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Progression-free survival as surrogate endpoint of overall survival in esophageal squamous cell carcinoma: a real-world data and literature-based analysis

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Abstract

Background: The surrogacy of progression-free survival (PFS) for overall survival (OS) in esophageal squamous cell carcinoma (ESCC) remains unelucidated. This study aimed to determine the validity of PFS as a surrogate endpoint for OS in ESCC patients treated with definitive radiotherapy or definitive chemoradiotherapy (dRT/dCRT), as well as characterize the prognostic factors and survival of such patients.

Methods: A total of 3662 patients from 10 cancer centers were enrolled. One-, 2-, and 3-year PFS (PFS12, PFS24, and PSF36, respectively) were used as time points for analysis. At each time point, ESCC-specific mortality and OS were characterized using competing risk and conditional survival models, while correlation between PFS and OS was evaluated by linear regression.

Results: At PFS12, PFS24, and PFS36, a progressive decrease in 5-year ESCC-specific mortality (35.2%–13.4%) and increase in 5-year OS (46.6%–62.9%) were observed. Regardless, the OS of patients remained markedly lower than those of the age- and sex-matched Chinese general population. TNM stage remained a significant prognostic factor at PFS36. Strong correlation was found between 3-year PFS and 5-year OS, which was further externally validated.

Conclusions: Three-year PFS may act as a potential surrogate endpoint for 5-year OS. TNM stage was considered a significant prognostic factor for OS, and may represent the optimal prognostic tool to guide clinical decision-making and post-treatment follow-up.

Keywords: esophageal cancer, overall survival, progression-free survival, radiotherapy, surrogate endpoint

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Background

Definitive concurrent chemoradiotherapy (dCRT) is one of the standard treatments for esophageal cancer (EC). However, despite recent advancements in radiotherapy (RT) techniques such as conformal RT and intensity-modulated RT (IMRT), the prognosis of EC remains poor.[1–3] For patients with inoperable local-advanced lesion, approximately 50% of them have demonstrated local-regional failure after receiving dCRT, of which over 90% occurred within 2–3 years of completing treatment.[4–6]

Overall survival (OS) represents the gold-standard endpoint for evaluating therapeutic efficacy in most prospective oncological trials, including

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those of inoperable or local advanced EC. However, OS as a clinical endpoint is limited by the need for long follow-up periods, which can delay the translation of potentially effective treatment to clinical practice and the adjustment of follow-up or intervention strategies. To address this, alternative endpoints with strong correlations to OS, which enable early prognostic evaluation and prompt clinical application of potential treatments, without concerns of confounding by subsequent treatment, would be ideal.

Progression-free survival (PFS) has been proposed as a reliable surrogate endpoint for OS in multiple cancer types.[7–11] However, the relationship between OS and PFS in the context of EC has not been fully elucidated, and lack of studies on effects of prognostic factors based on duration of PFS. Our study therefore aimed to evaluate the correlation between OS and PFS, and determine the validity of PFS as a surrogate endpoint for OS in esophageal squamous cell carcinoma (ESCC) patients treated with definitive radiotherapy (dRT) or dCRT, as well as characterize the prognostic factors and survival of such patients.

Materials and methods

Patient population

A total of 4236 ESCC patients treated with dRT/dCRT at 10 cancer centers (centers A–J) in China between 2003 and 2017 were retrospectively evaluated. The inclusion criteria were as follows: (1) no history of radical intended surgery, due to diagnosis of inoperable lesions or refusal for surgery; (2) lack of other malignancies ⩾5 years prior to dRT/dCRT, (3) Karnofsky performance score ⩾70 with no distant metastases, (5) underwent either three-dimensional conformal RT, IMRT, or volumetric modulated arc therapy, and not two-dimensional RT, (5) cumulative radiation dose, converted to equivalent dose in 2 Gy/f (EQD2), between 50 and 70 Gy, and (6) available at first follow-up. For patients conform with the above criteria, dCRT is considered preferable. dRT is also considered as one of the alternative treatment approaches with acceptable toxicities and relative favorable survival to those who tends more likely to discontinue the concurrent chemoradiotherapy due to general status such as advanced age and presence of complications, or tumor status such as high tumor burden (e.g. long primary tumor or multi-station-regional lymph nodes metastases) and large planning target volume with accompanied relative high lung irritation volume or individual indication such as concerns about the treatment-related toxicities and preference for relative moderate treatment modality.

Patients were followed up until death or October 2021, whichever occurred first. Data collected included primary tumor and treatment characteristics.

