

# Clinicopathological features and prognosis of patients <45 years old with esophageal adenocarcinoma comparing to other age groups

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**Background:** To analyze the clinicopathological features and prognosis of younger patients with esophageal adenocarcinoma (EAC).

**Methods:** A total of 2,601 patients diagnosed with EAC between 1988 and 2011 were selected from the Surveillance, Epidemiology, and End Results (SEER) database. All patients underwent primary tumor resection and regional lymphadenectomy without preoperative radiotherapy. The patients were into four age groups (<45, 45–59, 60–74, ≥75), with 94, 813, 1,272 and 422 patients in each group respectively.

**Results:** Patients in the age <45 group were more likely to have lymph node (LN) metastasis (P=0.002), postoperative radiotherapy (P<0.001) and advanced T and N stage (P=0.003, 0.014) compared to the other three groups. We then conducted two Cox proportional hazards model adjusted for the sex, race, number of LNs examined, histological grade, postoperative radiation. The hazard ratio (HR) was higher in patients <45 y and the survival rate were paradoxically lower compared to the patients between 45–60 years old (P=0.046, 0.039).

**Conclusions:** The patients <45 y had the most aggressive clinicopathological features of EAC and poorer survival rate after radical esophagectomy.

**Keywords:** Esophageal adenocarcinoma (EAC); young patients; the Surveillance, Epidemiology, and End Results (SEER); prognosis

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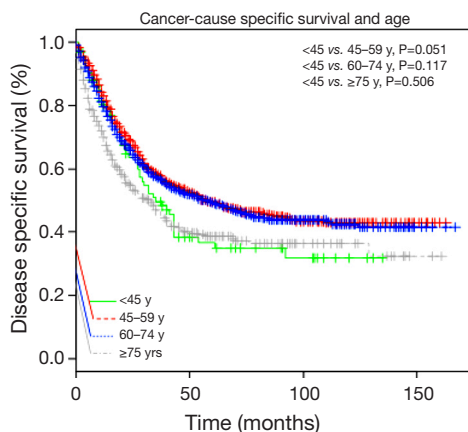
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## Introduction

Esophageal carcinoma is one of the most lethal malignant tumor throughout the world (1). The two main histological types are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Although the incidence of EAC is significant lower than ESCC in East Asia, it has increased rapidly in the western world within last

30 years, and become the predominant type in America and European countries (2,3).

Ageing is one of the risk factors for EAC (4). However, the incidence of EAC in each age group, particularly in young people has risen significantly according to epidemiological studies (5-7). Despite some reports about EAC of young patients have been published, there are



**Figure 1** Unadjusted cancer-cause specific survival between each group.

still controversial on whether young patients have more advanced stage at presentation and worse prognosis than the older patients (8-11).

In this retrospective study, we intended to analyze the clinicopathologic features and the prognosis of young patients with EAC using a population based cohort.

## Methods

The Surveillance, Epidemiology, and End Results (SEER) of the National Cancer Institute are the largest population-based cancer registry in the United States, including approximately 26% of the US population (12). The study cohort was created from the available data in the SEER-Medicare 2011 release. To identify the population of interest, SEER data from 1988 to 2011 were collected and reported using codes as documented by the North American Association of Central Cancer Registries (NAACCR). Only those who underwent esophagectomy and lymphadenectomy with or without gastrectomy, and histologically confirmed EAC (ICD-O-3 codes 8140, 8141, 8144, 8210, 8211, 8255, 8260, 8261, 8263, 8310, 8323, 8480, 8481, 8574, 8576) were included in our study. Patients who had preoperative radiation therapy or unknown radiation-surgery sequence, and those who underwent local tumor excision or unknown surgery method were excluded; Patients who did not have complete clinicopathologic data were also ruled out. In total, 2,601 patients whose medical data met the selection criteria were included in our study. According to the American Joint Commission on Cancer stage (7<sup>th</sup> edition), pT and pN were restaged.

