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Comparison and Prognostic Analysis of Elective Nodal Irradiation Using Definitive Radiotherapy versus Chemoradiotherapy for Treatment of Esophageal Cancer

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ABSTRACT

Objective: To investigate the prognostic factors for esophageal cancer (EC) patients treated by elective nodal irradiation (ENI) using chemo radiotherapy (CRT) and radiotherapy (RT)-alone.

Methods: Data from 340 patients with EC were randomized to receive RT-alone or CRT between January 2008 and December 2012. All patients received ENI either with late course RT or simultaneous integrated boost (SIB) - Intensity Modulated Radiotherapy (IMRT). The impact of clinic pathological factors and treatment modality on the overall survival (OS), and progression-free survival (PFS) were analyzed using Log-rank test, Cox proportional regression model, and propensity score matching (PSM). $P<0.05$ was considered statistically significant.

Results: A total of 340 patients were included, 174 patients (51.2%) underwent RT- alone and 166 patients (48.8%) received CRT. After the PSM, the median OS and median PFS times were 37.3 and 13.0 months for the RT–group, while those of the CRT-group were 39.0 and 16.2 months, respectively. The 5-year OS rates was 32.9% for the RT-group, while those of the CRT-group was 31.3%, respectively ($\chi2=0.002$, $p=0.961$). The 5-year PFS rate was 7.8% for the RT - group whereas, those of the CRT- group was 22.9%, respectively ($\chi2=3.911$, $p=0.048$). Subgroup analysis showed that, late-course RT was significantly associated with improve PFS in CRT – group for patients within ≤ 60 years, female gender with cT3-4, N0- status, cTNM- stage III-IV, T- length> 5 cm, SCC subtype, GTV volume >30 cm3, ($p<0.05$ for all analysis).

Conclusion: Compared with RT- alone, ENI using CRT and late- course RT provides a PFS benefit to EC patients, especially in those within ≤ 60 years old, cT3-4, N0- status, cTNM- stage III-IV, SCC subtype, T- length >5 cm, and GTV- volume >30 cm3 but it did not improve OS. Therefore, this finding could be of a particularly important pathway to the stratification parameters for a personalized treatment.

Abbreviations: CRT: Chemo Radiotherapy; CTV: Clinical Target Volume; EC: Esophageal Cancer; ENI: Elective Nodal Irradiation; GTV: Gross Volume Tumor; GTV-nd: Gross Volume Tumor- Nodes; OS: Overall Survival; PFS: Progression-Free Survival; PSM: Propensity Score Matching; PTV: Planning Target Volume; RT: Radiotherapy; SIB-IMRT: Simultaneous Integrated Boost - Intensity Modulated Radiotherapy; TNM: Tumors Nodes Metastasis.

INTRODUCTION

Esophageal cancer (EC) is a major cause of cancer morbidity and mortality throughout the world. In China, there were an estimated 477,900 new cases and, despite notable technical advances in diagnosis and treatment, 375,000 deaths occurred due to EC in 2015 [1]. Although the overall prognosis of patients has been improved among digestive cancers, the 5-year overall survival (OS) remains dismal about 10-20% [2,3]. Evidence indicates that surgery significantly improves survival in patients with

early-stage EC. While in advanced forms, its role becomes limited to palliative indications for patients comfort rather than the survival improvement [4]. As in surgery, chemoradiotherapy (CRT) has been well established as a standard approach to treat EC [3,4]. However, the two treatments methods are often limited because of patients' poor general conditions, advanced age or comorbidities. In this clinical situation, definitive radiotherapy (RT) - alone remains the only curative treatment option. In contrast, the 5-year OS rates after RT-alone has been usually associated with disappointing (OS range: 0% to 20%) [5]. However, the main concern today is three-fold. First, the definition of the target volume for the primary lesion. Second, the target volume delineation for the lymph nodes. Three, the optimal radiation therapy dose prescription. Recently, some researchers favorable to an elective node irradiation (ENI) claim their position, in addition to the high risk of micro metastatic invasion of the regional nodes at diagnosis, on the high frequency of relapses in the non-irradiated lymph node zones [6-9]. Studies from the radiotherapy-oncology group (RTOG 85-01/94-05) suggested that a combination of CRT and ENI might reduce the locoregional relapse rate in conventional fractionation compared with RT-alone [5,6]. In contrast, substantial late toxicities with the concomitant combination of chemotherapy may alleviate its benefits of quality of life and on the patient survival [5,6-11]. Therefore, the decision for ENI using CRT should depend on the primary tumor volume, clinical TNM- stage and tumor localization. Nowadays, there is no clear consensus regarding whether ENI should be required as a standard in the curative treatment for EC. For instance, the target volume delineation at the author's institution is defined according to the habits and experience of the physician. In this setting, we sought to retrospectively analyze the clinicopathological characteristics and identify prognostic factors for OS, and progression-free survival (PFS) in EC patients treated by ENI using CRT and RT- alone.

MATERIALS AND METHODS

Patient's characteristics

Data from patients who were treated at the Fourth Affiliated Hospital of Hebei Medical University from January 2008 to December 2012 were screened and 924 patients with EC were analyzed retrospectively. Of these, 340 patients who received ENI were included according to the following selection criteria: histological diagnosis of EC; Performance status of 0-2; Clinical stage T1-4, N0-1, M0 according to the TNM staging system proposed by the American Joint Committee on Cancer (7th edition); Patients with no history of malignancy or prior surgical treatment related to EC. All patients diagnosed with tracheoesophageal or esophagomediastinal fistula or with a documented distant metastasis (Lung, Liver and Bone) were excluded from the study

