

Conditional Survival of Patients Who Underwent Curative Resection for Esophageal Squamous Cell Carcinoma

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Objective: To analyze conditional survival estimates of patients with esophageal cancer who underwent curative resection.

Summary Background Data: Conditional survival reflects dynamic prognosis updated to the current status and is a more relevant indicator for current healthcare and life decisions.

Methods: This study included 1883 patients who underwent complete resection for esophageal squamous cell carcinoma at a tertiary cancer center from 1994 to 2016. We calculated 5-year (5Y) conditional overall survival

(COS), conditional recurrence-free survival (CRFS), and conditional relative survival (CRS) estimates from diagnosis to 5 years of survival.

Results: The 5Y COS, CRFS, and CRS increased from 63.7%, 65.2%, and 70.2% at diagnosis to 75.8%, 91.9%, and 86.4 at 5 years after diagnosis, respectively. While there were large differences with different stages (stage I, II, III) at diagnosis (81.2%, 64.9%, and 37.3% for COS; 85.1, 65.1%, and 67.9% for CRFS; 89.2%, 72.1%, and 41.1% for CRS), the gap decreased with time; rates were similar after 5 years (77.1%, 75.7%, and 72.6% for COS; 91.7%, 90.6%, and 94.5% for CRFS, and 89.3%, 85.4%, and 78.3% in CRS, respectively). The 5Y COS, CRFS, and CRS were persistently lower in older patients even after 5 years.

Conclusions: Conditional survival estimates generally increase over time, and the largest improvements were observed for patients with advanced stage. Availability of updated prognosis at various time points allows clinicians to better guide their patients. Our results also imply substantial residual risk of recurrence and sustained excess mortality compared to the general population even after 5 years.

Keywords: cancer survivor, conditional survival, esophageal cancer, Korea, prognosis

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Esophageal cancer is increasing in incidence and ranked seventh in terms of incidence (572,000 new cases) and sixth in mortality worldwide (509,000 deaths) as of 2018.¹ The US had around 18,440 new cases and 16,170 deaths from esophageal cancer in 2019.² The highest incidence rate of esophageal cancer is found in Eastern Asia,¹ and there were 2499 incident cases and 1524 deaths in Korea in 2016.³

Survival of esophageal cancer is very poor; 5-year (5Y) relative survival was only 17% in the US in 2014⁴ and 9.8% in Europe in 1995 to 1999.⁵ US SEER cancer registry data of patients diagnosed with esophageal cancer showed overall survival (OS) of 29%, 15%, and 3% for localized, regional, and distant stage, respectively.⁴ However, the survival of esophageal cancer recently improved with multimodal treatment strategies.^{6,7} In Sweden, 5-year relative survival increased from 5.0 in 1961 to 1969 to 10.3 in 2000 to 2008.⁸ In Korea, the 5-year relative survival estimate was 12.1% in 1993 to 1995; it increased to 34.6% in 2009 to 2013 with the introduction of a national gastric cancer screening program.⁶ Furthermore, the proportion of patients who underwent surgical treatment increased,⁷ and survival for local esophageal cancer receiving surgery improved dramatically during the last several decades.⁷

With increased survival, there is also increasing interest in quality of life for esophageal cancer survivors and their survivorship care. However, there is limited information on conditional survival estimates. This reflects dynamic prognosis updated to the current status and is a more relevant indicator for

current healthcare and life decisions⁹ than traditional 5-year overall survival (OS) or recurrence-free survival (RFS) rates calculated from baseline (time of diagnosis or surgery).

Few studies have examined the conditional survival of patients with esophageal cancer. Using US SEER cancer registry data, Kim et al analyzed 64,433 patients diagnosed with esophageal cancer from 1988 to 2011 and showed that conditional survival improves over time.⁴ One Japanese cancer registry study reported conditional 5-year survival of as part of a multicancer study, but did not consider any prognostic variables, such as age or stage.¹⁰ Other cancer registry studies reporting conditional survival of multiple cancers did not include esophageal cancer at all because it is relatively rare.^{11–15}

To the best of our knowledge, no study has specifically examined the conditional survival of patients with esophageal cancer who underwent curative resection. In this study, we analyzed conditional survival estimates of patients with esophageal cancer who underwent curative resection. We report 5Y conditional overall survival (COS), conditional recurrence-free survival (CRFS), and conditional relative survival (CRS) estimates from baseline to 5 years of survival in 1-year intervals stratified by age, stage, histology, and year of diagnosis.

