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Research Article

Prognostic Factors in Patients after Definitive Radiotherapy using Simultaneous Integrated Boost-Intensity Modulated Radiotherapy (SIB-IMRT) and Late-Course Boost to Gross Tumor Volume (LCBGTV)

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ABSTRACT

Objective: To assess pre-treatment factors that can predict the outcome of simultaneous integrated boost- intensity-modulated radiotherapy (SIB-IMRT) or Late-course boost to gross tumor volume (LCBGTV) and help to choose treatment strategies appropriate for individual patients.

Methods: Data obtained from 174 esophageal cancer (EC) patients, including 51 patients in the SIB-IMRT group and 123 patients in LCBGTV-IMRT group were reviewed between 2008 and 2012. The primary outcome was overall survival (OS) and progression-free survival (PFS) comparison.

Results: After the Propensity Score Matching (PSM) analysis, the 5 year OS rates and median survival in SIB-IMRT group and LCBGTV-IMRT group were 52.4%, and 62.2 months and 37.7%, and 49.6 months, respectively (p=0.491). The 5 year PFS rate was better in the SIB-IMRT group (27,6%; 95% CI: 12.2 to 25.8 months) than in the LCBGTV-IMRT group (6.7%; 95% CI: 8.5 to 15.5 months). Cox regression analysis revealed cTNM-stage to be the single independent prognostic factor for OS ($p<0.05$). Subgroup analysis suggested that male patients, >60 years, cT3-4 stage, N0/N1+2 status, cTNM-stage I-II, middle and lower tumor location, tumor length >5 cm, GTV (≤ 30 cm^3) and radiation dose of >62Gy were more likely to demonstrate PFS and OS benefit from SIB-IMRT.

Conclusion: Compared with LCBGTV- IMRT, ENI using SIB-IMRT provides both PFS and OS benefit to EC patients, especially in the following subgroup: male >60 years, cTNM-stage I-II, middle and lower tumor location, tumor length >5 cm, GTV volume ≤ 30 cm^3 and radiation dose of >62Gy, respectively.

Keywords: Esophageal cancer; Simultaneous integrated boost; Intensity-modulated radiotherapy; Late-course radiotherapy; Prognostic factors

INTRODUCTION

The treatment outcomes of patients with Esophageal Cancer (EC) have remained unchanged over the past three decades, with the 5-year overall survival (OS) rate range of 15%-20%. Surgery and radiotherapy (RT) have always been the main treatment methods [1]. However, the majority of patients cannot undergo surgery because of either the extent of their primary lesion or the medical comorbidities [2]. So far, most published studies of patients who are medically unfit for surgery and in whom chemotherapy is contraindicated, the 5 year OS rates ranged from 0%-10% [3,4]. For those patients with unresectable disease treated by RT-alone, the OS rate is 0% at 5-year, far inferior to the chemoradiotherapy (CRT) rates of 27% [5]. Despite the current therapies can be quite effective in some cases, local disease control, specifically within the GTV, remains a substantial concern. Moreover, whether ENI for RT treatment should be performed has always been remain questionable [6-8]. The effectiveness of dose-escalation in EC was first evaluated in the United States, in the Intergroup (INT)

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0123/Radiation Therapy Oncology Group (RTOG) 94-05 trial. In this largest trial, escalating dose up to 64.8Gy did not improve locoregional control or overall survival (OS) [5]. Moreover, increased toxicity was observed in the high dose group of this trial. However, since the completion of this trial, notable technical advances in RT treatment planning and delivery have taken place, including image guidance, and the use of Intensity Modulated Radiation Therapy (IMRT) [9,10]. With this advent of technology capable of producing more high precision, radiation oncologists have hypothesized that higher radiation doses may improve local tumor control without increasing radiation-related morbidity and offers the potential for significant improvement in outcomes. In this context, some investigators have demonstrated acceptable toxicity with IMRT and dose up to 60Gy can be delivered safely if a strict dose-volume limitations are applied to critical structures [10]. The current study was designed to retrospectively identify the predictive factors for EC patients treated by ENI using LCBGTV and SIB-IMRT and to help us to choose treatment strategies appropriate for individual patients (Figure 1).