Potential prognostic factors of ESCC

Potential prognostic factors included TNM stage, location, and length of the primary tumor, all of which were determined by multimodal clinical imaging. TNM stage was assessed based on the American Joint Committee on Cancer (AJCC) staging system (6th edition), with tumor (T) stage determined by endoscopic ultrasonography and computed tomography (CT), while nodal (N) and metastatic (M) stages determined by CT of the neck, chest and abdomen, endoscopic ultrasonography, and, if available, positron emission tomography/CT. Primary tumor location and length were determined by barium esophagography and esophagogastroduodenoscopy. Patients with M1 stage in current study only included those who with periesophageal cervical nodes or celiac nodes metastasis, those who with other non-regional lymph nodes or distant organs metastasis were excluded. The M1a stage was defined as primary tumors located in the upper-third esophagus and periesophageal cervical lymph node metastasis, or primary tumors located in the lower-third esophagus and celiac lymph node metastasis, without other distant metastases. The M1b stage was defined as primary tumors located in the upper-/middle-third esophagus and celiac lymph node metastasis, or primary tumors located in the middle-/lower-third esophagus and periesophageal cervical lymph node metastasis, and those who with other non-regional lymph nodes or distant organs metastasis were excluded.

Statistical analyses

OS and PFS were calculated from the date of dRT/dCRT initiation to the date of death, disease progression (recurrence of primary tumor, regional lymph node, or distant lymph nodes or organs), or the last follow-up date, whichever occurred first. Competing risk analysis was performed to estimate ESCC-specific mortality, with

competing risk defined as death due to other causes (including complications, comorbidities, accidents, new primary cancers, and other unknown causes). Landmark PFS time points, including PFS12, PFS24, and PFS36, were used for analysis, and corresponded to the months during which patients remained progression-free after the date of dRT/dCRT initiation. Subsequent OS was defined as the time from each PFS landmark to death from any causes. Expected survival was estimated using the 'survexp' function in R (package survival), with age- and sex-matched Chinese general population set as the reference group. Observed and expected OS were compared at each PFS time point using conditional survival analysis and standardized mortality ratios.

Linear regression analysis (LRA) was performed to evaluate the relationship between 1-, 2-, 3-, 5-year PFS and 5-year OS. The correlation coefficient (r value) of LRA, ranging from −1 to 1, was used to measure the linear association. −1 indicates a perfectly negative linear correlation, 0 indicates no linear correlation, and 1 indicates a perfectly positive linear correlation. The further away r is from zero, the stronger the relationship between the two variables. The correlation is considered to be strong if the absolute value of r is greater than 0.75. Survival information of multicenter data was applied to evaluate the correlation between 1-, 2-, 3-, 5-year PFS and 5-year OS. All patients were grouped based on cancer center (centers A–J), with those from centers F–J merged into one due to small sample size. Patients in each group were subsequently divided based on definitive treatment received (the dRT and dCRT group). In all, 11 patient subgroups were eventually formed to perform the LRA. For external validation, PFS and OS data from the literature were further collected. A literature search was performed on PubMed using the following keywords: ((esophag*[Title]) OR (oesophag*[Title])) AND ((radiotherapy[Title]) OR (chemoradiotherapy[Title]) OR (chemotherapy[Title]) OR (radiation therapy[Title])) NOT ((neoadjuvant[Title]) OR (preoperative[Title]) OR (surgery[Title]) OR (esophagectomy[Title]) OR (oesophagectomy[Title]) OR (resection[Title]) OR (postoperative[Title]) OR (adjuvant[Title]) OR (trimodality[Title]) OR (Salvage[Title])) AND (5 year[Title/Abstract]). All papers were screened for relevance by title and abstract, and by definition of relevant endpoints. Linear correlation between the 1-, 2-, 3-, and 5-year PFS and 5-year OS was evaluated using correlation coefficient (r), with weight depending on the sample size of our patient group and those from the literature. All statistical tests were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

All statistical analyses were performed using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 3662 patients were eventually enrolled in our study (Supplemental Figure 1), majority of whom were males (72.3%). Over one-third (33.6%) of patients were aged ⩾70 years, and 77.6% were diagnosed with AJCC stage III-IV ESCC. dRT and dCRT were performed in 55.3% and 44.7% of patients, respectively. The clinicopathological characteristics of all patients are summarized in Table 1. With a median follow-up period of 57.2 months, The 1-, 2-, 3-, and 5-year OS were 70.6%, 47.5%, 38.6%, and 31.0%, respectively, and the median survival period was 22.1 months.

