Treatment and Survival Analysis for 40-year SEER Data on Upper Esophageal Cancer

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Research Article

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Abstract

Background: Upper esophageal cancer (UEC) is rare in western countries. We elucidated the survival outcomes of UEC and analyzed factors associated with prognosis of UEC using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Cases of UEC (C15.3 and C15.0) arising during the period from 1973 to 2013 were identified and selected. Esophageal cancer-specific survival (ECSS) and overall survival (OS) rate were calculated by Kaplan–Meier method. Cox proportional hazard regression was used to analyze predictive factors.

Results: Since 1973, there has been a significant increase (1973-1982 vs. 2004-2013) in median OS (7 months vs. 10 months, p<0.001) and median ECSS (7 months vs. 11months, p < 0.001) among patients with UEC. The ECSS and OS of surgery without radiation (SWR) and radiation plus surgery (R+S) were superior to those of radiation without surgery (RWS). For patients with localized disease, ECSS and OS were highest among patients treated with SWR, compared with patients with R+S and RWS. For patients with regional disease, ECSS and OS were highest among patients with R+S, compared with SWR or RWS. Among patients with regional-stage squamous cell carcinoma (SCC), OS was higher with neoadjuvant radiotherapy or adjuvant radiotherapy, compared with SWR. Multivariate analysis showed that radiotherapy sequence was dependently associated with OS among patients with regional-stage SCC.

Conclusion: Although survival of patients with UEC has gradually increased since 1973, the long-term survival among this patient population remains poor. Effective treatments for UEC include surgery, radiotherapy, and combination of surgery and radiotherapy.

Introduction

Esophageal cancer rarely affects the upper esophagus, which includes cervical and upper thoracic esophagus. Upper esophageal cancer (UEC) cancer accounts for only 5–10% of all cases of esophageal cancer [1–3]. Compared with carcinoma affecting the middle or lower segments of the esophagus, carcinoma of upper esophagus is challenging. Multidisciplinary treatment is always required because of the complicated anatomy of the upper esophagus and because carcinoma affecting the upper esophagus is typically advanced at the time of diagnosis, with a tendency to invade surrounding anatomical structures when being diagnosed [2–5]. Thus, UEC is associated with a poorer prognosis than any other type of esophageal cancer [5].

In general, treatment of UEC includes surgery, radiotherapy (RT), chemotherapy, or a combination of these approaches. Surgery was once the major management of UEC. The surgical method used most commonly to UEC is the McKeown approach (tri-incisional esophagectomy) [6], which always requires cervical or total esophagectomy. A pharyngo-laryngo-esophagectomy (PLE) is required in the case of high disease burden [4]. Therefore, postoperative complications are common, and the 5-year overall survival (OS) for surgical resection is low (12–33%) [7, 8].

Previous reports have found similar OS after surgery, radiotherapy (RT) and definitive chemoraidotherapy (CRT) [4, 9]. RT and CRT gradually became the preferred treatments for UEC in many countries and regions, including the United States [2, 10, 11]. However, among patients with resectable tumors, long-term outcomes were significantly improved for those who underwent surgery, compared with those who received only received definitive CRT [12]. Surgery may also result in improvements in prognosis, quality of life, and post-treatment dysphagia symptoms [9, 13]. The centers included in these studies continue to rely on surgery as primary treatment for UEC [4, 7, 12].

The surgical procedure for esophageal cancer has changed dramatically in recent years with the development of medical skills and instruments. For example, many centers have adopted minimally invasive esophagectomy. The advantages of minimally invasive esophagectomy, compared with open esophagectomy, include decreased postoperative pain, decreased length of hospital stay, and fewer complications [14]. Furthermore, surgical robots have been used widely to perform esophageal cancer operations, with positive clinical outcomes [15]. Technological advancement has also brought numerous improvements to RT and chemotherapy [1, 11]. UEC patients must now choose carefully when deciding upon a treatment plan.

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is a cancer database covering approximately 26% of the total U.S. population. This database includes information on the incidence of cancer in 18 areas of the U.S. [16]. The aim of this study was to use information from the SEER database to analyze long-term survival trends of UEC in the U.S. and to identify independent predictors of associated mortality. We also compared the effects of different treatments on long-term survival, in order to provide a reference for patients seeking to determine how best to treat UEC.

Methods

Database and patients

This study was performed using data from the SEER database. Data were collected during the period from 1973 to 2013 (available at: www.seer.cancer.gov) based on the November 2015 submission using SEER*Stat software, version 8.3.5.

The outcomes of interest in this study were OS and esophageal cancer–specific survival (ECSS), according to specific codes. We collected information for patients with UEC diagnosed during the period from 1973 to 2013. All patients included in the study had a primary site-labeled recode diagnosis of "C15.0- Cervical esophagus and C15.3-Upper third of esophagus" (from the lower margin of the sixth cervical vertebra to the superior margin of the sixth thoracic vertebrae). Exclusion criteria were multiple primary carcinomas, unknown number of survival months, and diagnosis < 1 month prior to death. Tumors were classified as squamous cell carcinoma (SCC) (8050-8082), adenocarcinoma (AC) (8140-8573) or "other" pathological type. Criteria for SEER historical stage A (localized, regional, and distant) were adopted in order to comply with a unified tumor staging system across all years of the study.