METHODS

Study Population

All patients who received curative resection for esophageal squamous cell carcinoma in a comprehensive cancer center in Korea between September 1994 and December 2016 were included in this study (N = 2773). Patients with adenocarcinoma, which is rare in east Asia (<5%),^{6,16,17} were not included because this is a different disease entity^{1, 17} with different prognosis.¹⁸ This study excluded patients who had history of other cancers before esophageal cancer diagnosis (N = 187), received neoadjuvant chemo or radiotherapy before surgery (N = 567), had stage IV disease according to the 7th American Joint Committee on Cancer (AJCC) (N = 16), and did not have R0 resection (N = 120). This resulted in 1883 patients for final analyses.

This study proposal was approved by the ethics committee of our hospital, which waived the need for informed consent from each individual patient (IRB no. SMC 2019-01-159-001).

Data Collection and Follow-Up

Data were obtained from electronic medical records (EMR), including age, sex, surgical procedure, tumor histologic type, pathologic stage (TNM classification and AJCC stage), and treatment history other than surgery. Patients were scheduled for routine follow-up every 3 to 4 months for the first 2 years and every 6 months for the next 3 years; some high risk patients were followed-up for even longer at their surgeon's discretion. Routine follow-up tests to detect recurrence include chest CT scan and upper gastrointestinal endoscopy. If recurrence was suspected, additional workup was performed with PET/CT. Most patients were transferred back to a regional hospital after 5 years, but those who wanted to stay at our center were followed once per year.

Follow-up information for recurrence or death was also obtained from the EMR. Recurrence was defined by any clinical or pathologic evidence of local or distant recurrence documented in the EMR. Vital status was ascertained on December 31, 2018 by linkage to the death registry of the Korean National Statistical Office.

Statistical Analysis

Study outcomes were CRFS, COS, and CRS, which is conditional on years already survived.

The 5Y conditional survival was calculated as the proportion surviving 5 additional years: when $S(t)$ is (overall or recurrence-free) survival at time t , conditional survival is $S(x + 5)/S(x)$. For example, 5-year CS conditional on surviving 3 years is calculated by dividing 8-year survival by 3-year survival. Relative survival is calculated as the ratio of observed survival to that of the expected survival of the general population with the same age, sex, and calendar years. RS is an approximation of disease-specific survival that overcomes the limitation of inaccurate causes of death on death certificates. Data for expected mortality rates of the general population were retrieved from the life table of National Statistics Korea. The 5Y CRS rates were also calculated by dividing relative survival at $(x + 5)$ years by relative survival at x years.

This study presents 5Y COS, CRFS, and CRS from diagnosis (identical to traditional overall survival, recurrence-free survival, and relative survival) to 5 years after diagnosis at 1-year intervals. The 95% confidence intervals (CI) were also calculated assuming that conditional survival follows a normal distribution.

For the stratified analyses, patients were categorized into 5 groups by age at cancer diagnosis: 20 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥ 70 years. Years of diagnosis were classified into 3 groups: 1994 to 1999, 2000 to 2010, and 2011 to 2016. Histology of NSCLC was categorized as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others or mixed. Stages at diagnosis were classified as I, II, and III using the AJCC VII pathologic staging scheme.

All analyses were conducted using Stata version 15.0 (Stata-Corp LP, College Station, TX). All statistical tests were 2-sided, and P -values <0.05 were considered significant.

RESULTS

Subject Characteristics

Mean (SD) age of study participants was 64.6 (8.2) years. Most patients (93.2%) were male, and 43% of patients were stage I. The most common surgical approaches were transthoracic (95.4%), open surgery (84.9%), stomach conduit reconstruction (96.3%), and 2-field operation (84.5%) (Table 1).