Failure pattern and salvage treatments for disease progression

Disease progression was observed in 2287 patients. Among the patients with disease progression, 56.8%, 20.5%, and 44.1% of them recurred in esophagus, regional lymph nodes and distant lymph nodes/organs, respectively (Supplemental Figure 2(a)). Chemotherapy, RT, and best supportive care was applied as salvage treatment in 68.3%, 10.7%, and 10.8% of the patients with progression in esophagus, 67.6%, 15.1%, and 7.2% of the patients with progression in regional lymph nodes, 74.4%, 8.2%, and 8.3% of the patients with progression in distant lymph nodes/organs, respectively (Supplemental Figure 2(b)–(d)).

Risk of ESCC-specific mortality based on PFS time points

From the date of dRT/dCRT initiation, the 5-year ESCC-specific mortality and mortality due to other causes were 54.3% and 14.7%, respectively (Figure 1(a)). At the last follow-up, disease progression was observed in 2287 (62.5%) patients,

Table 1. Baseline clinicopathological characteristics of the included patients.

Characteristics	No (%)
Age	
<70 years	2432 (66.4%)
⩾70 years	1230 (33.6%)
Median (IQR)	64 (57–72)
Sex	
Male	2647 (72.3%)
Female	1015 (27.7%)
T stage	
T1	55 (1.5%)
T2	544 (14.9%)
T3	1411 (38.5%)
T4	1652 (45.1%)
N stage	
N0	960 (26.2%)
N1	2702 (73.8%)
M stage	
M0	2801 (76.5%)
M1a	386 (10.5%)
M1b	475 (13.0%)
TNM stage	
I	14 (0.4%)
IIA	535 (14.6%)
IIB	271 (7.4%)
III	1981 (54.1%)
IV A	386 (10.5%)
IV B	475 (13.0%)
Primary tumor site	
Cervical	167 (4.6%)
Upper thoracic	1044 (28.5%)
Middle thoracic	1739 (47.5%)
Lower thoracic	712 (19.4%)
Primary tumor length	
<5 cm	1145 (31.3%)
⩾5 cm	2517 (68.7%)
Median (IQR)	5.0 (4.0–7.0)
Induction chemotherapy	
No	3543 (96.8%)
Yes	119 (3.2%)
Definitive treatment	
dRT	2024 (55.3%)
dCRT	1638 (44.7%)
Consolidated chemotherapy	
No	3156 (86.2%)
Yes	506 (13.8%)
Radiation dose (EQD2)	
50–59.9 Gy	533 (14.6%)
60–69.9 Gy	3088 (84.3%)
70 Gy	41 (1.1%)
Median (IQR)	60.0 (60.0–61.8)

dCRT, definitive chemoradiotherapy; dRT, definitive radiotherapy; IQR, interquartile range.

majority of which occurred in the first 3 years (1-, 2-, and 3-year cumulative rates of 50.8%, 69.3%, and 74.6%, respectively). The 5-year ESCC-specific mortality at PFS12, PFS24, and PFS36 were 35.2%, 19.2%, and 13.4%, respectively, while 5-year mortality due to other causes were 18.2%, 23.3%, and 23.7% (Figure 1(b)–(d)).

In terms of prognostic factors, the 5-year competing event-related mortality was similar between patients with stage I-III and III-IV ESCC, upper-third and middle-/lower-third lesions, and tumor length <5 cm and ⩾5 cm (15.3% *versus* 14.6%, $p=0.50$; 13.7% *versus* 15.3%, $p=0.53$; and 13.3% *versus* 15.5%, $p=0.23$, respectively). However, the 5-year ESCC-specific mortality of patients with stage III-IV ESCC, middle-/lower-third lesions, and tumor length ⩾5 cm was

