SYSTEMATIC REVIEWS AND META-ANALYSIS

Stage-Specific Survival From Esophageal Cancer in China and Implications for Control Strategies: A Systematic Review and Meta-Analyses

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BACKGROUND AND AIMS: Esophageal cancer claims more than 500,000 deaths worldwide, with half occurring in China. We aimed to synthesize existing evidence on stage-specific survival from this cancer in China to inform cancer control strategies. **METHODS:** English and Chinese literature databases were systematically searched to identify original research published up to May 31, 2019 that reported stage-specific survival from esophageal cancer in China. Two meta-analyses were performed using random-effects models to summarize stage-specific survival differences on relative and absolute scales. The number of esophageal cancer deaths that might have been prevented by early detection in China, in 2018, was estimated assuming 2 different downstaging scenarios. **RESULTS:** One hundred fifty eligible studies were identified, 97 had non-overlapping study populations (83,063 participants), 47 were included in the meta-analysis of hazard ratios, and 26 in the meta-analysis of survival probabilities. Late-stage (III–IV) was associated with 92% higher hazard of death compared with early-stage (0–II) (95% confidence interval 1.62–2.28), corresponding to an absolute 5-year survival difference of 31.2% (29.9%–32.4%). In all, 5.2% esophageal cancer deaths could have been prevented in China, in 2018, if the observed stage distribution at diagnosis (∼50% early-stage) was shifted to the real-life conditions of a population-based endoscopic screening program (∼60% early-stage) and 26.9% if shifted to that observed in the controlled setting of a randomized trial (∼90% early-stage). **CONCLUSION:** Shifting downwards the stage distribution of esophageal cancer through screening would bring moderate reductions in mortality from the disease. Treatment improvements for early-stage patients are needed to reduce further mortality from this cancer.

Keywords: Esophageal cancer; Stage-specific survival; Systematic review; Meta-analysis; Avoidable deaths

Esophageal cancer (EC) claims 544,000 deaths worldwide, with half occurring in China.[1] Its incidence and mortality rank sixth and fourth, respectively, in the country.[2] Survival is universally poor with 5-year age-standardized relative survival for patients diagnosed in 2000–2014 being less than 30% in nearly all countries in the latest global cancer survival surveillance.[3] Primary prevention and early detection programs have been implemented in high-risk areas in China since the early 1970s,[4]

with successive national plans advocating early detection and the adoption of guidelines for early diagnosis and treatment of this cancer. Despite these efforts, 5-year age-standardized relative survival from EC in China has remained poor, although increased from 20.9% in patients diagnosed in 2003–2005 to a predicted estimate of 30.3% for those diagnosed in 2012–2015.[5]

The success of early detection programs for EC, either through screening of asymptomatic disease or downstaging of symptomatic disease, relies on the assumption that a shift toward early detection results in survival gains and, ultimately, mortality reductions. The American Joint Committee on Cancer (AJCC) has shown large variations in 5-year survival from ∼50% to ∼70% for stages 0 and I to less than 20% for stage IV based on "average" estimates from 33 centers across several countries.[6] Estimates of stage-specific survival from EC in China may differ from these because of differences in tumor biology (eg, predominance of squamous cell carcinoma [SCC]) and access to, and quality of, healthcare. Population-based cancer registries in mainland China do not report stage-specific survival. Hence, the only available information on stage-specific survival from EC in the country comes from hospital-based studies, which vary markedly in study design, patient source, sample size, follow-up approach, and analytical methodology.

In the absence of population-based studies on stage-specific survival in China, we conducted a systematic review aiming to (i) bring together all published estimates on stage-specific survival from EC in China and synthetize the evidence; (ii) quantify differences in stage-specific survival on both relative and absolute scales; (iii) investigate potential sources of heterogeneity; and (iv) estimate the

number of deaths that could potentially be prevented through effective early detection interventions. The review will provide an up-to-date snapshot on stage differences in EC survival in China and a baseline against which to monitor the likely impact of future early detection interventions.

Methods

The systematic review followed the principles highlighted in the Cochrane Handbook for systematic reviews (Text S1, Table S1).[7]

Eligibility Criteria

Papers were eligible if they provided information on stage-specific survival of primary EC in China in the form of median survival time, Kaplan-Meier (KM) curves or hazard ratios (HRs) (Text S1). Papers were excluded if they (i) reported research conducted in non-humans; (ii) reported studies carried out outside China or in non-Chinese ethnic populations; (iii) were not original articles; (iv) did not enroll incident cases with primary EC; (v) did not report or provide data for deriving stage-specific survival estimates for EC; and/or (vi) included only rare histological types other than SCC or adenocarcinoma (AC). No restrictions were imposed on year of publication, language, study design, follow-up method, or outcome definition.

Search Strategy

We systematically searched MEDLINE, Embase, Web of Science, and Wanfang (a major Chinese medical literature database) for original studies reporting stage-specific survival from EC in China (including Taiwan, Hong Kong, and Macao) published up to May 31, 2019, using appropriate search terms (Table S2). Annual reports of the National Central Cancer Registry of China (2010–2018), and of Taiwan (2003–2017), Hong Kong (2009–2017), and Macao (2003–2016) cancer registries, were also searched.

The titles and abstracts of papers identified were screened by one author (Y.H.) to assess potential eligibility, with a random sample of 200 independently screened by another author (Id.S.S.). The full texts of all papers deemed potentially eligible were then retrieved and screened, with the reasons for exclusion recorded (Figure 1).

Data Extraction and Quality Assessment

A data extraction form was developed to extract relevant information from the eligible papers including author, publication year, study area, study design, participants' characteristics, tumor features, follow-up (eg, active/passive, losses), death ascertainment method, analytical method, and reported stage-specific survival estimates.

To assess study quality, we modified the Cochrane criteria[7] to assess 7 domains in methodology that are pertinent to time-to-event studies (Table S3): (i) study design; (ii) recruitment approach; (iii) follow-up method, (iv) losses to follow-up; (v) definition of survival time; (vi) analytical method; and (vii) availability of data on other key prognostic variables.