Conditional Overall Survival

The 5Y COS increased from 63.7% at baseline to 75.8% at 5 years after surgery (Fig. 1, Supplementary Table 1, <http://link-s.lww.com/SLA/C607>). It continuously increased from 70.8 to 86.1 in the group with age <60, but it increased slightly initially (eg, 56.4% at diagnosis to 63.5% at 3 years) and decreased thereafter (to 57.6% at 5 years) in the group with age ≥ 70 . The 5Y COS increased for males (62.3%–75.6%), but did not increase for women (82.9%–76.9%). There were large differences by stage at baseline (81.2%, 64.9%, and 37.3% for stage I, II, and III, respectively), but rates became similar after 5 years (77.1%, 75.7%, and 72.6%, respectively). COS continued to be higher for those who recently underwent surgery (Fig. 2).

Conditional Recurrence-Free Survival

The 5Y CRFS increased from 65.2% at baseline to 91.9% at 5 years after surgery. Younger (age < 60) and older groups (age ≥ 70) showed slightly higher 5Y CRFS across the survival period. Females had significantly higher 5Y CRFS than males from baseline (81.6% vs 64.0%) to 5 years (100% vs 91.2%). 5Y CRFS rates were significantly lower in patients with stage II (65.1%) and III (33.9%) disease than those with stage I (85.1%) disease at baseline, but the gap disappeared after 5 years of survival (90%–95%). CRFS at 2 years after diagnosis was significantly lower in patients treated in earlier years (1994–1999), but the difference

TABLE 1. Baseline Characteristics of Patients with Esophageal Cancer at Time of Surgery (N = 1883)

Characteristics	N (%)	Characteristics	N (%)
Age, yr		Surgical Procedure	
Mean (SD)	63.6 (8.2)	Transthoracic, Rt.	1797 (95.4)
20–59	563 (29.9)	Transthoracic, Lt.	7 (0.4)
60–64	439 (23.3)	Transhiatal	74 (3.9)
65–69	407 (21.6)	Transabdominal	3 (0.2)
≥ 70 yr	474 (25.2)	Cervical	2 (0.1)
Sex		Surgical Approach	
Male	1755 (93.2)	Open	1598 (84.9)
Female	128 (6.8)	VATS	107 (5.7)
Year of diagnosis		Robot	178 (9.5)
1994–1999	135 (7.2)	Conduit reconstruction	
2000–2009	699 (37.1)	Stomach	1813 (96.3)
2010–2016	1,049 (55.7)	Colon	44 (2.3)
Stage at diagnosis		Pedicled jejunum	24 (1.3)
I	808 (42.9)	Free jejunum	2 (0.1)
II	537 (28.5)	Anastomosis	
III	538 (28.6)	1 field operation	92 (4.9)
		2 field operation	1,591 (84.5)
		3 field operation	195 (10.4)
		Unknown	5 (0.3)

disappeared after 3 years. There were no significant differences between 2000 to 2009 and 2010 to 2016 periods (Fig. 3).

Conditional Relative Survival

The 5Y CRS increased from 70.2% at baseline to 86.4% at 5 years after surgery. It was initially similar (baseline to 2 years), but there was a significant difference after 4 to 5 years (~90% in age < 65 group vs ~80% in age ≥ 65 group). The 5Y CRS increased in men (68.8%–86.2%), but slightly decreased in women (87.5%–83.2%). There were large differences by stage at baseline (89.2%, 72.1%, and 41.1% for stage I, II, and III, respectively), but the gap decreased after 5 years (89.3%, 85.4%, and 78.3%, respectively). Patients treated after 2000 continued to show higher CRS than those who were treated in earlier years (1994–1999) until 5 years after diagnosis, although the gap decreased with time (Fig. 4).

DISCUSSION

To the best of our knowledge, this is the first study to focus on conditional survival of patients who underwent curative resection for esophageal squamous cell carcinoma. Traditional survival estimates calculated from the time of diagnosis are less meaningful and may even be misleading for patients who have already survived for a certain amount of time after cancer diagnosis because the prognosis of each individual patient changes over time.