## Statistical analysis

The continuous variables were reported as mean  $\pm$  SD whereas the categorical variables as percentages. Comparisons between groups were performed using *t*-test for continuous variables and chi-square test for categorical variables. Generalized smoothing splines with knot locations generated automatically in generalized additive models (13) were used to explore the shape of the dose-response relation between N status and age by R package mgcv and ggplot2. Disease specific survival were estimated using the Kaplan-Meier method, and a Cox proportion hazard model were used to calculate hazard ratios (HR) and 95% confidence interval (95% CI). A two-sided statistical significance was defined as  $P < 0.05$ . All analyses were performed with R Project software version 3.1.2 (<http://www.R-project.org>).

## Results

### Age grouping method

In order to find the threshold for the “young” patients, we used the Kaplan-Meier to compare the survival rate using different grouping methods. We found the prognosis of patients with age  $<45$  y was worse than patients of other age groups (Figure 1). All the 2,601 patients were dividing into four groups based on age: 94 (3.6%) patients were younger than 45 y, 813 (31.3%) patients were between the age of 45–59 y, 1,272 (48.9%) patients were between the age of 60–74 y, and 422 (16.2%) patients were older than 75 y. The average age of younger patients was  $39.1 \pm 5.2$  years old.

### Clinicopathological features

As shown in Table 1, all the clinicopathological features of each group were showed significant differences. White male patients comprised the majority of the whole cohort. Overall, the patients  $<45$  y had fewer lymph nodes (LN) examined ( $13.8 \pm 9.0$ ,  $P = 0.046$ ), but had a higher incidence of LN metastasis (LNM) (60.6%,  $P = 0.002$ ) and more advanced pT and pN stage ( $P = 0.003$ , 0.014). The proportion of advanced pT stage (T3, T4), pN stage (N3, N4) and LNM rate was highest among patients  $<45$  y. Figure 2 have manifested a downtrend between age and LNM.

### Postoperative radiotherapy and survival

Younger patients were more likely to received postoperative radiotherapy compared to patients  $>45$  y (43.6%,  $P < 0.001$ ).

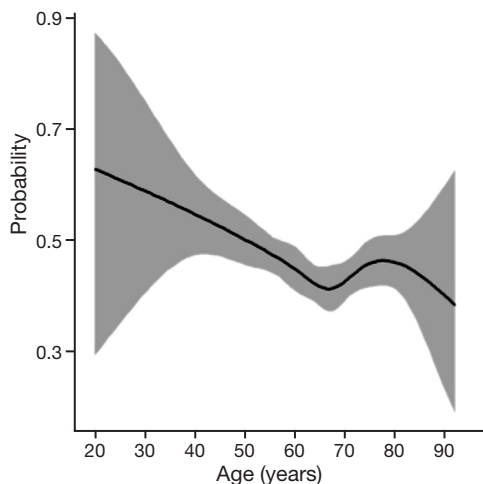
**Table 1** Clinicopathological features of patients in four different age groups