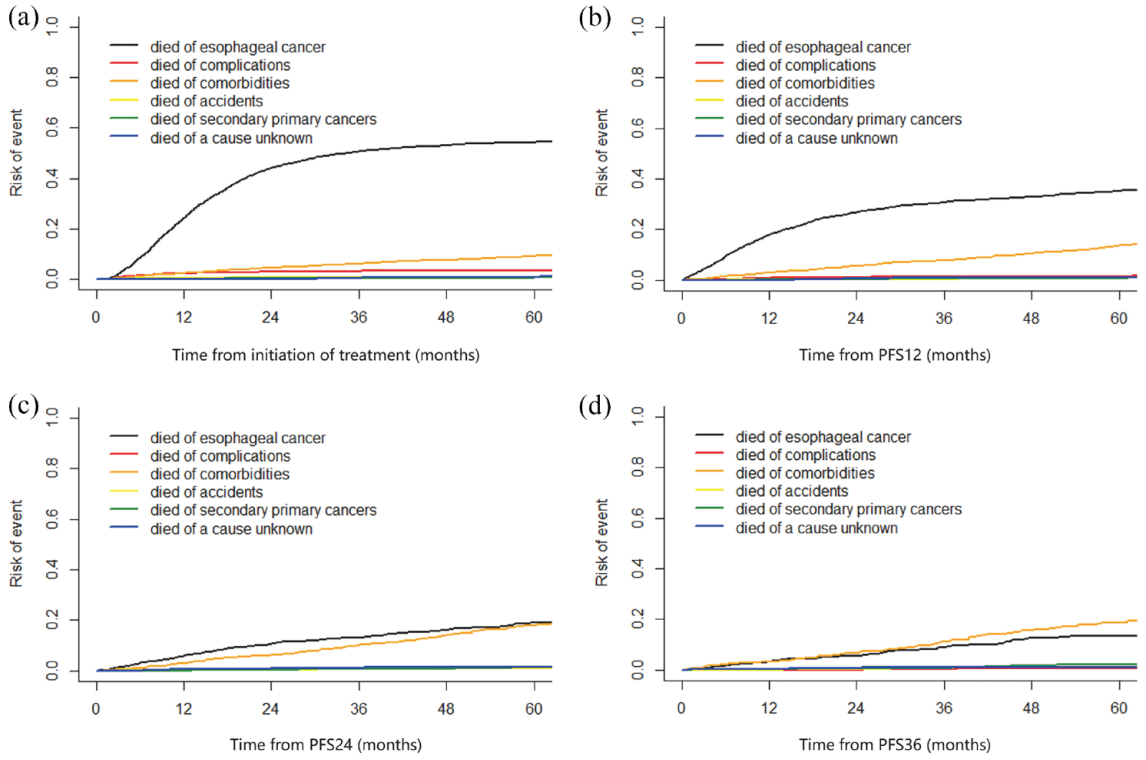

Figure 1. ESCC-specific and competing event-related mortality of our patients at treatment initiation (a), PFS12 (b), PFS24 (c), and PFS36 (d).
For patients treated dRT/dCRT in 10 cancer centers, the 5-year ESCC-specific mortality decrease continually from treatment initiation to PFS36 (from 54.3% to 13.4%), while the 5-year mortality due to other causes remained in relatively stable level (ranged 14.7% to 23.7%). PFS12, PFS24, and PFS36, were corresponded to the months during which patients remained progression-free after the date of dRT/dCRT initiation.
dCRT, definitive chemoradiotherapy; dRT, definitive radiotherapy; ESCC, esophageal squamous cell carcinoma; PFS, progression-free survival.

significantly higher than their counterparts (58.5% *versus* 39.6%, $p<0.01$; 56.7% *versus* 49.3%, $p<0.01$; and 56.8% *versus* 48.7%, $p<0.01$, respectively). The same was seen at PFS12 (39.2% *versus* 24.9%, $p<0.01$; 37.9% *versus* 30.4%, $p<0.01$; and 38.8% *versus* 28.6%, $p<0.01$, respectively). At PFS24, the 5-year ESCC-specific mortality of patients with middle-/lower-third lesions was similar to those with upper-third lesions (21.1% *versus* 16.0%, $p=0.23$; Supplemental Figure 2(a)–(d)). At PFS36, the 5-year ESCC-specific mortality of patients with tumor length ⩾5 cm was similar to those with tumor length <5 cm (15.4% *versus* 9.8%, $p=0.39$; Supplemental Figure 3(a)–(d)). At PFS24 and PFS36, however, the 5-year ESCC-specific mortality of patients with stage III-IV ESCC remained significantly higher than those with stage I-II ESCC (20.5% *versus* 16.3%, $p=0.03$; and 14.8% *versus* 10.3%, $p=0.04$, respectively; Supplemental Figure 4(a)–(d)).

Comparison of OS between ESCC patients and the Chinese general population

The 5-year OS of our patients at treatment initiation, PFS12, PFS24, and PFS36 were 31.0%, 46.6%, 57.5%, and 62.9%, respectively. Although significantly improvement was achieved at PFS36, the 5-year OS observed remained markedly lower than that of the age- and sex-matched Chinese general population (62.9% *versus* 96.4%) (Figure 2(a)–(d)).

