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Quality of life and survival outcomes of patients with inoperable esophageal squamous cell carcinoma after definitive radiation therapy: A multicenter retrospective observational study in China from 2015 to 2016



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ABSTRACT

Objectives: To investigate the health-related quality of life (HRQL) of long-term survivors of inoperable esophageal squamous cell carcinoma (ESCC) treated with definitive radiation therapy, the real-world trends in the use of advanced radiation techniques, and their impact on the survival outcomes of ESCC patients.

Methods: In this multicenter retrospective observational study, the medical records related to demographics and treatment of ESCC patients who were treated with definitive radiation therapy at 14 provincial hospitals in China from 1 January 2015 to 31 December 2016 were analyzed. A HRQL questionnaire was completed by survivors and collected by doctors at the final follow-up. The difference in quality of life between patients with or without recurrence was compared using the Wilcoxon–Mann–Whitney test. Overall survival (OS) was estimated using the Kaplan–Meier method and the group differences were assessed by unstratified log-rank test. The Cox proportional hazards model with Efron's method of tie handling was used to calculate the risk factors for OS.

Results: The data of a total of 3,308 patients were collected for this study, 248 were excluded because of missing data, and a final of 3,060 patients were included in the analysis. Most patients (2,901; 94.8%) received intensity-

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modulated radiotherapy (IMRT)/volumetric-modulated arc therapy (VMAT)/tomotherapy (TOMO). The 5-year OS rate was 30%. Patients who received either two-dimensional radiotherapy (2DRT; HR, 2.43 [95% CI, 1.70–3.47]; $P < 0.001$) or three-dimensional radiotherapy (3DRT; HR, 1.45 [95% CI, 1.14–1.84]; $P = 0.003$) had a significantly increased risk of death compared to those who received IMRT/VMAT/TOMO. Of the 716 (23.4%) long-term survivors who completed the HRQL questionnaire, nearly 70% patients were still able to swallow normally or almost normally, and >80% patients did not experience weight loss. Nearly 80% patients found life very enjoyable or were fairly enjoying life.

Conclusions: This large, multicenter retrospective study on ESCC patients who received definitive radiation therapy found that most ESCC survivors are satisfied with their quality of life. Most patients received advanced radiation technology. Patients who received either 2DRT or 3DRT had a significantly increased risk of death compared to those who received advanced radiation technology.

1. Introduction

According to data from the Cancer Registry of the National Cancer Center of China, esophageal cancer has the sixth highest incidence and fifth highest mortality rate among all malignant tumors.¹ In China, esophageal squamous cell cancer (ESCC) are the most common histological type, accounting for more than 90% of esophageal cancer patients.² Apart from surgery, the benefit of radiation therapy, administered either preoperatively or definitively, has been established in several randomized trials.^{3–5}

According to a survey on the basic information of personnel and facilities of radiotherapy in Chinese mainland in 2019, esophageal cancer patients rank second following lung cancer among all patients treated with radiation therapy.⁶ However, due to the imbalance of economic development, there are regional differences in the distribution of departments of radiation oncology, as well as linear accelerators. Approximately 40% of cancer patients who should have been treated with radiation therapy did not receive this treatment.⁶

With the development of chemoimmunotherapy drugs and radiation techniques, such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), tomotherapy (TOMO), and proton beam therapy (PBT), the survival rate of patients with ESCC has been improved from 8–15% to 20–40% since the 1980s.^{5,7–10} Compared with surgery, definitive radiation therapy is inferior in survival outcome but superior in health-related quality of life (HRQL) measures, although the definitive radiation therapy group has more cases with poorer prognostic factors, such as more advanced clinical stages, older ages, or more comorbidities. Nevertheless, treatment-related comorbidities of definitive chemoradiotherapy (dCRT), including esophageal stenosis, radiation pneumonitis, and cardiopulmonary toxicities, etc.,^{11–13} may likely occur in long-term survivors, resulting in a decrease in the physical quality of life. In addition, some researchers reported that socio-demographic factors such as age, socioeconomic status, and cancer-related treatment are associated with depression and anxiety in breast cancer patients,^{14,15} and may affect psychophysiological functions and further interfere with one's ability to cope effectively with cancer.¹⁶ However, the HRQL in terms of physical well-being, family support, and psychophysiological status of inoperable Chinese ESCC patients with long-term survival for whom radiation has been effective is unknown. Furthermore, real-world survey data are also lacking for the use of allopatric treatment, frequency of reexamination, and the coverage of medical insurance for patients with ESCC in a large sample size in China.

The primary objective of this study was to investigate the real-world HRQL of survivors with inoperable ESCC at 14 provincial hospitals in China treated with definitive radiation therapy between 2015 and 2016. The secondary objectives were to investigate the overall survival (OS), use of advanced radiation techniques, treatment type, local or allopatric treatment, frequency and location of patient reexamination, as well as the sources of medical expenses of ESCC patients in that period.

2. Materials and methods

2.1. Study population

In this retrospective observational study, the medical records related to demographics and treatment of patients with inoperable ESCC at 14 provincial hospitals in China treated with definitive radiation therapy between 2015 and 2016 were investigated, with a HRQL questionnaire for survivors.