Characteristics	Age (years) (%)				P
	<45	45–59	60–74	≥75	
Number	94 (3.6)	813 (31.3)	1,272 (48.9)	422 (16.2)	
Age*	39.1±5.2	53.8±3.9	66.8±4.3	78.7±3.3	<0.001
LN examined*	13.8±9.0	15.8±15.1	14.7±13.7	13.6±13.5	0.046
Survival (M)*	38.7±35.0	43.9±40.1	37.5±35.7	28.8±32.9	<0.001
Race					0.003
White	84 (89.4)	778 (95.7)	1,220 (95.9)	408 (96.7)	
Black	5 (5.3)	20 (2.5)	15 (1.2)	3 (0.7)	
Others and unknown	5 (5.3)	15 (1.8)	37 (2.9)	11 (2.6)	
Gender					0.009
Male	84 (89.4)	736 (90.5)	1,144 (89.9)	357 (84.6)	
Female	10 (10.6)	77 (9.5)	128 (10.1)	65 (15.4)	
Grade					0.016
Well	8 (8.5)	63 (7.7)	107 (8.4)	27 (6.4)	
Moderately	40 (42.6)	296 (36.4)	465 (36.6)	143 (33.9)	
Poor	38 (40.4)	370 (45.5)	570 (44.8)	206 (48.8)	
Undifferentiated	4 (4.3)	17 (2.1)	22 (1.7)	21 (5.0)	
Unknown	4 (4.3)	67 (8.2)	108 (8.5)	25 (5.9)	
Radiotherapy					<0.001
Yes	41 (43.6)	213 (26.2)	261 (20.5)	54 (12.8)	
No	53 (56.4)	600 (73.8)	1,011 (79.5)	368 (87.2)	
LNM					0.002
Yes	57 (60.6)	390 (48.0)	543 (42.7)	187 (44.3)	
No	37 (39.4)	423 (52.0)	729 (57.3)	235 (55.7)	
pN stage					0.014
pN0	37 (39.4)	423 (52.0)	729 (57.3)	235 (55.7)	
pN1	17 (18.1)	170 (20.9)	231 (18.2)	81 (19.2)	
pN2	24 (25.5%)	125 (15.4)	179 (14.1)	64 (15.2)	
pN3	16 (17.0)	95 (11.7)	133 (10.5)	42 (10.0)	
pT stage					0.003
pT1	24 (25.5)	308 (37.9)	515 (40.5)	130 (30.8)	
pT2	12 (12.8)	111 (13.7)	179 (14.1)	61 (14.5)	
pT3	44 (46.8)	329 (40.5)	490 (38.5)	192 (45.5)	
pT4	14 (14.9)	65 (8.0)	88 (6.9)	39 (9.2)	

\*, mean ± SD. LNM, LN metastasis.

Despite this additional treatment modality, their survival rate was relatively poor ( $38.7 \pm 35.0$  months,  $P < 0.001$ ). After a median follow up duration of 25 months (interquartile range, 10–56 months), EAC-specific death occurred in 54 patients (57.4%) in the age <45 y group, 371 patients (45.6%) in the 45–59 years group, 562 patients (44.2%) in the 60–74 years group, 211 patients (50.0%) in the age  $\geq 75$  years group, respectively. Cancer-cause specific survivals of each group were shown in *Figure 2*, the survival of patients <45 and  $\geq 75$  y were worse compared to that of patients between 45–74 y.

For age group comparison, we used the patients group between 45–59 y as the reference group, because this cohort had the best prognosis. Compared with the reference group of 45–59 y, the HR (95% CI) of other three groups were



**Figure 2** The shape of the dose-response relation between N status and age and their 95% confidence intervals (CI) (shape scope), which using generalized smoothing splines with five knots (13).

1.34 (1.01–1.78) for the age <45 y cohort, 1.06 (0.93–1.21) for the 60–74 y cohort and 1.48 (1.25–1.75) for the age  $\geq 75$  y cohort using the Cox proportional hazards model adjusted for sex, race (shown in *Table 2*, Model 1). When the data was further adjusted the number of LN examined, histological grade and postoperative radiation, the results were unchanged (shown in *Table 2*, Model 2). These two statistically models confirmed that the prognosis of patients younger than 45 y was significantly worse compared to patients between 45–59 y ( $P = 0.046, 0.039$ ).

## Discussion

EAC is uncommon in young people (14), but the incidence among younger patients with EAC has increased substantially over the past three decades (11,15). This observation partly attributed to the increasing risk factor among younger adults such as obesity, lack of physical activity and gastroesophageal reflux disease (GERD) (16–18). Some researchers try to investigate whether age influences the clinicopathological features and prognosis of EAC, but the results of previous studies were inconsistent.

Some researchers believe that EAC among younger patients may have more aggressive biology and metastatic risk. Thus, Oezcelik *et al.* reported that patients <40 y had a higher prevalence of stage IV disease and a poorer survival (9). Portale *et al.* reported that patients  $\leq 50$  y were more likely to present with advanced stage and a more than 70% LNM rate, significantly higher than patients >50 y. However, the survival rates were having no significant difference (11). Hashemi *et al.* reported that patients  $\leq 50$  y were more likely to have LNM but had similar survival rate compared with patients >50 y (19). Moreover, some other reports showed

