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Dose escalation in radical radio(chemo)therapy for cervical and upper thoracic esophageal cancer with 3DCRT/IMRT (ChC&UES): a multicenter retrospective study

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Abstract

Background Cervical and upper thoracic esophageal cancer (ESCA) presents treatment challenges due to limited clinical evidence. This multi-center study (ChC&UES) explores radical radio(chemo)therapy efficacy and safety, especially focusing on radiation dose.

Method We retrospectively analyzed clinical data from 1,422 cases across 8 medical centers. According to the radiation dose for primary gross tumor, patients were divided into standard dose radiotherapy (SD, 50–55 Gy) or high dose (HD, > 55 Gy) radiotherapy. HD was further subdivided into conventional- high-dose group (HD-conventional, 55–63 Gy) and ultra-high-dose group (HD-ultra, ≥ 63 Gy). Primary outcome was Overall Survival (OS).

Results The median OS was 33.0 months (95% CI: 29.401–36.521) in the whole cohort. Compared with SD, HD shown significant improved survival in cervical ESCA in Kaplan-Meier ($P = 0.029$) and cox multivariate regression analysis ($P = 0.024$) while shown comparable survival in upper thoracic ESCA ($P = 0.735$). No significant difference existed between HD-conventional and HD-ultra in cervical ($P = 0.976$) and upper thoracic ($P = 0.610$) ESCA. Incidences of radiation esophagitis and pneumonia from HD were comparable to SD ($P = 0.097$, 0.240), while myosuppression risk was higher($P = 0.039$). The Bonferroni method revealed that, for both cervical and upper thoracic ESCA, HD-ultra enhance the objective response rate (ORR) compared to SD ($P < 0.05$).

Conclusion HD radiotherapy benefits cervical but not upper thoracic ESCA, while increasing bone marrow suppression risk. Further dose escalating (≥ 63 Gy) doesn't improve survival but enhances ORR.

Keywords Cervical esophageal cancer, Upper thoracic esophageal cancer, Radiotherapy, Dose-escalation, Intensity modulated radiation therapy, Three-dimensional conformal radiation therapy

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Esophageal cancer (ESCA) stands as one of the most prevalent malignancies globally, ranking 7th in terms of incidence and 6th in terms of fatality rates [1]. ESCA can be categorized into cervical and thoracic ESCA based on the primary tumor's location [2]. Cervical and upper thoracic ESCA, originating from the upper part of the esophagus, are relatively uncommon, accounting for 8.8–19.6% of all ESCA cases [3–6]. These upper ESCA are closely linked and often involve adjacent areas, distinguishing them from middle and lower thoracic ESCA in terms of both anatomy and biological behavior. Firstly, in terms of anatomy, cervical and upper thoracic ESCA's primary sites are situated above the aortic arch, and their neighboring anatomical structures and lymphatic drainage patterns share similarities [7–9]. Secondly, regarding biological behavior, squamous cell carcinoma is the predominant pathological type, while adenocarcinoma is rare. These upper ESCA tend to exhibit greater local invasiveness and lower susceptibility to distant metastasis [10, 11]. Some researchers have noted that the genetic characteristics of cervical and upper thoracic ESCA are more akin to those of head and neck malignant tumors [12, 13]. Hence, it is imperative to investigate cervical and upper thoracic ESCA as a distinct subgroup.

The optimal radiation dose for radical radiotherapy in ESCA is currently a subject of ongoing investigation. The RTOG9405 study established a standard dose of 50–50.4 Gy for radical radiation therapy in ESCA using conventional radiotherapy [14]. However, with the advancement of radiation technology, such as intensity modulated radiation therapy (IMRT) or three-dimensional conformal radiation therapy (3DCRT), which offer better conformality and allow for the delivery of higher radiation doses to the target area without causing additional toxicities [15], more and more physicians have been exploring the use of higher radiation doses to achieve improved outcomes. Recent published randomized controlled studies have indicated that the efficacy of standard radiation dose is equivalent to doses of 60 Gy or higher, even when modern radiation techniques are employed [16–18]. However, it's important to note that these studies had limited inclusion of upper thoracic ESCA, and cervical ESCA was often excluded from their data. A lot of physicians believe that higher radiation doses are more appropriate for cervical and upper thoracic ESCA. Retrospective studies have suggested that for cervical ESCA, a radiotherapy dose of 60 Gy or higher can lead to better local control and survival rates [19, 20]. Some researchers have even proposed that, given the biological behavior similarities between cervical and upper thoracic ESCA and head and neck malignancies, radiation doses of up to 66 Gy might be considered [11, 17]. However, because of the rarity of this kind of disease, these theories have not yet been confirmed through head-to-head randomized controlled trials (RCTs).

The China cervical and upper thoracic ESCA multicenter retrospective study (ChC&UES) aimed to explore the real-world efficacy of radical radio(chemo)therapy in cervical and upper thoracic ESCA with 3DCRT/IMRT, and explore the optimal radiotherapy dose and combination therapy model, which in conjunction with 8 centers, which was the largest study of the disease.