Treatment protocol

RT-planning and target volume definition

The images of enhanced computed tomography and endoscopic representation were used to define the range of GTV volume. The irradiated fields were extended from the supraclavicular fossa to the esophagogastric junction, including the total mediastinum and the drainage region. The GTV was contoured on the planning CT by referring to the CT-scanning images and barium esophagography. The clinical target volume (CTV) margin was routinely created by expanding the GTV by 3.0-5.0 cm in the craniocaudal direction and 0.5-1.0 cm in the other four directions for the primary lesion. When metastatic lymph node was distant from the primary oesophageal lesion, the lymph node was contoured alone and noted as GTV-nd. The criterion for lymph node involvement was at least one of the following: diameter of the short axis ≥ 10 mm, the diameter of the long axis ≥ 15 mm on CT images. The presence of extra-nodal tumor extension and peripheral enhanced lymph node helped us to determine metastatic status. The planning target volume (PTV/PTV-nd) was created by expanding the CTV and the GTV-nd by a minimum of 0.5-1.0 cm radial margin. The nodal region that received ENI was noted as CTV1. Elective treatment of nodal regions depended upon the primary lesion location: 1-Primary lesion localized to the cervical and upper thoracic esophagus, 2-Primary lesion localized to the middle thoracic esophagus, 3 Primary lesion located in the lower thoracic esophagus [12]. The PTV1 margin was created by expanding the CTV1 by a minimum of 0.5-1.0 cm radial margin. All patients were treated with 3DCRT/IMRT, and the total dose of RT was delivered using a linear accelerator with beams 6 MeV photon. Treatment plans were generated with a three-dimensional planning system (ADAC-Pinnacle 3, version 5.0). Patients were treated 5 days a week, for those who had SIB- IMRT, the prescribed dose was 58.05-65.1Gy/28-31 fractions of 1.95-2.15 Gy, with the requirement that 95% of the PTV receives the prescribed dose, and 95% PTV1 receive 48.6-57.6Gy/28-31 fractions with a single dose of 1.7-1.8Gy. For those who received late- course RT: 95% PTV1 received 46-54 Gy/23-28 fractions, with a single dose of 1.8-2Gy during the first course of RT. For the late course, a booster dose was further administered to the primary esophageal lesion and the metastatic lymph nodes up to a total dose of 58-66 Gy/29-33 fractions at a single dose of 1.8-2Gy.

Systemic therapy regimen

With respect to chemotherapy in the entire group, a total of 166 patients (48.8%) had chemotherapy, including concurrent CRT 88 patients (53.0%) and sequential chemoradiotherapy 78 patients (47.0%). For patients who received concurrent CRT, the first course was started from the first day of irradiation. For those receiving sequential CRT, the first course began 1 week after the RT was completed. Typically, the main protocol consisted of platinum-based chemotherapy with combined 5-fluorouracil and a taxane (docetaxel or paclitaxel). According to the protocol in our cancer institute, three weeks for a cycle of chemotherapy and each patient received at least 2 cycles. Before and after every cycle of chemotherapy, a complete blood count was obtained. If the

white blood cell (WBC) down to 2000/mm^3 to 2500/mm^3 after the CT, patients were treated with the Recombinant Human Granulocyte Colony-stimulating Factor Injection. If there was a grade 4 hematological reaction or grade 3/4 gastrointestinal reactions or radiation-induced pneumonitis/esophagitis occurred, symptomatic treatment was delivered and the CRT dose was adjusted in the subsequent course of therapy.

Statistical analysis

Patients treated with RT-alone were compared with those treated with CRT using the χ^2 test, Fisher's exact or Student test according to the type of data. The treatment response evaluation was performed 4 to 12 weeks after the end of RT or CRT. The events considered to define event-free survival were: locoregional relapse, distant metastases, and all deaths. The OS was defined as the time from diagnosis to death date or the latest news of patients lost to follow-up. The PFS was defined as the time interval between the starting date of first-line treatment and the date of disease progression, last follow-up or death of any cause. Propensity score matching (PSM) was performed for further comparison. The OS and PFS rates were calculated with the Kaplan Meier method, and both groups were compared using the log-rank test. All survival curves were generated by the Kaplan-Meier method and compared with the Log-rank test. The potential prognostic factors for OS and PFS at 1, 3 and 5 years were investigated in univariate analysis. Prognostic factors with $p < 0.05$ were further evaluated in a multivariate Cox regression analysis. All these analyses were possible with SPSS software version 22.0 P <0.05 was considered statistically significant.

RESULTS

Description of the whole cohort

From January 2008 to December 2012, altogether 924 patients with pathologically- proven EC were investigated at the Fourth Affiliated Hospital of Hebei Medical University. Of these, 584 patients (63.2%) received involved - field radiotherapy. These patients were not included in this study. Case histories of the remaining 340 patients (36.8%) were available in the hospital archives and all of them were also fitted to our inclusion criteria **Figure 1**.

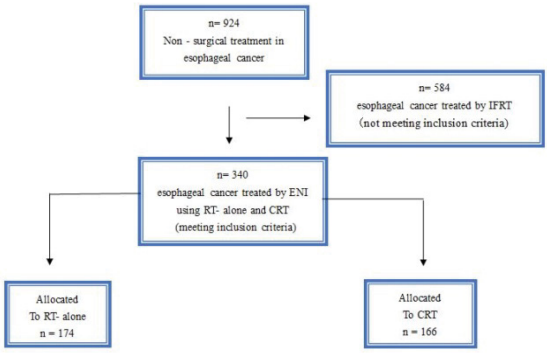

Figure 1. Diagram showing flow of participants through the study (IFRT: Involved-field radiotherapy; ENI: Elective nodal irradiation; RT: radiotherapy; CRT: radiochemotherapy).

Clinicopathological characteristics (**Table 1**).

Table 1. Characteristics of All Patients, According to Treatment Groups (n=340).

Characteristics	*Whole cohort (n=340)*	*RT- alone (n=174)*	*CRT (n=166)*	χ^2	*P*
	n%	n%	n%		
*Age (mean) years	64.4 ± 0.4	65.6 ± 0.6	63.1 ± 0.7	18.808	0
Min - Max	41 - 85	42 - 85	41 - 80		
≤ 60	113 (33.2)	39 (22.4)	74 (44.6)		
>60	227 (66.8)	135 (77.6)	92 (55.4)		
*Sex (sex- ratio M/F)	1.9	1.5	2.5	5.85	0.016
Female	118 (34.7)	71 (40.8)	47 (28.3)		
Male	222 (65.3)	103 (59.2)	119 (71.7)		
*cTNM stage				4.114	0.043
I-II	187 (55.0)	105 (60.3)	82 (49.4)		
III-IV	153 (45.0)	69 (39.7)	84 (50.6)		
Histology				0.106	0.745
Non-sq. carcinoma	33 (9.7)	16 (9.2)	17 (10.2)		
SCC	307 (90.3)	158 (90.8)	149 (89.8)		
T- location				0.381	0.537
CUT	184 (54.1)	97 (55.7)	87 (52.4)		
MLT	156 (45.9)	77 (44.3)	79 (47.6)		