A 10% random sample of full-text papers in English was independently reviewed by another author (Id.S.S.) to check eligibility, extract relevant data, and assess study quality. Only minor between-reviewer inconsistencies were identified and resolved among all authors.
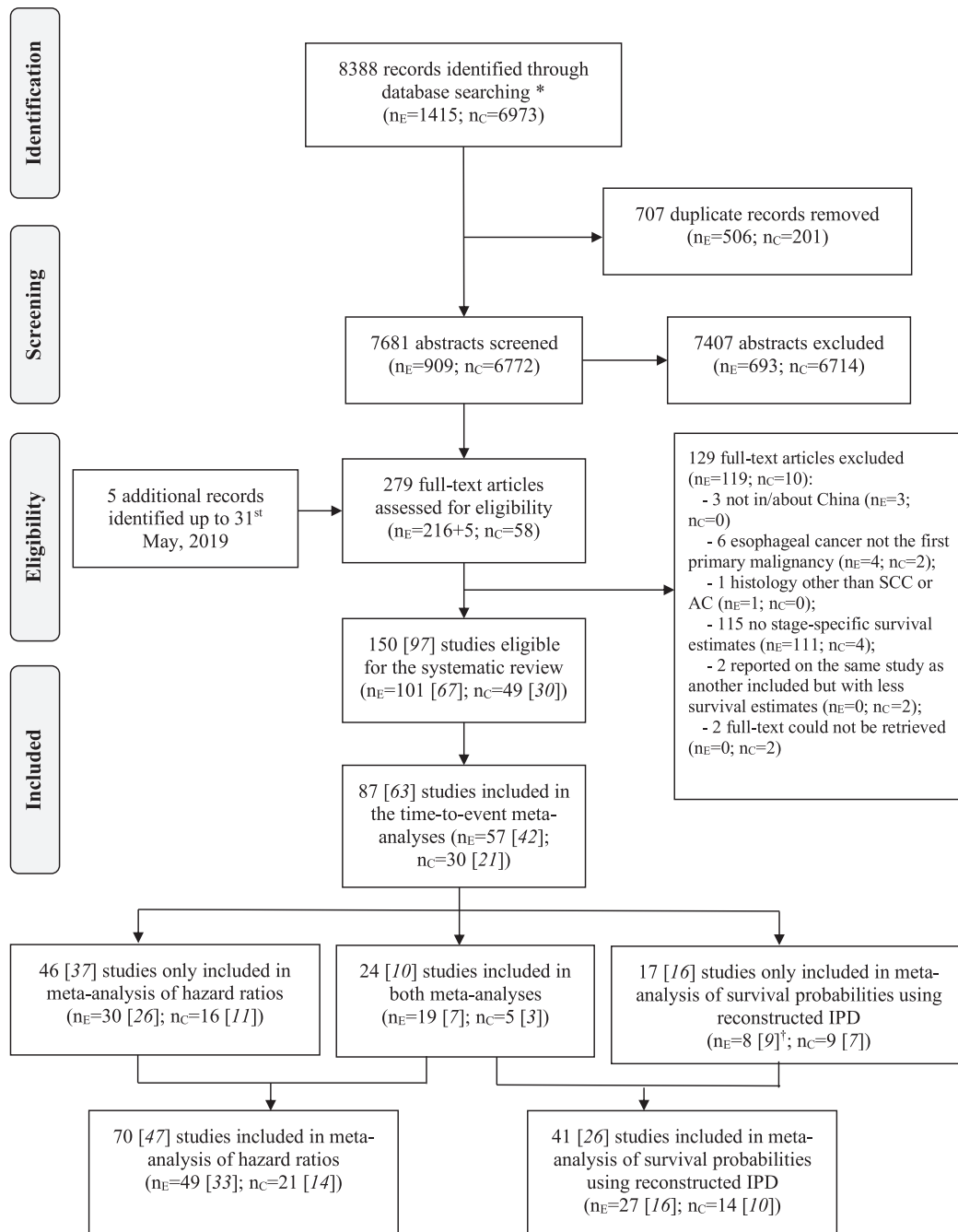
Outcomes

Stage-specific HRs and stage-specific survival probabilities were the primary outcomes of interest for quantification of summary differences in stage-specific survival on relative and absolute scales, respectively. The number of EC deaths that could potentially have been prevented in China, if the observed stage distribution was shifted downwards, was taken as a secondary outcome of interest.

Non-overlapping Studies

Several studies had potentially overlapping populations as they recruited patients from the same hospital or used data from the same cancer registry, in overlapping time periods. Albeit the inclusion/exclusion criteria were often different, it was difficult to establish the degree to which their study populations might have overlapped; thus, only the single study with the broadest inclusion criteria, the longest study period, and/or the largest sample size were considered. Hereafter, this subset of studies is referred to as "non-overlapping studies".

Statistical Analysis

Two meta-analyses were performed to quantify the relative and absolute summary differences in stage-specific survival, respectively. For the first meta-analysis, aggregate HRs (or log HRs) and their variances were extracted, or derived, using the approach by Tierney et al.[8] We used random-effects models to estimate summary pooled HRs (pHRs) and forest plots to visualize study-specific HRs (R software version 3.6.2). Between-study heterogeneity was assessed using the I^2 statistic.[9] Small-study effects and funnel plot asymmetry were examined using the Egger's test.[10] Meta-regression of study-specific HRs was performed to identify independent sources of between-study heterogeneity. Covariates with relative change (RC) $\geq$ 1.2 or $P <$ .2 in the univariable models were incorporated into a multiple meta-regression model and dropped one at a time. The final multiple meta-regression model was selected based on the adjusted R-squared value (Stata version 15.0). For the one-step meta-analysis on absolute differences in stage-specific survival, individual patient data (IPD) were reconstructed from the published KM survival curves by (i) extracting the coordinates for each survival curve using the DigitizeIt software (version 2.5, from https://www.digitizeit.de/) and (ii) reconstructing individual-level time-to-event data from the extracted coordinates using the Guyot et al[11] algorithm (R software version 3.6.2) and extracting their study-level covariates. Mixed-effects hazard regression models were then used to summarize stage-specific survival probabilities, accounting for study-level clustering.[12] Variables with a $P <$ .05 in the univariable hazard regression models were included in the multiple regression model. The final multiple hazard regression model was selected based on the Akaike Information Criteria.[13] Postestimation was used to calculate survival probabilities for each IPD record at 1, 3, and 5 years since diagnosis, which were then averaged over defined groupings of stage (0–II/III–IV, 0–I/II/III/IV) to obtain summary stage-specific survival probabilities and absolute

Identification

8388 records identified through database searching *
(n_E=1415; n_C=6973)

→ 707 duplicate records removed
(n_E=506; n_C=201)

Screening

7681 abstracts screened
(n_E=909; n_C=6772)

→ 7407 abstracts excluded
(n_E=693; n_C=6714)

Eligibility

5 additional records identified up to 31st May, 2019

279 full-text articles assessed for eligibility
(n_E=216+5; n_C=58)

→ 129 full-text articles excluded
(n_E=119; n_C=10):
   - 3 not in/about China (n_E=3; n_C=0)
   - 6 esophageal cancer not the first primary malignancy (n_E=4; n_C=2);
   - 1 histology other than SCC or AC (n_E=1; n_C=0);
   - 115 no stage-specific survival estimates (n_E=111; n_C=4);
   - 2 reported on the same study as another included but with less survival estimates (n_E=0; n_C=2);
   - 2 full-text could not be retrieved (n_E=0; n_C=2)

150 [*97*] studies eligible for the systematic review
(n_E=101 [*67*]; n_C=49 [*30*])

Included

87 [*63*] studies included in the time-to-event meta-analyses (n_E=57 [*42*]; n_C=30 [*21*])

46 [*37*] studies only included in meta-analysis of hazard ratios
(n_E=30 [*26*]; n_C=16 [*11*])

24 [*10*] studies included in both meta-analyses
(n_E=19 [*7*]; n_C=5 [*3*])

17 [*16*] studies only included in meta-analysis of survival probabilities using reconstructed IPD
(n_E=8 [*9*][†]; n_C=9 [*7*])

70 [*47*] studies included in meta-analysis of hazard ratios
(n_E=49 [*33*]; n_C=21 [*14*])

41 [*26*] studies included in meta-analysis of survival probabilities using reconstructed IPD
(n_E=27 [*16*]; n_C=14 [*10*])

Figure 1. PRISMA flowchart of retrieved, excluded, and included studies in the systematic review and in the meta-analyses of relative and absolute stage-specific differences in survival from esophageal cancer in China (numbers in italics within square brackets refer to the number of non-overlapping studies—see Methods section).
*No eligible records were identified by the search of annual reports of the National Central Cancer Registry (2010–2018) and Taiwan (2003–2017), Hong Kong (2009–2017), and Macao (2003–2016) cancer registries.
†One study retrieved from the English databases contributed to both meta-analyses of hazard ratios and survival probabilities when these were based on all eligible studies but only to the meta-analysis of survival probability when they were based on non-overlapping studies. n_E and n_C, number of papers retrieved from the English and Chinese databases, respectively.

summary survival differences. A similar approach was used to estimate summary stage-specific survival probabilities and corresponding absolute differences by the study-level covariates included in the final multiple hazard regression model.