METHODS AND MATERIALS

Data source

We reviewed records for all patients with histologically-proven EC treated by definitive RT at the Fourth Affiliated Hospital of Hebei Medical University between January 2008 to December 2012. The data included data for 174 patients who were enrolled in a retrospective study.

Eligibility criteria

Patients had to have: (1) confirmation of EC by histology; (2) measurable or assessable disease receiving non- operative definitive RT; (3) A Karnofsky performance status of 0-2; (4) Primary tumor grouped according to the AJCC TNM 6th edition staging method; (5) Tumors proved to be located either in cervical and upper or middle and lower thoracic esophagus by endoscopy; (6) No prior history of malignancy or surgical treatment related to thoracic cancers. Patients with a documented distant metastasis (Lung, liver, and bone), tracheoesophageal or esophagomediastinal fistula were excluded. The initial evaluation consisted of a history and physical examination; complete blood cell count; liver function tests; renal function tests; barium esophagography and computed tomography. For financial reasons, details regarding, PET-CT scan were not used for the pretreatment staging and for the eligibility criteria in this study.

Radiation therapy techniques

All patients who were recruited for this study were treated for definitive RT intent, and all received ENI using IMRT. The radiation treatment plans were generated with 3-dimensional planning system (ADAC-Pinnacle 3, version 5.0). The GTV was contoured on the planning CT-scans by using all available resources, including data from barium esophagography, endoscopic images, and diagnostic CT images. The GTV was defined as any visible esophageal lesion and clinically involved node (GTV-nd). The primary criterion for the node metastases was based upon the size: diameter of the short axis ≥ 1.0 cm; diameter of the long axis ≥ 1.5 cm on CT scans. 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. The Planning Target Volume for the lymph node (PTV-nd) was created by expanding the GTV-nd by a minimum of 0.5-1.0 cm radial margin. The PTV was defined as the CTV plus a 0.5-1.0 cm margin. The nodal regions that received ENI were noted as CTV1. Elective treatment of nodal regions depended upon the primary esophageal lesion location (cervical, upper thoracic, middle or lower thoracic esophagus). All organs at risk were outlined including, the total lung volume (and mean lung dose). The heart was contoured from the apex to the base of the right pulmonary artery. In general, patients who had LCBGTV, the prescribed dose was ranged from 46-54Gy/23-28 fractions of 1.8-2Gy, with the requirement that 95% PTV1 receive the prescribed dose during the first-course of RT. The planning objectives placed the highest priority on achieving target volume reduction to the primary esophageal lesion and the metastatic lymph nodes up to a total dose of 58-66Gy/29-33 fractions at a single dose of 1.8-2Gy, with the requirement that 95% GTV/95% GTV-nd receive the prescribed dose during the late- course boost to GTV. For patients receiving SIB-IMRT the GTV and the GTV-nd were simultaneously escalated up to 58.05-65.1Gy/28-31 fractions of 1.95-2.15Gy, with the requirement that 95% PTV/95% PTV-nd receive the prescribed dose, and 95% PTV1 receive 48.6-57.6Gy/28-31 fractions with a single dose of 1.75-1.8Gy. The dose volume parameters of the target area and the organs-at-risk are evaluated based on the isodose curve profile and