Statistical analysis

Continuous variables were compared with Student's t test; Categorical variables were compared with Pearson's chi-square test. Kaplan-Meier (KM) methods were used to estimate survival time for time to event endpoints, OS, and ECSS. The log-rank test and Cox proportional hazards models were used to conduct univariate and multivariate analysis, respectively. Multivariate analysis included only those variables that were significantly associated with survival in univariate analysis. All p values were 2-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS version 20.0.

Results

Patient characteristics

A total of 4424 patients who met our inclusion criteria were included in the study (Supplementary Table 1). Mean age was 66.8 years. Males accounted for 66.5% of all patients. Most patients had regional (37.6%) or distant (31.4%) stages of disease at the time of diagnosis. Patients were divided in 4 groups according to the year of diagnosis, (Supplementary Table 2). Although SCC (85.3%) remained the most common pathological type of UEC, the proportion of AC gradually increased over the study period (from 3.6% to 11.8%, $p < 0.001$). Most patients had undergone RT (75.7%) and only a few (13.3%) had been treated with surgery. While patients with localized or regional stages of disease were more likely to receive surgery ($p < 0.001$). RT was more commonly used in patients with regional-stage disease ($p < 0.001$ Supplementary Table 3). The rate of surgical resection was higher for AC, compared with SCC. Patients with SCC were more likely to receive RT than were patients with AC ($p<0.001$ for all, Supplementary Table 4).

Treatments

Patients were divided in four groups based on the type of treatment received (Supplementary Table 5). Patients with localized disease were more likely to undergo SWR, while patients with regional-stage tumors tended to choose R+S ($p<0.001$). Patients who chose neither surgery nor radiotherapy tended to have advanced-stage disease ($p < 0.001$).

In order to evaluate the effect of RT sequence on survival among patients who underwent surgery, we divided patients into 3 groups (Supplementary Table 6): SWR, neoadjuvant radiotherapy (NRT), and adjuvant radiotherapy (ART). The proportion of SCC was lower in the SWR group, compared with the ART and NRT ($p < 0.001$). The number of patients who elect to undergo NRT has increased over recent decades ($p < 0.001$). SWR was most likely to be performed for patients with localized disease ($p < 0.001$). While ART was most commonly used in the treatment of patients with regional-stage ($p < 0.001$), NRT was most commonly used in patients with distant-stage ($p < 0.001$).

Patient survival

Overall

Median OS was approximately 9.0 months (95% CI: 8.65–9.35). Overall ECSS was also approximately 9.0 months (95% CI: 8.60–9.40). OS at 1, 3, and 5 years was 37.0%, 13.2%, and 10.0% respectively; ECSS at 1, 3, and 5 years was 40.8%, 17.9%, and 14.1%, respectively.

OS values at 1, 2, 3, and 5 years, respectively, increased further for each year that elapsed between 1973 and the time of diagnosis (Figure 1A). OS and ECSS differed significantly among these four groups ($p < 0.05$ for all, Figure 1B and Figure 1C). These results indicate significant increases (1973-1982 vs. 2004-2013) in median OS (7 months vs. 10 months, $p < 0.001$) and median ECSS (7 months vs. 11 months, $p < 0.001$) since 1973.

The OS and ECSS were greater for AC than for SCC ($p < 0.001$ for all, Figure 2A and Figure 2B). OS was higher among females, compared with males ($p < 0.001$; Figure 2C). ECSS was also higher among females, compared with males ($p < 0.001$; Figure 2D). Univariate (Supplementary Table 7) and multivariate (Supplementary Table 8) Cox analyses identified the following independent factors associated with ECSS as well as OS: date of diagnosis, ethnicity, sex, age, marital status, histologic subtype, SEER historic stage, surgical treatment, and RT, were.

Survival analysis

Median OS for the control, RWS, SWR, and R+S groups was 3 months, 9 months, 15 months, and 15 months, respectively. ECSS and OS were improved among patients who underwent RT or surgery, compared with patients who did not receive treatment ($p < 0.001$ for all, Figure 3A and Figure 3B). ECSS and OS were lower in the RWS group, compared with the SWR and R+S groups ($p < 0.001$ for all, Figure 3A and Figure 3B).

Subgroup analyses by SEER historical stage A revealed that, for patients with localized disease, ECSS and OS were greatest in the SWR group (Figure 3C and Figure 3D). For patients with regional disease, ECSS and OS were highest in the R+S group (Figure 4A and Figure 4B). Univariate (Supplementary Table 9) and multivariate (Table 1) analysis demonstrated that treatment strategy was independently associated with both ECSS and OS.

Radiation sequence with surgery

No significant difference in ECSS or OS was found among the SWR, NRT, and ART groups ($p > 0.05$ for all, Figure 5A and Figure 5B).

Sub-group analysis by SEER stage showed that, for patients with localized disease, OS was highest in the SWR group. Among patients with regional disease, OS was lowest in the SWR group, compared with the ART and NRT groups. However, multivariate analysis did not reveal a significant difference in OS in localized or regional sub-groups.

