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Results and prognostic factors of 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy for esophageal carcinoma

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The aim of this study was to summarize the outcomes and prognostic factors of 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) for esophageal carcinoma in our institute. Five hundred ninety-two patients received radiotherapy for esophageal carcinoma (123 with 3D-CRT, 469 with IMRT) from January 2002 to March 2012. Three hundred sixty patients received radiotherapy alone and 232 patients received radiotherapy and chemotherapy. The endpoints were overall survival (OS), progression-free survival (PFS). Kaplan-Meier analysis was used to calculate endpoints, the log-rank test for univariate analysis, and multivariate analysis to identify independent prognostic factors. The median follow-up time was 22.6 months and the median dose was 60 Gy. The 1-year OS, PFS were 65.3%, 52.1%; the 3-year OS, PFS were 34.0%, 28.0%; and the 5-year OS, PFS were 23.5%, 19.6%. The median OS was 20 months (95% CI: 17.9-22.1 months) and the median PFS was 14 months (95% CI: 11.8-16.2 months). Univariate analysis indicated that sex, N-stage, M-stage, TNM stage, radiotherapy dose, weight loss before treatment, smoking, and drinking affected OS and PFS ($p < 0.05$ for all). T-stage affected OS ($p = 0.042$), but no significant influence on PFS ($p = 0.101$). The independent prognostic factors for better OS and PFS were early clinical TNM stage, high radiotherapy dose, and female sex ($p < 0.05$ for all). The results of esophageal carcinoma patients treated with 3D-CRT and IMRT with or without chemotherapy were promising. Clinical TNM stage, radiotherapy dose and sex were the independent prognostic factors for OS and PFS.

Key words: esophageal carcinoma, 3-dimensional conformal radiotherapy, intensity-modulated radiotherapy, prognostic factor

There were 455784 new cases of esophageal cancer and 400156 esophageal cancer deaths world-wide in the year 2012 [1]. In the same year, there were 223306 new cases of esophageal cancer and 197472 esophageal cancer deaths in China [1]. Thus, esophageal cancer is one of the most common cancers in China and the survival rate is poor. Surgery has long been the primary treatment for early-stage esophageal cancer, but is only suitable for about 25% of patients. Radiotherapy is usually given to patients with locally advanced esophageal cancer who have inoperable disease or who refuse surgery [2]. However, the 5-year survival rate from conventional 2-dimensional (2D) radiation therapy alone is less than 10% [3-8]. Worni et al. [9] reported that the 5-year OS following definitive radiotherapy alone for treatment of esophageal carcinoma was 11.2%, and was 12.9% for stage IIA patients, 14.2% for stage IIB patients, and 9.1% for stage III patients. The reason for the poor OS after conventional 2D radiation treatment of esophageal cancer is not known, but it seems likely that the radiation dose received by the tumor target is inadequate. Multiple factors must be investigated to resolve this issue.

The development of advanced imaging technologies, such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and positron emission tomography (PET), has led to improved tumor staging and more precise irradiation field design and delivery. In particular, based on CT, 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) can provide better dosimetry, with improved tumor coverage and sparing of surrounding normal tissues. We have previously assessed the dosimetric advantages of using 3D-CRT, rather than conventional 2D radiation, for treatment of esophageal carcinoma [10]. However, further studies are

needed to confirm the efficacy of these new techniques in terms of survival.

The purpose of this study was to summarized outcomes and prognostic factors of patients diagnosed with esophageal carcinoma who were treated with 3D-CRT or IMRT in our institute over a period of 10 years.

Patients and methods

Patient selection. From January 2002 to March 2012, 592 consecutive patients who received 3D-CRT (mainly before November 2005) or IMRT (mainly after November 2005) radiotherapy for esophageal carcinoma were enrolled. All patients had new diagnoses of esophageal carcinoma at in our institute, and complete medical records of all patients were available. All patients had inoperable or unresectable disease and were ineligible for surgery. None of the patients had distant viscera metastasis. All patients gave written informed consent to accept before treatment.

Pretreatment evaluation. All patients received necessary examinations and tests before radiotherapy. These included barium swallow, CT of the chest, and abdomen, ultrasound of the neck, abdomen, liver, and kidney, head MRI, bone scintigraphy, and laboratory tests. Esophagoscopy and/or endoscopic ultrasonography have been available since April 2004. Clinical staging was according to the 2002 UICC *TNM Classification of Malignant Tumors, 6th edition* [11]. Multifocal esophageal carcinoma was considered to be the stage of the main lesion. At first the patients with locally advanced esophageal carcinoma were considered to treat with definitive chemoradiotherapy unless the patients had worse physical condition (KPS<70), more than 68 age, large volume of target, severe obstruction, double lung V20≤ 28% and refusal of concurrent chemotherapy.

Treatment. A total of 360 patients (60.8%) were treated with radiotherapy alone, and 232 patients (39.2%) were treated with combined chemotherapy and radiotherapy. The radiation treatment consisted of 3D-CRT for 123 patients (20.8%) and IMRT for 469 patients (79.2%).