Patients who met the following inclusion criteria were included in the survey: (1) received definitive radiotherapy (dRT) alone or dCRT with or without induction chemotherapy (IC); (2) without surgery due to unresectable disease or contraindication of operation or refusal of surgical treatment; (3) pathologically or cytologically confirmed ESCC; (4) clinical staging at any T, any N, M0–1 (American Joint Committee on Cancer, version 8, M1 limited to supraclavicular lymph node metastasis); and (5) radiation dose to primary tumor ≥ 50 Gy (Fig. 1). Patients with histological types other than ESCC, distant lymph node or organ metastasis and radiation dose < 50 Gy, or who underwent neoadjuvant or postoperative radiation therapy were not included in data collection.

2.2. Data collection

The data of patients with ESCC who received definitive radiation therapy in 14 provincial hospitals in China from 1 January 2015 to 31 December 2016 was collected (Fig. 2). Baseline information of patients was obtained through electronic forms at all participating centers using the same template consisted of patient characteristics (age, sex, and clinical stage), treatment type (dRT, dCRT or IC followed by dRT/dCRT [IC + dRT/dCRT]), radiation techniques (two-dimensional radiotherapy [2DRT], three-dimensional radiotherapy [3DRT], or IMRT/VMAT/TOMO), and received allopatric medical treatment across or within provinces or municipality. The questionnaire was completed by survivors and collected by doctors through phone calls or a WeChat mini program at the final follow-up from June 2021 and December 2021. Two parts comprised the questionnaire. The first part consisted of frequency and location of follow-up, the sources of medical expenses, and use of Traditional Chinese Medicine therapy or not. The second part was an HRQL questionnaire including physical well-being, family support, emotional and functional status, as well as swallowing and eating ability, according to the Assessment of Cancer Therapy-General (FACT-G) and the Functional Assessment of Cancer Therapy-Esophageal (FACT-E).^{17,18} Because of the complexity of the questionnaire, a representative physician from each participating center voted for 15 most concerned issues to constitute the HRQL survey items. A five-point Likert-type scale from 0 (not at all) to 4 (very much) was used for the HRQL at the final follow-up, and a higher score indicated better quality of life.

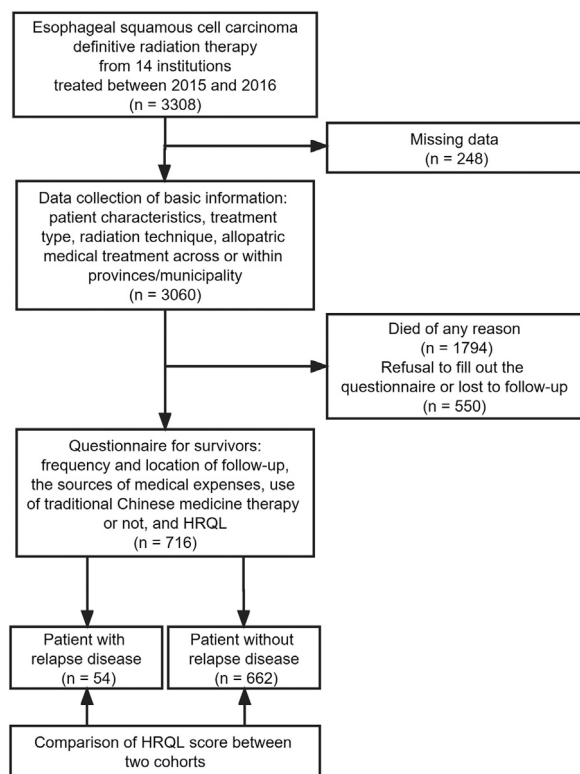


Fig. 1. CONSORT diagram of patient selection. HRQL, health-related quality of life.

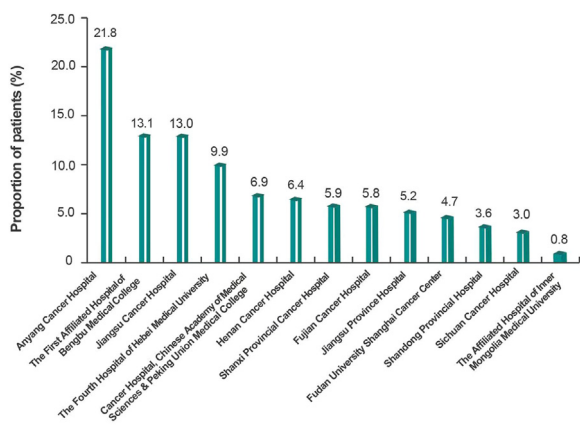


Fig. 2. Proportion of patients in each participating centers.

2.3. Statistical analysis

Quality of life was described using frequency and percentage. The difference in quality of life between patients with recurrence and those without recurrence was compared using the Wilcoxon–Mann–Whitney test.

The OS was defined as the time interval between the start of radiotherapy or IC and death of any cause. Data for patients who were alive or lost to follow-up were censored for OS at the time they were last known to be alive. OS was estimated using the Kaplan–Meier method, and 95% confidence intervals (CIs) for the median were calculated using the Brookmeyer–Crowley method. The 5-year survival duration was estimated using the Kaplan–Meier method. Duration of follow-up was estimated using the reverse Kaplan–Meier method. An unstratified log-rank test was used to assess the group differences in OS and calculate the *P* value. Investigated factors included sex, age, stage, treatment type, and

Table 1
Baseline characteristics of patients included in the study (n = 3,060).