Next, we performed sub-group analysis by histologic subtype. For the SCC subgroup, among patients with regional disease, OS was lower with SWR (median OS: 9 months, 95% CI: 6.34–11.67), compared with NRT (median OS:17 months, 95% CI: 11.79–22.21) and ART (median OS:15 months, 95% CI: 11.42–18.59; Figure 5C). Multivariate analysis for this subgroup also demonstrated that RT sequence was an independent factor for OS (SWR as reference, HR of NRT: 0.633, 95% CI: 0.427–0.938, $p = 0.023$; HR of ART: 0.635, 95% CI: 0.453–0.889, $p = 0.008$, Supplementary Table 10). No other subgroup analysis yielded statistically significant results.

Comment

Although the long-term survival of patients with UEC remains extremely low, this figure gradually increased in the U.S. during the period from 1973 to 2013. This trend may reflect advancements in medical equipment, surgical technique, and related adjuvant therapy. OS and ECSS were higher among females, compared with males, perhaps due to gender-based differences in lifestyle. Use of alcohol and cigarette smoking are more common among males, and both are common causes of esophageal cancer [17].

Recent decades have also seen a dramatic rise in the incidence of esophageal adenocarcinoma (EAC) in western countries [18, 19]. The results of our study indicate a similar rise in the prevalence of UEC. Notably, AC was rarely found in upper esophagus [20, 21]. And the histogenesis of AC in upper esophagus remains unclear. The pathogenesis of AC in middle and/or lower esophagus is typically related to gastroesophageal reflux or Barrett's esophagus. However, the pathogenesis of AC in upper esophagus is different from that of AC in middle or lower esophagus. Previous studies have revealed that AC in upper esophagus may arise from esophageal glands or heterotopic gastric mucosa (HGM), the latter of which may be related to infection with Helicobacter pylori [21]. Our results presented above identified histologic type as an independent prognostic factor in UEC. Survival was higher for AC than for SCC, as reported previously [22]. Among patients with regional or distant disease, SCC was more common than AC (Supplementary Table 4). This finding is concordant with results described above, which found lymph node metastasis was more commonly associated with SCC than with AC [22].

In most countries and regions including the U.S., first-line strategies for UEC are CRT and RT [1, 2, 10, 11]. Our study revealed that RT was commonly used. For SCC, this proportion reached 70.6%. Previous studies have reported no significant difference in outcomes after combined surgery and RT, compared with CRT alone [4]. However, among patients with resectable UEC, long-term outcomes appear to be better with surgery, compared with definitive CRT alone. Patients who underwent surgery also had improvements in prognosis, quality of life, and post-treatment dysphagia [9, 13]. OS and ECSS were higher among the SWR and R + S groups, compared with the group of patients that underwent RT alone. Among patients with localized disease, survival was highest with surgery alone, compared with RWS and R + S. Notably, RT may decrease the patient's own resistance and increase risk for postoperative complications [23, 24]. Furthermore, use of RT alone was likely insufficient to entirely eliminate the primary lesion. For patients with regional disease, highest OS was found in the R + S group. This finding is similar to those published in a previous report [12]. Importantly, R + S, in addition to removing the lesion, eliminates any potential unresected lesions.

Surgery may afford reasonable OS and improve quality of life for UEC patients [25]. Surgery may also significantly reduce local tumor recurrence and improve dysphagia [13]. The surgical method used most commonly to treat UEC is the McKeown approach (tri-incisional esophagectomy) [6]. Surgery is not recommended for tumors < 20 cm from the incisors, because UEC at this site always requires a pharyngo-laryngo-esophagectomy, which is associated with poor quality of life post-operatively because of the loss of vocal function [26]. Previous studies also showed that long-term survival was similar in the CRT and surgery groups for patients with lesions that were positioned more superiorly [13, 27]. Thus, CRT gradually became the main strategy for these patients. However, prognosis for these UEC patients who underwent definitive CRT alone was always unsatisfactory because of insufficient local disease control; salvage surgery was always needed for these patients [26]. In recent years, studies have sought to elaborate a larynxpreserving surgery that would preserve vocal function in patients with UEC[26, 28]. Furthermore, larynxpreserving surgery, compared with non-preserving procedures, was associated with improved prognosis and decreased complications [26]. However, comparison of larynx-preserving surgery and CRT alone showed no significant difference in long-term survival [28]. Compared with CRT alone, surgery decreases risk for local recurrence and improves dysphagia symptoms [13]. Therefore, larynxpreserving surgery may be an acceptable surgical approach for UEC proximal to the larynx.

Grass et al. performed a similar investigation using the SEER database, with a focus on cervical esophageal cancer [4]. The authors found that ECSS was higher among patients who had RT alone, compared with surgery alone. ECSS was also higher with surgery plus RT, compared with RT alone. These results differed from those presented in this study, perhaps because of methodological discrepancies. One difference between studies was the criteria used for inclusion and exclusion. Grass et al. included SCC and AC cervical esophageal cancer, and excluded patients with distant metastases. Grass et al. did not conduct subgroup analysis by SEER historical stage, and studied only patients diagnosed during the period from 1998 to 2008.

