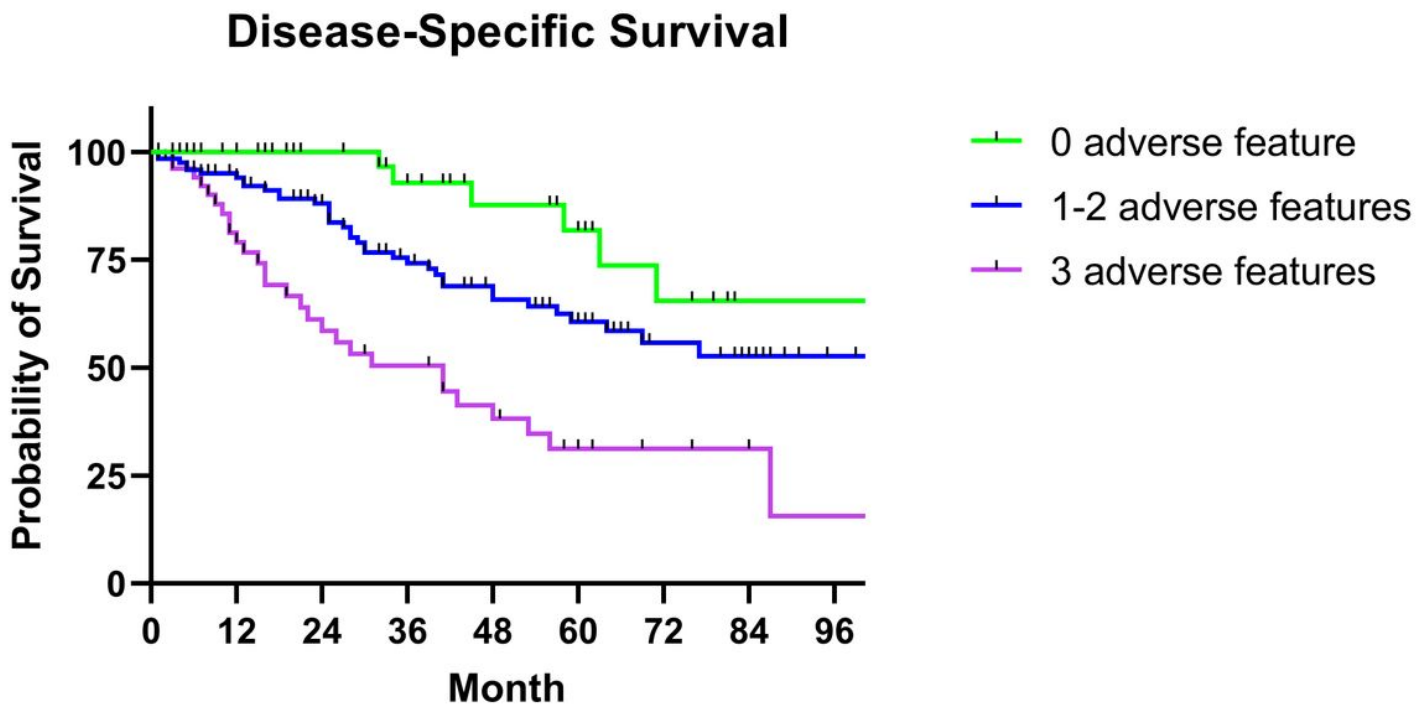

Figure 2. Disease-specific survival in patients with AEG after radical resection.

Figure 2

Disease-specific survival in patients with AEG after radical resection. Green line: Patients with no pathological adverse feature Blue line: Patients with 1 or 2 pathological adverse features Purple line: Patients with 3 pathological adverse features Black dot in each line: Censored cases

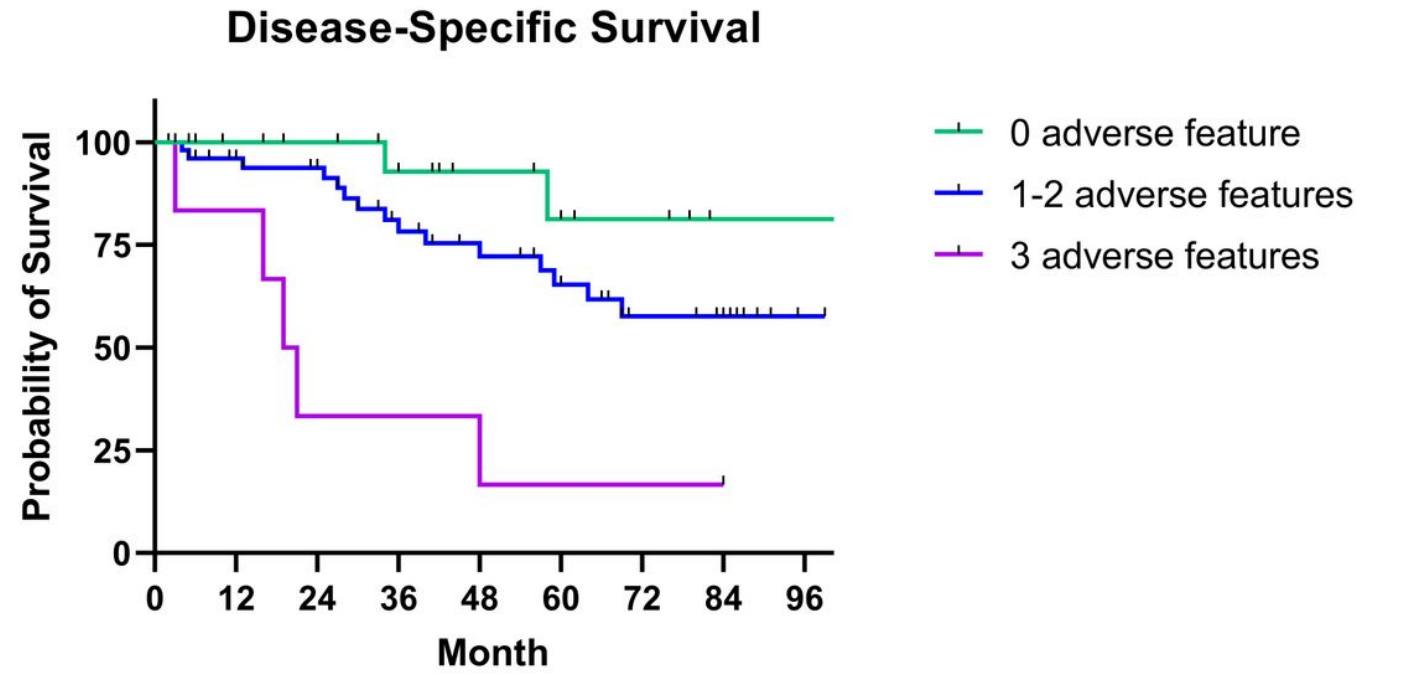

Figure 3. Disease-specific survival in stage II patients with AEG after radical resection.

Figure 3

Disease-specific survival in stage II patients with AEG after radical resection. Green line: Patients with no pathological adverse feature Blue line: Patients with 1 or 2 pathological adverse features Purple line: Patients with 3 pathological adverse features Black dot in each line: Censored cases