All patients were given simulation CT scans (5 mm slices) while immobilized in the supine position with a thermoplastic body mask. The target was identified as previously described. [2] In particular, the gross tumor volume (GTV) was delineated according to the esophageal lesion length (based on barium swallow or endoscopy results) and tumor location was based on chest CT results. The clinical treatment volume (CTV) included the GTV with an extension of 0.5-0.8 cm in the radial directions, 3-5 cm in the superior and inferior directions, involved nodes, and elective nodal regions. The planning target volume (PTV) was 0.5 cm larger than the CTV in all dimensions. The organs at risk (OARs) included the lung, heart, and spinal cord. The planning risk volume was defined as the spinal cord plus a 5 mm margin.

Radiotherapy was delivered using 6 MV X-rays from a linear accelerator with the Pinnacle planning systems (Philips Healthcare, Madison, WI). The dose prescribed for radiotherapy alone was 60-64Gy at 95% PTV at 2Gy per fraction, once per day, five days per week. The dose prescribed for concurrent chemoradiotherapy was 56-60Gy at 95% PTV at 1.8-2.20 Gy per fraction, once per day, five days per week. Shrinking volume to primary lesion and involved lymph node could be given a boosted dose 0-10Gy according to change of lesion in the course of treatment and physical condition of patients at that time.

Radiation planning claimed prescribed dose covered 95% PTV or more. Dose homogeneity was defined as PTV receiving 93% to 107% of the prescribed dose. The dose to critical normal organs was constrained as follows: mean dose of bilateral lungs≤13Gy, V20 of the bilateral lungs≤30Gy at the time of radiotherapy alone, V20 of the bilateral lungs≤28Gy at the time of concurrent chemoradiotherapy, the spinal cord planning risk volume≤45Gy, V30 of the heart≤ 40%, V40 of the heart≤ 30%. V20, V30 and V40 was defined as the volume of organ receiving 20Gy, 30Gy and 40Gy radiation dose, respectively. Cone beam CT or portal images were performed and used daily during the first week and once per week thereafter.

5-6 weeks of weekly paclitaxel(40-45mg/m^2) of plus a platinum-based drug(cisplatin 20mg/m^2 or nedaplatin 25mg/m^2) after February 2007 or 2cycles of paclitaxel (135mg/m^2) plus a platinum-based drug (cisplatin 50 mg/m^2 or nadaplatin 50mg/m^2,21days ervery cycle) and 2 cycles of cisplatin(25-30-mg/m^2, day 3-5) plus 5-fluorouracil(450-500mg/m^2, day 1-5, continuous, 28 days every cycle) were the main chemotherapy regimen in patients given concurrent chemoradiotherapy. Three weeks of paclitaxel(175mg/m^2 d1) or docetaxel(75mg/m^2 d1) or 5-fluorouracil(800mg/m^2 d1-5) plus a platinum-based drug(cisplatin 75mg/m^2, d1 or nadaplatin 80-100mg/m^2) were the main chemotherapy regimen in patients given sequential chemotherapy and radiotherapy.

Treatment toxicity and follow-up. All patients were evaluated weekly during treatment. Acute toxicity was graded with the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring system [12]. All patients were required to be followed-up after completion of treatment: 1 month after completion of treatment, every 3 months in the first 2 years, every 6 months from the third to fifth years, and annually thereafter. At each follow-up, emphases were on evaluation the treatment related to toxicities and complete examination.

Statistical analysis. The endpoints were overall survival (OS), progression-free survival (PFS). OS was defined as the duration from the start of radiotherapy to death from any cause, date of censor, or the last follow-up. PFS was defined as the duration from the start of radiotherapy to disease recurrence or progression, death from any cause, date of censor, or date of the last follow-up. Local failure was defined as the recurrence or progression of an esophageal lesion. Regional failure included regional lymph node. Distant failure included the distant viscera and no regional lymph nodes. The Kaplan-Meier method was used to estimate endpoints, the

log-rank test was used to compare different outcomes, and Cox multivariate analysis was used for factor analysis. $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics. Table 1 shows the demographic characteristics, clinical characteristics, and radiotherapy regimens of all 592 esophageal cancer patients. 1 patient with a cervical esophageal carcinoma received 80 Gy (50 Gy as preoperative radiotherapy and 30 Gy because the patient refused surgery at 4 weeks after completion of the initial radiotherapy).

Overall survival, progression-free survival. Figure 1 shows the OS, PFS for all 592 patients. The 1-year, 3-year and 5-year OS rates were 65.3%, 34.0%, and 23.5%, respectively; the median OS was 20 months (95% CI 17.9-22.1 months).

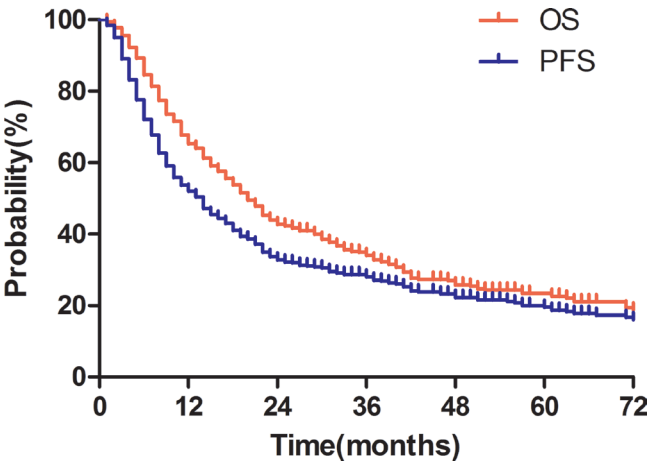

Figure 1. Overall survival, progression-free survival for the 592 patients.