Clinical practice has recently seen the increased use of adjuvant and neoadjuvant therapies for the treatment of esophageal cancer. However, the role of adjuvant and neoadjuvant therapies remains controversial. Previous studies reported that NRT, compared with surgery alone, may improve 5-year OS and increase the curative resectability of tumors [29]. However, other researchers found no increase in resectable rate or OS among patients treated with NRT [30]. Notably, none of these studies studied UEC alone.

In our study, NRT was mainly used in patients with advanced disease (Supplementary Table 5, $p < 0.001$), suggesting that NRT may improve tumor resection rate. However, in the SWR group, there was no significant effect of NRT or ART on OS or ECSS ($p > 0.05$ for all). Sub-group analysis of patients with localized disease revealed higher OS in the SWR group, compared with the other two groups. Adjuvant use of NRT and ART may increase the difficulty of surgery and, therefore, risk for postoperative complications. OS for patients with regional disease was higher in the ART and NRT groups, compared with the SWR group. This finding was expected because lymph node metastasis is observed in almost all patients with regional disease but not in as high a proportion of patients with localized disease. NRT and ART may eliminate potentially metastatic lesions and thus reduce tumor recurrence.

RT sequence was not an independent factor in the NRT and ART subgroups. In a previous analysis of the SEER database, NRT was beneficial to long-term survival and an independent factor for OS [29]. However, this previous analysis did not study UEC alone. In our study, which did investigate UEC alone, RT sequence was an independent factor for OS among patients with regional SCC.

Current treatment for UEC typically includes CRT or surgery plus CRT. However, we could not assess the effect of chemotherapy on patent survival, as these data were not available in the SEER database. RT methods, radiation dose, and surgical methodology are also reported to have significant effects on patient prognosis [1, 11, 14]. However, the SEER database does not include these data. The database did not register information related to smoking, drinking, or postoperative complications. Finally, we used SEER historical stage A (localized: confined to primary site; regional: spread to regional lymph nodes; distant: cancer metastasis) in order to comply with unified tumor staging criteria across all years of the study. SEER historical stage A differs from the staging criteria provided by the American Joint Committee on Cancer [3]. Any of the factors mentioned above may have resulted in a deviation in the research results.

Conclusion

UEC is a rare esophageal cancer associated with a poor prognosis. Our investigation of the SEER database showed that surgery and radiation in combination, or alone may improve OS and ECSS among patients with UEC. Surgery appears to be more effective for the treatment of localized and regional disease. For patients with regional SCC, NRT or ART is more effective than surgery or RT alone. Additional clinical studies are needed to identify the optimal treatment strategies for UEC.

Declarations

Acknowledgements

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Conflict of interest

Ming-Chuang Zhu, Guo-Liang Li, Peng Xiong, Min Zhu, authors of the paper referenced above, have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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Table

Table 1: Multivariate analysis of ECSS and OS across treatments.

Variable	ECSS			OS		
	HR	*95% CI of HR*	P value	*HR*	*95% CI of HR*	*P value*
Group						
None	***Reference***			***Reference***		
RWS	***0.514***	***0.468–0.564***	***<0.001***	***0.501***	***0.459–0.547***	***<0.001***
SWR	***0.380***	***0.316–0.457***	***<0.001***	***0.383***	***0.324–0.452***	***<0.001***
R+S	***0.362***	***0.309–0.424***	***<0.001***	***0.367***	***0.317–0.424***	***<0.001***
Year of diagnosis						
1973~1983	***Reference***			***Reference***		
1984~1993	0.773	0.688–0.869	***<0.001***	0.789	0.709–0.879	***<0.001***
1994~2003	0.665	0.596–0.742	***<0.001***	0.662	0.597–0.733	***<0.001***
2004~2013	0.485	0.435–0.542	***<0.001***	0.488	0.440–0.541	***<0.001***
Ethnicity						
White	***Reference***			***Reference***		
Black	1.160	1.064–1.266	***0.001***	1.165	1.074–1.264	***<0.001***
Other	0.997	0.877–1.133	0.959	0.969	0.859–1.093	0.607
Unknown	1.419	0.734–2.742	0.298	1.260	0.652–2.432	0.492
Sex (Male)						
Male	***Reference***			***Reference***		
Female	0.845	0.782–0.913	***<0.001***	0.843	0.784–0.906	***<0.001***
Age						
≤45	***Reference***			***Reference***		
>45,≤65	1.576	1.262–1.968	***<0.001***	1.669	1.351–2.061	***<0.001***
>65,≤80	1.619	1.296–2.024	***<0.001***	1.805	1.460–2.231	***<0.001***
>80	1.878	1.473–2.393	***<0.001***	2.172	1.728–2.731	***<0.001***
Marital status						
Married	***Reference***			***Reference***		
Single (unmarried)	1.138	1.027–1.261	***0.013***	1.128	1.025–1.242	0.014
Separated/Divorced /Widowed	1.148	1.057–1.248	***0.001***	1.123	1.039–1.213	0.003
Unknown	1.140	0.947–1.372	0.167	1.064	0.892–1.268	0.492
SEER historic stage						
Localized	***Reference***			***Reference***		
Regional	1.522	1.378–1.681	***<0.001***	1.434	1.310–1.571	***<0.001***
Distant	2.279	2.054–2.529	***<0.001***	2.064	1.874–2.273	***<0.001***
Unstaged	1.249	1.117–1.398	***<0.001***	1.204	1.087–1.333	***<0.001***