Conditional survival is most meaningful for patients treated with curative intent,⁹ as most patients with advanced cancer do not receive curative surgery. In addition, elderly patients may forgo surgery because of short life expectancy or multiple comorbidities, even if they have local or regional disease. Patients treated with chemoradiation have lower survival than patients treated with surgery, and the conditional survival

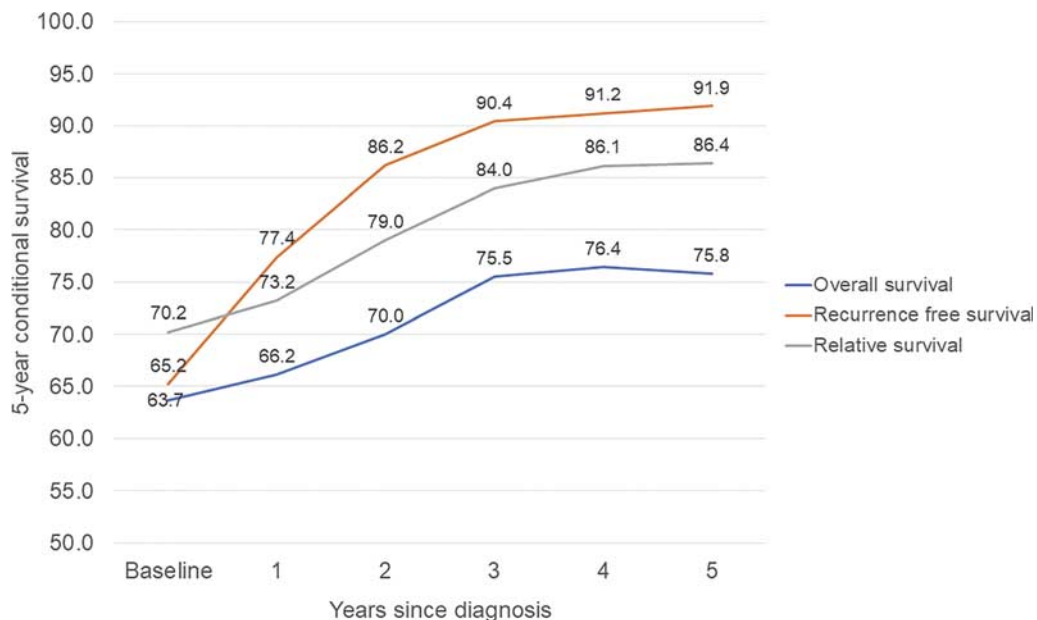


FIGURE 1. Conditional survival estimates in all patients who underwent curative surgery for esophageal squamous cell cancer.