Characteristics	Number of patients
Age, median (IQR), years	67.0 (61.0, 74.0)
Age group, No. (%), years	
< 50	133 (4.3)
50–59	495 (16.2)
60–69	1,238 (40.5)
70–79	928 (30.3)
≥ 80	266 (8.7)
Sex, No. (%)	
Male	2,080 (68.0)
Female	980 (32.0)
Stage, No. (%)	
I	86 (2.8)
II	1,004 (32.8)
III	1,234 (40.3)
IVa	366 (12.0)
IVb	370 (12.1)
Treatment type, No. (%)	
dRT	909 (29.7)
IC-dRT/dCRT	539 (17.6)
dCRT	1,612 (52.7)
Radiation technique, No. (%)	
IMRT/VMAT/TOMO	2,901 (94.8)
3D	113 (3.7)
2D	46 (1.5)

Abbreviations: 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy; dCRT, definitive chemoradiotherapy; dRT, radiotherapy alone; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; IQR, interquartile ratio; TOMO, tomotherapy; VMAT, volumetric-modulated arc therapy.

radiation technique. The Cox proportional hazards model with Efron’s method of tie handling was used to calculate hazard ratios (HRs) and corresponding 95% CIs for OS. Factors that achieved significance at *P* < 0.05 were entered into the multivariable analyses via the Cox regression model to identify the predictive factors of OS. All statistical analyses were performed using the R software, version 4.1.2 (R Foundation).

3. Results

3.1. Patient characteristics

Of the 3,308 patients, 248 patients were excluded from the study because of missing data. Finally, a total of 3,060 patients were included in the analysis (median age 67 years [interquartile range, 61.0–74.0]; 68.1% male; male-to-female ratio, 2.1:1). Table 1 showed the characteristics of patients enrolled in the analysis. Of the total patients enrolled, 39% were older than 70 years. Most patients (1,970; 64.4%) had stage III–IV ESCC at the initial diagnosis. DRT was performed in 909 patients (29.7%), and the remaining patients received a combination with chemotherapy, including dCRT (1,612; 52.7%) or IC+dRT/dCRT (539; 17.6%). Most patients (2,901; 94.8%) received IMRT/VMAT/TOMO. No patients received immunotherapy. In total, 15.4% (472 patients) received allopathic medical treatment across provinces or municipality, while the rest received medical treatment within provinces or municipality.

Among the 3,060 patients, a total of 716 (23.4%) survivors completed the questionnaire. Among them, 63.8% (457) were followed up every three to six months within two years after the end of treatment, 34.5% were followed up every 6 months within 3–5 years, and 24.4% were followed up every one year after five years. As for the follow-up location, 31.8% (228) patients returned to the original treatment hospital, 13.5% (97) visited a hospital near their place of residence, and 48.3% (346) chose both. In terms of the source of medical expenses, 94.7% (678) of patients used medical insurance expenditure (including medical plus commercial insurance), and 5.3% (38) paid for the medical expenditure themselves. Three (0.4%) patients were interrupted during

Table 2
Results of health-related quality of life questionnaire reported by survivors (n = 716).

Issue	No. ^a	Item	Not at all, No. (%)	A little bit, No. (%)	Somewhat, No. (%)	Quite a bit, No. (%)	Very much, No. (%)
Physical well-being	1	I have a lack of energy.	516 (72.1)	140 (19.6)	29 (4.1)	12 (1.7)	19 (2.7)
	2	I have pain.	593 (82.8)	95 (13.3)	17 (2.4)	6 (0.8)	5 (0.7)
	3	I am bothered by the side effects of treatment.	499 (69.7)	155 (21.6)	42 (5.9)	15 (2.1)	5 (0.7)
Family well-being	4	I get emotional support from my family.	4 (0.6)	41 (5.7)	52 (7.3)	180 (25.1)	439 (61.3)
	5	My family has accepted my illness.	2 (0.3)	5 (0.7)	74 (10.3)	194 (27.1)	441 (61.6)
	6	Family communication about my illness is poor.	3 (0.4)	8 (1.1)	64 (8.9)	211 (29.5)	430 (60.1)
Emotional well-being	7	I am losing hope in the fight against my illness.	555 (77.5)	113 (15.8)	33 (4.6)	7 (1.0)	8 (1.1)
	8	I feel nervous.	460 (64.2)	203 (28.4)	42 (5.9)	10 (1.4)	1 (0.1)
	9	I worry about dying.	382 (53.4)	255 (35.6)	54 (7.5)	22 (3.1)	3 (0.4)
Functional well-being	10	I have been able to work (including housework).	50 (7.0)	110 (15.4)	158 (22.1)	228 (31.8)	170 (23.7)
	11	I am able to enjoy life “in the moment”.	12 (1.7)	45 (6.3)	94 (13.1)	248 (34.6)	317 (44.3)
	12	I am content with the quality of my life right now.	17 (2.4)	40 (5.6)	111 (15.5)	263 (36.7)	285 (39.8)
Swallowing and eating	13	I am able to eat the foods that I like.	13 (1.8)	41 (5.7)	176 (24.6)	260 (36.3)	226 (31.6)
	14	I can swallow naturally and easily.	26 (3.6)	53 (7.4)	143 (20.0)	223 (31.1)	271 (37.8)
	15	I am losing weight.	581 (81.1)	100 (14.0)	22 (3.1)	8 (1.1)	5 (0.7)

^a Items 1–12 were derived from Functional Assessment of Cancer Therapy-General (FACT-G). Items 13–15 were derived from Functional Assessment of Cancer Therapy-Esophageal (FACT-E).

anticancer treatment due to economics. We also found that 20.7% (148) patients received traditional Chinese medicine during anticancer treatment.