Dysphagia (Grades)				0.005	0.946
0 - 2	144 (42.4)	74 (42.5)	70 (42.2)		
3-4	196 (57.6)	100 (57.5)	96 (57.8)		
T- length (mean) cm	5.4 ± 0.1	5.3 ± 0.1	5.5 ± 0.2	0.017	0.895
Min-Max	1.4 - 15.9	1.9 - 11.7	1.4 - 15.9		
≤ 5	179 (52.6)	91 (52.3)	88 (53.0)		
>5	161 (47.4)	83 (47.7)	78 (47.0)		
GTV- volume (mean) cm^3	40.4 ±1.4	37.4 ± 1.6	43.6 ± 2.4	0.881	0.247
(Min - Max)	4.7- 222.3	4.7 -117.9	5.43 - 222.3		
≤ 30	146 (42.9)	80 (46.0)	66 (39.8)		
>30	194 (57.1)	94 (54.0)	100 (60.2)		
***RT- techniques**				17.872	0
SIB- IMRT	137 (40.3)	51 (29.3)	86 (51.8)		
Late course RT	203(59.7)	123 (70.7)	80 (48.2)		
RT dose (mean) Gy	62.0 ± 13.2	61.9 ± 18.2	62.1 ± 19.2	3.714	0.054
(Min- Max)	50.4 - 66	52.0 - 66.0	50.4 - 66.0		
50.4 - 62	182 (53.5)	102 (58.6)	80 (48.2)		
>62	158 (46.5)	72 (41.4)	86 (51.8)		

cTNM: Clinical Tumor Node; Metastasis; **SCC:** Squamous cell carcinoma; Non-sq. cell carcinoma: Non-squamous cell carcinoma=adenocarcinomas, Small cell carcinoma; T-location : Tumor - location; **CUT:** Cervical and upper thoracic; **MLT:** Middle and lower thoracic ; T- length: Tumor length; **GTV:** Gross tumor volume; RT- techniques: Radiotherapy techniques; **SIB- IMRT:** Simultaneous integrated boost – IMRT; **Late course RT:** Late-course radiotherapy; **RT- dose:** Radiotherapy dose; *P<0.05.

Survival outcomes

The mean age in the entire group was 64 ± 0.4 (range: 41-85 years), with a relatively higher mean age in RT- group (65.6 ± 0.6 *vs*. 63.1 ± 0.7 years, if CRT, χ^2=18.808, p=0.000). Over 65.3% (n=222 patients) of patients were male, and the M/F sex ratio was high in CRT- group (2.5 *vs*. 1.4, if RT- alone, χ^2=5.850, p=0.016). The percentages of patients with cTNM- stage III-IV was 50.6% (n=84 patients) in CRT-group *vs*. 39.7% (n=69 patients) in RT- group (χ^2=4.414, p=0.043). Two hundred and three patients experienced late- course RT including, 123 patients (70.7%) in RT-group *vs*. 80 patients (48.2%) in CRT-group (χ^2=17.872, p=0.000). The most common digestive toxicity was esophagitis, including 88 patients (50.6%) of grade 1-2 esophagitis in RT-group *vs*. 110 patients (66.3%) of grade 1-2 esophagitis in CRT-group (χ^2=8.950, p=0.011). The incidence of hematological toxicities was obviously higher in patients who had CRT rather than those who had RT-alone, especially for grade 3-4 anemia (18.1% *vs*. 3.4%; χ^2=24.217, p=0.000).

During the study period, the median OS time for the whole group was 38.2 ± 3.4 months (range: 31.6-44.8 months). The median and 5-year OS rate for those patients treated with RT- alone was 35.2 ± 4.9 months (95% CI: 31.6-44.8 months) and 33.4%, compared to 43.0 ± 3.3 months (95% CI: 36.0-49.9 months) and 31.2% for those treated with CRT. There was no statistical difference between the two groups (χ^2=0.337, p=0.562; **Figure 2**).

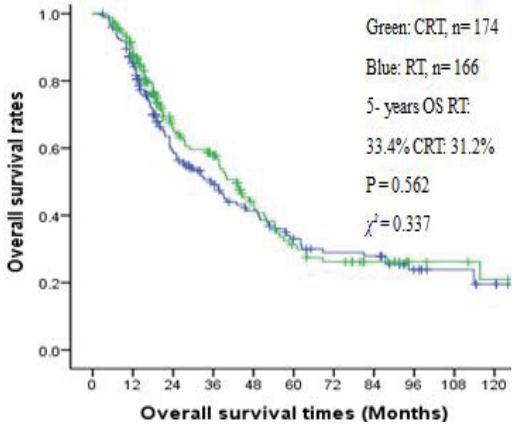

Figure 2. Kaplan Meier curves comparing overall survival for oesophageal cancer patients treated by ENI using RT- alone and CRT (n=340). The 5-year Kaplan-Meier showed that no significant difference was observed between RT- group and CRT- group, OS rates (33.4% and 31.2%, χ^2=0.337, P=0.562).

By contrast, the median and 5-year PFS in patients who had CRT was relatively longer than those who had RT- alone, with the median PFS of 16.7 ± 1.4 months (95% CI, 13.9-19.5 months) and the 5- year PFS rate of 22.7% for those who had CRT vs. 13.0 ± 0.9 months (95% CI, 11.3–14.7 months) and 10.8%, if RT- alone. This finding was statistically significant (χ2=6.099, p=0.014; **Figure 3**).

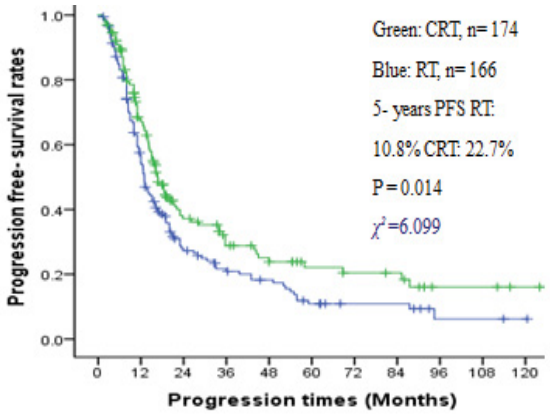

Figure 3. Kaplan Meier curves comparing progression-free survival for oesophageal cancer patients treated by ENI using RT- alone and CRT (n=340). The 5-year Kaplan-Meier showed that a significant difference was observed between RT- group and CRT- group, PFS rates (10.8% and 22.7%, χ^2=6.099, P=0.014).