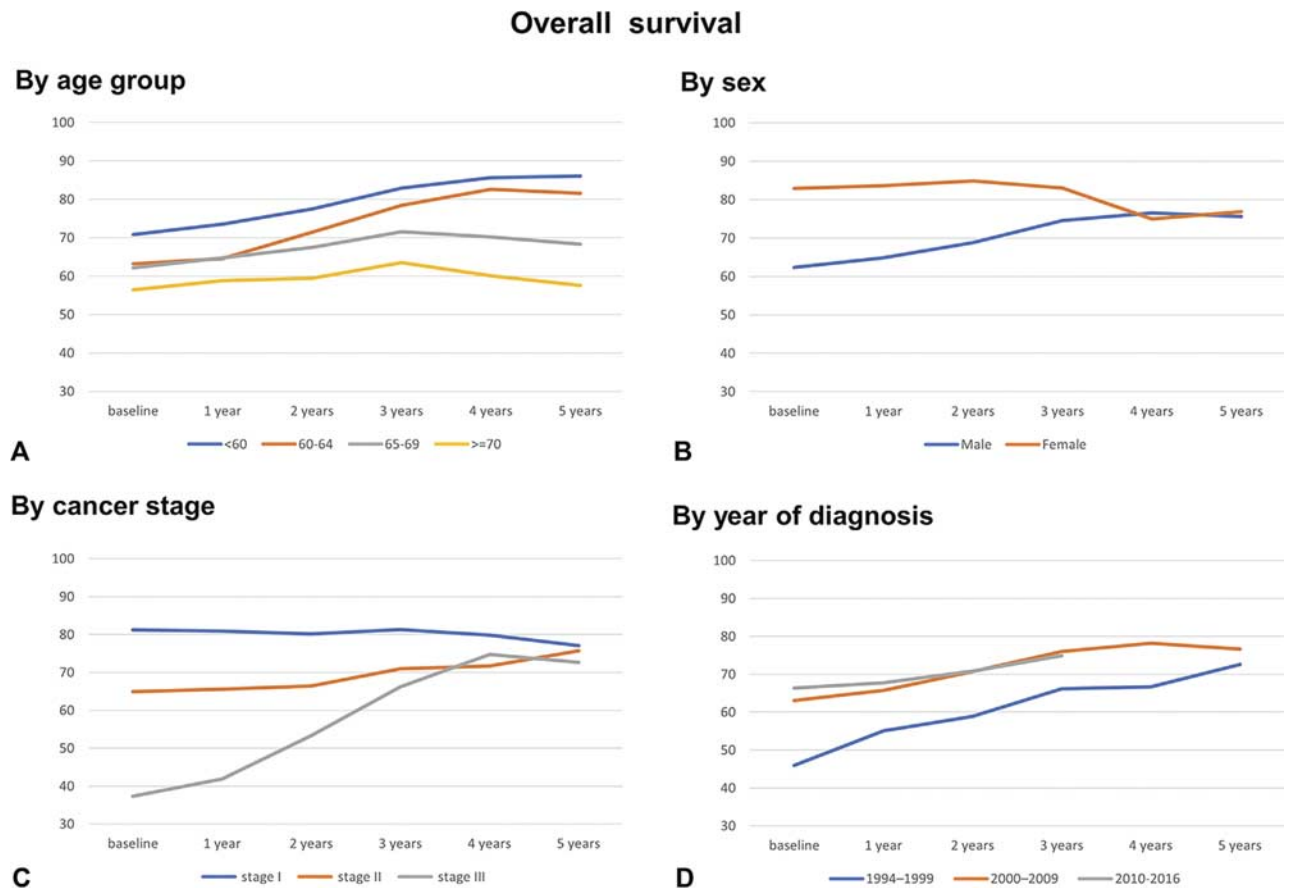


FIGURE 2. Conditional survival estimates in all patients who underwent curative surgery for esophageal squamous cell cancer stratified by patient characteristics.

of overall patients with esophageal cancer is much lower than that of surgically treated patients.¹⁹ Therefore, conditional survival estimates for patients who underwent curative surgery would be very useful for thoracic surgeons.

The 5Y OS and RFS at diagnosis in our study for stage I, II, and III cancer were 81.2%, 64.9%, 37.3% and 85.1%, 65.1%, 33.9%, respectively. These rates are similar to or slightly lower than estimates from 206 patients who received surgery for esophageal squamous cell carcinoma in a single Japanese cancer center between 2003 and 2013. Those 5Y OS and RFS rates were reported as 80.0%, 78.2%, and 45.7% and 74.0%, 65.8%, and 38.5% for stage I, II, and III cancer, respectively.¹⁶ These are much higher than rates obtained in Western countries.^{8,19} This might be due to early detection of esophageal cancer through a national gastric cancer screening program and the wide availability of upper gastrointestinal endoscopy at local clinics in Korea, which has the highest incidence of gastric cancer in the world.

In our study, 5Y relative survival rates at baseline were 89.2%, 72.1%, and 41.1% for stage I, II, and III cancer, respectively. 5Y relative survival estimates of esophageal cancer from the Korean Cancer Registry data are 58.8%, 29.2%, and 7.3% for localized, regional, and distant SEER stage. While AJCC stage is not directly comparable to SEER summary stage, localized stage group is mostly stage I (ranging stages I and II), regional stage group is mostly stages II and III (ranging stages I–IV), and distant stage group is mostly stage IV (ranging stage I–IV).