Figures

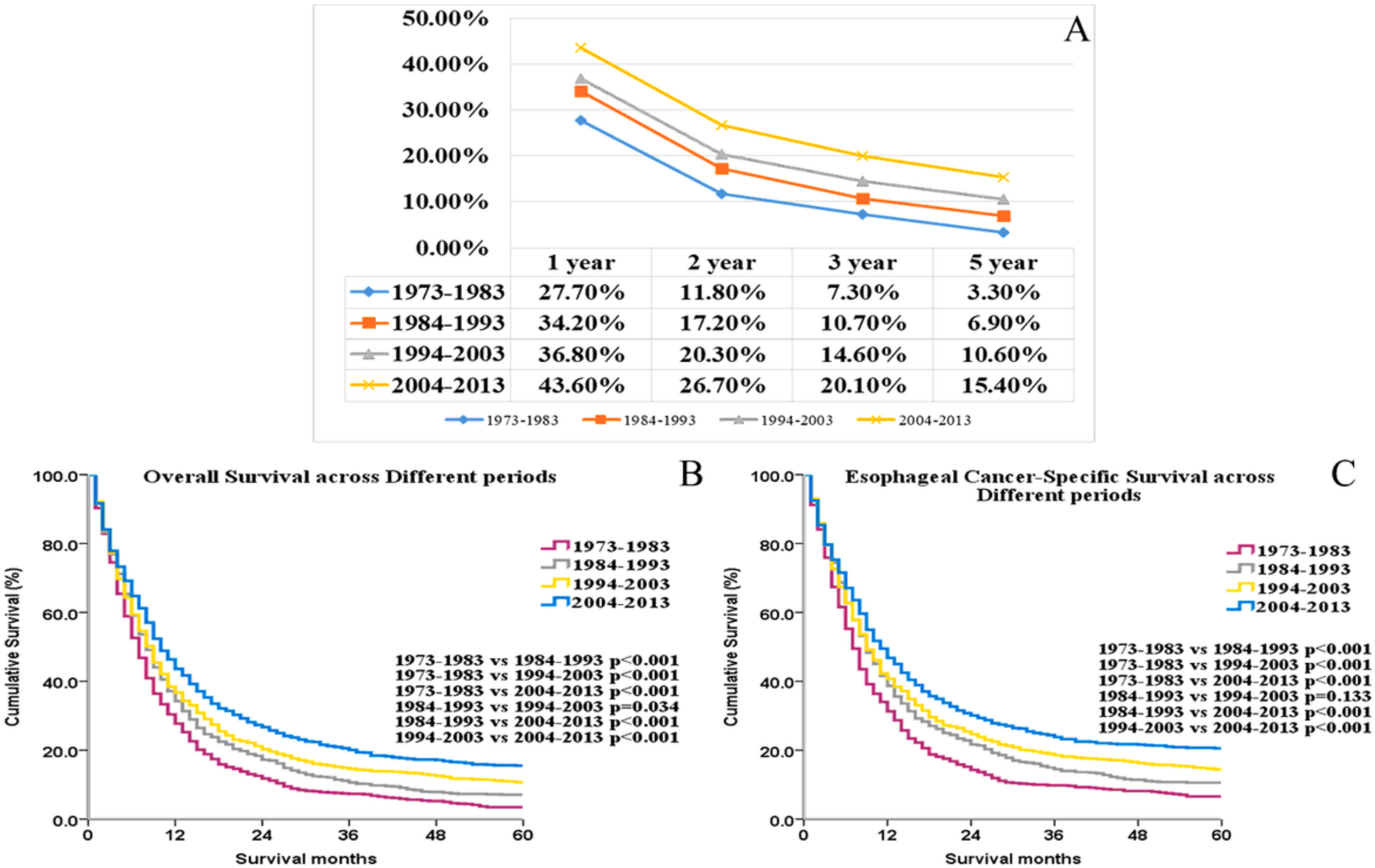

Figure 1

Figure 1

The trends of the 1-, 2, -3- and 5-year overall survival rate, and ECSS and OS across different periods.