Method

Patient population and study design

This retrospective study analyzed all eligible patients diagnosed with cervical and upper thoracic ESCA from 8 medical centers (Tianjin Cancer Hospital, Cancer Hospital of the Chinese Academy of Medical Sciences, Fujian Cancer Hospital, Fudan University Shanghai Cancer Center, Shandong Cancer Hospital, Jiangsu Cancer Hospital, Jiangsu Provincial People's Hospital, and the Fourth Hospital of Hebei Medical University) in China between June 2004 and July 2016. Basic clinical information, including age, gender, ECOG score, pathological type, smoking and drinking history, radiotherapy dose, radiotherapy modality(IMRT/3DCRT), radiotherapy range, physical parameters (including gross tumor volume, lymph node volume, tumor length), concurrent chemotherapy modality, chemotherapy sequence, immunotherapy, targeted drug usage, treatment efficacy assessment, toxicity effects and survival time was collected. Randiation range was categoried into elective-field irradiation (ENI) or involved-field irradiation (IFI). ENI means radiation is delivered not only to the visible tumor but also high-risk lymphatic drainage area (generally extends from the supraclavicular region to the upper mediastinal lymph nodes). IFI means radiation is focused specifically on the visible tumor. The standard-dose (SD) group was defined as those prescribed a radiotherapy dose for primary gross tumor of ≥50 and ≤55 Gy, while high-dose (HD) group gross tumor received a prescribed dose exceeding 55 Gy. Furthermore, the HD was subdivided into conventional-high-dose group (HD-conventional, with a prescription dose of 55–63 Gy) and ultra-high-dose group (HD-ultra, with a prescribed dose of ≥63 Gy) in subgroup analysis. Clinical staging was determined using the AJCC/UICC stage classification system, 8th edition. Overall Survival (OS) was defined as the time from the start of treatment to either death or the last contact with the patient. The ChC&UES study was registered in Chictr.org.cn and conducted in accordance with the principles of Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Fourth Hospital of Hebei Medical University. Informed consent from patients was waived because of the retrospective nature of this study.

Inclusion and exclusion criteria

Inclusion Criteria.

1. Age 18 and older.
2. Confirmation of esophageal cancer through histopathology or cytology.
3. Primary tumor location within the cervical or upper thoracic segment, cervical esophageal cancer is defined as tumor with its center located 15–20 cm from the incisors through the esophagoscope. While upper thoracic esophageal cancer is defined as tumor with its center located 20–25 cm from the incisors.
4. Absence of distant metastasis.
5. Patients unable or unwilling to undergo surgical treatment for various reasons.
6. Receipt of radical radiotherapy as the first-line treatment, with or without chemotherapy, immunotherapy, or targeted therapy.
7. Undergoing conventional radiation therapy (1.8–2.0 Gy per session, once per day).
8. Receiving 3DCRT or IMRT radiotherapy.
9. Availability of complete radiotherapy prescription dose information and follow-up records.

Exclusion Criteria.

1. Receipt of radiation dose below 50 Gy.
2. History of other malignancies (except for cured cancer in situ and malignancies cured for over 5 years) or laryngeal invasion.
3. Diagnosis of double primary esophageal cancer.
4. Prior chest radiation therapy within the past 5 years.
5. Recurrent or metastatic esophageal cancer.
6. Receipt of 2D radiotherapy, large fractionation, or hyper-fractionation radiotherapy.
7. Patients with incomplete radiotherapy dose and follow-up data.

Assessment of treatment-related adverse effects and treatment efficacy

We employed the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, to assess treatment-related adverse effects during and after the course of treatment. The treatment efficacy was categorized into four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response (OR) denotes the proportion of patients whose tumors have exhibited a reduction in size for a specific duration, encompassing CR and PR cases. While Non-objective response including progressive disease (PD) and stable disease (SD).

Follow up

All enrolled patients were regularly reviewed and followed up, which mainly included hospital, telephone and online follow-up. Reexamination imaging such as ultrasound, CT or MRI and cytology were performed. The examination took place every 3 to 6 months after the completion of treatment.

Statical analysis

GraphPad Prism 9.3.1 was applied for graphs generation. SPSS 26.0 statistical software was used for statistical analysis, count data were represented by component ratio, χ^2 test or Fisher test were used for statistical analysis, and the difference in component ratio between multiple groups of data was compared by Bonferroni method. Kaplan-Meier method was used to calculate OS, survival differences were assessed using the log-rank test. Univariate analysis was conducted via Cox regression modeling, with variables demonstrating P values <0.1 being included in multivariate analysis. A significance level of two-sided $P<0.05$ was considered statistically significant.

Result

Patients characteristics

Between June 2004 and July 2016, 1,422 patients were enrolled from 8 medical centers, including the Cancer Hospital of the Chinese Academy of Medical Sciences, Tianjin Cancer Hospital, and Shandong Cancer Hospital. The median follow-up period was 31 months. Of these, 326 had cervical ESCA, and 1,096 had upper thoracic ESCA. Squamous cell carcinoma constituted 98.3%, with 3 cases of adenocarcinoma, 5 cases of small cell carcinoma, 6 cases of poorly differentiated carcinoma, and 10 cases of unidentifiable or other types. The median prescribed radiotherapy dose was 60 Gy, ranging from 50 to 70 Gy. High-dose radiotherapy was administered to 85.5% of patients (1,216), while 14.5% (206) received standard-dose radiotherapy. In cervical ESCA, 10.1% (33) received standard-dose radiotherapy, and 89.9% (293) received high-dose radiotherapy. In upper thoracic ESCA, 15.8% (173) received standard-dose radiotherapy, and 84.2% (923) received high-dose radiotherapy. The median radiation dose in the standard-dose (SD) group was 52 Gy (range: 50–55 Gy), and in the high-dose (HD) group, it was 62 Gy (range: 56–70 Gy). demographic and clinical characteristics information is provided in Table 1.