We showed that 5Y COS, 5Y CRFS, and 5Y CRS estimates generally increase over time, indicating that residual risk of recurrence

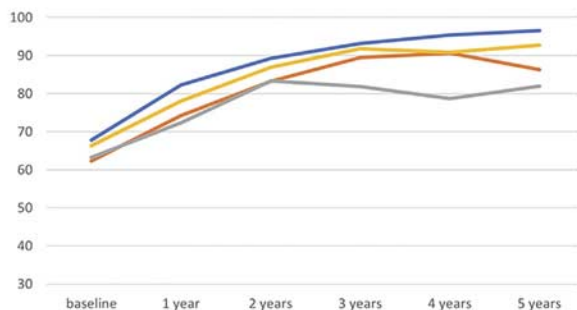
or death substantially diminishes over time. As with many cancers, the greatest incidence of recurrence or death occurs during the first year after diagnosis and then decreases rapidly with several years of survival (Supplementary Fig. 1, <http://links.lww.com/SLA/C606>). Availability of updated prognosis at various time points would allow clinicians to better guide their patients based on updated risk profiles and to reduce anxiety and fear regarding cancer recurrence.

The 5Y CRFS increases rapidly with time to exceed 90% 3 years after diagnosis. However, 5Y CRFS was 91.9% and did not reach 100%. This indicates that even after 5 years, there is a small risk of recurrence (1%–2% annual rate). In comparison, 5Y COS increased rather slowly, and even decreased after 4 years. This trend reflects older age and death from other causes. When stratified by age, younger patients (age < 65) showed continued increases in 5Y COS, whereas older patients (age ≥ 75) showed no increase even in the early survivorship period.

The 5Y CRS, which considers the mortality of the general population, increased with time, but only reached 86.4%. This is different from what is seen with many other cancer types, such as gastric,^{10,15} colorectal,^{10,12,15} gallbladder,¹⁰ and kidney cancer,¹⁰ which often exceed 90% survival after 5 years. In general, the mortality of a patient group is considered comparable to that of the general population when 5Y CRS exceeds 95%.^{12,15} Excess mortality 5 years after surgery indicates that higher health risk persists in long-term survivors of surgically treated esophageal cancer. This is probably due to comorbidities (eg, chronic obstructive pulmonary disease or cardiovascular disease from long smoking history), second

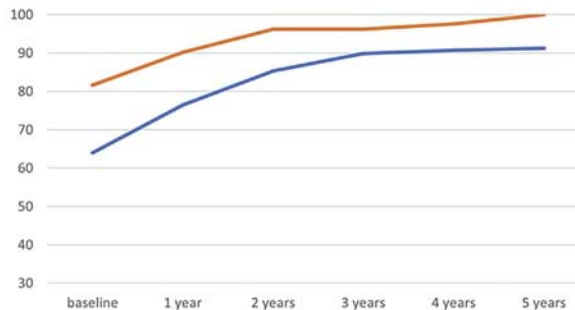
Recurrence-free survival

By age group



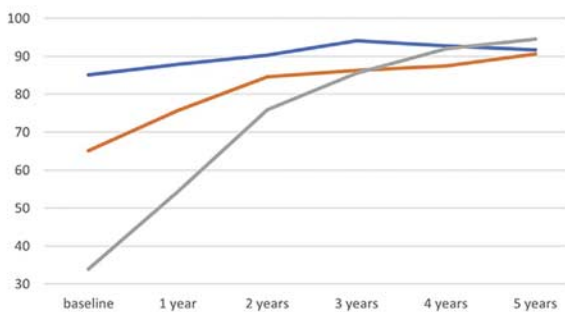
A

By sex



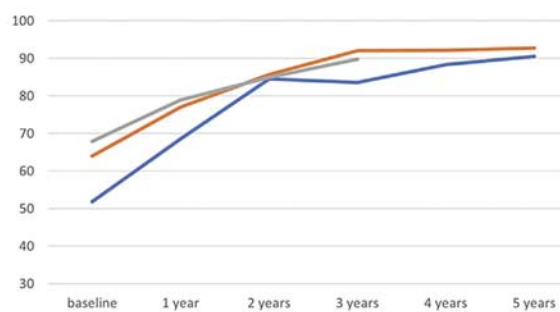
B

By cancer stage



C

By year of diagnosis



D

FIGURE 3. Conditional recurrence-free survival estimates in all patients who underwent curative surgery for esophageal squamous cell cancer stratified by patient characteristics.

primary cancer, and late effect of treatment (eg, malnutrition from surgery or cardiotoxicity from chemotherapy). Currently, there is no clear guidance for clinical follow-up of esophageal cancer, especially after 5 years. CRS estimates from our study suggest the need for continued surveillance and comprehensive care in long-term survivors of esophageal cancer. Additional evidence is required to guide follow-up in this group.