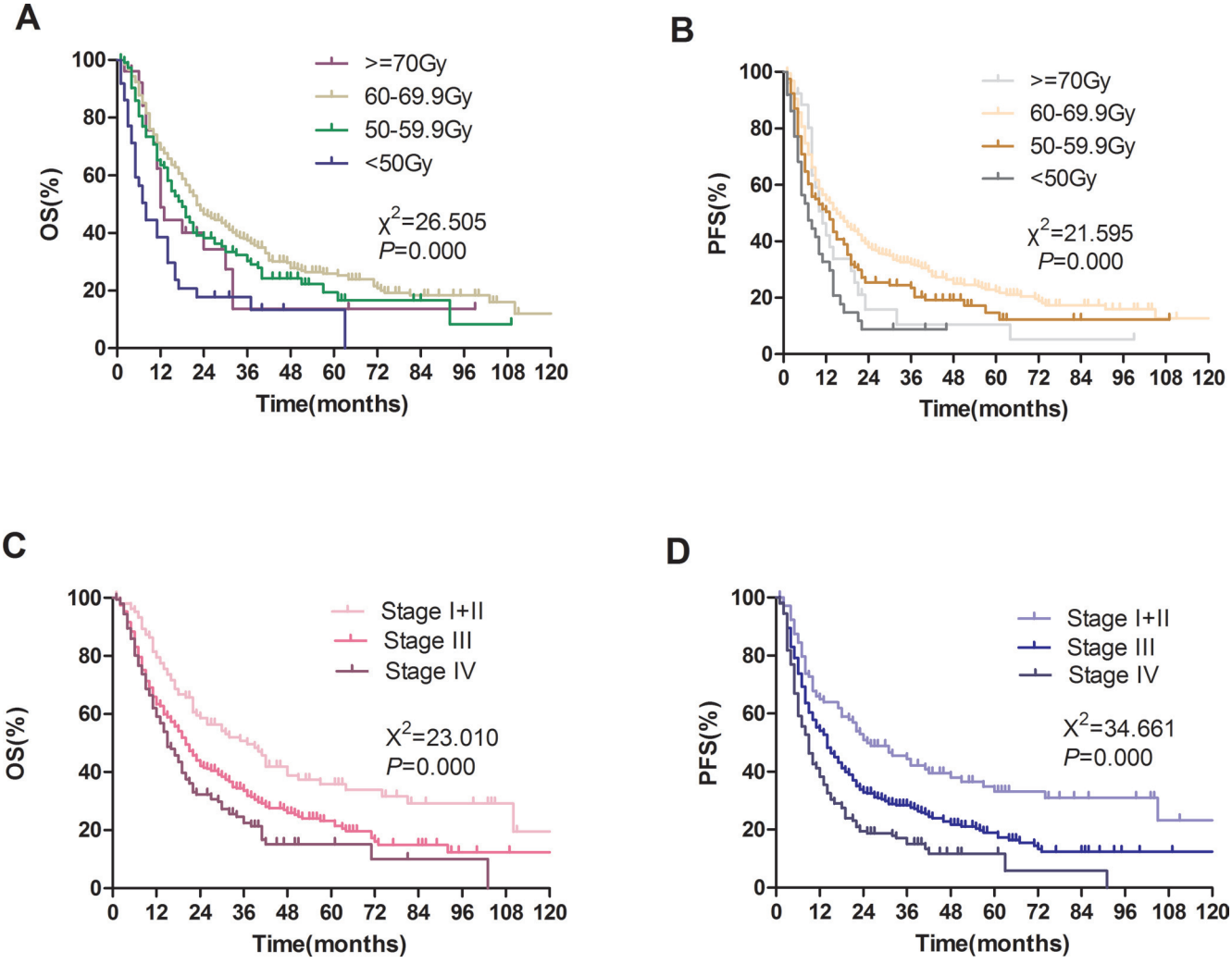

Figure 2. The influence of different radiotherapy dose and TNM stage on overall survival (A,C) and progression-free survival (B, D) rates for the 592 patients.

Table 1. Characteristics of 592 patients with esophageal carcinoma

Patient characteristics	N	%
Sex		
Male	479	80.9
Female	113	19.1
Age(y) Median 64(34-96)		
≤60	227	38.4
>60	365	61.6
Location		
Cervical	46	7.8
Upper thoracic	159	26.9
Middle thoracic	284	48.0
Lower thoracic	67	11.3
Multi-focal	36	6.1
Histology		
Squamous cell carcinoma	578	97.6
Adenocarcinoma	4	0.7
Small cell carcinoma	8	1.4
Undifferentiated carcinoma	2	0.3
Histological grading (245 cases)		
Well	35	5.9
Moderately	109	18.4
Poorly	101	17.1
Tumor length(cm)		
≤3	72	12.2
3.1-7	373	63.0
<7	147	24.8
Clinical T stage		
T1	19	3.2
T2	64	10.8
T3	243	41.0
T4	266	44.9
Clinical N stage		
N0	119	20.1
N1	473	79.9
Clinical M stage		
M0	442	74.7
M1	150	25.3
2002UICC TNM stage		
I	7	1.2
IIA	64	10.8
IIB	38	6.4
III	333	56.3
IV	150	25.3
Radiotherapy dosage(Gy)		
<50	37	6.3
50-59.9	118	19.9
60-69.9	411	69.4
≥70	26	4.4
Radiotherapy technique		
3D-CRT	123	20.8
Radiotherapy alone	94	76.4
SCR	4	3.3
CCRT	24	19.5
SC+CCR	1	0.8
IMRT	469	79.2
Radiotherapy alone	266	56.7
SCR	28	6.0
CCRT	140	29.9
SC+CCR	35	7.5
Treatment		
Radiotherapy alone	360	60.8
SCR	32	5.4
CCRT	164	27.7
SC+CCRT	36	6.1
KPS Median 80(60-90)		
<80	84	14.2
≥80	508	85.8
Smoking		
No	233	39.4
Yes	359	60.6
Drinking		
No	273	46.1
Yes	319	53.9
Weight lose before treatment		
No	380	64.2
Yes	212	35.8