Propensity-score matching

In order to minimize the error caused by the influencing factors and to make the results more reliable, the clinicopathological characteristics and the potential prognostic factors for both groups were reassessed for further comparison. The PSM models were then developed for each comparative level. In this context, PSM confirmed the absence of a statistically significant difference in OS between the two groups (p>0.05; **Figure 4**).

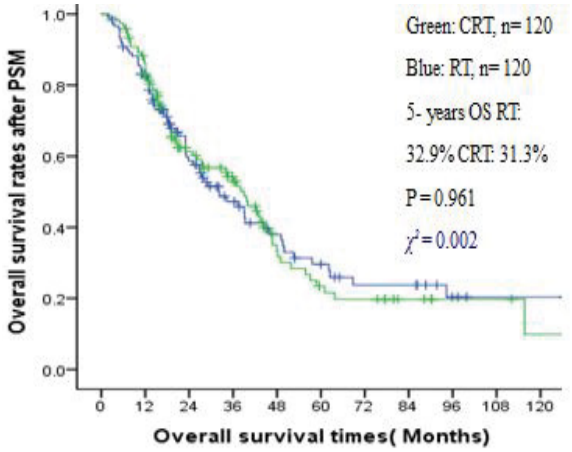

Figure 4. Propensity-matched Kaplan Meier curves comparing overall survival for oesophageal cancer patients treated by ENI using RT- alone and CRT (n=240). The 5-year Kaplan-Meier after matching score showed that no significant difference was observed between RT- group and CRT- group, OS rates (32.9% and 31.3%, χ^2=0.002, P=0.961).

Additional analysis was also performed for PFS. Overall, the CRT- group was remained associated with improving PFS, with a 5-year PFS rate of 7.8% in RT- group and 22.9% in CRT- group, respectively (χ^2=3.911, p=0.048, **Figure 5**).

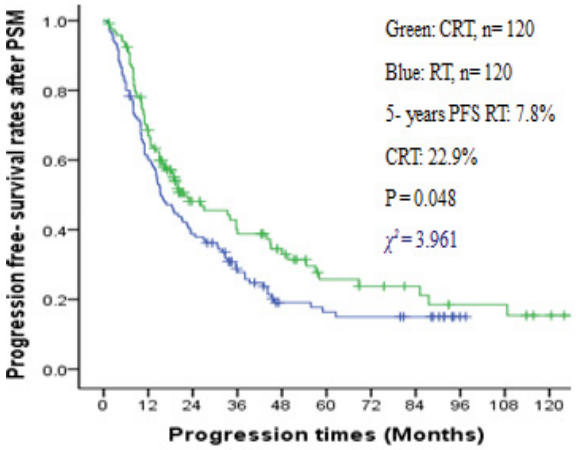

Figure 5. Propensity-matched Kaplan Meier curves comparing progression-free survival for oesophageal cancer patients treated by ENI using RT- alone and CRT (n=240). The 5-year Kaplan-Meier after matching score showed a significant difference was observed between RT- group and CRT- group, PFS rates (7.8% and 22.8%, χ^2=3.961, P=0.048).

Prognostic factors for the whole cohort after PSM

The group analysis conducted in order to reexamine the effect of the treatment on potential prognostic factors. After propensity score matching, 240 well-balanced pairs of patients were available for outcome comparison. In univariate analysis, prognostic factors identified were (χ^2=4.445, p=0.035), cT- stage (χ^2=11.477, p=0.001), cTNM - stage (χ^2=19.180, p=0.000), T-length (χ^2=6.170, p=0.013) **Table 2**.

Table 2. Characteristics of Patients After Matching, According to Treatment Group (n= 240).

Characteristics	Whole cohort (n=240)	RT- alone (n=120)	CRT (n=120)	χ^2	P
	n%	n%	n%		
Age (mean) years	64.4 ± 0.5	64.9 ± 0.7	68.3 ± 0.8	0.077	0.781
Min - Max	41 - 80	42 - 80	42 - 85		
≤ 60	76 (31.7)	37 (30.8)	39 (32.5)		
>60	164 (68.3)	83 (69.2)	81 (67.5)		
***Sex (sex- ratio M/F)**	2.1	2.1	2.1	0	1
Female	78 (32.5)	39 (32.5)	39 (32.5)		
Male	162 (67.5)	81 (67.5)	81(67.5)		
cTNM stage				1.1366	0.242
I-II	133 (55.4)	71 (59.2)	62 (51.7)		
III-IV	107 (44.6)	49 (40.8)	58 (48.3)		
Histology				0.69	0.406
Non-sq. carcinoma	26 (10.8)	11 (9.2)	15 (12.5)		
SCC	214 (89.2)	109 (90.8)	105 (87.5)		
T- location				0.602	0.438
CUT	126 (52.5)	66 (55.0)	54 (45.0)		
MLT	114 (47.5)	60 (50.0)	60 (50.0)		
Dysphagia (Grades)				0.158	0.691
0 - 2	93 (38.8)	48 (40.0)	45 (37.5)		
3-4	147 (61.3)	72 (60.0)	75 (62.5)		
T- length (mean) cm	5.4 ± 0.1	5.2 ± 2.0	5.6 ± 0.2	2.024	0.155
Min- Max	1.4 - 15.9	1.9 - 11.7	1.4 - 15.9		
≤ 5	127 (52.9)	69 (57.5)	58 (48.3)		
>5	113 (47.1)	51 (42.5)	62 (51.7)		
GTV volume (mean) cm^3	40.8 ± 1.8	37.6 ± 1.9	41.1 ± 2.9	0.425	0.514
(Min - Max)	5.4 - 222.3	9.8 - 10.2.7	5.43 - 222.3		
≤ 30	103 (42.9)	54 (45.0)	49 (40.8)		
>30	137 (57.1)	66 (55.0)	71 (59.2)		
RT- techniques				271	0.602
SIB- IMRT	104 (43.3)	50 (41.7)	54 (45.0)		
Late- course RT	136 (56.7)	70 (58.3)	66 (55.0)		
RT dose (mean) Gy	61.9 ± 15.1	61.8 ± 21.6	62.2 ± 20.9	3.29	0.07
(Min- Max)	52.0 - 66.0	58.5 - 66	52.0 - 66.0		
50.4 - 62	130(54.2)	72 (60.0)	58 (48.3)		
>62	110 (45.8)	48(40.0)	62 (51.7)		

cTNM: Clinical Tumor Node; Metastasis; SCC: Squamous cell carcinoma; Non- sq. cell carcinoma: Non- squamous cell carcinoma = adenocarcinomas, Small cell carcinoma; T-location : Tumor –location; CUT: Cervical and upper thoracic; MLT: Middle and lower thoracic ; T-length: Tumor length; GTV: Gross tumor volume; RT- techniques: Radiotherapy techniques; SIB- IMRT: Simultaneous integrated boost- IMRT; Late course RT: Late- course radiotherapy; RT- dose: Radiotherapy dose;*P<0.05.