Kaplan-Meier survival analysis according to radiation dose

For entire cohort, the median OS was 33.0 months (95% CI: 29.401–36.521). The 3-year OS rate and 5-year OS rate were 47.2% and 35.3%, respectively. In the case of cervical ESCA, the median OS was 34.0 months (95% CI: 29.524–38.524), with 3-year and 5-year OS rates of 46.7% and 34.8%, respectively. For upper thoracic ESCA, the

Table 1 Clinical characteristics between standard dose (SD, 50–55 gy) group and high dose (HD, >55 gy) group

Characteristics	Total	Cervical ESCA (*N* = 326)				Upper thoracic ESCA (*N* = 1096)			
		SD (*N* = 33)	HD (*N* = 293)	χ^2	*P*	SD (*N* = 173)	HD (*N* = 923)	χ^2	*P*
Age(years)									
≤ 65	899	19	200	1.535	0.215	108	572	0.013	0.910
>65	523	14	93			65	351		
Sex									
Male	1059	28	218	1.748	0.186	130	683	0.120	0.730
Female	363	5	75			43	240		
KPS scores									
<90	768	16	166	1.997	0.158	86	500	8.116	0.004
≥ 90	523	17	105			87	314		
Unknown	131								
Smoking history									
Yes	947	22	192	0.017	0.896	118	615	0.164	0.686
No	475	11	101			55	308		
Drinking history									
Yes	863	22	180	0.345	0.557	110	551	0.920	0.382
No	559	11	113			63	372		
Clinical TNM Stage									
1–2	303	9	74	0.064	0.801	33	187	0.127	0.127
3–4	1119	24	219			140	736		
Clinical T stage									
1–2	289	8	66	0.050	0.823	31	184	0.375	0.540
3–4	1133	25	227			142	739		
Clinical N stage									
0	357	8	73	0.007	0.932	36	240	2.085	0.149
N+	1065	25	220			137	683		
Combination of chemotherapy									
YES	1187	31	267	0.299	0.585	134	755	1.793	0.181
No	235	2	26			39	168		
Chemotherapy modality									
Single-agent	223	8	50	1.529	0.216	36	129	3.403	0.065
Doublet-agent	801	17	186			94	504		
Unknown	398								
Double-agent modality									
Taxanes + Platinum	533	13	119	0.413	0.521	73	328	5.894	0.015
5-fu + Platinum	269	5	65			21	178		
Others	220								
Single-drug modality									
5-FU	129	3	11	0.356	0.551	27	88	1.835	0.176
Cisplatin	36	3	13			2	18		
Sequence of chemotherapy									
Simultaneous	1072	26	243	1.612	0.204	111	692	10.131	0.001
Concurrent	115	5	24			23	63		
Radiotherapy modality									
IMRT	1157	27	225	0.427	0.513	141	764	0.163	0.686
3DCRT	265	6	68			32	159		
Radiotherapy range									
ENI	502	11	153	2.349	0.125	57	281	1.268	0.260
IFI	611	12	86			72	441		
Unknown	309								
Gross tumor volumn (cm3)									

Table 1 (continued)

Characteristics	Total	Cervical ESCA (*N* = 326)				Upper thoracic ESCA (*N* = 1096)			
		SD (*N* = 33)	HD (*N* = 293)	χ^2	*P*	SD (*N* = 173)	HD (*N* = 923)	χ^2	*P*
≤ 33cm^3	521	8	106	1.599	0.206	70	337	0.304	0.581
>33cm^3	533	15	112			64	342		
Unknown	368								
Metastatic lymph node volumn (cm^3)									
≤ 1.25	249	5	55	0.897	0.344	20	169	0.445	0.505
>1.25	311	8	50			32	221		
Unknown	862								
Gross tumor length (cm)									
≤ 4	469	9	109	4.796	0.029	57	294	0.015	0.902
>4	605	18	116			78	393		
Unknown	348								
Utility of Nimotuzumab									
Yes	82	4	16	2.285	0.131	19	43	10.91	0.001
No	1340	29	277			154	880		
Utility of immunotherapy									
Yes	51	1	32	0.288	0.592	4	14	0.571	0.450
No	1371	5	288			169	909		
Number of chemotherapy cycles									
≤ 4	592	15	146	3.133	0.077	85	346	0.822	0.365
>4	115	0	31			13	71		
Unknown	707								
Objective response									
OR	616	12	142	3.421	0.064	60	402	3.236	0.072
Non-OR	313	11	58			44	200		
Unknown	493								

Note: ESCA: esophageal cancer; KPS: Karnofsky Performance OR: Objective response

median OS was 33.0 months (95% CI: 28.211–37.803), and the 3-year and 5-year OS rates were 47.3% and 35.5%, respectively. There was no significant difference in overall survival between cervical and upper thoracic ESCA (χ^2=1.730, *P*=0.188). In the case of cervical ESCA, the median OS was 34.000 months (95% CI: 29.542–38.458), the 3-year and 5-year OS was 47% and 35%. In HD group, the median OS in HD was 35 months (95% CI: 27.006–42.994), with 3-year and 5-year OS rates of 48.3% and 37.3%, respectively. For SD group, the median OS was 25.00 months (95% CI: 19.960–30.040), with 3-year and 5-year OS rates of 29.5% and 9.8%, respectively, there was a significant difference in survival time between HD and SD groups for cervical ESCA (χ^2=4.950, *P*=0.026). For upper thoracic ESCA, the median survival was 32 months (95% CI: 27.336–36.664), with 3-year and 5-year OS rates of 47.7% and 35.2% in HD group. In SD group, the median survival time was 33 months (95% CI: 24.852–61.151), with 3-year and 5-year survival rates of 50.6% and 37.9%, respectively. There was no significant difference in survival time between HD and SD groups for upper thoracic ESCA (χ^2=0.116, *P*=0.734), as shown in Fig. 1.