3.2. Quality of life

Table 2 showed the results of 716 patients who completed the HRQL questionnaire. In terms of physical condition, at the time of the questionnaire completed by survivors, 72.1% and 82.8% of survivors did not feel insufficient energy or have pain at all in the previous week, and 69.7% were not bothered by the side effects of treatment at all.

Regarding family support, 86.4% of patients felt emotionally supported by their families, 88.7% of survivors believed that their families had accepted their illness, and 89.6% were very (60.1%) or quite (29.5%) satisfied with the ways their families communicated with them about their illness.

In terms of emotional well-being, 77.5% of patients never lost hope in the fight against the disease, and 64.2% did not feel nervous at all. Most patients were not worried (53.4%) or were a little bit worried (35.6%) about dying.

Regarding the functional well-being, >50% survivors did well (23.7%) or better (31.8%) at jobs (including housework). Most survivors (78.9%) were very enjoyable (44.3%) or enjoyed life quite a bit (34.6%). In total, 39.8% of survivors were very satisfied and 36.7% were quite satisfied with their current quality of life.

Approximately 67.9% of patients could eat their favorite food and swallow normally or relatively normally. No weight loss was observed in 81.1% of survivors.

Of the 716 patients who completed HRQL questionnaire, 54 patients (7.5%) were alive with recurrence until the questionnaire was returned. Patients without recurrence reported better results than those with recurrence in terms of physical condition (including not feeling lack of energy, being able to work, being able to swallow normally, being able to eat their favorite foods, not losing weight, and not feeling pain). Patients without recurrence had better psychological states than relapsed patients in terms of “not feeling nervous”, “not bothered by the side effects of treatment”, “not losing hope in the fight against my illness”, and “not worried about dying”. However, scores for family support were not significantly different among patients with or without recurrence (Table 3).

3.3. Overall survival

Patients were followed up until August 31, 2021; the median follow-up time was 63 months (95% CI, 62.1–63.8). The median OS duration

was 25.9 months (95% CI, 24–27.6). The 1-year, 2-year, 3-year, 4-year, and 5-year OS rates were 75.2%, 52.0%, 40.7%, 34.1%, and 30.0%, respectively. A total of 1,794 patients died, of which 1,528 (85.2%) patients died of cancer, 91 (5.1%) of comorbidities, 81 (4.5%) of post-treatment complications, 5 (0.3%) of accidents, and 89 (5.0%) of unknown reasons.

In either univariate or multivariate analysis, age, sex, clinical stage, treatment type of chemoradiotherapy, and radiation techniques were associated with OS (Table 4). Patients aged ≥ 80 years had a 57% increased risk of death compared to younger patients (95% CI, 1.19–2.07; $P < 0.008$; Fig. 3). The 5-year OS was better in female than in male patients (HR, 0.81 [95% CI, 0.74–0.90]; $P < 0.0001$). The median OS of patients at stages I, II, III, and IV ESCC were 67 months, 37.4 months, 22.9 months, and 22.1 months, respectively (Fig. 4). Patients with supraclavicular lymph node metastasis who were assigned to Stage IVb, had the worst median OS of 20.5 months. Patients who underwent dCRT (35.8%; HR, 0.64 [95% CI, 0.57–0.72]; $P < 0.001$) or IC+dRT/dCRT (31.1%; HR, 0.72 [95% CI, 0.62–0.84]; $P < 0.001$) had significantly better survival outcomes than those who received dRT (Fig. 5). Patients who received either 2DRT (HR, 2.43 [95% CI, 1.70–3.47]; $P < 0.001$) or 3DRT (HR, 1.45 [95% CI, 1.14–1.84]; $P = 0.003$) had a significantly increased risk of death compared to those who received IMRT/VMAT/TOMO (Fig. 6).

4. Discussion

This is the first and largest survey report focusing on HRQL of patients with ESCC survived more than five years after definitive radiation therapy in multiple medical centers in China. The results are comprehensive and include radiation technique, local or allopatric treatment, as well as frequency and location of patient reexamination, etc.

The average life expectancy in China reached 76.3 years in 2015, 1.5 years higher than that in 2010.¹⁹ The aging population has increased and is more prone to serious illness. In recent years, the number of elderly cancer patients gradually increased. Our survey results show that patients with esophageal cancer who received definitive radiation therapy from 2015 to 2016 had a median age of 67 years, and 39% of them were ≥ 70 years, much higher than the median age of operable patients in the NEOCRTEC5010 and CROSS trials (56–61.4 years).^{4,20}

With the development of radiation technology, the 5-year OS of patients who receive dCRT for esophageal cancer in China has reached 20–44%.^{5,8} In the era of conventional 2DRT, the ⁶⁰Co machine was used, and subsequently, linear accelerator was used to deliver external irradiation. The radiation field comprises a three-field isocenter arrangement employing one front and two rear radiation fields or a four-

Table 3
Comparison of quality-of-life scores in patients with and without relapse tumor.

Issue	No. ^a	Item ^a	Relapsed ^b , median	Relapse-free ^b , median	P value ^c
Physical well-being	1	I have a lack of energy.	2	3	< 0.001
	2	I have pain.	2	3	< 0.001
	3	I am bothered by the side effects of treatment.	2	3	< 0.001
Family well-being	4	I get emotional support from my family.	4	4	0.188
	5	My family has accepted my illness.	4	4	0.669
	6	Family communication about my illness is poor.	4	4	0.960
Emotional well-being	7	I am losing hope in the fight against my illness.	2	3	< 0.001
	8	I feel nervous.	2	3	< 0.001
	9	I worry about dying.	2	3	< 0.001
Functional well-being	10	I have been able to work (including housework).	1	3	< 0.001
	11	I am able to enjoy the life at the moment.	3	3	< 0.001
	12	I am content with the quality of my life right now.	3	3	< 0.001
Swallowing and eating	13	I am able to eat the foods that I like.	2	3	< 0.001
	14	I can swallow naturally and easily.	2	3	< 0.001
	15	I am losing weight.	2	3	< 0.001

^a Items 1–12 were derived from Functional Assessment of Cancer Therapy-General (FACT-G). Items 13–15 were derived from Functional Assessment of Cancer Therapy-Esophageal (FACT-E).