The number of deaths from EC that could have been potentially prevented in China in 2018, among patients diagnosed in the previous 5 years, was estimated assuming that although the country experienced the same stage-specific survival yielded by the present meta-analysis, the corresponding

stage distribution had been shifted downwards under 2 different scenarios. In scenario 1, we assumed early detection resulted in a tumor stage distribution similar to that reported by the nationwide cancer registry in South Korea (30.3%, 28.6%, 26.6%, and 14.5%, respectively, for stage 0–I, II, III, and IV)[14] where a population-based endoscopic screening program was implemented in 2002.[15] In scenario 2, we assumed that early detection led to a more marked tumor downstaging, resulting in a distribution similar to that observed in the screening arm of a cluster randomized trial of one-off endoscopic screening (70.97%, 19.35%, 6.45%, and 3.23%, respectively, for stages 0–I, II, III, and IV) in China[16] (Text S2 provides full estimation methods).

The primary statistical analyses were conducted within the subset of non-overlapping studies, whereas sensitivity analyses were conducted based on all eligible studies.

Results

The search identified 8388 potentially eligible records (1415 and 6973, respectively, from the English and Chinese databases and none from the Cancer Registry reports). After removal of duplicate records, title/abstract screening, full-text screening, and 150 eligible studies were identified (Figure 1).

Characteristics of the Studies

The 150 eligible studies (n = 127,042) included 101 studies from the English database and 49 from the Chinese database (Figure 1). The summary characteristics of these studies are shown in Table 1. In all, 72.7% of the eligible studies had a retrospective design, 51.3% had a sample size < 300, 90% were conducted in urban areas, and 82% recruited patients from a cancer, tertiary, or other specialized hospital (Table 1). Relative to the studies from the English database, a higher proportion of those from the Chinese database had a retrospective design, recruited both SCC and AC patients, and used a national staging system[17–24] or its own staging system[25] (Table S4).

The individual characteristics of each eligible study, and their reported stage-specific survival estimates, are shown in Table S5. Patient eligibility was restricted to a particular tumor stage in 51 studies: 35 studies excluded patients with distant metastasis at diagnosis,[17,26–59] 8 included only patients at inoperable or medium/late stage,[18,19,23,24,60–63] 1 included only stage I patients,[64] 2 included only stage II patients,[65,66] 2 included only stage III patients,[67,68] and 3 included only stage IV patients.[69–71] (Table S5).

Ninety seven (n = 83,063) of the 150 eligible studies were deemed nonoverlapping studies. The characteristics of the latter were similar to those described above for all eligible studies (Figure 1; Table 1 and Table S5).

Study Quality Assessment

More than 95% of the eligible studies were at high risk of bias in one or more domains. In particular, a large proportion of studies did not specify how participants were recruited (66%), the follow-up method used (35.3%), or losses to follow-up (57.3%). Yet appropriate survival analytical methods were adopted by 96% of the studies. Similar proportions were observed within the subset of non-overlapping studies (Table S6).

Study-Specific Survival Estimates

The 150 eligible studies varied markedly in the survival estimates they reported both in terms of their metric (eg, median, overall survival, cancer-specific survival, HRs) and their time frame (eg, 1, 3, 5 years) (Table S5). Nevertheless, they all showed consistently that survival for early-stage disease was better than that for later-stage disease but with distinct between-study variability in the magnitude of the survival differences.

Meta-Analysis and Meta-Regression of Hazard Ratios

Forty seven non-overlapping studies were included in the meta-analysis of HRs (Figure 1). Stage III–IV patients had a 92% higher hazard of death compared to stage 0–II patients, but with moderate between-study heterogeneity (17 studies [n = 4670]; pHR 1.92, 95% confidence interval [CI] 1.62–2.28, I^2 = 49.4%; Figure 2A). Relative to stage 0–I, the hazard of death increased progressively for stage II (4 studies [n = 24,676]; pHR 1.85, 1.40–2.45), III (5 studies [n = 15,553]; 3.14, 2.19–4.49), and IV (2 studies [n = 720]; 10.88, 0.35–334.7) (Figure 2C–E). The 17 studies (n = 11,555) which treated stage as a continuous variable showed an 83% increase in the hazard of death for every category increment in stage (pHR 1.83, 1.43–2.35) but with substantial between-study heterogeneity (I^2 = 90.3%) (Figure 2F).

The meta-regression analysis identified sample size and recruitment ward as independent sources of between-study heterogeneity. Studies with a sample size ≥ 300 and those that included patients from radio/oncological wards reported higher hazards of death for late-stage disease vs early-stage than, respectively, those with smaller sample sizes (adjusted RC = 1.40, 95% CI 1.01–1.94) and those that only included surgical patients (adjusted RC = 1.26, 0.87–1.82) (Table S7).

Sensitivity analyses based on all 70 eligible studies for the meta-analysis of HRs (Figure 1) yielded similar pHRs (Figure S1) and identified the same independent sources of between-study heterogeneity (data not shown) as seen within the subset of non-overlapping studies.

Among the non-overlapping studies there was little evidence of small-study effects on reported HRs among studies comparing stage III–IV vs 0–II ($t = 0.18$, $P = .597$), stage III vs 0–I ($t = -0.23$, $P = .820$), and stage II vs 0–I ($t = -1.28$, $P = .241$). In contrast, there was evidence of small-study effect among studies that analyzed stage as a continuous variable ($t = 5.46$, $P < .001$). Similar findings were observed

Table 1. Summary Characteristics of the 150 Eligible Studies and the 97 Non-overlapping Studies in the Systematic Review

| | All eligible studies | | | | Non-overlapping studies[a] | | | |
| | Studies | | Patients | | Studies | | Patients | |
	N	%	N	%	N	%	N	%
Study design								
PB+PC + RCT/PSM[b]	28	18.7	39,947	31.4	14	14.4	9268	11.2
Retrospective cohort	109	72.7	84,227	66.3	72	74.2	71,282	85.8
Other designs	3	2.0	640	0.5	2	2.1	385	0.5
Not reported	10	6.7	2228	1.8	9	9.3	2128	2.6
Study years								
Before 2005	40	26.7	20,634	16.2	28	28.9	17,072	20.6
Spanning across 2005	44	29.3	56,560	44.5	30	30.9	50,068	60.3
After 2005	64	42.7	49,579	39.0	37	38.1	15,654	18.8
Not reported	2	1.3	269	0.2	2	2.1	269	0.3
Study size								
< 300	77	51.3	11,693	9.2	56	57.7	8085	9.7
≥ 300	73	48.7	115,349	90.8	41	42.3	74,978	90.3
Median follow-up time								
< 3 y	34	22.7	17,886	14.1	20	20.6	5222	6.3
≥ 3 y	33	22.0	15,419	12.1	20	20.6	8322	10.0
Not reported	83	55.3	93,737	73.8	57	58.8	69,519	83.7
High-risk EC area								
No	59	39.3	52,630	41.4	37	38.1	21,548	25.9
High-risk or mixed	91	60.7	74,412	58.6	60	61.9	61,515	74.1
Study region								
East	88	58.7	38,941	30.7	55	56.7	25,187	30.3
Central	22	14.7	45,085	35.5	15	15.5	43,413	52.3
West	12	8.0	2939	2.3	12	12.4	2939	3.5
Taiwan/Hong Kong/mix	24	16.0	37,551	29.6	12	12.4	9154	11.0
Not reported	4	2.7	2526	2.0	3	3.1	2370	2.9
Study area								
Urban	135	90.0	123,621	97.3	84	86.6	79,937	96.2
Rural	12	8.0	2953	2.3	10	10.3	2658	3.2
Mixed	3	2.0	468	0.4	3	3.1	468	0.6
Type of health facility								
Cancer hospital	67	44.7	35,304	27.8	38	39.2	23,427	28.2
Tertiary/other specialist hospital	56	37.3	53,628	42.2	46	47.4	50,218	60.5
Secondary hospital	7	4.7	1479	1.2	5	5.2	1184	1.4
Mixed	20	13.3	36,631	28.8	8	8.2	8234	9.9
Recruitment ward								
Surgical only	107	71.3	93,951	74.0	69	71.1	71,059	85.5
Radiological/oncological only	30	20.0	11,504	9.1	19	19.6	3051	3.7
Both	10	6.7	20,308	16.0	7	7.2	8176	9.8
Not reported	3	2.0	1279	1.0	2	2.1	777	0.9
Mean age at diagnosis								
< 60 y	70	46.7	49,808	39.2	37	38.1	17,742	21.4
≥ 60 y	53	35.3	17,604	13.9	40	41.2	13,283	16.0
Not reported	27	18.0	59,630	46.9	20	20.6	52,038	62.6
Male-to-female ratio								
≤ 3.3	76	50.7	67,711	53.3	51	52.6	58,441	70.4
> 3.3	75	50.0	58,667	46.2	47	48.5	23,958	28.8
Not reported	1	0.7	664	0.5	1	1.0	664	0.8
Staging classification								
AJCC/UICC TNM (7th)	52	34.7	73,483	57.8	36	37.1	56,080	67.5
Other staging systems	63	42.0	39,643	31.2	35	36.1	17,526	21.1
Not reported	35	23.3	13,916	11.0	26	26.8	9457	11.4
Stage grouping categories								
0/I/II/III/IV	61	40.7	96,922	76.3	38	39.2	65,765	79.2
Early/late	23	15.3	7920	6.2	18	18.6	4593	5.5
Other categorisations[c]	60	40.0	20,251	15.9	38	39.2	11,921	14.4
Not applicable[d]	6	4.0	1949	1.5	3	3.1	784	0.9