COX regression analysis for OS

Factors affecting OS in Univariate Cox regression analysis were included in multivariate analysis. Multivariate regression analysis identified independent prognostic factors for cervical ESCA, including drinking, clinical T stage, clinical N stage, combination of chemotherapy, and radiation dose (*P*=0.044,0.033,0.019,0.000,0.024, respectively). For upper thoracic ESCA, independent prognosis factors affecting OS included clinical T stage, clinical N stage, gross tumor length and the combination of chemotherapy (*P*=0.008, 0.000, 0.022, 0.033), detailed in Table 2.

Subgroup analysis for radiation dose in high dose group

Among cervical ESCA, 211 (72.01%) were in the HD-conventional group, and 82 (27.99%) were in the HD-ultra group. In the HD-conventional group, the 5-year survival rate was 41%, with a median survival time of 35 months (95% CI: 22.33–47.67). In the HD-ultra group,

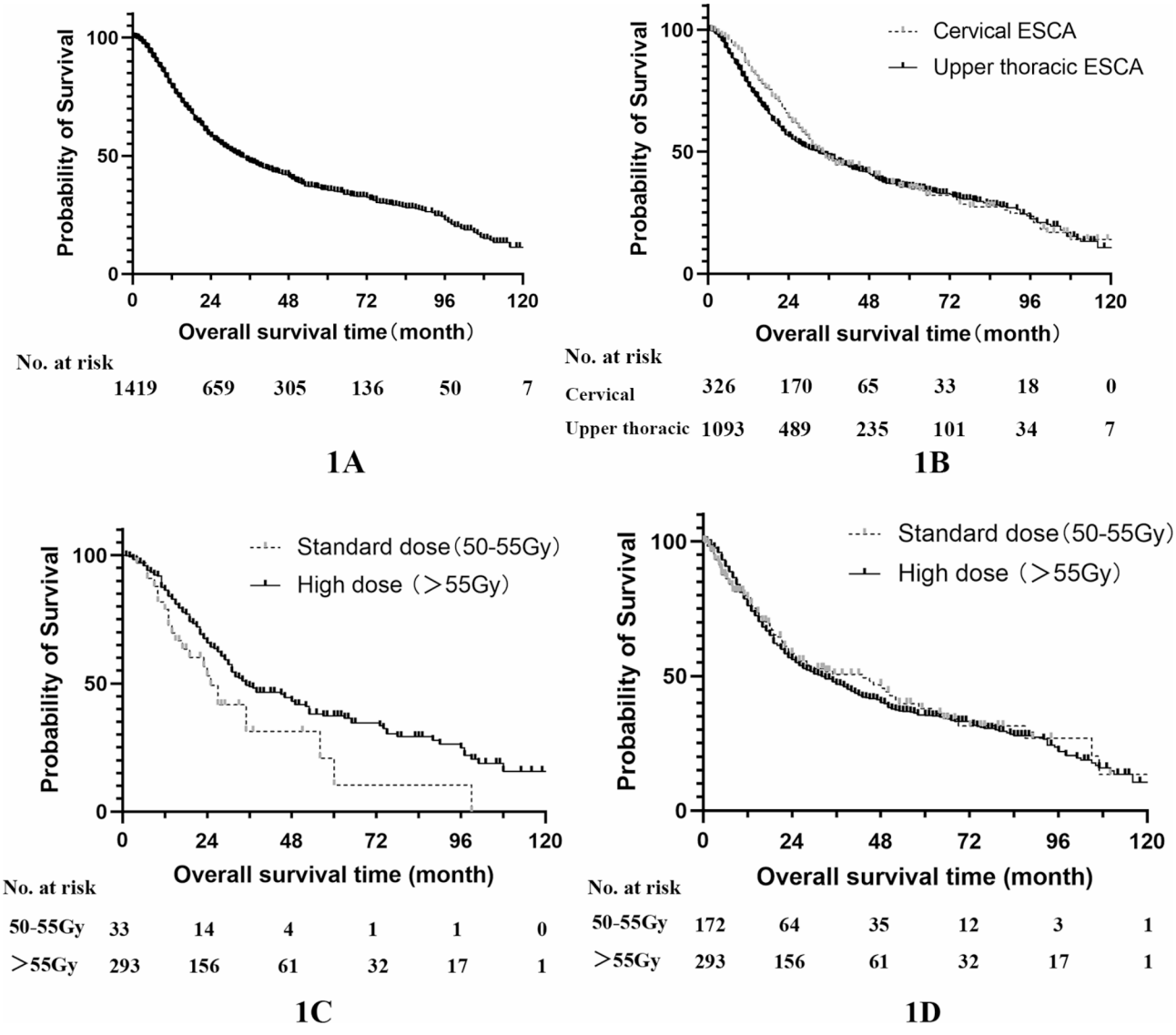

Fig. 1 The overall survival of: (**A**) the whole cohort. (**B**) cervical/upper thoracic ESCA. (**C**) standard dose(50–55 Gy)and high dose (>55 Gy) for cervical ESCA. (**D**) standard dose (50–55 Gy) and high dose (>55 Gy) for upper thoracic ESCA. ESCA: Esophageal cancer

the 5-year survival rate was 47.3%, with a median survival time of 36 months (95% CI: 25.36–46.64). No significant survival benefit was observed from HD-ultra(χ^2=0.001, P=0.976). Among upper thoracic ESCA patients, 695 (75.30%) were in the HD-conventional group. The median survival time in this group was 33 months (95% CI: 27.738–38.262), with 5-year survival rates of 34.8%. In the HD-ultra group, the median survival was 27 months (95% CI: 17.85–36.15), with a 5-year survival rate of 35.8%. No significant difference was observed in survival between the HD-conventional and HD-ultra groups for upper thoracic ESCA (χ^2=0.008, P=0.929), Fig. 2.