UICC: the International Union Against Cancer; SC: sequential chemotherapy; CCRT: concurrent chemoradiotherapy; SCR: sequential chemotherapy and radiotherapy

The 1-year, 3-year and 5-year PFS rates were 52.1%, 28.0%, and 19.6%, respectively; the median PFS was 14 months (95% CI: 11.8-16.2 months).

Effect of radiation dose on OS, and PFS. Analysis of patients treated with different radiotherapy doses also indicated a significant effect of radiation dose on OS ($\chi^2 = 26.505$, $p < 0.001$) and PFS ($\chi^2 = 21.595$, $p < 0.001$) (Fig2. A,B). Except for patients who received 70 Gy or more (n = 26, 4.4%), increasing dose was associated OS and PFS.

Influence of TNM stage on OS and PFS. Patients with stage I/II cancer had significantly better 1-year, 3-year and 5-year OS and PFS than those with stage III cancer or stage IV cancer (OS for stage I/II *vs.* III: $\chi^2 = 23.010$, $p < 0.001$; OS for stage I/II *vs.* IV: $\chi^2 = 34.661$, $p < 0.001$) (Fig2. C,D).

Univariate and multivariate analysis of factors that affected OS and PFS. We evaluated the value of various potential prognostic factors include age, sex, lesion location, histological grading, tumor length, T stage, N stage, M stage, TNM stage, radiotherapy dose, radiotherapy technique, CCRT, KPS, smoking, drinking and weight lose on predicting OS and PFS. The results are shown in Table 2, 3. For radiotherapy technique (3D-CRT or IMRT) and CCRT had no effect on outcomes in this analysis, we compared the characteristics of patients in these two groups. The results indicated that prognostic factors on OS and PFS include N stage, M stage, TNM stage and radiotherapy dose had significantly statistical difference in 3D-CRT group and IMRT group. The same results were observed in radiotherapy alone group and CCRT group, in addition to radiotherapy dose without difference. Table 4, 5 show the details.

Toxicities. The most frequently acute toxicities were mainly Grade 1 or Grade 2. 76 patients (12.8%) had Grade 3

Table 2. Univariate analysis for overall survival (OS) and progression-free survival (PFS) in 592 patients with esophageal carcinoma treated with 3D-CRT/IMRT

Factors	5y-OS			5y-PFS		
	%	HR(95% CI)	*p*	%	HR(95% CI)	*p*
Sex						
Male	21.3	-	-	16.5	-	-
Female	32.7	0.65(0.50-0.85)	0.002	20.2	0.62(0.48-0.80)	0.000
Age(y)						
≤60	22.3	-	-	18.3	-	-
>60	24.4	0.08(0.69-1.02)	0.084	20.6	0.82(0.67-0.99)	0.040
Location			0.260			0.482
Cervical	19.3	-	-	20.8	-	-
Upper thoracic	25.3	0.98(0.67-1.45)	0.929	21.3	0.98(0.67-1.43)	0.912
Middle thoracic	25.5	0.91(0.63-1.31)	0.601	21.3	0.95(0.66-1.36)	0.790
Lower thoracic	16.8	1.26(0.82-1.95)	0.291	15.4	1.21(0.79-1.85)	0.379
Multi-foca	15.6	1.16(0.70-1.91)	0.574	-	1.20(0.73-1.95)	0.472
HG (245 cases)						
G1,2	24.1	-	-	21.5	-	-
G3	22.3	1.07(0.79-1.45	0.681	18.5	1.12(0.83-1.51)	0.462
Tumor length(cm)			0.387			0.549
≤3	24.5	-	-	21.4	-	-
3.1-7	24.3	0.94(0.70-1.27)	0.693	19.3	1.01(0.76-1.35)	0.946
>7	20.5	11.11(0.80-1.5)	0.544	19.3	1.14(0.82-1.58)	0.434
Clinical T stage			0.042			0.101
T1	55.6	-	-	46.3	-	-
T2	20.0	2.12(1.04-4.35)	0.040	17.5	1.89(0.95-3.75)	0.069
T3	24.1	2.10(1.07-4.10)	0.031	20.4	1.91(1.01-3.62)	0.046
T4	20.9	2.45(1.26-4.80)	0.009	17.3	2.14(1.14-4.05)	0.019
Clinical N stage						
N0	35.9	-	-	31.8	-	-
N1	20.3	1.61(1.25-2.09)	0.000	16.3	1.63(1.27-2.09)	0.000
Clinical M stage						
M0	19.8	-	-	22.4	-	-
M1	15.2	1.47(1.18-1.83)	0.001	11.8	1.65(1.34-2.04)	0.000
2002 UICC TNM stage			0.000			0.000
I+II	35.8	-	-	33.1	-	-
III	23.1	1.61(1.22-2.13)	0.001	18.9	1.62(1.23-2.13)	0.001
IV	15.2	2.10(1.54-2.87)	0.000	11.8	2.38(1.76-3.23)	0.000
Radiotherapy dosage(Gy)			0.000			0.000
<50	13.4	-	-	-	-	-
50-59.9	19.5	0.50(0.33-0.75)	0.001	14.8	0.61(0.40-0.91)	0.016
60-69.9	25.9	0.40(0.27-0.58)	0.000	22.4	0.47(0.32-0.68)	0.000
≥70	13.7	0.55(0.31-0.99)	0.047	10.6	0.66(0.38-1.14)	0.135
Radiotherapy technique						
3D-CRT	26.5	-	-	20.5	-	-
IMRT	22.6	1.11(0.87-1.43)	0.932	19.3	1.09(0.86-1.38)	0.473
Treatment			0.953			0.484
Radiotherapy alone	22.4	-	-	18.2	-	-
SCR	27.5	1.12(0.72-1.73)	0.619	22.8	1.26(0.83-1.91)	0.287
CCRT	26.3	0.99(0.80-1.25)	0.977	24.9	1.05(0.85-1.30)	0.649
SC+CCRT	23.2	1.07(0.70-1.62)	0.768	15.5	1.28(0.87-1.89)	0.217
KPS						
<80	19.5	-	-	16.5	-	-
≥80	24.4	0.87(0.67-1.14)	0.306	20.2	0.91(0.70-1.18)	0.470
Drinking						
No	24.2	-	-	21.8	-	-
Yes	22.6	1.42(1.17-1.73)	0.000	17.7	1.42(1.17-1.71)	0.000
Smoking						
No	23.3	-	-	21.7	-	-
Yes	23.0	1.31(1.07-1.60)	0.009	18.0	1.32(1.09-1.60)	0.005
Weight lose before treatment						
No	25.1	-	-	20.5	-	-
Yes	21.0	1.26(1.03-1.54)	0.024	18.3	1.25(1.03-1.51)	0.026