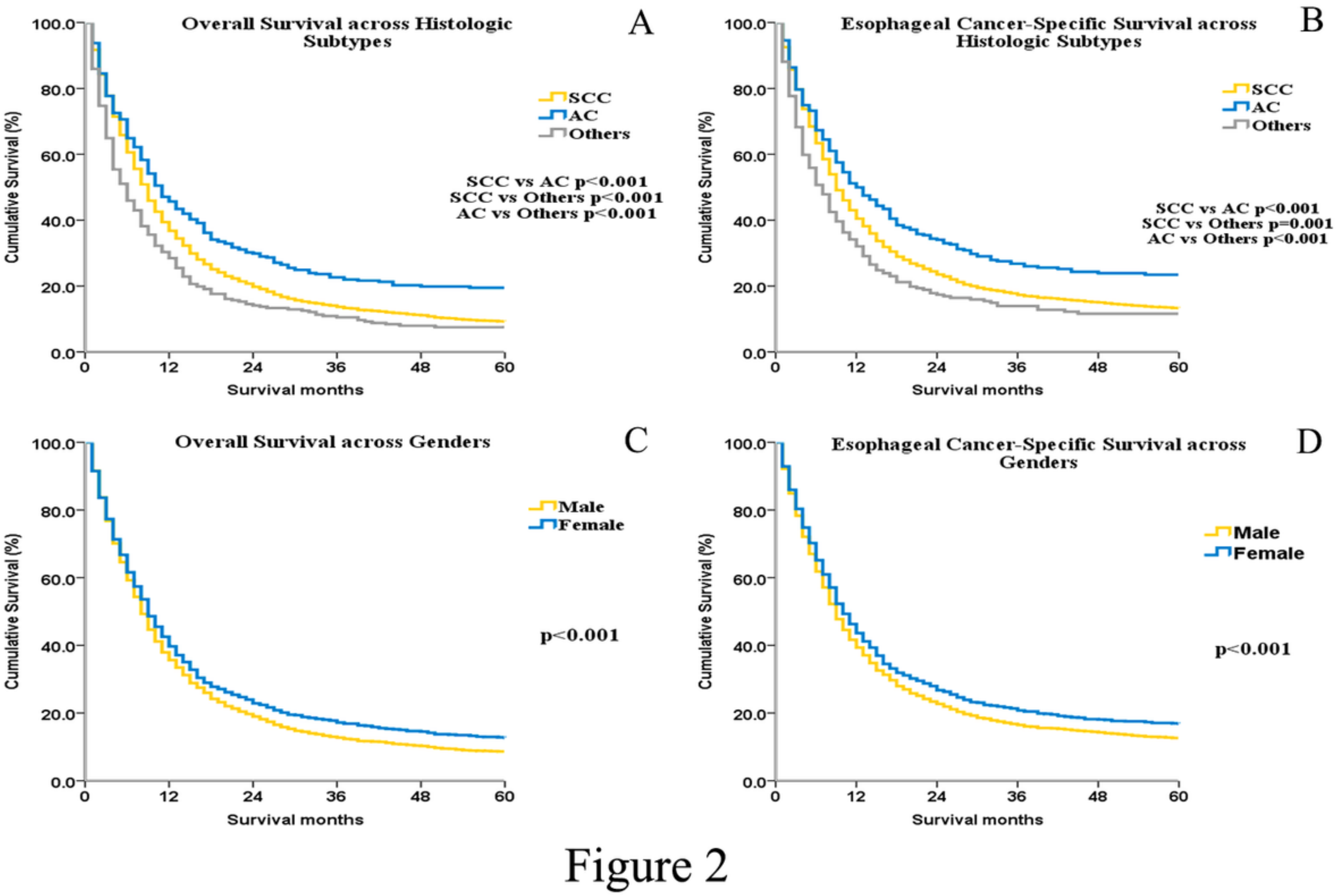

Figure 2

ECSS and OS for patients across histological subtypes and across genders.