^b A five-point Likert-type scale from 0 (not at all) to 4 (very much) was used. Higher score indicates better quality of life.

^c P value was calculated using Wilcoxon–Mann–Whitney test and P < 0.05 was considered as statistically significant.

Table 4
Results of univariate and multivariate Cox regression analyses.

	Median OS (95% CI)	5-year OS rate (95% CI)	Univariate Cox regression		Multivariate Cox regression	
			HR (95% CI)	P ^a	HR (95% CI)	P ^b
Age group, years						
< 50	23.3 (18.7–33.7)	32.9 (24.9–43.5)	Reference		Reference	
50–59	23.9 (20.2–27.9)	29.7 (25.6–34.6)	1.07 (0.81–1.38)	0.632	1.13 (0.88–1.43)	0.327
60–69	30.4 (27.2–34.1)	33.8 (31.0–36.9)	0.92 (0.72–1.17)	0.493	1.02 (0.81–1.27)	0.893
70–79	25.0 (22.3–28.1)	29.2 (26.0–32.7)	1.08 (0.84–1.39)	0.546	1.19 (0.94–1.50)	0.156
≥80	18.1 (15.8–21.2)	14.7 (10.6–20.5)	1.57 (1.19–2.07)	0.001	1.63 (1.23–2.16)	<0.001
Sex						
Male	24.1 (22.6–26.0)	27.4 (25.3–29.6)	Reference		Reference	
Female	30.8 (26.7–35.1)	35.7 (32.5–39.2)	0.81 (0.74–0.90)	<0.001	0.76 (0.68–0.84)	<0.001
Stage						
Stage I	67.0 (32.8-NA)	54.1 (42.9–68.2)	Reference		Reference	
Stage II	37.4 (32.7–42.5)	37.1 (33.8–40.7)	1.39 (0.97–1.98)	0.073	1.38 (0.96–1.97)	0.008
Stage III	22.9 (20.6–25.5)	27.7 (25.1–30.6)	1.88 (1.32–2.67)	<0.001	1.96 (1.38–2.79)	<0.001
Stage IVa	21.6 (18.7–25.2)	23.5 (18.9–29.2)	2.09 (1.44–3.04)	<0.001	2.16 (1.49–3.13)	<0.001
Stage IVb	20.5 (18.3–23.6)	22.0 (17.7–27.2)	2.11 (1.46–3.05)	<0.001	2.28 (1.58–3.31)	<0.001
Treatment type						
dRT	19.1 (17.8–21.2)	19.2 (16.5–22.3)	Reference		Reference	
IC-dRT/dCRT	25.8 (23.4–31.1)	31.1 (26.9–35.9)	0.72 (0.62–0.82)	<0.001	0.72 (0.62–0.84)	<0.001
dCRT	31.8 (28.8–35.0)	35.8 (32.2–38.5)	0.62 (0.56–0.69)	<0.001	0.64 (0.57–0.72)	<0.001
Radiation technique						
IMRT/VMAT/TOMO	26.6 (25.1–28.8)	30.7 (28.9–32.6)	Reference		Reference	
3DRT	16.7 (12.1–21.1)	21.1 (13.9–31.9)	1.45 (1.14–1.84)	0.002	1.44 (1.13–1.83)	0.003
2DRT	8.9 (5.9–13.8)	13.8 (6.2–31.1)	2.41 (1.70–3.42)	<0.001	2.43 (1.70–3.47)	<0.001

^a P value was calculated using univariate Cox regression and P < 0.05 was considered as statistically significant.

^b P value was calculated using multivariate Cox regression and P < 0.05 was considered as statistically significant.

Abbreviations: 2DRT, two-dimensional radiotherapy; 3DRT, three-dimensional radiotherapy; CI, confidence interval; dCRT, definitive chemoradiotherapy; dRT, radiotherapy alone; HR, hazard ratio; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; OS, overall survival; TOMO, tomotherapy; VMAT, volumetric-modulated arc therapy.

field consisting of anteroposterior-posteroanterior plus oblique radiation fields. However, 2DRT has shown 5-year OS of only 8.4–15.5% and a locoregional failure rate of 60–80% in unresectable ESCC patients after dCRT.^{9,10} In 2001, the 3DRT was first used in China. Xiao *et al.* used the 3DRT planning system to evaluate the dose distribution in conventional 2DRT for esophageal cancer and found that although the prescribed dose of planning target volume was 60 Gy, only 36.6% of gross target volume and 27% of clinical target volume were covered, whereas with 3DRT these values reached 100% and 95%, respectively.²¹ Theoretically, 3DRT improves the locoregional control rate after obtaining the prescribed dose in the radiation area. Furthermore, IMRT presented significantly better conformality and homogeneity than 3DRT. Specifically, IMRT planning was superior to 3DRT planning in protecting the normal tissue. The present study found that during 2015–2016,