3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; HR: hazard ratio; UICC: the International Union Against Cancer. HG: histological grading; SC: sequential chemotherapy; CCRT: concurrent chemoradiotherapy; SCR: sequential chemotherapy and radiotherapy

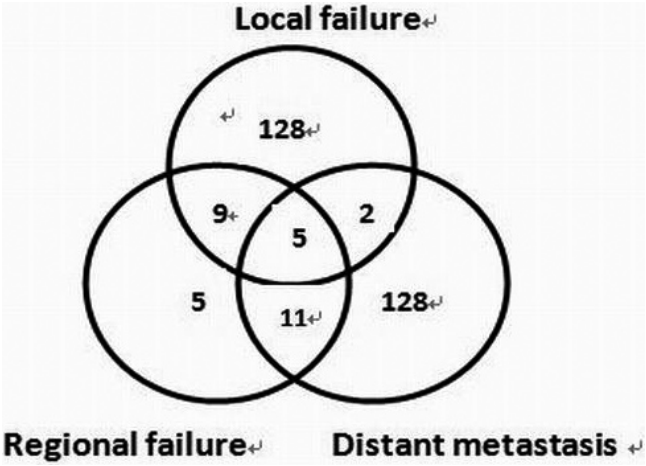

Figure 3. Failure patterns in 311 patients with esophageal carcinoma treated with 3D-CRT/IMRT

esophagitis, and 9 patients (1.5%) had Grade 4 esophagitis. In addition, 17 patients (2.9%) had grade 3 pneumonitis, and no patients had grade 4 pneumonitis. Grade 3/4 leukopenia, hemoglobin deficiency and thrombocytopenia were 5.1/0.2%, 0.7/0.2%, 1.9/0.7%, respectively. 30 patients developed esophageal stricture in which 7 patients required intervention (esophageal dilation, gastrostomy, insertion of enteral feeding tube).

Follow-up and failure patterns. The last follow-up was in Jan 2014. Follow-ups were available for 535 cases (90.4%), with a duration range of 0.9 to 135 months (median: 22.6 months). At the last follow-up, 117 patients were alive and without disease and 8 patients were alive with disease.

At last follow-up, treatments failure occurred in 311 patients (52.5%). 167, 30 and 169 patients had developed local failure (28.2%), regional failure (5.1%) and distant metastasis (28.5%), respectively. Distant metastasis included distant lymph node metastasis in 29 patients and hematogenous metastasis in 140 patients, from which 58 patients with lung metastasis were seen most frequently. The details of failure patterns were shown in Figure 3. The main failure pattern was local failure, followed by hematogenous metastasis.

Discussion

Radiotherapy is one of the main treatments for locally advanced esophageal cancer, but the 5-year survival rate is less than 10% for conventional 2D radiotherapy. Previous research reported that the target volume often does not cover the entire esophageal lesion with conventional 2D radiotherapy, because 82% of lesions had asymmetric infiltrating growths of different sizes, leading to low-dose regions within the tumor [13-15]. Xiao et al. [10] reported that the GTV and CTV covered by prescription dose (D_T of 60 Gy) were 37% and 27% for conventional 2D radiotherapy. However, 3D-CRT and IMRT use CT-based simulation to more accurately localize all lesions of the esophagus and involved lymph nodes. With these newer methods, 95% of the PTV is covered by the prescription dose, the radiation has a more even distribution within the tumor volume, and normal tissues are spared [10].