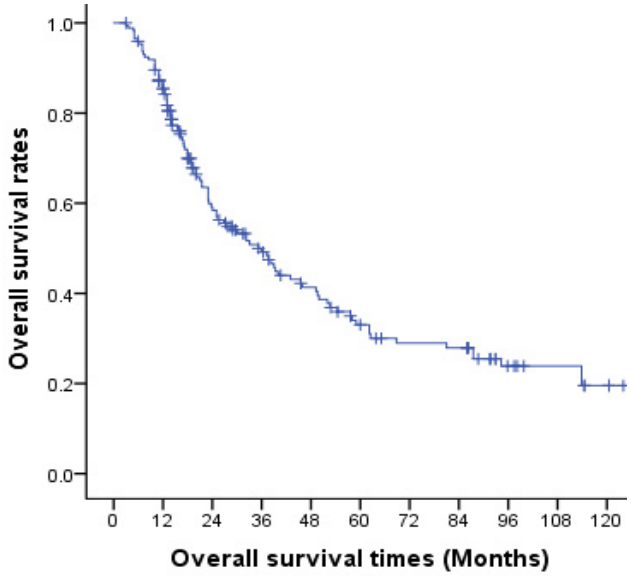

Figure 1: Kaplan-Meier estimates of overall survival for all patients.

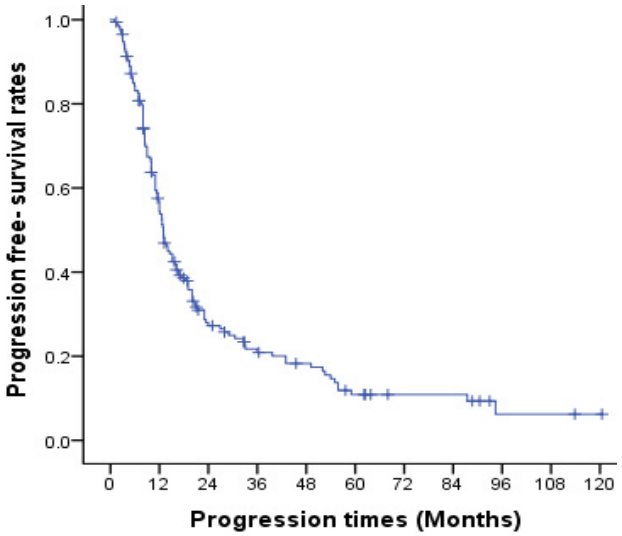

Figure 2: Kaplan-Meier estimates of progression free survival curve for all patients.

Dose Volume Histogram (DVH). The general requirements were 95% PTV/95% PTV1 volume to receive 100% of the prescribed dose, lungs V5 ≤ 60%, V20 ≤ 30%, V30 ≤ 20%, heart Dmean ≤ 30Gy, V25 ≤ 50%, V40 ≤ 30%, spinal cord Dmax ≤ 45Gy (Figure 2).

Surveillance protocol

Most patients were clinically examined by radiation oncologists 1 to 3 months after completion of RT treatment. Chest CT scans and upper part of the abdomen were performed every 3 months for the first 2 years, followed by every 6 months for the subsequent 3 years. We used World Health Organization criteria including Complete Response (CR), Partial Response (PR), No Response (NR), and Progressive Disease (PD) for assessment after completion of RT [11]. All collected data were entered into a database and updated at regular intervals. Complete follow-up information was available for all participants.

Surveillance analysis

Patients' characteristics and acute toxicity of RT regimen were compared using the χ^2 test. Fisher's exact test was used to analyze categorical variables. The actuarial survival rates and time to locoregional or disease progression were the endpoints of this analysis and were dated from the initiation of the RT treatment. Two different types of survival were analyzed; OS and Progression-Free Survival (PFS). The OS was determined as the time between the first day of therapy and the last follow-up or the date of death. The locoregional relapse was determined by a radiologist if there was a significant increase in the volume of the tumor within the esophagus when compared with the previous CT scan. The PFS was defined as the time interval between the starting date of the RT treatment and the date of disease progression, last follow-up or death of any cause. The median OS and PFS were calculated using the Kaplan-Meier method. We used the Kaplan-Meier method to draw survival curves and the log-rank test was employed to evaluate the difference in survival curves between LCBGTV-IMRT and SIB-IMRT groups. Propensity Score Matching (PSM) was performed to reduce selection bias. A 1:1 matched study group was created with the use of the nearest approach for further comparison. To improve the accuracy of statistical results, if significant or trending towards significance on univariate analysis, it was included in the multivariate analysis. The Cox-regression model was used to identify independent prognostic factors for both groups. All these analyses were performed using SPSS (version 22, IBM SPSS). P<0.05 was considered statistically significant.