Correlation between PFS and OS and validation from the literature

The 1-, 2-, 3-, and 5-year PFS of our patients ranged between 43.3–64.2%, 26.0–46.0%, 23.6–41.7%, and 16.2–33.6%, respectively, while the 5-year OS was 21.4–46.2%. Based on linear regression models (Figure 3(a)–(d)), a sharp increase in correlation coefficient was observed between 1- and 3-year PFS (*r* value, 0.375 and 0.771,

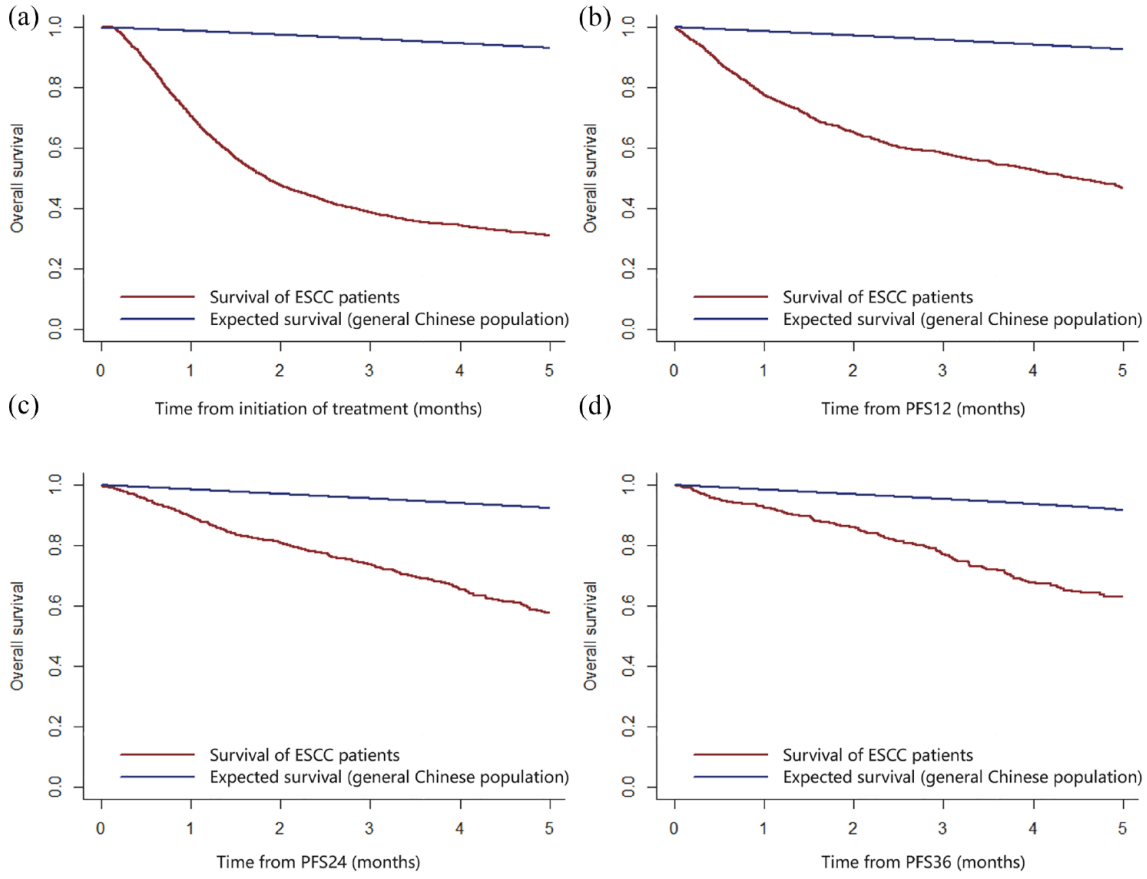

Figure 2. Comparison of OS between our patients and the age- and sex-matched Chinese general population at treatment initiation (a), PFS12 (b), PFS24 (c), and PFS36 (d).
For patients treated dRT/dCRT in 10 cancer centers, the 5-year OS increased continually from treatment initiation to PFS36 (from 31.0% to 62.9%), but still markedly lower than that of the age- and sex-matched Chinese general population (96.4%). PFS12, PFS24, and PFS36 were corresponded to the months during which patients remained progression-free after the date of dRT/dCRT initiation.
dCRT, definitive chemoradiotherapy; dRT, definitive radiotherapy; OS, overall survival; PFS, progression-free survival.

respectively), followed by a slight increase at 5-year PFS (*r* value, 0.800). In addition, linear regression models in RT- and CRT-treated patients' subgroups analogously showed correlation coefficients increased sharply between 1- and 3-year PFS (Supplemental Figure 6 and 7, *r* value, 0.532 and 0.776 in RT group, 0.501 and 0.762 in RT group, respectively) and increased slightly at 5-year PFS (*r* value, 0.850 in RT group, 0.856 in CRT group, respectively). According to this, four linear regression formulas using 1-, 2-, 3-, and 5-year PFS were established to predict the 5-year OS of our patients.