Treatment efficacy analysis

Out of 326 patients with cervical ESCA, 223 were assessed for efficacy, and 154 achieved an objective response, resulting in an ORR of 69.1%. Among the 1,096 patients with upper thoracic ESCA, 706 were evaluated for efficacy, and 462 showed an objective response, leading to an ORR of 65.4%.

An analysis of the ORR based on radiotherapy dose indicated that the radiotherapy dose had a significant impact on the ORR for both cervical ESCA and upper thoracic ESCA (P=0.036, 0.017). The Bonferroni method revealed that, for both cervical and upper thoracic ESCA a radiation dose≥63 Gy could enhance the ORR compared to a radiation dose≤55 Gy (P<0.05), as shown in Table 3.

Toxic effect according to radiation dose

The occurrence of radiation esophagitis was documented in 1,200 patients, with 437 (30.7%) experiencing grade

Table 2 Univariate and multivariate analysis for overall survival in ESCA

Characteristics	Cervical ESCA				Upper thoracic ESCA			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Exp (B)	*P*	Exp (B)	*P*	Exp (B)	*P*	Exp (B)	*P*
Gender (Male vs. Female)	0.345	0.854			1.239	0.165		
Age (≥ 65 vs.<65)	1.246	0.159			0.874	0.109		
KPS scores (<90 vs.≥90)	1.281	0.111			1.054	0.543		
Smoking history (Yes vs.No)	1.036	0.829			1.272	0.007		
Drinking history (Yes vs.No)	0.768	0.082	0.685	0.044	1.027	0.747		
Clinical T Stage (T1 -T2 vs. T3-T4)	1.687	0.005	1.715	0.033	1.753	0.000	1.853	0.008
Clinical N stage (N0 vs. N+)	1.507	0.018	1.656	0.019	1.595	0.000	2.581	0.000
Gross tumor volume (continuous variable)	1.006	0.041	1.004	0.181	1.003	0.035	0.107	0.996
Metastatic lymph node volume (continuous variable)	1.004	0.676			1.004	0.180		
Gross tumor length (continuous variable)	1.021	0.770			1.087	0.026	1.075	0.022
Combination of chemotherapy (Yes vs.No)	0.209	0.000	0.213	0.000	0.742	0.000	0.533	0.003
Chemotherapy modality (Single-agent vs. Doublet-agent)	0.771	0.194			0.917	0.482		
Double-agent modality (taxanes + platinum vs. 5-fu + platinum)	0.982	0.927			0.929	0.519		
Single-drug modality (5-FU vs. Cisplatin)	1.721	0.212			1.058	0.869		
Chemotherapy Sequence (Concurrent vs. Simultaneously)	0.998	0.994			1.006	0.967		
Utility of Nimotuzumab (Yes vs.No)	1.172	0.661			1.043	0.822		
Utility of immunotherapy (Yes vs.No)	1.239	0.831			0.856	0.662		
Number of chemotherapy cycles (≤ 4 vs.>4)	1.014	0.834			1.135	0.436		
Objective response (OR) (OR vs. .Non-OR)	1.537	0.019	1.243	0.251	1.264	0.021	1.232	0.237
Radiation coverage (ENI vs. IFI)	0.867	0.411			0.885	0.190		
Radiotherapy modality (IMRT vs. 3DCRT)	0.795	0.189			0.876	0.208		
Radiation dose (≤ 55 Gy vs.>55 Gy)	0.613	0.029	0.552	0.024	1.041	0.735	1.203	0.458

IMRT: intensity modulated radiation therapy; 3DCRT: Three-dimensional conformal radiation therapy; ENI: elective-field irradiation; IFI: involved-field irradiation

1 radiation esophagitis, 315 (22.2%) with grade 2 radiation esophagitis, and 87 (6.1%) with grade 3 radiation esophagitis. Myelosuppression was recorded in a total of 987 patients, while 307 (21.6%) did not experience myelosuppression. Among those with myelosuppression, 279 patients (19.6%) had degree 1 myelosuppression, 243 patients (17.1%) had degree 2 myelosuppression, and 158 patients (11.1%) had grade≥3 myelosuppression. Additionally, the occurrence of radiation pneumonia was observed in 1,152 individuals, with 73 having grade 1, 20 with grade 2, and 13 with grade≥3.

Analyze the correlation between the radiation dose and the likelihood of encountering toxic effects, the study's findings indicated that there was no significant difference in the frequency of radiation esophagitis and radiation pneumonia among the SD, HD-conventional, and