Table 1. Continued

| | All eligible studies | | | | Non-overlapping studies[a] | | | |
| | Studies | | Patients | | Studies | | Patients | |
	N	%	N	%	N	%	N	%
Histology								
SCC only	106	70.7	109,014	85.8	68	70.1	72,064	86.8
AC only	2	1.3	315	0.2	2	2.1	315	0.4
Mixed	35	23.3	14,171	11.2	21	21.6	7393	8.9
Not reported	7	4.7	3542	2.8	6	6.2	3291	4.0
High risk of bias								
Study design	121	80.7	86,690	68.2	82	84.5	73,390	88.4
Participant accrual	99	66.0	70,920	55.8	69	71.1	61,306	73.8
Losses to follow-up	86	57.3	78,097	61.5	58	59.8	66,957	80.6
Follow-up method	53	35.3	15,759	12.4	42	43.3	12,176	14.7
Survival time scale	39	26.0	17,635	13.9	33	34.0	15,139	18.2
Survival analysis method	6	4.0	7650	6.0	6	6.2	7650	9.2
Key prognostic variables	49	32.7	20,164	15.9	36	37.1	16,798	20.2
Total	150	100.0	127,042	100.0	97	100.0	83,063	100.0

AC, adenocarcinoma; AJCC, American Joint Committee on Cancer; EC, esophageal cancer; NR, not reported; PB, population-based; PC, prospective cohort; PSM, propensity-score matched study; RCT, randomized controlled trial; SCC, squamous cell carcinoma; UICC, Union for International Cancer Control.
[a]Studies with nonoverlapping study populations (Methods section).
[b]All population-based studies were conducted using data from the cancer registry of Taiwan.
[c]Stage treated as a continuous variable or categorized in a way that do not allow regrouping as per the standard TNM stages (Table S5).
[d]Not applicable for studies which restricted recruitment of participants to those with a specific stage (eg, stage IV, only).

when all 70 eligible studies were considered (data not shown).

Meta-Analysis Using Reconstructed Individual Patient Data

Twenty six non-overlapping studies (n = 15,415) were included in the reconstructed IPD analysis (Figure 1), with 7915 early-stage and 7500 late-stage patients, followed up for a median of 63.1 (interquartile range 53.4–105.7) months. A total of 10,278 deaths occurred during follow-up (4469 and 5809, respectively, among early-stage and late-stage patients), corresponding to a median survival time of 27.8 (11.1–99.3) months.

The final multiple hazard regression model included tumor stage, study design, and sample size. Estimated summary stage-specific survival probabilities are shown in Table 2 and Figure S2. The probability of surviving EC declined gradually with more advanced stage, resulting in an absolute survival difference between stages 0–II and stages III–IV of 31.2% (95% CI 29.9%–32.4%) at 5 years after diagnosis [44.5% (43.4%–45.5%) vs 13.3% (12.6%–14.0%)] (Table 2).

Prospective studies reported lower survival estimates at all 3 time points for both early and late stage compared to retrospective studies. Studies with sample size < 300 reported lower survival estimates compared to studies with sample size ≥ 300 for early stage but higher survival estimates for late stage (Table 2).

Sensitivity analyses of survival probabilities based on all 41 eligible studies (n = 34,934; Figure 1) yielded similar summary survival probabilities (Table S8; Figure S3).

Number of Deaths Potentially Prevented by Early Detection

Using the summary stage-specific survival estimates based on the subset of non-overlapping studies, we estimated that 5.2% and 26.9% of deaths from EC in China, in 2018, among cases diagnosed in the previous 5 years, could potentially have been prevented if the stage distribution at diagnosis observed in the current review (*status quo*: 10.8%, 40.0%, 46.5%, and 2.7%, respectively, for stages 0–I, II III, and IV) had been shifted, respectively, to the stage distribution reported in South Korea (scenario 1) or to the stage distribution observed in an endoscopic screening trial (scenario 2) (Figure 3). These estimates were robust to different assumptions (Text S2, Figure S4).