Of this statistical significance persisted only for cTNM - stage (p=0.000) upon multivariate analysis. However, although there was no statistically significant difference in OS for cT- stage, N- status and the GTV- volume, there was a trend toward a higher ratio of 5- year OS in favor of cT1-2 (39.6% *vs*. 14.5%, if cT3-4, χ^2=11.477, p=0.001), N0- status (35.3% *vs.* 29.9%, if N^{1+2} - status, χ^2=3.383, p=0.066) and the GTV- volume ≤ 30 cm^3 (39.8% *vs.* 25.4%, if GTV- volume >30 cm^3; χ^2=3.667, p=0.055, **Table 3**).

Table 3. Univariate analysis of the effect of potential prognostic factors on OS oesophageal cancer patients treated by ENI using RT- alone and CRT after PSM.

Prognostic factors	n	Overall survival (%)			χ^2	P
		1 y	3 y	5 y		
Age						

≤ 60	76	89.3	55.6	37.1	0.417	0.518
>60	164	89.4	54.4	29.2		
***Sex**						
Male	162	87.9	49.3	27.1	4.445	0.035
Female	78	92.3	65.6	41.2		
***cT- stage**						
T1-2	110	93.6	58.7	39.6	11.477	0.001
T3- 4	130	769	44.1	14.5		
***N- status**						
N0	98	95.9	63.8	35.3	3.383	0.066
N1+2	142	84.8	48.6	29.9		
***cTNM - stage**						
I-II	133	92.3	65.7	43.7	19.18	0
III-IV	107	85.6	41.2	17.3		
T- location						
CUT	126	89.4	56.9	28.1	0.021	0.884
MLT	114	89.3	52.8	35.6		
Histology						
Non- sq. carcinoma	26	88.5	55.3	22.5	0.154	0.695
SCC	214	89.4	54.8	32.9		
***T- length (cm)**						
≤ 5	127	91.8	61.8	39.5	6.17	0.013
>5	113	86.6	47.5	24.2		
Dysphagia (Grade)						
0- 2	93	87.8	61.8	34.5	0.948	0.33
03-Apr	147	90.3	50.7	30.6		
CT- cycles						
≤ 4	206	89.1	52.6	31.2	0.513	0.474
>4	34	91	69.6	37.4		
***GTV- volume (cm^3)**						
≤ 30	103	87.9	55.4	39.8	3.667	0.055
>30	137	90.4	54.9	25.4		
RT- techniques						
Late course RT	136	88.7	52.4	30.3	0.879	0.348
SIB- IMRT	104	90.1	58.2	35.5		
RT- dose (Gy)						
50.4 - 62	130	88.9	56.4	30.3	0.009	0.923
>62	110	89.8	52.9	34.1		

cT- stage: Clinical Tumor stage; N- status: Node-status; cTNM: Clinical Tumor Node; Metastasis; SCC: Squamous cell carcinoma; Non- sq. cell carcinoma: Non- squamous cell carcinoma = adenocarcinomas, Small cell carcinoma; T-location : Tumor –location; CUT: Cervical and upper thoracic; MLT: Middle and lower thoracic ; T- length: Tumor length; GTV: Gross tumor volume; RT- techniques: Radiotherapy techniques; SIB-IMRT: Simultaneous integrated boost – IMRT; Late course RT: Late- course radiotherapy; RT- dose: Radiotherapy dose; *P<0.05.

Additional PSM was also performed for PFS in the whole group and the outcomes revealed that male – gender was an unfavorable prognostic factor for PFS (p=0.034, **Tables 4 and 5**).

Table 4. Univariate analysis of the effect of potential prognostic factors on PFS in patients with esophageal cancer treated by ENI using RT- alone and CRT after PSM (n=240).

Prognostic factors	n	Progressive free- survival (%)			χ^2	P
		1 y	3 y	5 y		
Age						
≤ 60	76	61.1	27.9	14.1	0.013	0.909
>60	164	61.1	22.5	14.4		
***Sex**						
Male	162	55.4	22..8	11.6	4.594	0.032
Female	78	72.5	27.6	18.5		
cT- stage						
T1-2	110	62.6	24.1	11.1	0.002	0.966
T3-4	130	59.8	24.4	17.8		
N- status						

N0	98	62.9	19.4	11	0.054	0.816
N1+2	142	59.9	28.2	16.9		
cTNM - stage						
I-II	133	63.6	24.6	13.3	0.583	0.445
III-IV	107	58	23.8	16.2		
T- location						
CUT	126	60.1	21.8	10.1	0.788	0.375
MLT	114	62.2	27.2	18.3		
Histology						
Non- sq. carcinoma	26	56.9	34.1	34.1	1.18	0.277
SCC	214	61.7	22.9	11.8		
T- length (cm)						
≤ 5	127	64.8	23.3	11.5	0.002	0.962
>5	113	57	26	18.3		
Dysphagia (Grade)						
01-Feb	93	66.7	19.2	8.8	1.275	0.259
03-Apr	147	57.7	27.5	17.9		
CT- cycles						
≤ 4	206	61.1	25.3	14.8	0.118	0.731
>4	34	61.1	19.2	11.6		
GTV- volume (cm3)						
≤ 30	103	64.5	20.1	11.3	0.113	0.736
>30	137	58.6	28	16.9		
RT- techniques						
Late course RT	136	62.9	24.9	11.3	0.597	0.44
SIB- IMRT	104	58.8	23.3	19.3		
RT- dose (Gy)						
50.4- 62	130	62	26.6	15.5	0.052	0.82
>62	110	62.3	21.2	12.5		

cT- stage: Clinical Tumor stage; N- status: Node-status; cTNM: Clinical Tumor Node; Metastasis; SCC: Squamous cell carcinoma; Non- sq. cell carcinoma: Non- squamous cell carcinoma=adenocarcinomas, Small cell carcinoma; T-location : Tumor –location; CUT: Cervical and upper thoracic; MLT: Middle and lower thoracic ; T- length: Tumor length; GTV: Gross tumor volume; RT- techniques: Radiotherapy techniques; SIB- IMRT: Simultaneous integrated boost–IMRT; Late course RT: Late- course radiotherapy; RT- dose: Radiotherapy dose; *P< 0.05.