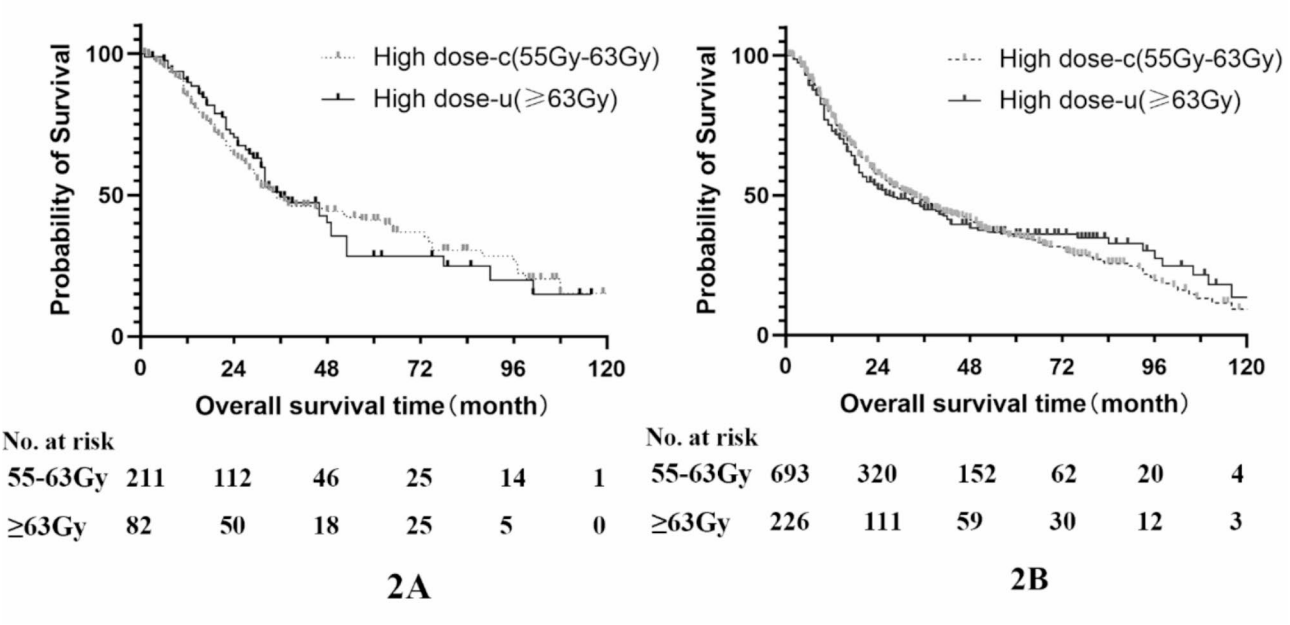

Fig. 2 The overall survival of conventional-high-dose (HD-conventional, 55–63 Gy) and ultra-high-dose (HD-ultra, ≥ 63 Gy) in cervical ESCA (**A**) and upper thoracic ESCA (**B**). ESCA: Esophageal cancer

Table 3 Treatment efficacy according to radiation dose

Treatment efficacy	SD (≤55 Gy)	HD-conventional (55–63 Gy)	HD-ultra (≥ 63 Gy)	χ^2	*P*
Cervical ESCA				6.635	0.036
ORR	50% (12) a*	68.7% (103) a, b*	79.6% (39)b*		
Non-ORR	50% (12) a*	31.3% (47) a, b*	20.4% (10)b*		
Upper thoracic ESCA				8.204	0.017
ORR	57.0% (61)a*	64.8% (302) a, b*	74.4% (99)b*		
Non-ORR	43.0% (46)a*	35.2% (164) a, b*	25.6% (34)b*		

ESCA: Esophageal cancer; SD: Standard dose; HD: High dose; OR: Objective response rate; Non-OR: Non-objective response rate

*: Each subscript letter denotes a subset of radiation dose categories whose column proportions do not differ significantly from each other at the 0.05 level

HD-ultra groups (χ^2=10.71, *P*=0.09; χ^2=7.98 *P*=0.24). However, the frequency of myelosuppression was lower in the SD group compared to the HD-conventional and HD-ultra groups (χ^2=13.25, *P*=0.04), as detailed in Table 4.

Discussion

This study gathered real-world data of radical radiotherapy for cervical and upper thoracic ESCA from 6 medical centers in China with the application of 3DCRT/IMRT, exploring the clinical efficacy of radiation dose escalation. The results showed that 3DCRT/IMRT was effective in the treatment of cervical and upper thoracic ESCA, achieving a 3-year OS rate of 47.2% and a 5-year OS rate of 35.3%. The survival outcomes for upper thoracic ESCA were slightly better than those for cervical ESCA, although the difference was not statistically significant. Notably, the 5-year survival rate in this study exceeded that reported in previous two-dimensional radiotherapy studies such as those by Bruce D et al. (3-year OS rates ranged from 25 to 33%) [14] and Shulian W et al. (5-year OS rate was 18.6%) [11], These outcomes were comparable to the data obtained from 3DCRT/IMRT studies, where the 5-year OS rate typically ranged from about 22–40% [8, 21–23]. It's worth highlighting that 78.7% of the patients in this study were diagnosed at stage 3–4, considering the advanced clinical stage of these patients, the survival results in this study were quite promising.

Notably, this study delves into the optimal radiotherapy dose for cervical and upper thoracic ESCA. While the standard radical radiation dose for ESCA is conventionally considered to be 50–50.4 Gy [14], the unique anatomical location and biological characteristics of cervical and upper thoracic ESCA may necessitate different optimal radiotherapy doses compared to other thoracic ESCA cases. Data from the National Cancer Database (NCDB) reveals that 73% of physicians tend to prescribe a radiation dose exceeding 50.4 Gy for cervical