Discussion

This systematic review, with meta-analyses, is the first to synthetize all the available evidence to yield stage-specific survival, on both absolute and relative scales, from EC in China. Using its survival figures, we estimated that between 5% (based on the real-life downstaging estimates observed in South Korea, where a population-based EC screening program was implemented) and 27% (based on the
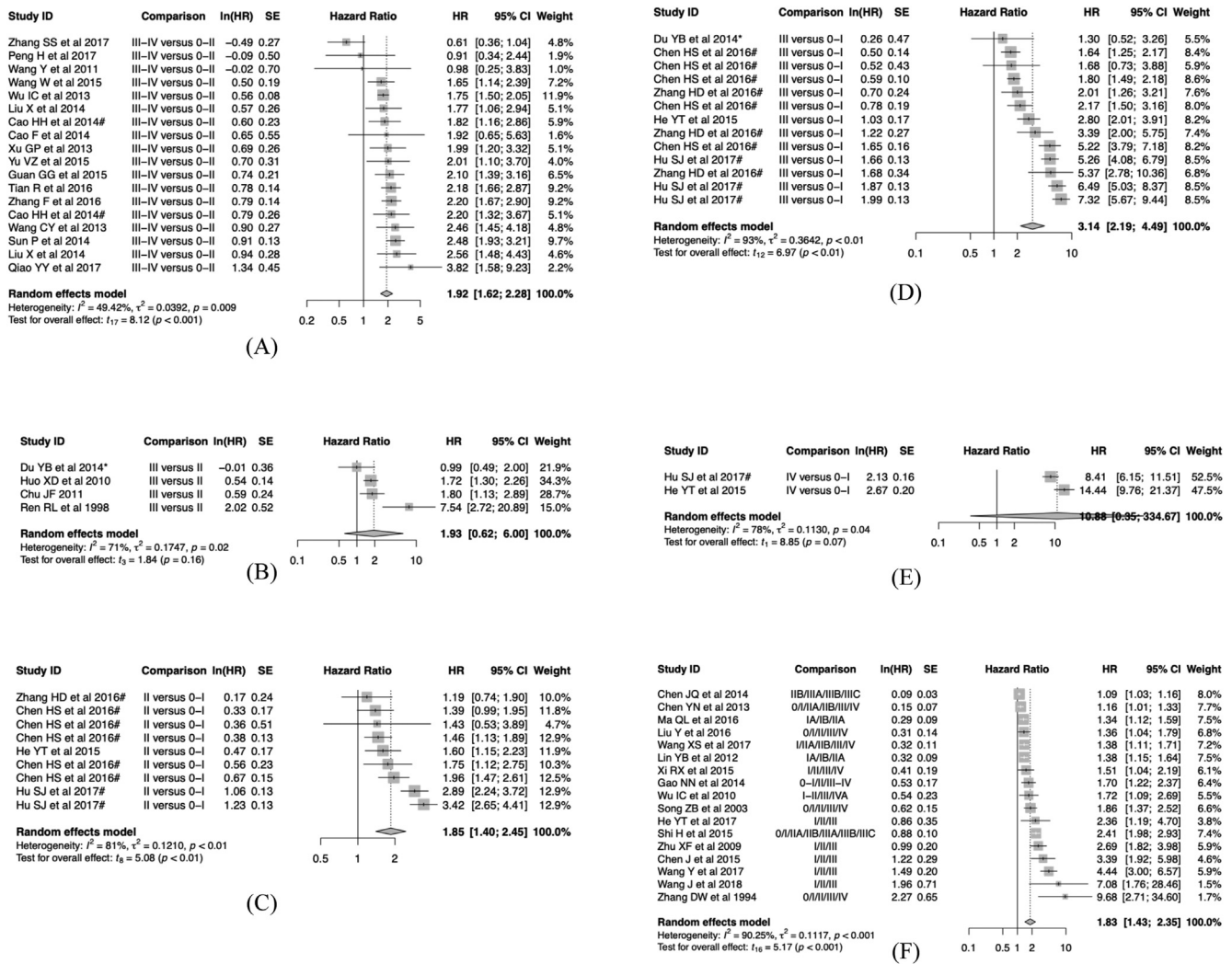
Figure 2. Study-specific hazard ratios and summary pooled estimates of the effect of tumor stage on mortality after a diagnosis of esophageal cancer in China based on the subset of non-overlapping studies (Methods section): (A) stage III–IV vs stage 0–II; (B) stage III vs stage II; (C) stage II vs stage 0–I; (D) stage III vs stage 0–I; (E) stage IV vs stage 0–I; and (F) per one unit increment in stage category (stage taken as a continuous variable). Comparisons based on stage groupings with less than 5 studies are omitted.

*The HRs reported in the original publication used late stage as the reference group; hence, HRs using early stage as the reference group were derived by inverting the reported HR values.

#Several study-specific HR estimates from a single study included in the meta-analyses as they corresponded to different (nonoverlapping) patient subgroups (eg, different treatment modalities).

downstaging estimates seen in the controlled setting of a randomized trial) of EC deaths in China, in 2018, among patients diagnosed in the previous 5 years, could have been potentially prevented by early detection efforts.

This systematic review has several strengths. Its inclusive search strategy, covering both English and Chinese bibliographic databases and annual cancer registry reports, ensured all relevant publications were included. Meta-analysis of study-level time-to-event data was used to synthesize HRs of late-stage vs early-stage disease. In addition, we applied a novel method to reconstruct individual-level time-to-event data from published KM curves, although this novel approach does not obtain individual-level data on covariates.

This review also has some limitations. First, only 150 studies were eligible for the qualitative synthesis. Second, it was very difficult to gauge the degree of overlap in study populations across studies. We used strict criteria to exclude all studies with potentially overlapping populations from the main analyses, which might have resulted in under-representation of certain subsets of patients. Reassuringly, sensitivity analyses based on all eligible studies yielded similar results. Third, the review was largely based, out of necessity, on hospital-based studies. But as appropriate staging work-up (eg, endoscopy with biopsy) can only be done in hospital settings, hospital-based estimates of stage-specific survival are unlikely to be less reliable than

Table 2. Summary Survival Probability Estimates for Early-Stage and Late-Stage Esophageal Cancer at 1, 3, and 5 Years After Diagnosis of Esophageal Cancer, and Corresponding Absolute Differences, From Reconstructed Individual Patient Data Based on 26 Non-overlapping Studies (15,415 Patients)

	Summary survival (S) and absolute differences (AD)[a]								
	1 y (95% CI)			3 y (95% CI)			5 y (95% CI)		
All									
Early-stage (0–II) (S)	83.17	82.58	83.74	56.60	55.62	57.56	44.48	43.43	45.53
Late-stage (III-IV) (S)	61.98	61.08	62.86	23.60	22.76	24.45	13.31	12.62	14.01
Early-stage vs late-stage (AD)	21.19	20.13	22.25	32.99	31.71	34.28	31.17	29.91	32.44
0–I (S)	88.85	87.93	89.70	69.38	67.32	71.34	59.32	56.86	61.69
II (S)	81.76	81.09	82.42	53.96	52.84	55.06	41.62	40.44	42.79
III (S)	61.92	61.01	62.82	23.86	22.99	24.73	13.58	12.86	14.31
IV (S)	57.03	53.61	60.29	18.73	15.71	21.97	9.68	7.51	12.16
0–I vs II (AD)	7.09	5.98	8.19	15.42	13.13	17.72	17.70	15.02	20.39
0–I vs III (AD)	26.93	25.66	28.19	45.52	43.33	47.72	45.74	43.22	48.26
0–I vs IV (AD)	31.82	28.36	35.28	50.65	46.92	54.37	49.64	46.29	52.99
By study design:									
PB/PC/RCT studies									
Early-stage (S)	76.57	75.56	77.54	42.95	41.31	44.57	29.47	27.83	31.13
Late-stage (S)	55.77	54.63	56.88	15.75	14.81	16.71	6.91	6.28	7.59
Early-stage vs late-stage (AD)	20.80	19.30	22.30	27.20	25.31	29.08	22.56	20.78	24.34
Retrospective studies									
Early-stage (S)	85.76	85.20	86.29	61.95	60.94	62.94	50.37	49.25	51.47
Late-stage (S)	71.29	70.29	72.27	35.38	34.09	36.68	22.90	21.71	24.11
Early-stage vs late-stage (AD)	14.47	13.34	15.59	26.56	24.93	28.20	27.47	25.83	29.10
By sample size:									
< 300									
Early-stage (S)	80.23	78.95	81.45	50.57	48.39	52.71	37.85	35.63	40.07
Late-stage (S)	66.86	65.12	68.54	28.96	26.85	31.10	17.20	15.41	19.08
Early-stage vs late-stage (AD)	13.37	11.25	15.48	21.62	18.58	24.65	20.65	17.76	23.53
≥ 300									
Early-stage (S)	83.54	82.94	84.11	57.35	56.33	58.35	45.31	44.21	46.41
Late-stage (S)	61.25	60.31	62.18	22.81	21.93	23.70	12.73	12.03	13.45
Early-stage vs late-stage (AD)	22.28	20.80	23.77	34.54	32.33	36.75	32.58	30.53	34.64

PB, population-based; PC, prospective cohort; RCT, randomized controlled trial.
[a]Survival probability estimated from a mixed-effects hazard regression model which included stage, study design, and sample size (section entitled "Meta-analysis using reconstructed individual patient data") and expressed as a percentage (0–100).

population-based estimates from cancer registry data. Fourth, tumor-staging methodology might have varied across health facilities. However, only type of recruitment ward was identified as a source of between-study heterogeneity with studies including radio/oncological patients reporting higher HRs for late vs early stage than studies recruiting surgical patients only (Table S7). This might reflect genuine differences in disease stage, with nonsurgical late-stage patients being diagnosed at a more advanced stage than surgical late-stage patients and/or differences in the staging approach (eg, pathological staging for surgical patients vs clinical staging for nonsurgical patients). Fifth, the low quality of many of the included studies might have biased the pooled survival estimates. Reassuringly, however, the pooled 5-year all-stage survival estimates from IPD of 19 studies (n = 7349) that did not restrict recruitment to any particular stage (41.1%, 95% CI 40.1%–42.1%) were similar to that reported in a recent systematic review and meta-analysis of hospital-based studies in China (40.1%, 33.7%–46.4%),[72] albeit higher

than the estimates reported by the National Cancer Registry for 2003–2005 (18.4%)[73] and most regional cancer registries (Table S9).