94.8% Chinese patients with ESCC received IMRT-based advanced radiation technology that resulted in a corresponding 5-year OS rate of 30% and a median OS of 25.9 months, which was significantly better than the results of 3DRT (21.1%, 16.7 months) and 2DRT (13.8%, 8.9 months). Lan *et al.* reviewed 388 patients with ESCC receiving IMRT or 3DRT from 2010 to 2017, and found that IMRT was significantly associated with better OS (P = 0.001) and progression-free survival (PFS, P = 0.008) and lower risk of radiation pneumonitis (5.4% vs 23.1%, P < 0.001) compared to 3DRT.²² Therefore, we recommend that IMRT-based photon radiotherapy should be used as far as possible in esophageal cancer to improve OS and reduce the occurrence of side effects. PBT can provide the same radiation dose in the tumor area, while further reducing the dose to surrounding normal tissues. Xi *et al.* reported PBT improved OS and PFS compared with IMRT for stage III

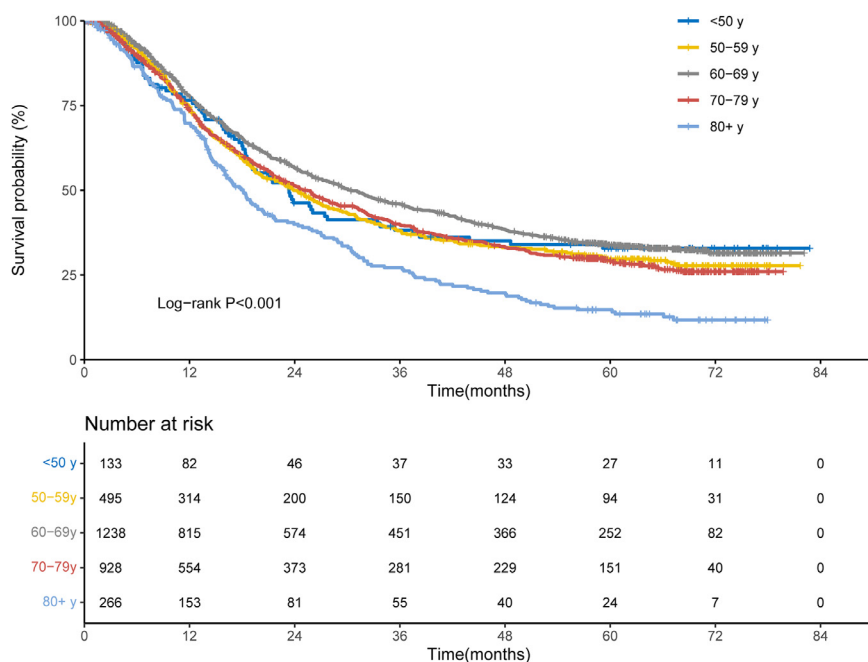


Fig. 3. Overall survival of inoperable esophageal patients after definitive radiation therapy according to age group. Y, years.

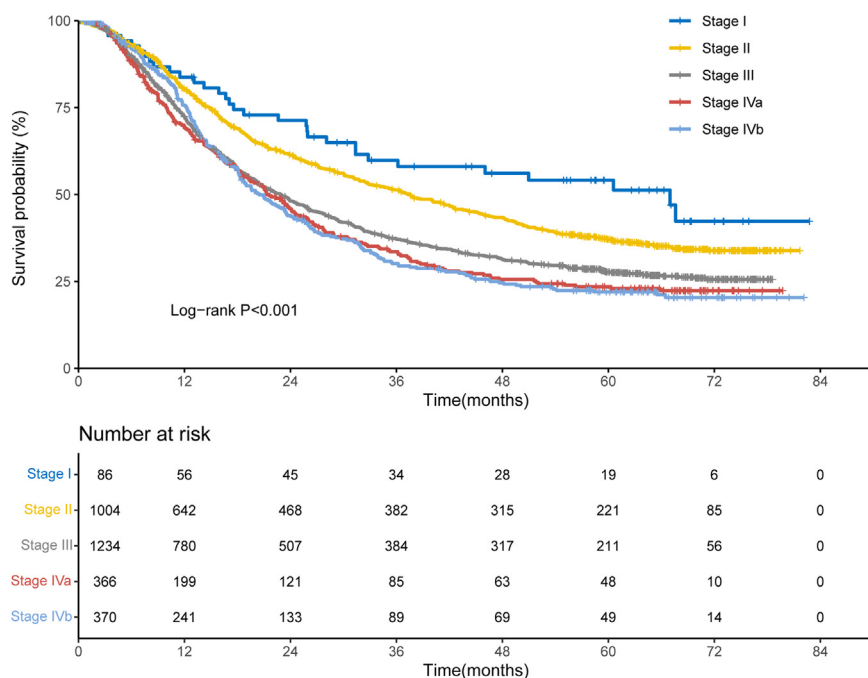


Fig. 4. Overall survival of inoperable esophageal patients after definitive radiation therapy according to clinical stage.

esophageal cancer patients receiving dCRT.²³ However, a study with a large sample size or prospective studies are needed to confirm this conclusion.