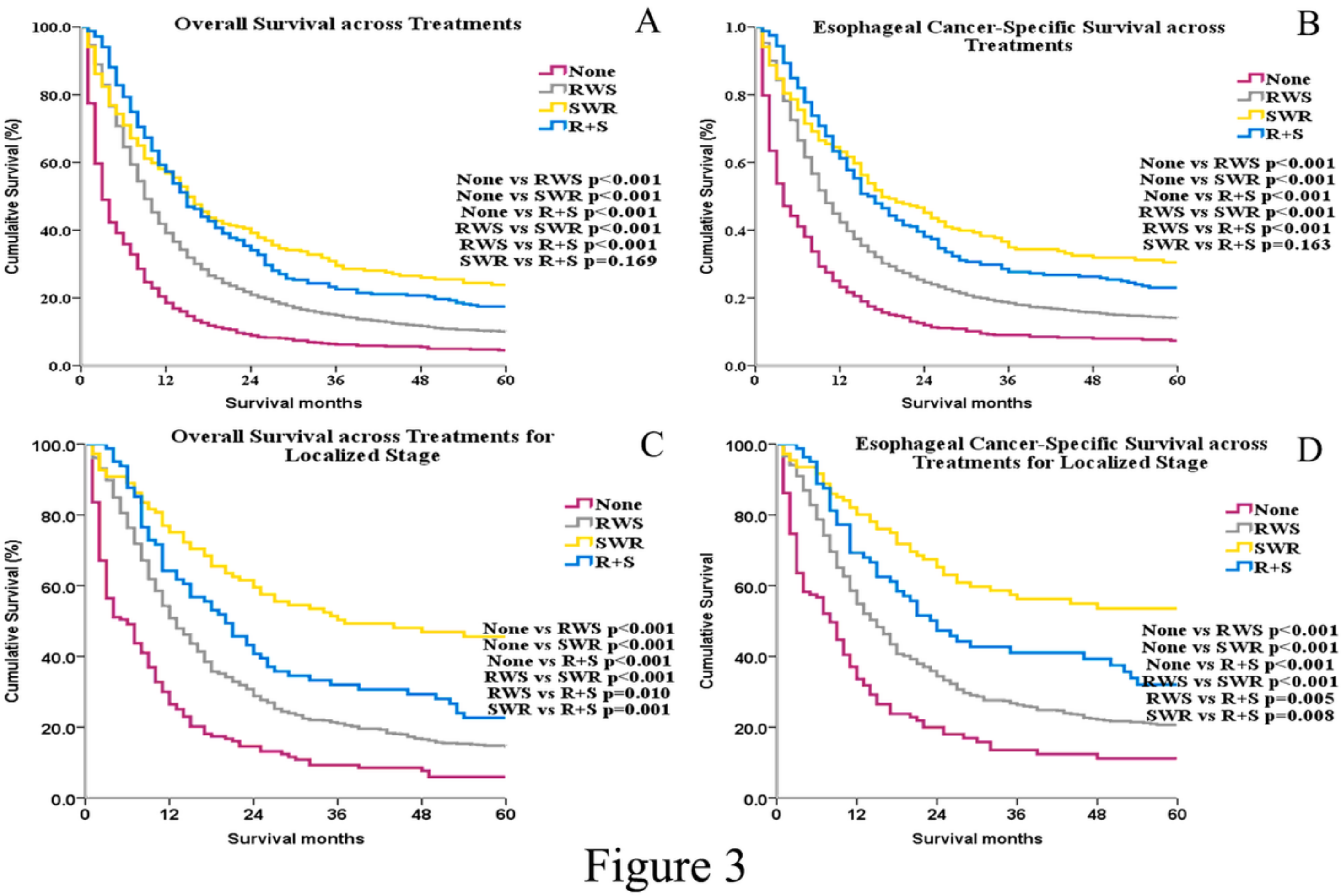

Figure 3

ECSS and OS across treatments for all patients and for localized stage subgroup.