**Table 2** HRs for death due to EAC by age group

Age (years)	N	No. with outcome (%)	Model 1		Model 2	
			HR (95% CI) <sup>a</sup>	P value <sup>b</sup>	HR (95% CI) <sup>a</sup>	P value <sup>b</sup>
<45	94	54 (57.4)	1.34 (1.01–1.78)	0.046	1.35 (1.02–1.80)	0.039
45–59	813	371 (45.6)	Reference	—	Reference	—
60–74	1,272	562 (44.2)	1.06 (0.93–1.21)	0.413	1.11 (0.97–1.26)	0.137
$\geq 75$	422	211 (50.0)	1.48 (1.25–1.75)	<0.001	1.52 (1.28–1.81)	<0.001

<sup>a</sup>, hazard ratio estimated using the Cox proportional hazards model; <sup>b</sup>, derived from the log-rank test. Model 1, adjustment for sex, race; Model 2, adjustment for sex, race, number of LN examined, tumor grade, radiotherapy. HR, hazard ratio; EAC, esophageal adenocarcinoma.

there was no significant difference in the tumor pathology between different age group (8,20,21).

These conflicting results are difficult to reconcile. We speculate that one of the primary reasons is that the sample sizes of younger patients of EAC in these reports were usually quite small; Secondly, these studies did not adjust the variables among each group, and this may have led to some statistical bias; In addition, most studies defined only one or two thresholds for all age groups. Fewer groups may cause unprecise age stratification, and may have unknown effect on the prognosis of each group. To address the limitation of small sample size, we used the SEER database with a large sample size and the ability to perform cohort analysis among subgroups. Besides, generalized smoothing splines were used to show the relationship between age and LNM (Figure 1), this statistical method manifest a nonlinear relationship between continuous variable and categorical variable, and have a high fitting degree. Although the number of LN examined had no significant difference among each age subgroup, the ratio of metastatic LN compared to number of nodes examined decreased as the patient age increased. We also excluded the patients who received preoperative radiotherapy to reduce the impact on the pathological stage as much as possible. For more accurate comparison, we subdivided all the patients into four groups to make the age distribution more accurate. Although the unadjusted survival did not show significant difference when using Kaplan–Meier methods, we created Cox proportional hazards models to adjust the variables such as sex, race, the number of LN examined, tumor grade and radiotherapy, the results demonstrated patients <45 y had a higher HR and significantly worse survival compared to the patients between 45–59 y.

Portale *et al.* found that young patients with EAC were asymptomatic for a longer time before diagnosis (11), but this criterion may not be the only reason for a poor survival. A retrospective study by Hashemi *et al.* showed that patients ≤50 y were more likely than older patients to receive neoadjuvant or adjuvant therapy (19). Therefore despite lack of data on the use chemotherapy in SEER database is a shortcoming, we still considered the young patients were able to tolerate chemotherapy compared to older patients because of better physical condition and advanced pathological stage. But why young patients underwent more adjuvant or neoadjuvant therapy, but still have a worse prognosis is worth considering. Solomon *et al.* reported have find out that patients with localized EAC (confined to the organ of origin) without LM metastasis had no significant

survival benefit from additional chemotherapies using the Florida Cancer Data System (FCDS) (22). Vallböhmer *et al.* reported that patients ≤50 y had a significantly higher 5-year survival rate that they attributed to neoadjuvant therapy (10). However the pathological stage of young patients was similar to that of older patients receiving neoadjuvant therapy. Thus neoadjuvant therapy may lead the tumor downstage and an enhanced ability to perform complete surgery and have lower perioperative morbidity that may improve the prognosis of younger patients.

It is undeniable that our studies still have some limitations given its retrospective nature. Due to lack of some information such as lymph-vascular invasion, we do not know whether it is more prone to happen in young patients; Besides, we speculate that unknown gene influence were also could be the potential factor for poor survival.

## Conclusions

In conclusion, our study showed the patients <45 y presented with advanced stage and received more aggressive treatment after esophagectomy. Worse prognosis of these patients deserved considering, screening such as endoscopy should be performed in young people at high risk. In the future, additional prospective studies such as therapeutic strategies and fundamental research should be undertaken.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine.

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