Table 5. Multivariate analysis of the effect of potentials prognostic factors on OS and LRRFS in patients with esophageal cancer treated by ENI using RT- alone and CRT after PSM (n=240).

Parameters	Prognosis factors	B	SE	Wald	Sig
OS	Sex	-0.346	0.193	3.218	0.073
	cT- stage	0.251	0.997	0.318	1.285
	N- status	0.032	0.195	0.027	0.868
	*cTNM - stage	0.728	0.177	16.972	0
	T- length	0.082	0.232	0.124	0.724
	GTV- volume	-0.024	0.232	0.011	0.917
PFS	*Sex	-0.342	0.161	4.492	0.034

OS: Overall survival; PFS: Progression Free- survival; cT- stage: Clinical Tumor stage; N- status: Node-status; cTNM: Clinical Tumor Node; Metastasis; T- length: Tumor length; GTV: Gross tumor volume,

Prognostic factors for the subgroup after PSM

In order to ascertain the specific factors affecting PFS and OS, we conducted a further study of the clinical stage and radiation dose. For the subgroup, various prognostic factors were evaluated by log- rang test and the data indicated that age ≤ 60 years old (χ^2=7.074, p=0.008), cT3-4 (χ^2=3.901, p=0.048), N0 status (χ^2=7.449, p=0.006), cTNM stage III-IV (χ^2=3.833, p=0.050), SCC (χ^2=4.207, p=0.040), T- length >5 cm (χ^2=3.003, p=0.083), GTV- volume >30 cm^3 (χ^2=7.910, p=0.007), and late- course RT (χ^2=6.863, p=0.009) were marginally or significatively associated with a better PFS prognosis in CRT- group (**Table 6**).

Table 6. Subgroup Comparison of Patients with Different Characteristics (n=240).

Prognostic factors	Sub-groups	n	Progression free- survival (%)			χ^2	P
			1 y	3 y	5 y		
***Age**							
≤ 60	RT- alone	37	49.3	17.7	0	7.074	0.008
	CRT	39	72.6	37.5	28.7		

>60	RT- alone	83	60.5	21.8	11.6	0.347	0.556
	CRT	81	61.8	23.5	18.1		
Sex							
Male	RT- alone	81	51.3	19.7	1.6	2.588	0.108
	CRT	81	59.7	26.3	20.9		
Female	RT- alone	39	68.8	22.6	14.1	1.543	0.214
	CRT	39	76.3	33	24.1		
***cT- stage**							
T1-2	RT- alone	62	57.4	24.4	8.3	0.471	0.492
	CRT	48	70.4	27.5	18.8		
T3-4	RT- alone	58	56.6	15.1	7.6	3.901	0.048
	CRT	72	62.4	32.2	26.5		
***N- status**							
N0	RT- alone	51	54	11.2	4.5	7.449	0.006
	CRT	47	73	29.9	20.7		
N1+2	RT- alone	69	59.4	28.8	10.6	1.089	0.297
	CRT	73	60.3	27.7	22.6		
***cTNM stage**							
I- II	RT- alone	71	58.6	24.3	9.6	1.074	0.3
	CRT	62	69.5	25.1	18.7		
III- IV	RT- alone	49	54.8	13.9	4.6	3.833	0.05
	CRT	58	60.7	32.9	26.6		
T- location							
CUT	RT- alone	66	57.5	18.9	2.7	2.375	0.123
	CRT	60	63.2	25.3	21.1		
MLT	RT- alone	54	56.6	22.6	13.7	1.403	0.236
	CRT	60	67.6	31.6	22.8		
***Histology**							
Non-sq. carcinoma	RT- alone	11	52.4	41	40.7	0.004	0.947
	CRT	15	60	31	31.1		
SCC	RT- alone	109	57.5	18.9	5.8	4.207	0.04
	CRT	105	66.2	27.9	19.9		
***T- length (cm)**							
≤ 5	RT- alone	69	61.2	20.7	8.7	0.855	0.355
	CRT	58	69.1	27.3	15.2		
>5	RT- alone	51	51.5	22.1	7.4	3.003	0.083
	CRT	62	61.7	30	29.9		
Dysphagia							
Grade 0-2	RT- alone	48	63	16	4	1.252	0.263
	CRT	45	70.7	22.9	13.1		
Grade 3-4	RT- alone	72	53.2	23.5	10.5	2.688	0.101
	CRT	75	62.2	31.9	28.6		
***GTV volume (cm^3)**							
≤ 30	RT- alone	54	65.7	22.8	12.2	0.066	0.798
	CRT	49	63	16.6	9.9		
>30	RT- alone	66	50	18.5	3.1	7.19	0.007
	CRT	71	66.9	37.4	31.4		
***RT- techniques**							
Late course	RT- alone	70	54.7	18.8	3.8	6.863	0.009
	CRT	66	72.1	32.3	22.9		
SIB- IMRT	RT- alone	50	60.4	22.9	17.8	0.003	0.954
	CRT	54	57.3	23.7	20.3		
RT dose (Gy)							
50.4-62	RT- alone	72	54.6	24.4	8.9	2.383	0.123
	CRT	58	67.3	29.1	23.5		
>62	RT- alone	48	60.9	15.1	6.2	1.657	0.198
	CRT	62	63.5	27.2	19.4		

cT- stage: Clinical Tumor stage; N- status:Node-Status; cTNM: Clinical Tumor Node Metastasis; SCC: Squamous Cell Carcinoma; Non- sq. cell carcinoma: Non- Squamous Cell Carcinoma = adenocarcinomas, Small cell carcinoma; T-location : Tumor –location; CUT: Cervical and Upper Thoracic; MLT: Middle and Lower Thoracic ; T- length: Tumor Length; GTV: Gross Tumor Volume; RT- techniques: Radiotherapy Techniques; SIB-IMRT: Simultaneous Integrated Boost – IMRT; Late course RT: Late- Course Radiotherapy; RT- dose: Radiotherapy dose; *P<0.05.