Table 4 Toxic and side effect according to radiation dose

	SD (≤55 Gy)	HD-conventional (55–63 Gy)	HD-ultra (≥63 Gy)	χ^2	*P*
Radiation esophagitis				10.719	0.097
0 grade	58(30.5%)	285(36.4%)	94(41.2%)		
1 grade	51(26.8%)	242(30.9%)	68(29.8%)		
2 grade	65(34.2%)	199(25.4%)	51(22.4%)		
≥3 grade	16(8.4%)	56(7.2%)	15(6.6%)		
Radiation pneumonitis				7.977	0.240
0 grade	163(91.1%)	685(91.7%)	198(87.6%)		
1 grade	8(4.5%)	45(6.0%)	20(8.8%)		
2 grade	6(3.4%)	9(1.2%)	5(2.2%)		
≥3 grade	2(1.1%)	8(1.1%)	3(1.3%)		
Myelosuppression				13.249	0.039
0 grade	54(35.1%)	195(30.8%)	58(29.4%)		
1 grade	50(32.5%)	175(27.6%)	52(26.4%)		
2 grade	33(21.4%)	168(26.5%)	42(21.3%)		
≥3 grade	17(11%)	95(15%)	45(22.8%)		

SD: Standard dose; HD: High dose;

ESCA [24], whereas this percentage drops to only 34% for thoracic ESCA [25]. In Asian countries, particularly in China, there is a prevailing trend toward administering higher doses for cervical and upper thoracic ESCA [26, 27], a trend also reflected in this study, where 85.5% of physicians opt for a prescription dose≥55 Gy, with only 14.5% choosing the range of 50–55 Gy. There is a paucity of studies comparing radiotherapy doses in cervical and upper thoracic ESCA, and a dearth of prospective results. The studies conducted by Lachlan J. McDowell and Caineng Cao align with our findings, demonstrating that cervical esophageal cancer patients receiving higher radiotherapy doses (66–70 Gy) exhibited improved survival compared to those receiving conventional doses (50–54 Gy) [19, 28]. Conversely, B. De conducted a review of the National Cancer Database (NCDB) in the United States, which indicated no survival advantage with radiotherapy doses exceeding 50.4 Gy in comparison to doses within the range of 50–50.4 Gy. However, it's essential to note that the data in this particular study were relatively early, with only a small subset of patients receiving IMRT. Additionally, the baseline characteristics of the patients were not well-balanced. Notably, a more substantial proportion of patients in 50–50.4 Gy group presented with an earlier clinical stage and received chemotherapy compared to >50.4 Gy group. These imbalances may have introduced bias that obscured the impact of high-dose radiotherapy on tumor control [24]. Research for radiation dose escalation in upper thoracic ESCA was even rarer. Given the paucity of high-quality prospective evidence, we embarked on the current study, which stands as the largest investigation to address this question. Our results indicate that, for cervical ESCA, radiation dose>55 Gy outperforms 50–55 Gy, but further dose escalation >63 Gy does not confer a survival advantage. In the case of upper thoracic ESCA, survival outcomes were similar between 50 and 55 Gy and >55 Gy radiotherapy, consistent with the findings observed in the lower two-thirds of the ESCA cohort. However, it is worth noting that >55 Gy radiotherapy was associated with a better ORR. Jiaqi Zhang's research also suggests that radiation therapy with doses≥60 Gy yields a more favorable Complete Response (CR) and Partial Response (PR) rate [29], aligning with the results of our study. Nevertheless, in the context of upper thoracic ESCA, ORR did not translate into improved survival. This discrepancy may be attributed to the utilization of concurrent chemotherapy, which could potentially mask the local tumor control benefits conferred by radiotherapy.

This study collected data on the impact of different radiotherapy modalities on patients. 3DCRT and IMRTare the two most commonly used radiotherapy techniques today. Previous research has shown that IMRT can provide dosimetric advantages and improvements. These advantages allow for an increased tumor dose while protecting normal tissues [30, 31]. Some studies suggest that IMRT offers significant survival benefits over 3DCRT [32, 33], while others indicate that although IMRT trends towards improved survival, the difference is not statistically significant [34, 35]. Our study showed that the survival advantages of IMRT over 3DCRT did not reach statistical significance. Besides, compared with 3DCRT, IMRT can significantly reduce the probability of radiation pneumonia ($P=0.017$) but has no effect on the incidence of radiation esophagitis and myelosuppression ($P=0.328$, 0.153). Future studies should balance dose and physical parameters when comparing IMRT and 3DCRT for esophageal cancer.

On the other hand, there is considerable debate regarding the radiotherapy range for ESCA, specifically between

ENI and IFI. According to a recent meta-analysis that included 23 studies and 4120 patients, IFI achieved similar survival rates to ENI with significantly reduced side effects [36]. There are few studies comparing ENI and IFI specifically for cervical and upper thoracic esophageal cancer. Jianing Wang's study showed similar survival times between IFI and ENI. A subgroup analysis based on high or low radiotherapy doses (cut-off: 59.4 Gy) indicated no significant difference in OS between ENI and IFI across different dose groups [37]. Our study results indicate that IFI provides survival outcomes comparable to ENI, suggesting that IFI irradiation may be sufficient for cervical and upper thoracic esophageal cancer. Some studies have shown that some physical parameters, such as primary tumor volume, have prognostic significance for cervical and upper thoracic esophageal cancer [38, 39] Although we included several physical parameters in our study to explore their impact on prognosis, none reached statistical significance in multivariate regression analysis. However, the significant results of primary tumor volume and tumor length in univariate analysis suggest that future research should further explore the interaction between these physical parameters and other clinical variables to establish prognostic models for better diagnostic efficacy.