The RTOG8501 trial has confirmed that dCRT is more effective than dRT in esophageal cancer.⁷ Ji *et al.*, in a prospective phase III randomized controlled study on S-1 based dCRT vs dRT in elderly patients with ESCC, found that the addition of S-1 significantly improved 3-year OS (43.4% vs 28.4%, $P = 0.002$).²⁴ In the present study, the 5-year OS of patients who received dRT was only 19.2%, much lower than 35.8% in patients receiving dCRT or 31.1% in those who received IC + dRT/dCRT. According to the National Comprehensive Cancer Network guidelines, radiotherapy combined with chemotherapy is the standard neoadjuvant or definitive treatment for esophageal cancer with stage T2–4aN0–3M0. However, whether induction chemotherapy is needed before dCRT is

unclear. Liu *et al.* evaluated the efficacy of IC + dCRT vs dCRT in patients with inoperable thoracic ESCC in a single-center randomized phase II study.²⁵ No significant differences in 3-year OS and PFS were observed between patients receiving IC + dCRT and those receiving dCRT (41.8% vs 38.1%, $P = 0.584$; 30.6% vs 29.8%, $P = 0.770$), and grade ≥ 3 adverse events were similar between the two groups. While subgroup analysis showed that responders to IC had significantly more favorable survival compared with non-responders or with patients in the dCRT group (3-year OS, 80% vs 10% vs 38.1%, $P < 0.001$; 3-year PFS, 55.3% vs 10% vs 29.8%, $P < 0.001$). In addition, patients with stage III-IVa benefited from IC compared to those with stage II (OS, $P = 0.069$; PFS, $P = 0.058$).²⁵ Thus, ESCC patients with locally advanced stage may be suitable for IC + dCRT. Furthermore, IC may screen some patients for sensitivity to chemotherapy and have excellent

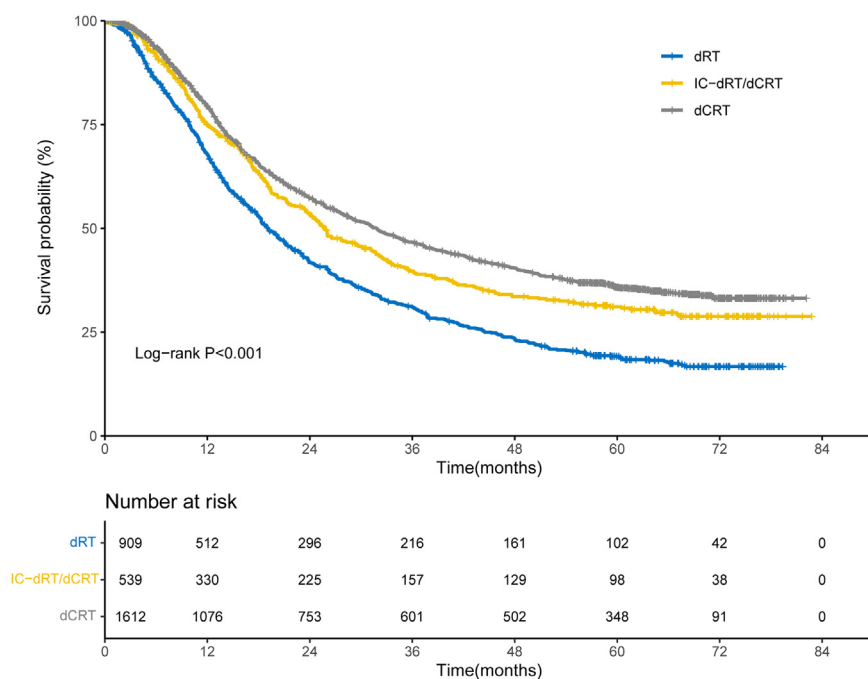


Fig. 5. Overall survival of inoperable esophageal patients according to treatment type. dCRT, chemoradiotherapy; IC-dRT, induction chemotherapy followed by radiotherapy or chemoradiotherapy; dRT, radiotherapy alone.

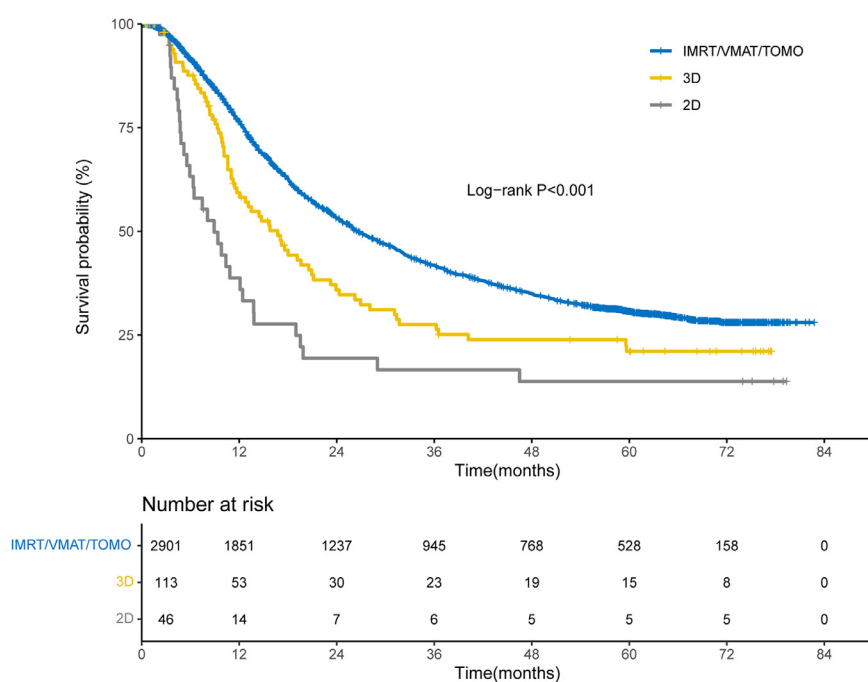


Fig. 6. Overall survival according to radiation technique. 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy; TOMO, tomotherapy; VMAT, volumetric-modulated arc therapy.