It seems likely that the improved dosimetry provided by IMRT and 3D-CRT could improve the OS and PFS of patients with locally advanced esophageal carcinoma. Our analysis of all 592 patients indicated that the 5-year OS and PFS were 23.5% and 19.6% respectively, and the median OS and PFS were 20 months and 14 months, respectively.

Table 3. Multivariate analysis for overall survival (OS) and progression-free survival (PFS) in 592 patients with esophageal cancer treated with 3D-CRT/IMRT

Factors	N	OS		PFS	
		HR(95% CI)	*p* value	HR(95% CI)	*p* value
Sex					
Male	479	-	-	-	-
Female	113	0.728(0.541-0.980)	0.036	0.723(0.543-0.964)	0.027
2002 UICC TNM stage			0.000		0.000
I+II	109	-	-	-	-
III	333	1.499(1.131-1.986)	0.005	1.531(1.163-2.016)	0.002
IV	150	1.943(1.419-2.662)	0.000	2.188(1.609-2.975)	0.000
Radiotherapy dosage(Gy)			0.000		0.001
<50	37	-	-	-	-
50-59.9	118	0.49 (0.324-0.750)	0.001	0.599(0.397-0.903)	0.014
60-69.9	411	0.41 (0.286-0.614)	0.000	0.087(0.334-0.709)	0.000
>=70	26	0.55 (0.309-1.002)	0.051	0.647(0.373-1.122)	0.121
Drinking					
No	273	-	-	-	-
Yes	319	1.226(0.982-1.530)	0.072	1.210(0.977-1.499)	0.081

3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; HR: hazard ratio; UICC: the International Union Against Cancer.

Our OS rates for IMRT and 3D-CRT are better than reported previously (5-year OS less than 10%) [3-8]. Dirix et al. [16-17] confirmed that IMRT and 3D-CRT improved the survival of patients with head-and-neck cancer due to improved dosimetry. Other studies reported better OS from IMRT and 3D-CRT than conventional 2D radiotherapy for treatment of esophageal cancer, regardless of survival rate and normal tissue sparing [18-21]. In particular, Kong et al. reported that the 5-year OS was 28% for patients treated with 3D-CRT and IMRT [21], similar to our results even though the patients with M1-stage (no hematogenous metastasis) were included. However, Lin SH et al [22] reported that the median survival time was 25.2 months for 3D-CRT and 43.2 months for IMRT, and that the 5-year OS was 34% for 3D-CRT and 44% for IMRT, better than achieved in our patients. The better results in the Lin et al. study may be explained by their enrollment of more patients with early-stage cancer (stage II: 34.6%, n = 234; stage IV: 7.7%, n = 52), and their exclusion of patients who received previous palliative RT or RT alone without chemotherapy. Our study included patients with more advanced cancer (stage III: 56.3%, n = 333; stage IV: 25.3%, n = 150) and patients who received palliative RT. Taken together with these previous studies, IMRT and 3D-CRT are more effective than conventional 2D radiotherapy for treatment of esophageal carcinoma, most likely because these new radiation modalities more effectively irradiate the target volume covered by the prescribed dose.

There is limited understanding of the prognostic factors associated with survival from esophageal carcinoma after treatment with 3D-CRT or IMRT. Our study showed that large radiotherapy dose, early clinical stage, and female sex were independent predictors of improved OS and PFS. In the domestic, prescribed dose was at least 60Gy, 56Gy for lesion at radiotherapy alone or concurrent chemoradiotherapy, respectively, which is different to the European and American countries. RTOG 94-05 indicated than higher radiation dose (64.8Gy verse 50.4Gy) did not increase the survival [23]. However, many previous studies indicated that the radiotherapy dose impacted the survival of the patients with esophageal cancer who were treated with conventional 2D radiotherapy, 3D-CRT, or IMRT [24-28]. Ohtake et al reported that 5-year survival rate in 124 curative cases given a dose more than 50Gy and combination with chemotherapy was 12.9%. The cases in the 5-year survivors were irradiated with ≥ 60Gy dose and the tumors showed a high response to irradiation [24]. The study from Sun et al indicated that an association between a higher radiation dose (60-69Gy verse 50-59Gy) and improved 5-year survival (10.6% vs.2%) at the patients with esophageal carcinoma treated with radiotherapy alone [34]. The efficacy and prognostic factors of definitive chemoradiotherapy for inoperable esophageal cancer were reported by Semrau et al. [27]. Radiation dose significantly correlated with OS/PFS in the univariate analysis. Moreover, multivariate analysis revealed radiation dose was an independent prognostic factor. Compared with patients receiving only 40-59.9Gy, patients

Table 4. Comparision of the characteristics of patients treated with 3D-CRT and IMRT