Furthermore, in addition to age ≤ 60 years old (χ^2=3.423, p=0.064), patients with N0-status (χ^2=3.025, p=0.082), cTNM stage III-IV (χ^2=2.776, p=0.096), and T- length ≤ 5 cm (χ^2=3.579, p=0.059) were also more likely to demonstrate an OS benefit from CRT without statistical significance **Table 7**. As well, it confirmed that non- squamous cell carcinoma was associated with improve OS after RT-alone (χ^2=5.687, p=0.017, **Table 7**).

Table 7. Subgroup Comparison of Patients with Different Characteristics (n=240).

Prognostic factors	Sub-groups	n	Overall survival (%)			χ^2	P
			1 y	3 y	5 y		
***Age**							
≤ 60	RT- alone	37	83.6	47.1	29.4	3.423	0.064
	CRT	39	94.7	63.9	44.3		
>60	RT- alone	83	92.5	54.8	34.5	1.955	0.162
	CRT	81	86.2	54.2	23.9		
Sex							
Male	RT- alone	81	89.7	50.9	26.9	0.192	0.661
	CRT	81	86.1	47.5	27.1		
Female	RT- alone	39	89.7	55.3	43	0.374	0.541
	CRT	39	94.8	76.4	39.7		
cT- stage							
T1-2	RT- alone	62	90	60.1	44.4	0.049	0.824
	CRT	48	91.2	62.8	41.5		
T3-4	RT- alone	58	84.5	42.1	22.3	1.331	0.249
	CRT	72	89.4	76.4	39.7		
N- status							
N0	RT- alone	51	96	56.6	32.5	0.576	0.448
	CRT	47	95.7	71.9	38.8		
N1+2	RT- alone	69	84.9	49.2	33.2	0.172	0.678
	CRT	73	84.6	47.8	26.7		
cTNM stage							
I- II	RT- alone	71	92.8	66.1	46.2	0.47	0.493
	CRT	62	91.7	65.2	40.9		
III- IV	RT- alone	49	85.3	32.4	12.6	2.353	0.125
	CRT	58	85.9	49.1	21.5		
T- location							
CUT	RT- alone	66	89.1	52.3	27.5	0.295	0.587
	CRT	60	89.7	62.5	29		
MLT	RT- alone	54	90.5	52.6	37.8	0.118	0.731
	CRT	60	88.2	52.9	33.5		
***Histology**							
Non- sq. carcinoma	RT- alone	11	90.9	80.2	80.2	5.687	0.017
	CRT	15	86.7	41.3	8.2		
SCC	RT- alone	109	89.6	49.9	30.3	0.815	0.367
	CRT	105	89.3	60.2	35.9		
T- length (cm)							
≤ 5	RT- alone	69	89.5	55	37.6	0.601	0.438
	CRT	58	94.6	70.2	41.5		
>5	RT- alone	51	90.1	49.8	26.5	0.14	0.708
	CRT	62	83.7	45.7	22.5		
Dysphagia							
Grade 0-2	RT- alone	48	87.1	62.2	34.6	0.009	0.925
	CRT	45	88.6	61.4	32.6		
Grade 3-4	RT- alone	72	91.5	46.6	31.9	0.026	0.871
	CRT	75	89.1	55.1	29.5		
GTV volume (cm^3)							
≤ 30	RT- alone	54	86.5	52	40.7	0.006	0.939
	CRT	49	89.5	59.5	38.2		
>30	RT- alone	66	92.3	53.9	23.9	0.163	0.686
	CRT	71	88.6	56.1	26.9		
RT- techniques							
Late course RT	RT- alone	70	86.8	46.7	27.3	0.313	0.516
	CRT	66	90.8	58.3	33.2		

SIB-IMRT	RT- alone	50	93.9	60.9	44.2	0.517	0.472
	CRT	54	86.7	54.9	26.7		
RT dose (Gy)							
50.4-62	RT- alone	72	91.4	53.9	31.4	0.086	0.769
	CRT	52	85.8	59.8	29.1		
>62	RT- alone	48	87.2	50.3	35.1	0.174	0.676
	CRT	62	91.8	55.1	33.2		

cT- stage: Clinical Tumor stage; N- status: Node-status; cTNM: Clinical Tumor Node Metastasis; SCC: Squamous Cell Carcinoma; Non- sq. cell carcinoma: Non-Squamous Cell Carcinoma = adenocarcinomas, Small cell carcinoma; T-location : Tumor –Location; CUT: Cervical and Upper Thoracic; MLT: Middle and Lower Thoracic ; T- length: Tumor Length; GTV: Gross Tumor Volume; RT- techniques: Radiotherapy Techniques; SIB-IMRT: Simultaneous Integrated Boost - IMRT; Late course RT: Late- Course Radiotherapy; RT- dose: Radiotherapy dose; *P<0.05.

DISCUSSION

In order to ascertain the specific factors affecting PFS and OS, we conducted a further study of the clinical characteristics and radiation dose. Our subgroup analysis also showed that, compared to RT- alone, CRT improved PFS in the following subgroups: age ≤ 60 years (χ^2=7.074, p=0.008), cT3-4 (χ^2=3.901, p=0.048), N0 -status (χ^2=7.449, p=0.006), cTNM stage III-IV (χ^2=3.833, p=0.050), SCC (χ^2=4.207, p=0.040), T-length >5 cm (χ^2=3.003, p=0.083), GTV-volume >30 cm^3 (χ^2=7.910, p=0.007), and late-course RT (χ^2=6.863, p=0.009) **Table 7**. Moreover, in addition to age ≤ 60 years (χ^2=3.423, p=0.064), patients with N 0-status (χ^2=3.025, p= 0.082), cTNM stage III-IV (χ^2=2.776, p=0.096), and T-length ≤ 5 cm (χ^2=3.579, p=0.059) were more likely to demonstrate an OS benefit from CRT rather than RT- alone, although the difference was not statistically significant **Table 6**. Indeed, we observe survival superiority of RT- alone in non- squamous esophageal carcinoma. One possible reason for this result might be that the number of non-squamous esophageal carcinoma included in the study was small (33 patients) compare to the SCC subtype (307 patients).