A total of 45 relevant publications were included (Supplemental Table 1). Based on linear regression models (Figure 4(a)–(d)), a similar sharp increase in correlation coefficient between predicted and observed 5-year OS was observed between 1- and 3-year PFS (*r* value, 0.365 and 0.897, respectively), followed by a slight increase at 5-year PFS (*r* value, 0.962).

Discussion

EC is among the most common causes of cancer-related mortality due to its poor prognosis and high recurrence rates. Local-regional failure often occurs despite standard dCRT, and the median survival time has been reported as ⩽27.3 months.[4] A surrogate endpoint which enables early prognostic assessment, administration of subsequent therapies if indicated, and the expedition of regulatory approval and clinical application is therefore of great importance.

In the current multicentered study, we first characterized the risk of ESCC-specific mortality, and

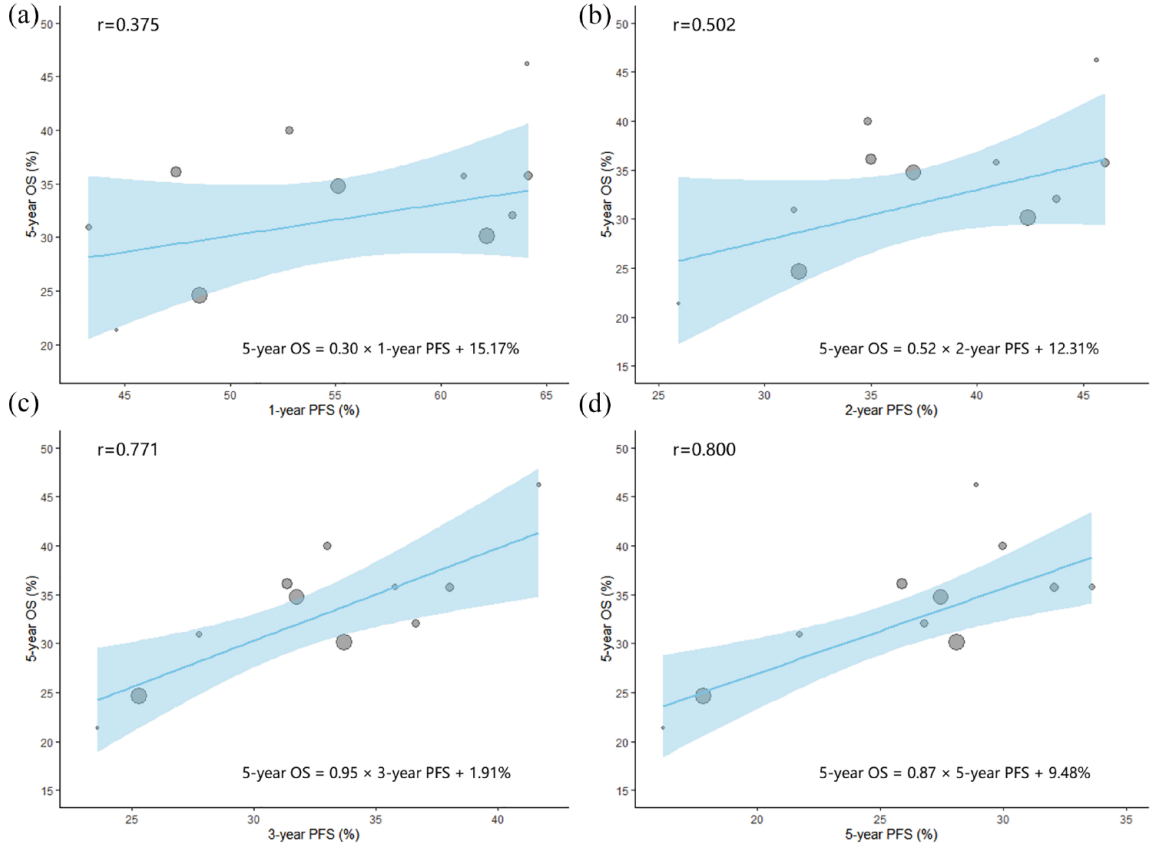

Figure 3. Linear regression models of the correlation between 5-year OS and 1 year (a) 2 years, (b) 3 years, and (c) 5 years. (d) PFS of multicenter patients.