The areas with the highest EC risk worldwide stretch from north-eastern Iran to China, where SCC represents more than 90% of cases. In contrast to high-income countries, where tobacco smoking and alcohol consumption are the most important risk factors for EC,[74] other risk factors have been reported in high-risk areas, such as consumption of hot tea, nitroso compounds in food, lack of access to piped water, and poor oral health.[75] Primary prevention aimed at reducing exposure to these risk factors has had a little impact and thus early detection, based on endoscopic screening, has been recommended in high-risk areas. Our estimation of the number of potentially preventable deaths through endoscopic screening under 2 contrasting scenarios showed that screening would lead to only modest-to-moderate reductions in mortality. These estimations rely on the assumption that downstaging is feasible with tumors diagnosed at a late stage having a similar natural history to
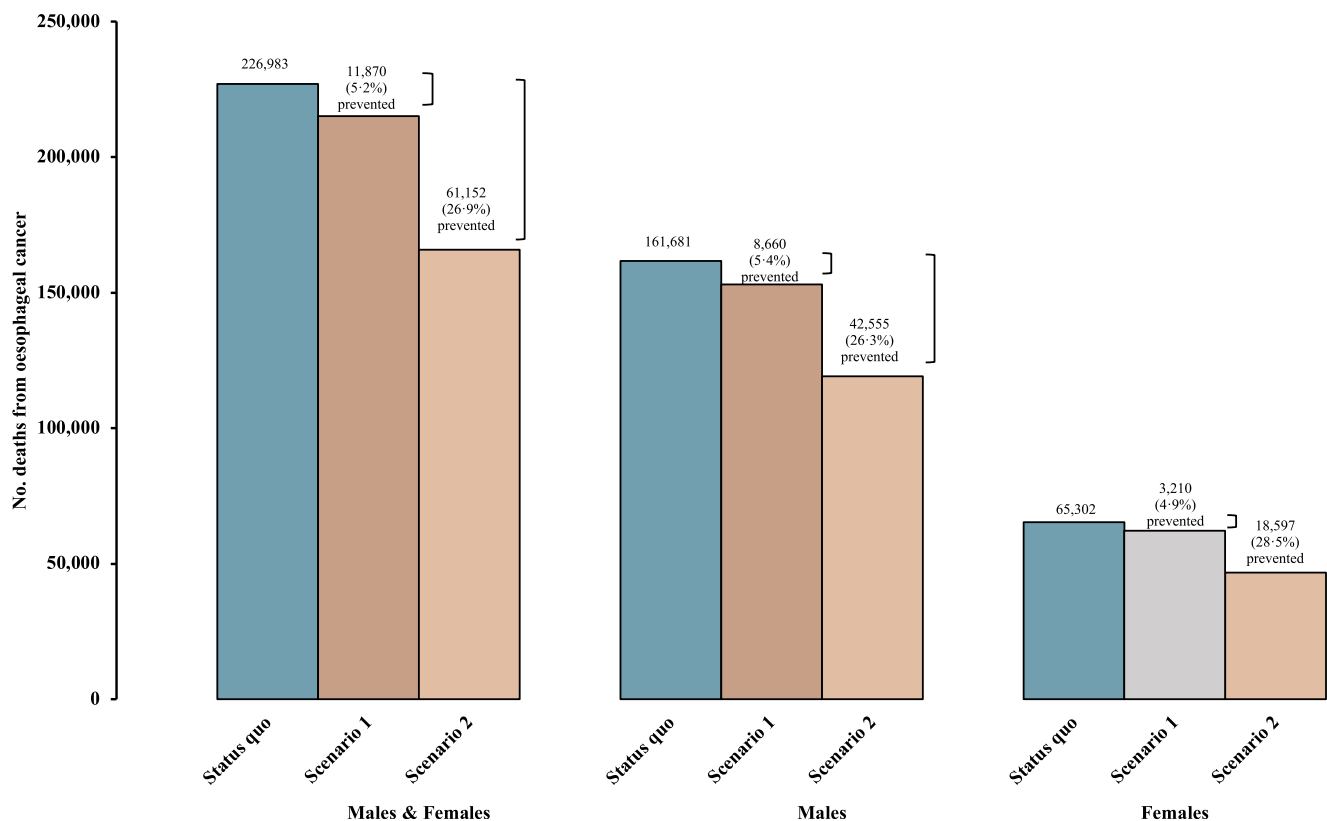
Figure 3. Number (%) of deaths from esophageal cancer that could potentially have been prevented in China, in 2018, among patients diagnosed in the previous 5 years, if the current stage distribution (*status quo*) were shifted downwards to: (i) *scenario 1*, the nationwide stage distribution in South Korea (30.3%, 28.6%, 26.6%, and 14.5% tumor diagnosed, respectively, at stages 0–I, II, III, and IV) and (ii) *scenario 2*, the stage distribution reported in the intervention arm of an intensive endoscopic screening trial in China (71.0%, 19.4%, 6.4%, and 3.2%, respectively, at stages 0–I, II, III, and IV) (estimations based on the stage distribution and stage-specific survival estimates yielded by the meta-analyses of non-overlapping studies; Text S2 provides full discussion of estimation methods and underlying assumptions).

those diagnosed at an earlier stage as opposed to being intrinsically more biologically aggressive. The estimations also rely on the assumption that gains in survival through early diagnosis will ultimately translate into mortality reductions rather than simply reflecting lead-time bias[76]—an issue that can only be answered by randomized controlled trials with the primary outcome being mortality.[77]

Even if proven to be effective, implementation of population-based endoscopic screening in China would be a huge challenge. In a randomized controlled trial aiming to assess the cost-effectiveness of endoscopic screening in high-risk areas (Endoscopic Screening for Esophageal Cancer in China, ESECC, NCT01688908),[77] the cost of a single screening procedure was found to be much higher than what was previously reported in other countries (eg, the United States, Japan, etc.) relative to local per capita gross domestic product (US $4246 in 2016 in Hua County, Henan Province, a well-recognized high-risk area of EC in China).[78] A simulation study concluded that endoscopic screening every 2 years was cost-effective in areas with high incidence of gastric cancer and EC but it relies on the national level of per capita gross domestic product (US $10,276 in China) as the threshold for willingness to pay,[79] which was much

higher than that for Hua County. Although the cost-effectiveness of endoscopic screening may be enhanced by adoption of risk prediction models,[80] and development of less invasive techniques, implementation of a population-based screening program would still impose a heavy financial and administrative burden on local governments.[78] The findings from the present study are also a reminder that for early detection to significantly reduce mortality, it needs to be coupled with effective treatment for early-stage disease. As EC is one of the commonest cancers in China, survival improvements for this cancer will be critical to achieving the Healthy China 2030 goal of a 15% increase in 5-year all-cancer survival by 2030.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.10.012.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality

worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–249.

2. He J. China cancer registry annual report 2018. Beijing, China: People's Medical Publishing House, 2019.

3. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018;391(10125):1023–1075.