RESULTS

a.) Patient's characteristics: of 174 patients, who were diagnosed between 2008 and 2012; 123 patients (70.7%) in LCBGTV-IMRT group and 51 patients (29.3%) in SIB-IMRT group, met the inclusion criteria and were included in this study. The clinical characteristics of the two groups are summarized in Table 1. The baseline characteristics were well balanced between the two groups except that LCBGTV-IMRT group had more patients treated with >62 (47.2% vs. 27.5%; χ^2=13.767, p=0.001), more deaths (65.9% vs. 47.1%; χ^2=5.322, p=0.021), and had more patients with PD (83.7% vs. 68.6%; χ^2=5.108, p=0.023) compared with SIB-IMRT group (Table 1)

b.) Toxicity: Esophagitis, anemia, and pneumonitis were the major treatment-induced acute toxicities shown in Table 2. No significant difference was found between patients in LCBGTV-IMRT group and those in the SIB-IMRT group who experienced grade 1-2 or grade 3-4 radiation-related toxicities

c.) Survival: For the whole group, the median OS and PFS were 35.2 months and 13.0 months, respectively. The 1, 3, and 5 year OS and PFS rates were 87.1%, 57.3%, and 50.6% and 21.9%, 33.4%, and 10.8%, respectively (Figures 1 and 2). For the 123 patients in the LCBGTV-IMRT group, the median OS was 32.3 months (95% CI: 21.8-43 months) with a 1,3 and 5 year OS rate of 84.2%, 46.4% and 29.7%, respectively; corresponding median OS time and OS rates for the 51 patients in SIB-IMRT group were 40 months (95% CI: 28.0-52 months), and 94.0%, 61.9% and 45.9%, respectively (χ^2=2.089, p=0.148; Figure 3). The median PFS rates in SIB-IMRT and LCBGTV- IMRT groups were 15.2 months and 12.7 months, respectively. The 1, 3 and 5 year PFS were 61.2%, 24.9% and 20.4% in SIB-IMRT group, corresponding rates of

Table 1: Clinicopathological characteristics of patients with esophageal cancer. According to treatment groups (n=174).

Characteristics	Whole cohort (n= 174)	SIB-IMRT (n=51)	LCBGTV-IMRT (n=123)	χ^2	P
	n%	n%	n%		
Age (mean) years	65.6 ± 7.8	64.7 ± 1.1	66.0 ± 0.7	1.878	0.171
Min-Max	42-85	42-80	44-85		
≤ 60	39 (22.4)	8 (15.7)	31 (25.2)		
>60	135 (77.6)	43 (84.3)	92 (74.8)		
Sex (sex-ratio M/F)	1.5	1.3	1.5	0.163	0.687
Female	71 (40.8)	22 (43.1)	49 (39.8)		
Male	103 (59.2)	29 (56.9)	74 (60.2)		
cTNM stage				2.068	0.15
I-II	105 (60.3)	35 (68.6)	70 (56.9)		
III-IV	69 (39.7)	16 (31.4)	53 (43.1)		
Histology				1.773	0.183
Non-sq. carcinoma	16 (9.2)	7 (13.7)	9 (7.3)		
SCC	158 (90.8)	44 (86.3)	114 (92.7)		
T-location				0.664	0.415
CUT	97 (55.7)	26 (51.0)	71 (57.7)		
MLT	77 (44.3)	25(49.0)	52 (42.3)		