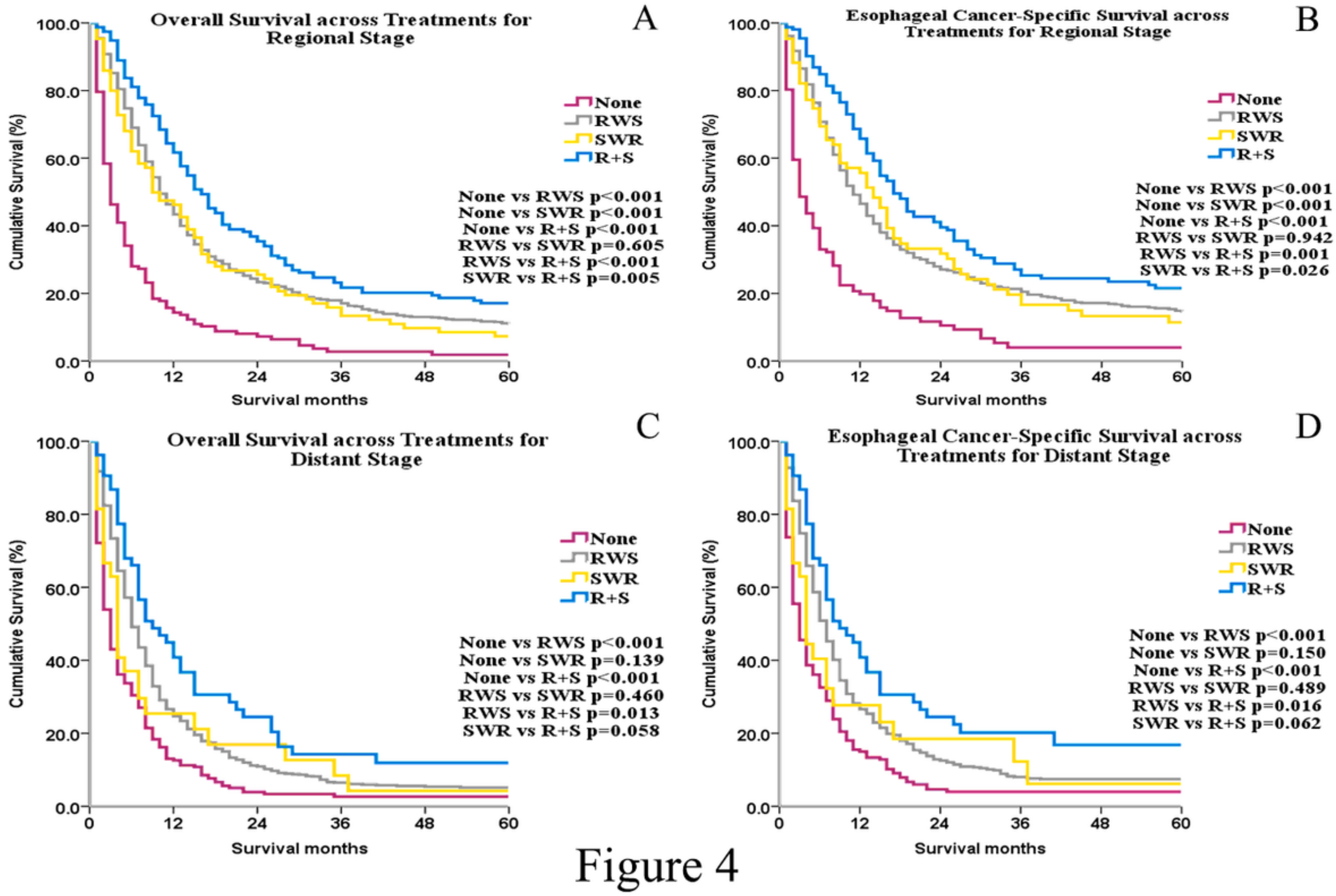

Figure 4

ECSS and OS across treatments for regional stage and for distant stage subgroups.

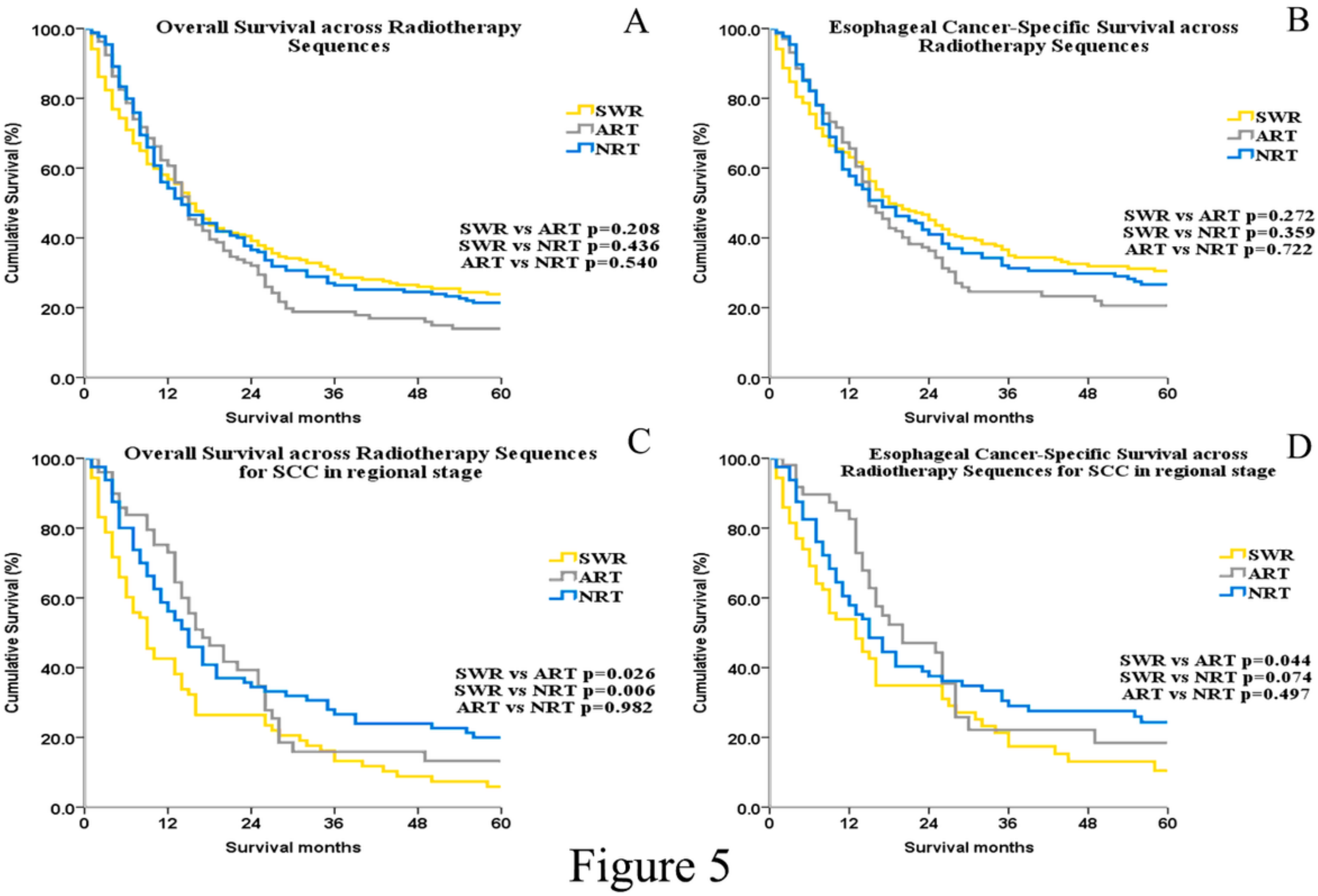

Figure 5

ECSS and OS across radiotherapy squences for all patients and for regional stage SCC.

Supplementary Files

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