4. Wei WQ. [Current status and challenges of prevention and control of esophageal cancer in China]. Zhonghua Yu Fang Yi Xue Za Zhi 2019;53(11):1081–1083.

5. Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018;6(5):e555–e567.

6. Esophagus and esophagogastric junction. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC cancer staging manual. 8 ed. New York: Springer, 2017:185–202.

7. The Cochrane Collaboration. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011. www.handbook.cochrane.org. Accessed June 7, 2019.

8. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

9. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557–560.

10. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–634.

11. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.

12. Charvat H, Belot A. Mexhaz: An R package for fitting flexible hazard-based regression models for overall and excess mortality with a random effect. J Stat Softw 2021; 98(14):1–36.

13. Akaike H. A new look at the statistical model identification. EEE Trans Automatic Control 1974;19(6):716–723.

14. Jung HK, Tae CH, Lee HA, et al. Treatment pattern and overall survival in esophageal cancer during a 13-year period: a nationwide cohort study of 6,354 Korean patients. PLoS One 2020;15(4):e0231456.

15. Shin A, Won YJ, Jung HK, et al. Trends in incidence and survival of esophageal cancer in Korea: analysis of the Korea central cancer registry database. J Gastroenterol Hepatol 2018;33(12):1961–1968.

16. Guan CT, Song GH, Li BY, et al. Endoscopy screening effect on stage distributions of esophageal cancer: a cluster randomized cohort study in China. Cancer Science 2018;109(6):1995–2002.

17. Chen JZ, Chen CZ, Li DR, et al. Verification of non-surgical clinical staging for esophageal carcinoma. China Cancer 2012;21(5):374–378.

18. Han C, Wang L, Zhu SC, et al. Evaluation of prognosis of clinical staging for esophageal carcinoma treated with non-surgical methods - addition with analysis of 225 patients. Zhonghua Fang She Zhong Liu Xue Za Zhi 2011;20(2):109–112.

19. Li HY, Zhu SC, Su JW, et al. An analysis of the influencing factors for long-term survival in patients with esophageal carcinoma undergoing radical chemo-radiotherapy. Zhonghua Fang She Zhong Liu Xue Za Zhi 2016;25(11):1177–1181.

20. Liu Y, Wang KL, Yuan L. Prognosis and investigation of clinical staging for esophageal carcinoma treated with non-surgical methods. Clin Med 2015;35(9):1–4.

21. Ren XJ, Wang L, Han C, et al. Long term survival analysis of middle and lower thoracic esophageal carcinoma of stage T4N(+) treated with 3DRT. Zhonghua Fang She Zhong Liu Xue Za Zhi 2017;26(1):29–34.

22. Wang HY, Kong LL, Wang F, et al. Effect of radiotherapy and prognostic factors in elderly patients with esophageal carcinoma. Acta Universitatis Medicinalis Anhui 2016;51(8):1188–1192.

23. Wang L, Kong J, Han C, et al. The evaluation of prognosis and investigation of clinical staging for esophageal carcinoma treated with non-surgical methods. Zhonghua Fang She Zhong Liu Xue Za Zhi 2012;21(4):330–333.

24. Wu EW, Qi HZ, Zhao HR, et al. Prognostic factors in 167 patients with advanced stage esophageal cancer after radiotherapy and chemotherapy. Mod Oncol 2017; 25(3):385–389.

25. Li J, Zhu SC, Wang YX, et al. Analysis the long-term effect of 375 patients with esophageal carcinoma treated by three-dimensional conformal radiotherapy. Zhonghua Fang She Zhong Liu Xue Za Zhi 2012; 21(4):334–338.

26. Chang CL, Tsai HC, Lin WC, et al. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effective for advanced-stage thoracic esophageal squamous cell carcinoma. Radiother Oncol 2017;125(1):73–79.

27. Chang Z, Gao M, Zhang W, et al. Beta-elemene treatment is associated with improved outcomes of patients with esophageal squamous cell carcinoma. Surg Oncol 2017;26(4):333–337.

28. Chao YK, Chen HS, Wang BY, et al. Prognosis of patients with pathologic T0 N+ esophageal squamous cell carcinoma after chemoradiotherapy and surgical Resection: results from a nationwide study. Ann Thorac Surg 2016;101(5):1897–1902.

29. Chao YK, Ku HY, Chen CY, et al. Induction therapy before surgery improves survival in patients with clinical T3N0 esophageal cancer: a nationwide study in Taiwan. Dis Esophagus 2017;30(12):1–7.

30. Chen HS, Wu SC, Hsu PK, et al. The prognostic impact of Preoperative and postoperative chemoradiation in clinical stage II and III esophageal squamous cell carcinomas: a population based study in Taiwan. Medicine 2015;94(25):e1002.

31. Chen HS, Hung WH, Ko JL, et al. Impact of treatment modalities on survival of patients with locoregional esophageal squamous-cell carcinoma in Taiwan. Medicine (Baltimore) 2016;95(10):e3018.

32. Chen JQ, Zhu KS, Zheng XW, et al. Prognostic analysis of cervical lymph node metastasis in patients with thoracic esophageal squamous cell carcinoma. Zhonghua Zhong Liu Za Zhi 2014;36(8):612–616.

33. Chen S, Yang X, Feng JF. A novel inflammation-based prognostic score for patients with esophageal

squamous cell carcinoma: the c-reactive protein/prognostic nutritional index ratio. Oncotarget 2016; 7(38):62123–62132.

34. Chen XH, Chen JQ, Zheng XW, et al. Prognostic factors in patients with thoracic esophageal carcinoma staged pT(1-4a)N(0)M(0) undergone esophagectomy with three-field lymphadenectomy. Ann Translational Med 2015; 3(19):282.

35. Feng JF, Yang X, Chen S, et al. Prognostic value of plasma d-dimer in patients with resectable esophageal squamous cell carcinoma in China. J Cancer 2016; 7(12):1663–1667.

36. Hao DX, Li X, Yang YY, et al. Neoadjuvant chemoradiotherapy versus chemotherapy and surgery for patients with locally advanced esophageal squamous cell carcinoma. Translational Cancer Res 2017;6(2):346–353.

37. Ho H-J, Chen H-S, Hung W-H, et al. Survival impact of total Resected lymph nodes in esophageal cancer patients with and without neoadjuvant chemoradiation. Ann Surg Oncol 2018;25(13):3820–3832.

38. Huang CJ, Li H, Chen YP. Clinical characteristics and prognostic factors of elder esophageal carcinoma patients treated with surgery. Zhongguo Lao Nian Xue Za Zhi 2016;36(19):4784–4787.

39. Huang Q, Luo K, Yang H, et al. Impact of alcohol consumption on survival in patients with esophageal carcinoma: a large cohort with long-term follow-up. Cancer Science 2014;105(12):1638–1646.

40. Huo XD, Wang HJ, Pang ZL, et al. Survival and prognostic analysis of 339 patients with advanced stage thoracic esophageal squamous cell carcinoma. J Pract Oncol 2010;25(3):273–277.

41. Li N, Wang J, Li J, et al. Prognosis of different postoperative treatment modalities in esophageal adenocarcinoma. Chin J Cancer Prev Treat 2016;23(6):378–383.

42. Li Q, Wu SG, Gao JM, et al. Impact of esophageal cancer staging on overall survival and disease-free survival based on the 2010 AJCC classification by lymph nodes. J Radiat Res 2013;54(2):307–314.

43. Li QQ, Liu MZ, Hu YH, et al. Clinical value of barium swallow in observing esophageal tumor regression during radiotherapy. Ai Zheng 2006;25(6):723–727.