The results of this population-based study reveal that the use of ENI using CRT is associated with significantly improved PFS for EC. After the propensity score matching, the median PSF times were 13.0 (95% CI:11.3-14.7) and 16.2 (95% CI:13.0-19.4) months in RT and CRT-group, respectively, and the 1, 3 and 5-year survival rates were 57.1%, 20.5, and 7.8% in RT-group and 65.5%, 28.5%, and 22.9% in CRT- group, respectively (χ^2=3.911, p=0.048). Patients within poor prognostic factors, including, age ≤ 60 years, with cT3-4, N1+2 - status, cTNM stage III-IV, SCC, T- length >5 cm, and GTV- volume >30 cm^3, were more likely to benefit from CRT and have trended toward better survival than those receiving ENI using RT- alone. However, our results highlighted the lack of a statistically significant difference in OS between the two groups. The 1, 3 and 5 year OS rate in RT – group were 87.1%, 50.6% and 33.4%, respectively *vs*. 90.1%, 58.9% and 31.2%, if CRT- group (χ^2=0.337, p=0.562, **Figure 5**). Pouliquen et al. and Walsh et al. [13,14], also reported the absence of survival benefit between the two treatment methods with ORR of 72% (95% CI, 0.53-0.97; p=0.05). Inversely, Herskovic et al. in a phase III study reported a superiority of CRT over RT- alone [15]. The results at one-year from the study describe an increase in locoregional control rate (38 *versus* 56%) as well as a significant increase in survival at 2 years (10 *versus* 38%). The number of metastases at 2 years decreased from 26 to 12%. By contrast, for some investigators, even though CRT may prevent elective nodal failure or improve local control, it is not clear whether the association of CRT and ENI improves OS [16]. These might mean that CRT using ENI contribute to increasing PFS benefit by controlling minor metastases, but does not contribute to increasing significantly OS.

Generally, it has been found that acute complications in patients undergoing CRT are more severe than those of patients receiving RT- alone. These complications include anemia, pneumonitis, and esophagitis along with other common symptoms like fatigue, nausea, vomiting, ulceration, epidermitis. Our results showed 31 patients (18.7%) of acute grade 3- 4 anemia in CRT- group *vs*. 10 patients (5.7%) in RT- group (χ^2=24.217, p=0.000) and 110 patients (66.3%) of grade 1-2 esophagitis in CRT –group *vs* 88 patients (50.6%), if RT-alone (χ^2=8.950, p=0.011). There were no patients with an esophageal stricture. Sang Jun Byun, et al. reported 11.6% of esophagitis, 2.3% of ulceration and 27.9% of esophageal stricture after CRT [17].

Regarding the prognostic role of clinical factors on OS, and PFS, several clinical characteristics related variables were identified in a univariate analysis by log-rank test. For the whole group, although cT- stage, N- status, cTNM stage, T-length, and GTV-volume were of significant prognostic relevance for OS, the propensity-matched analysis, concluded that cTNM- stage (p=0.000) was the only independent prognostic factor for OS (**Table 5**). Several studies have reported that the cTNM stage is one of the most important prognostic factors in estimating survival rates including depth of tumor invasion, nodal involvement, GTV-volume and distant metastases. However, although difficulties and variation in the TNM staging undoubtedly exist, the present finding was translated into a survival advantage for those patients with cTNM stage I-II. The 1, 3 and 5 years OS rates were 92.3%, 65.7% and 43.7%, respectively in patients with cTNM stage I-II *vs*. 85.6% 41.2% and 17.3% for those with cTNM stage III-IV, respectively (χ^2=19.180, p=0.000, **Table 3**). Besides, in the study by Boggs DH et al. [18] published in 2015, the GTV- volume was a significant predictor for improved OS (p=0.001). They concluded that GTV-volume was a more powerful predictor of patient outcome than the traditional TNM staging. This finding consistent with our result; however, the target volume in Boggs study was contoured as separate regions rather than together [18] Our finding suggests that the conventional T- classification only is not invariably the best indicator of the real nature of the disease; in addition to age, a classification based on the actual cTNM-stage and the primary GTV- volume could have a better prognostic value.

Furthermore, as many variables could potentially be responsible for the difference observed in PFS between the two groups. In accordance with previous findings, factor independently found in the present study to be predictive of improved PFS after PSM was female gender. The PFS rate in female patients was significantly better than in male patients (χ^2=4.594, p=0.032, **Table 4**). This result was also translated into a survival advantage for female patients. The OS rate at 3 and 5 years for the female patients were 65.6% and 41.2% *vs.* 49.3% and 27.1%, if male patients (χ^2=4.445, p=0.035) (**Table 3**). For Halperin EC et al. esophageal carcinoma in men tend to have a more aggressive nature with poorer outcomes [19].

To our knowledge, potential prognostic factors including cTNM stage, cT- stage, primary tumor location, histologic type, gender, patient age, tumor oxygenation and hemoglobin level before treatment have been already reported to possess prognostic value for EC [20,21]. In our subgroup analysis after PSM, in addition to female gender, age ≤ 60 years (χ^2=7.074, p=0.008), cT3-4 (χ^2=3.901, p=0.048), N 0-status (χ^2=7.449, p=0.006), cTNM- stage III-IV (χ^2=3.833, p=0.050), T- length >5 cm (χ^2=3.003, p=0.083), SCC (χ^2=4.207, p=0.040), GTV volume >30 cm^3(χ^2=7.190, p=0.007), and late- course RT technique (χ^2=6.863, p=0.009) were associated with a better PFS in CRT- group. Compared to others previously published studies, some authors have admitted that advanced age at diagnosis, the depth of tumor invasion, tumor length >5 cm, GTV–volume and middle and lower esophagus localization were correlated with a poor PFS prognosis in CRT- group [18,22-24]. However, the most important message in this study is that compared to RT- alone, ENI using CRT and late-course RT improved PFS prognosis in the following subgroups female gender, age ≤ 60 years, cT3- 4, N0- status, cTNM- stage III-IV, T- length >5 cm, SCC, GTV volume >30 cm^3. This could be a particularly important pathway to the stratification parameters for a personalized treatment.

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