survival outcomes from the subsequent dCRT. The 3-year OS of 80% in the IC + dCRT group reported in the above study²⁵ is even better than the results of neoadjuvant chemoradiotherapy trials followed by surgery in patients with esophageal cancer (3-year OS rate in the neoadjuvant chemoradiotherapy plus surgery arm in the NEOCRTEC5010 trial was 67% and the rate was 69.1% in the CROSS trial for ESCC patients).^{4,26}

According to the results of this survey, the coverage rate of medical insurance for radiotherapy patients during 2015–2016 reached 94.7%, which is similar to 96.5% as published in the Report of Medical and Health Development in China, 2016.¹⁹ At present, the coverage of medical insurance in China is constantly expanding, the scope of insurance coverage and compensation ratio are constantly increasing, and

the economic burden of residents’ medical treatment is gradually reduced. Simultaneously, in order to provide better medical insurance for residents, the government is encouraging the complete development of commercial insurance as a powerful supplement to medical insurance.

With advances in multidisciplinary diagnosis and treatment of esophageal cancer, the number of patients with long-term survival has gradually increased. Surgery remains the cornerstone of comprehensive treatment, but HRQL, including physical, psychological, emotional, and social support, is greatly affected after surgery in approximately 50% patients.^{27–29} Derogar *et al.* conducted a HRQL survey in 153 patients with esophageal cancer who survived more than 5 years after surgery and found that one-third of the patients with severe postoperative com-

plications still had severe insomnia and gastroesophageal reflux during follow-up.²⁹ Donohoe *et al.* found that, after a median follow-up of 70.3 months, the HRQL related to long-term dysphagia, regurgitation, pain, and cough of patients with disease-free survival after surgery was significantly lower than pre-treatment patients and healthy people.²⁸ Most studies that reported HRQL of patients after radiotherapy in esophageal cancer had a small sample size.^{30–32} In SCOPE-1, a prospective, controlled, phase III study that compared the efficacy of dCRT ± cetuximab in esophageal cancer,³³ the functional HRQL scores decreased significantly at 14 weeks after dCRT, and most recovered at 6 months and fully recovered at 2 years.³⁴ In our study, the HRQL survey of 716 ESCC patients surviving more than 5 years showed that nearly 70% patients were still able to swallow normally or almost normally, and > 80% patients did not experience weight loss. Nearly 80% patients enjoyed life very much or quite enjoyed life at the moment. More than 85% patients felt emotionally supported by their families. Currently, no study has compared HRQL results between dCRT-based and surgery-based comprehensive treatment for esophageal cancer in large-scale randomized controlled trials. Avery *et al.*, in a small sample size study, observed reduced HRQL outcomes in patients receiving both dCRT-based and surgery-based treatments, but found that dCRT had less impact on HRQL.³⁰

Based on the goal of achieving satisfactory prognosis and improving HRQL, organ-preserving treatment such as dCRT or IC + dCRT followed by active surveillance and salvage surgery should be considered for selected ESCC patients who respond to dCRT or IC. Recently, Qian *et al.* reported that the survival rate of patients with locally advanced ESCC who achieved clinical complete response after neoadjuvant chemoradiotherapy was not significantly different from those who received neoadjuvant chemoradiotherapy plus surgery and dCRT.³⁵ Active surveillance combined with diagnostic modalities in esophageal cancer are currently being assessed in the SANO trial.³⁶

This study has limitations. First, this is a retrospective study, and some variables are not detailed in the survey (i.e., radiation dose, chemotherapy drug, or cycles). Owing to the limitation in follow-up, only a few questions that physicians believed to have the most impact on patients' HRQL were selected to form the questionnaire. Because of this selection, our findings may ignore possible impact of radiotherapy on patients in certain aspects, such as activities of daily living, cognitive state, or depression.

In conclusion, this largest, multicenter survey of HRQL and long-term survival in ESCC patients treated with definitive radiation therapy between 2015 and 2016 in China showed that most ESCC survivors who received definitive radiation therapy were satisfied with their quality of life. Advanced radiation technology (IMRT/VMAT/TOMO) resulted in significant survival benefits in ESCC patients. This study also provides a basic reference for the HRQL and survival outcomes of ESCC patients who received definitive radiation therapy after China entered the era of immunotherapy after 2018.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Ethics statement

This study was conducted in compliance with the principles of the Declaration of Helsinki and was registered at clinicaltrials.gov (NCT05194371). It was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval number: YW2021-92-1). Informed consent was waived for the study given its retrospective nature.

Data availability

The datasets are available from the corresponding author upon reasonable request.

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Author contributions

L.H.W., K.Z. and X.W. designed this study. F.L. developed the methodology. X.M.W., Y.W., D.W., Y.C., J.L., Y.Z., B.S., Y.L., D.Y., X.G., J.S., G.Y., L.W., J.Z., W.J., N.B., Z.L.Y., Q.W., Z.Y., X.S., J.C., J.Z.C., H.G., J.W., X.Z., H.J., and Y.Z. conduct and collected the study and collected the data. X.W., F.L., X.M.W., Y.W., D.W., Y.C., and J.L. analyzed and interpreted the data. X.W. and F.L. drafted manuscript. L.H.W. and K.Z. revised manuscript and all authors finally approved the manuscript.

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