Factors	3D-CRT n(%)	IMRT n(%)	χ^2	*p*
N	123	469		
Sex				
Male	92(74.8)	387(82.5)	3.760	0.053
Female	31(25.2)	82(17.5)		
Age(y)				
≤60	32(26.0)	195(41.6)	9.981	0.002
>60	91(74.0)	274(58.4)		
Location				
Cervical	9(7.3)	37(7.9)	3.012	0.556
Upper thoracic	31(25.2)	128(27.3)		
Middle thoracic	65(52.8)	219(46.7)		
Lower thoracic	14(11.4)	53(11.3)		
Multi-foca	4(3.3)	32(6.8)		
HG (245 cases)				
G1,2	33(64.7)	111(57.2)	0.935	0.334
G3	18(35.3)	83(42.8)		
Tumor length(cm)				
≤3	17(13.8)	55(11.7)	0.454	0.797
3.1-7	77(62.6)	296(63.1)		
>7	29(23.6)	118(25.2)		
Clinical T stage				
T1	1(0.8)	18(3.8)	4.865	0.182
T2	16(13.0)	48(10.2)		
T3	56(45.5)	187(39.9)		
T4	50(40.7)	216(46.1)		
Clinical N stage				
N0	48(39.0)	71(15.1)	34.616	0.000
N1	75(61.0)	398(84.9)		
Clinical M stage				
M0	105(85.4)	337(71.9)	9.403	0.002
M1	18(14.6)	132(28.1)		
2002 UICC TNM stage				
I+II	38(30.9)	71(15.1)	20.245	0.000
III	67(54.5)	266(56.7)		
IV	18(14.6)	132(28.1)		
Radiotherapy dosage(Gy)				
<50	9(7.3)	28(6.0)	17.476	0.001
50-59.9	13(10.6)	105(22.4)		
60-69.9	89(72.4)	322(68.7)		
≥70	12(9.8)	14(3.0)		
Treatment				
Radiotherapy alone	94(79.4)	266(65.5)	8.506	0.004
CCRT	24(20.3)	140(34.5)		
KPS				
<80	28(22.8)	56(11.9)	9.376	0.002
≥80	95(77.2)	413(88.1)		
Drinking				
No	65(52.8)	208(44.3)	2.830	0.092
Yes	58(47.2)	261(55.7)		
Smoking				
No	48(39.0)	185(39.4)	0.007	0.932
Yes	75(61.0)	284(60.6)		
Weight lose before treatment				
No	89(72.4)	291(62.0)	4.507	0.034
Yes	34(27.6)	178(38.0)		

Table 5. Comparision of the characteristics of patients treated with radiotherapy alone and concurrent chemoradiotherapy

Factors	RA n(%)	CCRT n(%)	χ^2	*p*
n	360	164		
Sex				
Male	281(78.1)	139(84.8)	3.180	0.075
Female	79(21.9)	25(15.2)		
Age(y)				
≤60	86(23.9)	95(57.9)	57.734	0.000
>60	274(76.1)	69(42.1)		
Location				
Cervical	20(5.6)	23(14.0)	16.540	0.002
Upper thoracic	99(27.5)	40(24.4)		
Middle thoracic	184(51.1)	72(43.9)		
Lower thoracic	41(11.4)	14(8.5)		
Multi-foca	16(4.4)	15(9.1)		
HG (245 cases)				
G1,2	95(63.3)	37(56.1)	1.020	0.313
G3	55(36.7)	29(43.9)		
Tumor length(cm)				
≤3	39(10.8)	19(11.6)	0.099	0.952
3.1-7	232(64.4)	106(64.6)		
>7	89(24.7)	39(23.8)		
Clinical T stage				
T1	10(2.8)	4(2.4))	2.712	0.438
T2	42(11.7)	12(7.3)		
T3	150(41.7)	68(41.5)		
T4	158(43.9)	80(48.8)		
Clinical N stage				
N0	92(25.6)	23(14.0)	8.746	0.003
N1	268(74.4)	141(86.0)		
Clinical M stage				
M0	289(80.3)	115(70.1)	6.582	0.010
M1	71(19.7)	49(29.9)		
2002 UICC TNM stage				
I+II	82(22.8)	18(11.0)	13.351	0.001
III	207(57.5)	97(59.1)		
IV	71(19.7)	49(29.9)		
Radiotherapy dosage(Gy)				
<50	22(6.1)	12(7.3)	0.722	0.868
50-59.9	68(18.9)	32(19.5)		
60-69.9	252(70.0)	114(69.5)		
≥70	18(5.0)	6(3.7)		
Treatment				
3D-CRT	94(26.1)	24(14.6)	8.506	0.004
IMRT	266(73.9)	140(85.4)		
KPS				
<80	67(18.6)	11(6.7)	12.601	0.000
≥80	293(81.4)	153(93.3)		
Drinking				
No	183(50.8)	64(39.0)	6.306	0.012
Yes	177(49.2)	100(61.0)		
Smoking				
No	157(43.6)	54(32.9)	5.347	0.021
Yes	203(56.4)	110(67.1)		
Weight lose before treatment				
No	235(65.3)	102(62.2)	0.467	0.495
Yes	125(34.7)	62(37.8)		

who received ≥60Gy had a significantly higher 2-year OS (26.8% vs 7.5%, p=0.0001). PFS also was significantly higher in the group ≥60Gy (17.4% vs. 5.0%, p=0.0001). Our univariate and multivariate analyses showed that radiotherapy dose was an important prognostic factor for OS, PFS. In particular, patients who received a dose of 60-69.9 Gy had better 5-yr OS and PFS than patients who received 50-59.9 Gy, 70 Gy or more, and less than 50 Gy (OS: $\chi^2 = 26.505$, $p < 0.001$; PFS: $\chi^2 = 21.595$, $p < 0.001$).