Linear regression models showed a sharp increase in correlation coefficient between 1- and 3-year PFS (*r* value, 0.375 and 0.771, respectively), followed by a slight increase at 5-year PFS (*r* value, 0.800). Four linear regression formulas using 1-, 2-, 3- and 5-year PFS were established to predict the 5-year OS of our patients. Each circle represents a patient subgroup. The circle size represents its weight in the weighted linear regression model, which is proportional to the sample size of each patient subgroup. The straight line represents the fitted weighted linear regression line. The skyblue bands represent the corresponding 95% prediction intervals.

OS, overall survival; PFS, progression-free survival.

subsequently evaluated the validity of PFS as a surrogate endpoint for OS in ESCC patients treated with dRT/dCRT. We observed that disease progression commonly occurred in the first 3 years (cumulative rate, 74.6%). In addition, we found that ESCC-specific mortality diminished with increasing PFS and OS. When exceeding 3 years of PFS, the subsequent 5-year OS was found to increase at a steady rate (from 31.0% to 62.9%). Nevertheless, ESCC-specific mortality remained relatively high, at a rate nearly equivalent to that of mortality due to other causes. This correlated with our observation that the risk of death in ESCC patients remained higher than that of the age- and sex-matched Chinese general population. In view of its poor prognosis, clinical trials to optimize the current standard treatment of ESCC are warranted.

PFS has been proven as an appropriate surrogate endpoint for OS in several cancer types.[7–11] As for ESCC patients previously treated with dCRT, the outcomes of salvage treatment (esophagectomy, chemoradiotherapy, or supportive care) have been unfavorable. The mortality of salvage esophagectomy has ranged between 7% and 25%,[12–16] with 5-year OS of 5.7–15%.[13,14,17] The pooled analysis by Markar *et al.*[12] showed significantly higher incidences of anastomotic leak and pulmonary complications (23.97% *versus* 14.47%, and 29.75% *versus* 16.99%, respectively) and length of hospital stay (mean difference, 8.29 days) following salvage esophagectomy compared to planned esophagectomy with neoadjuvant CRT. In terms of salvage CRT, the retrospective analysis by Chen *et al.*[17] showed a 5-year OS of 3.1%, with the incidences