44. Lin CS, Liu CY, Cheng CT, et al. Prognostic role of initial pan-endoscopic tumor length at diagnosis in operable esophageal squamous cell carcinoma undergoing esophagectomy with or without neoadjuvant concurrent chemoradiotherapy. J Thorac Dis 2017;9(9):3193–3207.

45. Lin WC, Ding YF, Hsu HL, et al. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer 2017;123(20):3904–3915.

46. Luo QS, Gan CZ, Wang XH, et al. Clinical characteristics and prognostic factors of patients with lymph node metastasis of thoracic esophageal squamous cell carcinoma. Int J Clin Exp Med 2017;10(3):5307–5313.

47. Sheng LM, Ji YL, Du XH. Perineural invasion correlates with postoperative distant metastasis and poor overall survival in patients with PT1-3N0M0 esophageal squamous cell carcinoma. Oncotargets Ther 2015; 8:3153–3157.

48. Sun P, Chen C, Zhang F, et al. The ABO blood group predicts survival in esophageal squamous cell carcinoma in patients who ever smoked: a retrospective study from China. Tumor Biol 2014;35(7):7201–7208.

49. Sun P, Zhang F, Chen C, et al. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China. Oncotarget 2016; 7(27):42650–42660.

50. Sun P, Zhang F, Chen C, et al. Prognostic impact of body mass index stratified by smoking status in patients with esophageal squamous cell carcinoma. Oncotargets Ther 2016;9:6389–6397.

51. Tan H, Zhang H, Xie J, et al. A novel staging model to classify oesophageal squamous cell carcinoma patients in China. Br J Cancer 2014;110:2109–2115.

52. Wang BY, Chen HS, Hsu PK, et al. Clinical impact of the interval between chemoradiotherapy and esophagectomy in esophageal squamous cell carcinoma patients. Ann Thorac Surg 2015;99(3):947–955.

53. Wang BY, Hung WH, Wu SC, et al. Comparison between esophagectomy and definitive chemoradiotherapy in patients with esophageal cancer. Ann Thorac Surg 2019; 107:1060–1067.

54. Wang Y, Liu JF. Prognostic value of neutrophil-to-lymphocyte ratio in patients with esophageal adenocarcinoma. Zhonghua Shi Yan Wai Ke Za Zhi 2017; 34(12):2244–2248.

55. Wei RN, Shang ZQ, Leng J, et al. Increased expression of high-mobility group A2: a novel independent indicator of poor prognosis in patients with esophageal squamous cell carcinoma. J Cancer Res Ther 2016; 12(4):1291–1297.

56. Xi RX, Zhang XZ, Chen X, et al. Human papillomavirus 16 infection predicts poor outcome in patients with esophageal squamous cell carcinoma. Oncotargets Ther 2015; 8:573–581.

57. Yen YC, Chang JH, Lin WC, et al. Effectiveness of esophagectomy in patients with thoracic esophageal squamous cell carcinoma receiving definitive radiotherapy or concurrent chemoradiotherapy through intensity-modulated radiation therapy techniques. Cancer 2017;123(11):2043–2053.

58. Zhang HD, Liang HG, Gao YY, et al. Metastatic lymph node ratio demonstrates better prognostic stratification than pN staging in patients with esophageal squamous cell carcinoma after esophagectomy. Sci Rep 2016;6:38804.

59. Zhong H, Ma R, Gong L, et al. Comparison of the prognostic value of the seventh and eighth edition of the AJCC esophageal cancer staging system for the patients with stage II and III esophageal squamous cell carcinoma. Zhonghua Wai Ke Za Zhi 2017;55(12):903–908.

60. Chang WL, Lin FC, Yen CJ, et al. Tumor length assessed by miniprobe endosonography can predict the survival of the advanced esophageal squamous cell carcinoma with stricture receiving concurrent chemoradiation. Dis Esophagus 2011;24(8):590–595.

61. Chu JF. Clinical effects of three dimensional conformal radiotherapy for the treatment of esophageal carcinoma. J Huaihai Med 2011;29(5):411–413.

62. Hsieh HY, Yeh HL, Hsu CP, et al. Feasibility of intensity-modulated radiotherapy for esophageal cancer in definite chemoradiotherapy. J Chin Med Assoc 2016; 79(7):375–381.

63. Zhu ZQ, Zhu ZA, Cai HX. Continuous infusion of a large dose of CF (folinic acid) and 5-FU combined with CDDP in the treatment of advanced esophageal cancer. Int J Clin Pharmacol Ther 2017;55(5):397–402.

64. Huang GJ. Early detection and surgical treatment of esophageal carcinoma. Jpn J Surg 1981;11(6):399–405.

65. Liu SG, Qi B, Zhao BS, et al. Prognostic factors for patients with same pathological staging of esophageal carcinoma. China J Mod Med 2015;25(36):93–96.

66. Zhang DK, Su XD, Lin P. Survival analysis of patients with stage II squamous cell carcinoma of the thoracic esophagus after esophagectomy. Ai Zheng 2008;27(2):113–118.

67. Hu Y, Zheng B, Rong TH, et al. Prognostic analysis of the patients with stage III esophageal squamous cell carcinoma after radical esophagectomy. Chin J Cancer 2010;29(2):190–195.

68. Yang Q, Wang YX, He M, et al. Factors affecting on long-term survival in patients with stage III thoracic esophageal carcinoma with esophagectomy. Zhonghua Zhong Liu Za Zhi 2016;38(7):530–537.

69. Chen MQ, Xu BH, Zhang YY. Analysis of prognostic factors for esophageal squamous cell carcinoma with distant organ metastasis at initial diagnosis. J Chin Med Assoc 2014;77(11):562–566.

70. Huang CY, Wang L, Yang XB, et al. Expression of activated signal transducer and activator of transcription-3 as a predictive and prognostic marker in advanced esophageal squamous cell carcinoma. World J Surg Oncol 2015;13:314.

71. Yan XJ, Xia XM, Liu QL, et al. First-line chemotherapy of patients with advanced esophageal squamous cell carcinoma: a survival analysis of 139 cases. Acad J Chin PLA Med Sch 2015;36(7):671–674, 719.

72. Hou H, Meng Z, Zhao X, et al. Survival of esophageal cancer in China: a pooled analysis on hospital-based studies from 2000 to 2018. Front Oncol 2019;9:548.

73. Zhang SW, Zheng RS, Zuo TT, et al. Mortality and survival analysis of esophageal cancer in China. Zhonghua Zhong Liu Za Zhi 2016;38(9):709–715.

74. Lin Y, Totsuka Y, Shan B, et al. Esophageal cancer in high-risk areas of China: research progress and challenges. Ann Epidemiol 2017;27(3):215–221.

75. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015;21(26):7933–7943.

76. Hutchison GB, Shapiro S. Lead time gained by diagnostic screening for breast cancer. J Natl Cancer Inst 1968;41(3):665–681.

77. He Z, Liu Z, Liu M, et al. Efficacy of endoscopic screening for esophageal cancer in China (ESECC): design and preliminary results of a population-based randomised controlled trial. Gut 2019;68(2):198–206.

78. Li F, Li X, Guo C, et al. Estimation of cost for endoscopic screening for esophageal cancer in a high-risk population in rural China: results from a population-level randomized controlled trial. Pharmacoeconomics 2019;37(6):819–827. http://doi.org/10.1007/s40273-019-00766-9.

79. Xia R, Zeng H, Liu W, et al. Estimated cost-effectiveness of endoscopic screening for upper gastrointestinal tract cancer in high-risk areas in China. JAMA Netw Open 2021;4:e2121403.

80. Liu Z, Guo C, He Y, et al. A clinical model predicting the risk of esophageal high-grade lesions in opportunistic screening: a multicenter real-world study in China. Gastrointest Endosc 2020;91:1253–1260.e3.

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