Chemotherapy stands as one of the most crucial non-surgical treatment modalities for ESCA. The rationale behind combining chemotherapy and radiotherapy lies in its capacity to enhance radiosensitivity through several mechanisms: Chemotherapy can effectively eliminate hypoxic cells, inhibit tumor proliferation, impede sublethal radiation damage repair, ameliorate organ blood supply, and promote reoxygenation [40]. The landmark RTOG 8501 study solidified the role of concurrent chemoradiotherapy, with the cisplatin and 5-fluorouracil (PF) regimen being widely adopted in clinical practice as a first-line recommendation [41]. In China, however, the more prevalent regimen was the combination of paclitaxel and cisplatin (TP). Our study established that the utilization of chemotherapy independently influenced the prognosis for both cervical and upper thoracic ESCA patients. Remarkably, the TP regimen was most commonly administered, which was received by 52.1% patients. Nevertheless, no significant disparity in survival benefits among various chemotherapy regimens, which aligns with the findings from Dashan Ai's research [42]. The type of chemotherapy regimen (whether single-agent or double-agent), the chemotherapy modality, and the number of chemotherapy cycles (≤ 4 or >4) did not exhibit a significant impact on OS. Prospective randomized controlled trials and multicenter retrospective analyses have consistently indicated that the efficacy of single-agent chemotherapy does not markedly differ from that of double-agent chemotherapy in the setting of concurrent chemoradiotherapy for ESCA [43, 44]. Consequently, it is suggested that single-agent chemotherapy or a reduction in the number of chemotherapy cycles may be viable options for patients with a compromised general condition who had difficulty tolerating high-intensity chemotherapy regimens.

Recently, programmed cell death protein 1 (PD-1) / programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors have been widely adopted in immunotherapy for multiple malignancies. Nituzumab is an IgG1 monoclonal antibody targeting EGFR, which is commonly applied as a substitution for cetuximab in head and neck malignancy among China, and was utilized in cervical and upper thoracic ESCA in some physicians. An increasing number of evidence indicates that immunotherapy or Nituzumab, along with concurrent chemoradiotherapy, has demonstrated both safety and efficacy in the management of unresectable ESCA [45–48]. However, this study did not observe a survival benefit associated with immunotherapy or Nituzumab when analyzed using COX univariate analysis. It is important to note that the number of patients receiving immunotherapy or Nituzumab in this study was limited, confounding factors may have existed. Therefore, expanding the sample size is warranted to establish more robust conclusions.

Most studies have shown that with advanced radiotherapy techniques, radiotherapy dose escalation does not significantly increase the probability of treatment-related side effects. Xin Sun's meta-analysis, which encompassed 10,896 ESCA patients treated with 3DCRT/IMRT, found no increased incidence of grade 3–5 radiation-induced pneumonia, radiation esophagitis, or treatment-related mortality with radiotherapy dose escalation [49]. Similarly, M. Hulshof's randomized controlled trial (RCT) study indicated that administering higher doses of radiotherapy did not increase the risk of treatment-related side effects when compared to lower doses of radiotherapy [50]. However, the results presented by Y. Xu showed a higher incidence of grade 3 and above radiation-induced pneumonia in the radiotherapy dose escalation group compared to the standard dose group (7.5% vs. 3.1%, $P=0.03$) [17]. The results of this study showed that under the condition of 3DCRT/IMRT, high dose radiotherapy did not increase the probability of toxic side effects such as radiation pneumonia and radiation esophagitis. This can be partially explained by the fact that the lung tissue within the target of cervical and upper thoracic ESCA is limited to the region above the azygos vein. As a result, the majority of the lung tissue remains outside the radiation field, and a moderate increase in gross tumor dose does not substantially raise the risk of radiation-induced pneumonia. However, our study does suggest a potential heightened risk of myelosuppression associated with high-dose radiotherapy. Therefore, it is advisable to

exercise caution when considering high-dose radiotherapy for patients with a high risk of myelosuppression during chemotherapy.

This study represents the largest investigation of radical radio(chemo)therapy employing 3DCRT/IMRT technology for cervical and upper thoracic ESCA. Given the rarity of this disease, conducting large-scale prospective studies is challenging. This study gathered extensive data from eight medical centers in China, providing a comprehensive representation of Chinese patients with cervical and upper thoracic ESCA with radical radio(chemo) therapy. The outcomes were conducted from a real-world perspective, mainly encompassing considerations of radiotherapy dose escalation, chemotherapy regimens, and associated side effects. While this study was retrospective in nature, the SD group and HD group demonstrated a basic balance in clinical and pathological baseline characteristics, enhancing the objectivity of the results to some extent.

There are, however, some limitations to be acknowledged. Only the radiation dose for the gross tumor was documented, with less detailed information regarding the delineation of target areas like lymphatic drainage regions. Late side effects, including esophageal stenosis, ulcers, and cardiovascular events, were not comprehensively documented. Additionally, due to the absence of recurrence in some patients, progression-free survival could not be analyzed. Moreover, being a retrospective study, it carries inherent potential bias risks, and the research findings would benefit from further validation through prospective studies.

Conclusion

Under the background of 3DCRT/IMRT, radical radio(chemo)therapy has demonstrated favorable efficacy and safety in the management of cervical and upper thoracic ESCA, for cervical ESCA, radiotherapy doses exceeding 55 Gy demonstrated significant survival advantages compared to the 50–50 Gy, though no survival advantage was observed in upper thoracic ESCA. A higher risk of myelosuppression was observed with elevated doses. further escalation of radiotherapy dose beyond 63 Gy didn't contribute survival but improved ORR. Combination chemotherapy significantly improved OS, no survival advantage was found with different chemotherapy regimens or prolonged chemotherapy>4 cycles.

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Data availability
Research data are stored in an institutional repository and will be shared upon request by the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Committee of the Fourth Hospital of Hebei Medical University. Informed consent from patients was waived because of the retrospective nature of this study.

Consent for publication
All authors agreed the publication of this paper.

Competing interests
The authors declare no competing interests.

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