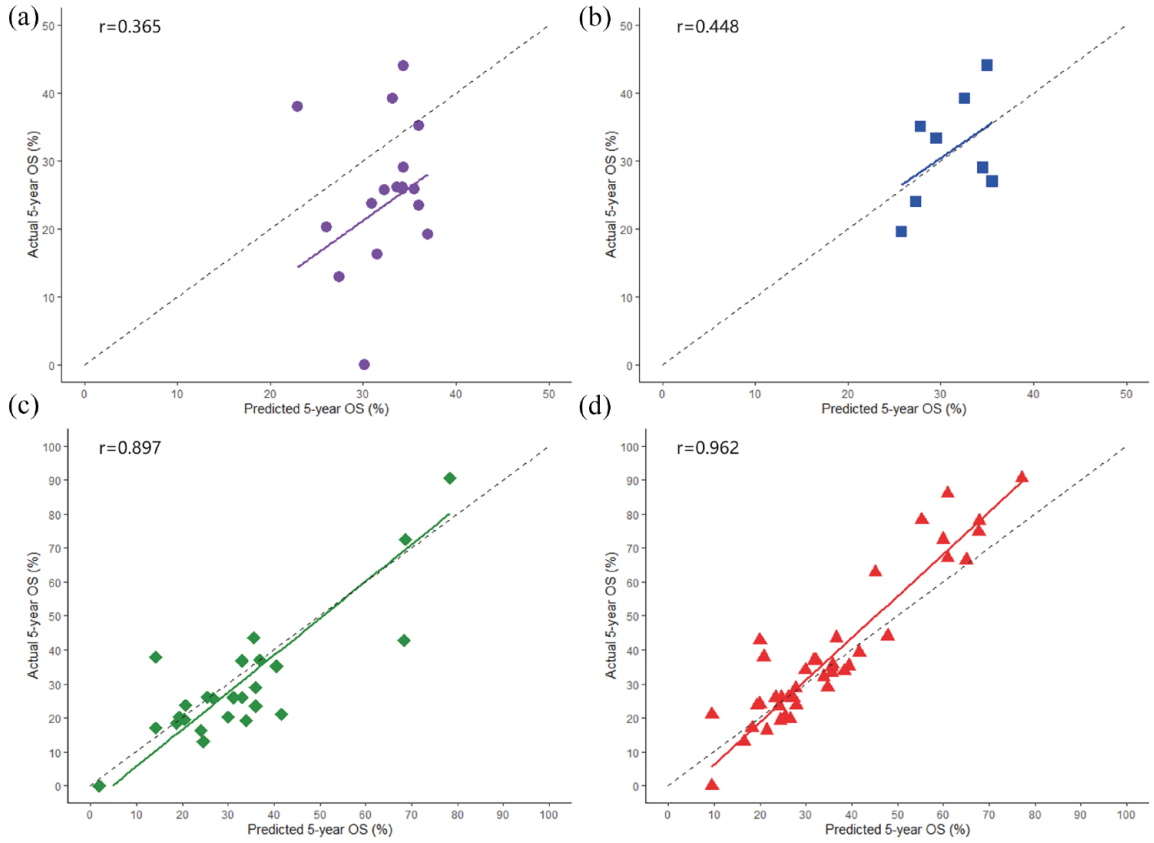

Figure 4. Linear regression models of the correlation between observed and predicted 5-year OS according to 1-year (a) 2-year, (b) 3-year, (c) and 5-year PFS (d) of literatures.
When applying the linear regression formulas established from our data to predict the 5-year OS according to 1-, 2-, 3-, and 5-year PFS of 45 online literatures, a sharp increase in correlation coefficient between predicted and observed 5-year OS was observed between 1- and 3-year PFS (r value, 0.365 and 0.897, respectively), followed by a slight increase at 5-year PFS (r value, 0.962). Each dot represents a patient subgroup in the literature. The solid straight lines represent the fitted linear regression line. The dash diagonal lines represent the condition that predicted OS was equal to observed OS.
OS, overall survival; PFS, progression-free survival.

of grade 2–4 esophagitis, grade 2–4 radiation pneumonia, and esophagotracheal fistula/esophageal perforation being 52.8%, 8.3%, and 19.4%, respectively. In line with this, the retrospective study by Zhou *et al.*[18] reported unsatisfactory efficacy and safety with salvage CRT, with 3-year OS of 21.8%, and grade 3 radiation pneumonia and esophageal fistula/perforation incidences of 5.45% and 20.0%, respectively. Majority of ESCC patients die within years of disease progression following definitive treatment, suggesting that the risk of ESCC-specific mortality may increase with increasing PFS. In our study, as a plateau in subsequent 5-year OS was observed after 3 years of PFS, it is reasonable to hypothesize that 3-year PFS may act as a potential surrogate endpoint for 5-year OS. Subsequent LRA revealed that the correlation with 5-year OS increased sharply from 1- to 3-year PFS, which then trended to a plateau. A similar pattern was observed with literature-based data. Based on these findings, we propose that 3-year PFS may be applied as a surrogate endpoint of 5-year OS in future prospective clinical trials.

TNM stage, location, and length of the primary tumor have been reported as significant prognostic factors for ESCC.[19,20] However, no studies have explored the impact of such prognostic factors on ESCC-specific survival based on the duration of PFS time points. Our study found that the effects of primary tumor location and length on ESCC-specific survival diminished with increasing PFS, while that of TNM stage remained significant. In line with the several prognosis-prediction models previously reported,[21,22] TNM stage is considered the optimal prognostic marker to guide

clinical decision-making and post-treatment follow-ups.

The main limitation of our study was its retrospective design, which may have introduced biases to the results and conclusion. Further validation with large-sample studies involving real-world data is therefore warranted. In addition, salvage treatment approaches were confounding in our study, prognosis of different salvage treatment modalities may affect subsequent survival and confound our results.

Conclusion

The prognosis of ESCC is poor, and the risk of death among ESCC patients treated with dRT/dCRT remained higher than the Chinese general population despite the attainment of PFS. Nonetheless, increased PFS may associate with OS benefits. TNM stage was found as a significant prognostic factor even after prolonged periods of PFS, and may represent the optimal prognostic marker in guiding clinical decision-making and post-treatment follow-up. Importantly, our findings suggest that 3-year PFS may act as a surrogate endpoint for 5-year OS among non-surgically treated patients, which carries the potential of expediting future prospective clinical trials on inoperable ECs.

Declarations

Ethics approval and consent to participate

This study was approved by the hospital's ethics committee (reference number: NCC2751). All patients had written informed consent.

Consent for publication

Not applicable.

Author contribution(s)

Weiming Han: Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft.

Lan Wang: Data curation; Investigation; Resources; Validation.

Chen Li: Data curation; Investigation.

Junqiang Chen: Investigation; Resources.

Wencheng Zhang: Investigation; Resources.

Xin Wang: Investigation; Resources.

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Shuchai Zhu: Investigation; Resources.

Chun Han: Data curation; Investigation; Resources; Validation.

Zefen Xiao: Conceptualization; Methodology; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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