The 5Y CRS was only slightly higher in the younger age group, but it diverged with longer survival time. Although the background mortality of the general population is considered, survival is generally reduced in older patients. This is because older patients have higher operative/postoperative mortality, are more subject to treatment toxicity, and are less likely to receive adjuvant therapies. Smaller difference in 5Y CRS in the early survivorship period might reflect that curative resection is offered to relatively healthy older patients.⁵

Women showed higher 5Y CRFS than males that was sustained through 5 years. Women also showed higher 5Y COS and CRS in the early survivorship period, although the gap disappeared after 4 years. Previous studies also reported favorable prognosis in women with esophageal cancer.^{17,19} Possible suggested mechanisms include inhibition of cancer cell growth by estrogen (ie, both endogenous and hormonal replacement therapy),^{18,20,21} fewer comorbidities,²² better lifestyle (eg, lower smoking and alcohol consumption rate²²), and health seeking behavior.¹⁷ However, only a very small portion of our patients (6.8%) were female, and additional studies with more female patients are needed to further elucidate sex differences.

All three measures of COS, CRFS, and CRS showed convergence of risk estimates with dramatic increases in conditional survival for stage III patients with more time elapsed since diagnosis. This is consistent with a previous US SEER study that showed the same pattern of COS by SEER stage in patients with esophageal cancer. It is also similar to patterns shown in other gastrointestinal tract cancers, such as stomach²³ and colorectal cancer.²⁴ While only a third of patients (37%) survive 5 years when diagnosed with stage III esophageal cancer, those that do have a 73% chance of surviving an additional 5 years, which is comparable to those who are still alive 5 years after diagnosis of stage I cancer (77.1%). This is meaningful information for patients who were diagnosed with more advanced disease, but have survived several years. This information may greatly reduce worry about poor initial prognosis.

Patients diagnosed after the year 2000 had better conditional survival estimates than those diagnosed in 1994 to 1999. This is consistent with the increased survival of patients who received surgical treatment in different time periods. A single US institution reported that 5Y overall survival increased from 18.8% in 1980 to 1987 to 42.3% in 1996 to 2004,²⁵ and a Swedish study reported that 5Y overall survival increased from 22% in 1990 to 1994 to 40% in 2010 to 2013.¹⁷ This is likely a result of advances in surgical technique and perioperative care, as well as multimodal therapy.^{17,25} In Korea, easy access to endoscopic examination through clinical care and a national stomach cancer screening program (launched in 2002) might influence early detection and treatment.^{6,26} However, there is no significant difference between 2000 to 2009 and 2010 to 2016. While conditional survival in