Second, our univariate and multivariate analyses indicated that the 2002 UICC/TNM stage was the most important factor in determining OS and PFS. In particular, patients with stage N0 and M0 had better OS and PFS than patients with stage N1 and M1. T stage influenced OS and PFS, but OS of different T stage had significant statistically difference, PFS of T stage was opposite. Patients with stage T2, T3, and T4 had similar OS and PFS, perhaps because of the superior tumor coverage provided by 3D-CRT and IMRT which could make the lesions of different T stage received enough prescribed radiation dose. Then the chance of different T stage on local failure, regional and distant lymph lode metastasis and hematogenous metastasis was reduced. Similar results were reported in a study of patients with nasopharyngeal carcinoma who were treated by IMRT [29]. These results suggest a common underlying pathogenesis for esophageal squamous cell carcinoma (ESCC) and head and neck squamous cell carcinoma (HNSCC) [30]. Our patients with stage I and II cancer had significantly better OS and PFS than those with stage III and IV cancer. For potentially resectable patients with stage III cancer who underwent 3D-CRT or IMRT in this study, the 5-year OS was 23.1%; this is similar to 5-year OS (~20%) for patients with stage III who were treated with surgery [31]. However, surgery is associated with postoperative morbidities. The most frequent adverse events after surgery were cardiopulmonary complications (30%) and anastomotic leakage (6%) [32]. In addition, the present study found that the 5-year OS of patients with stage IV cancer (no hematogenous metastasis) was 15.2%, which is quite promising. Most importantly, we showed that the 2002 UICC/TNM stage predicted prognosis for esophageal cancer in patients who were not given surgery. This is accordance with our previous study [33].

Finally, our results indicated that female sex was independently associated with better OS and PFS, similar to a previous study [34].Previous research [30] also indicated that the risk of esophageal squamous cell carcinoma correlated with alcohol consumption and that drinking was a prognostic factor for OS in univariate ($p = 0.010$) and multivariate analyses ($p = 0.037$). This is also in agreement with our results. Our univariate analysis indicated that drinking was negatively associated with OS ($p < 0.001$) and PFS ($p < 0.001$), and our multivariate analysis showed a tendency for negative associations of drinking with OS ($p = 0.072$) and PFS ($p = 0.081$). Lin et al reported significantly improved OS in IMRT compared with 3D-CRT esophageal cancer patients with inverse probability

weighted-adjusted method [22]. The median survival time was 25.2 months for 3D-CRT vs 43.2 months for IMRT and 5-year OS rate was 34% for 3D-CRT and 44% for IMRT. However, no statistically significant difference between the 2 groups was found when researchers analyzed the inverse probability of treatment weighted (IPW)-adjusted cancer-specific survival. In opposite with this study, we observed that 5-year OS/PFS of 3D-CRT (26.5%/20.5%) was more than IMRT (22.6%/19.3%) although with no significant statistically difference. In order to exclude the potential selection bias, we compared the characteristics of patients in the 2 groups. Statistically significant differences in the distribution of N stage, M stage, TNM stage, with or without radiotherapy dose on OS and PFS were observed in two groups. More advanced stage patients were observed in IMRT group, which influenced the efficacy of IMRT. We also observed more advanced stage patients distributed in CCRT group, perhaps which affected the outcomes of CCRT with slight improvement of OS/PFS without statistically significant differences. However, RTOG 8501 reported that combination of chemotherapy and radiotherapy group had a significantly better 5-year OS (26%) than radiotherapy alone (0%) [35]. This study showed combination of chemotherapy and radiotherapy treatment whether sequential chemotherapy, concurrent chemoradiotherapy or sequential chemotherapy and concurrent chemoradiotherapy had not statistical difference on OS and PFS comparing with radiotherapy alone or each other (OS: p=0.953; PFS: p=0.484). Chemotherapy theoretically enhances the effect of radiation and reduces the risk of distant metastatic diseases by eradication of micrometastases. However, selective bias existed in this prospective study and sequential chemotherapy group, sequential chemotherapy and concurrent chemoradiotherapy group included small numbers of patients. Then further research is needed for comparing the efficacy of 3D-CRT and IMRT or various combination of chemotherapy and radiotherapy for esophageal carcinoma with prospective study.

Our results showed that nearly all patients had acceptable tolerance of 3D-CRT and IMRT with or without chemotherapy. The most common acute toxicities were esophagitis, pneumonitis, and myelosuppression. The cases of acute esophagitis (grade 3: 12.8%, grade 4: 1.5%) and pneumonitis (grade 3: 2.9%, grade 4: 0%) could be handled easily. It seems likely that this favorable toxicity profile can be explained by the sparing of normal tissue, such as the esophagus and lung, due to the use of IMRT and 3D-CRT. In this study, most patients (60.8%) received radiotherapy alone, and 39.2% received chemotherapy and radiotherapy. Thus, some of the reported toxicities may also be attributable to chemotherapy. In addition, local failure and distant metastasis were mainly failure pattern. More efforts such as improved radiotherapy technique and radiotherapy combination with more effective chemotherapy drugs need to be done to control the disease of esophageal carcinoma.

In conclusion, the results of this study of nonsurgical patients with esophageal carcinoma who underwent 3D-CRT or IMRT with or without chemotherapy were promising and provided radiation treatments were well-tolerated. Furthermore, clinical TNM stage, radiotherapy dose and sex showed to be the independent prognostic factors for OS and PFS.

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