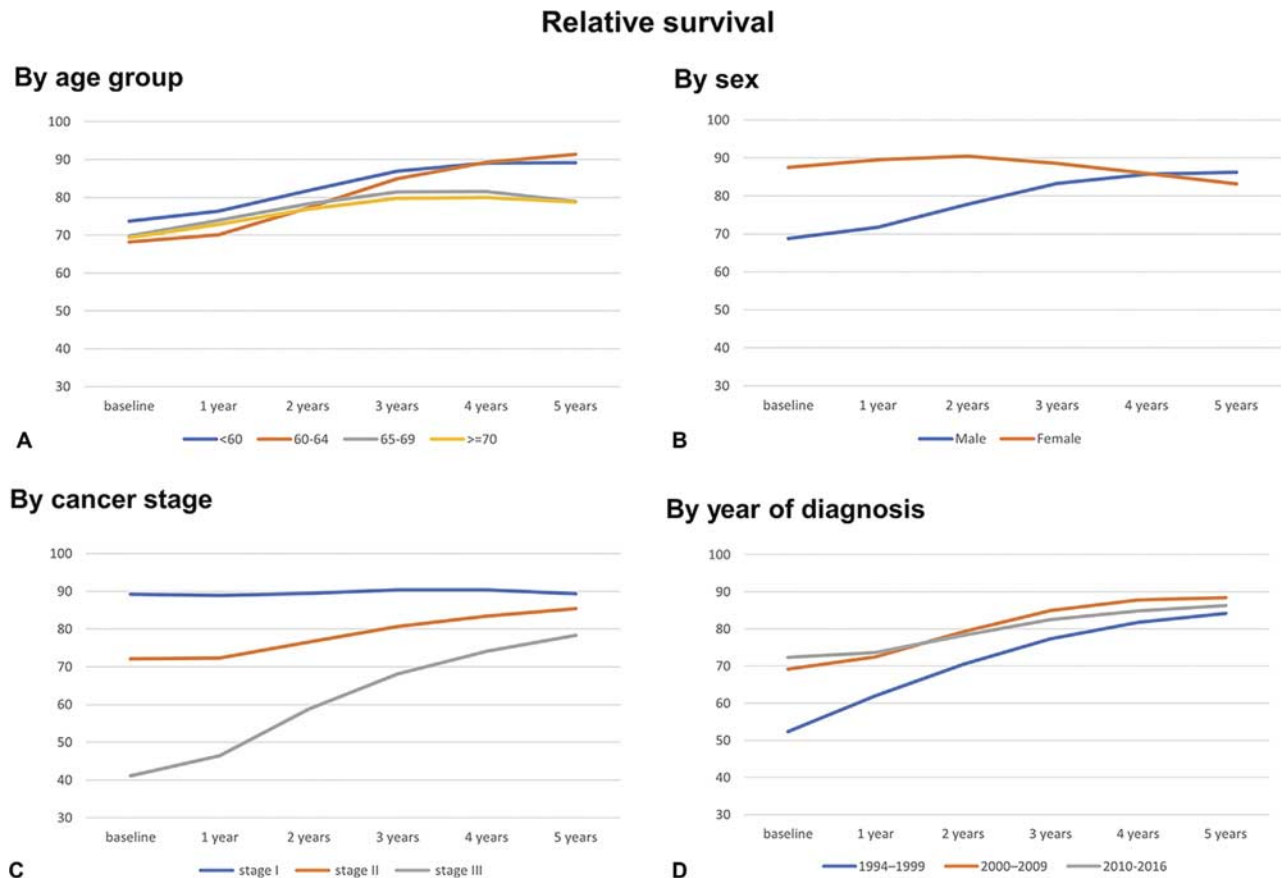


FIGURE 4. Conditional relative survival estimates in all patients who underwent curative surgery for esophageal squamous cell cancer stratified by patient characteristics.

the earlier survivorship period differed by time period of surgery, the gap decreased with more time elapsed since surgery. This indicates that better perioperative or short-term mortality with modern treatment does not necessarily translate to better long-term outcomes.⁷

One major strength of our study is inclusion of all types of survival estimates (5-year overall, recurrence-free, and relative survival). Other strengths include reliable data from extensive medical record review, linkage to a national death registration database, the relatively large number of patients, and longer inclusion period, which enabled examination of time trends.

However, there are also several limitations. First, this study may not be representative of the general population, as it was a retrospective analysis of a cohort from a single institution. The survival of study participants might be higher than at other centers, as our center has the highest volume of esophageal cancer surgery in Korea and a well-trained multidisciplinary team. Second, follow-up was relatively short (mean follow-up of 5.7 years, maximum follow-up of 22.8 years). Third, we did not include cases with other histologic types, such as adenocarcinoma, because the number of cases was too low to produce reliable estimates. Lastly, our data might not be generalizable to other countries with different epidemiologic and health system characteristics.

CONCLUSIONS

In conclusion, conditional survival estimates, including 5Y COS, 5Y CRFS, and 5Y CRS, generally increase over time. The

largest improvements in conditional survival were observed for patients with advanced stage disease. However, 5Y CRFS and 5Y CRS were 91.9% and 86.4%, respectively, implying substantial residual risk of recurrence and sustained excess mortality compared to the general population. Our data provide important probability estimates on a patient's evolving risk profile for health care decisions and suggests the need for continuing surveillance and care in long-term survivors of esophageal cancer.

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