T-length (mean) cm	5.3 ± 1.9	5.2 ± 0.3	5.4 ± 0.2		
Min-Max	1.9-11.7	1.9-11.7	2.0-10.0	0.602	0.438
≤ 5	91 (52.3)	29 (56.9)	62 (50.4)		
>5	83 (47.7)	22 (47.1)	61 (49.6)		
GTV-volume (mean) cm^3	37.4 ± 21.5	41.3 ± 3.0	35.8 ± 1.9		
Min-Max	4.7-117.9	11.3-102.7	4.7-117.9	1.114	1.114
≤ 30	79 (45.4)	20 (39.2)	59 (39.8)		
>30	95 (54.6)	31 (60.8)	64 (60.2)		
RT dose (mean) Gy	62.0 ± 2.4	61.6 ± 29.3	62.0 ± 22.7		
Min-Max	52.0-66.0	52.0-64.4	52.0-66.0		
50.4-60	51 (29.3)	12 (23.5)	39 (31.7)	13.767	0.001
60.1-62.0	51 (29.3)	25 (49.0)	26 (21.1)		
>62	72 (41.4)	14 (27.5)	58 (47.2)		
OS					
Alive	69 (39.7)	27 (52.9%)	42 (34.1)	5.322	0.021
Death	105 (60.3)	24 (47.1%)	81 (65.9)		
LRC					
Yes	44 (25.3)	16 (31.4)	28 (22.8)	1.425	0.49
No	130 (74.7)	35 (68.6)	95 (77.2)		
PD					
Yes	138 (79.3)	35 (68.6)	103 (83.7)	5.018	0.023
No	36 (20.7)	16 (31.4)	20 (16.3)		

Table 2: Acute toxicities of SIB-IMRT and LCBGTV-IMRT (n=174).

Characteristics	Whole cohort (n=174)	SIB-IMRT (n=51)	LCBGTV-ssIMRT (n=123)	χ^2	P
	n%	n%	n%		
Esophagitis (Grades)					
0	78 (44.8)	19 (37.3)	59 (48.0)	2.843	0.241
1-2	88 (50.6)	28 (54.9)	60 (48.8)		
3-4	8 (4.6)	4 (7.8)	4 (3.3)		
Pneumonitis (Grades)					
0	138 (79.3)	42 (82.4)	96 (78.0)	1.046	0.593
1-2	34 (19.5)	9 (17.6)	25 (20.3)		
3-4	2 (1.1)	0 (0.0	2 (1.6)		
Anaemia (Grades)					
0	110 (63.2)	30 (58.8)	80 (65.0)	0.645	0.725
1-2	54 (31.0)	18 (35.3)	36 (29.3)		
3-4	10 (5.7)	3 (5.9)	7 (5.7)		

55.6%, 20.6% and 8.0% for LCBGTV-IMRT group (χ^2=1.976, p=0.160 as shown in Figure 4). There was no significant difference observed between the groups.

Clinicopathological characteristics of the patients in whole group after propensity

Score Matching: Before matching, patients who received SIB-IMRT were younger, had less cTNM stage III-IV diseases, fewer patients treated with >62Gy, had significantly fewer patients with PD and fewer death rates (Table 1; all p<0.05). To reduce the bias in the study, the propensity score model was performed and have included 10 variables (age, sex, cT-stage, N-status, cTNM-stage, T-location, T-length, histology, GTV-volume, and radiation dose). Although the baseline data on PD showed a significant difference between the SIB-IMRT group and LCBGTV-IMRT group, the clinical stage before treatment were quite similar (Table 3).

Comparisons of OS and PFS in the whole group after propensity score matching

Figures 5 and 6 depicts OS and PFS curves for EC patients treated by ENI using SIB-IMRT or LCBGT-IMRT. For the whole group, the median OS and PFS duration were 49.6 months (95% CI: 19.1 to 80.1) and 13.1 months (95% CI: 9.2 to 17.0) respectively. The 5 year OS and PFS rates were 43.6% and 15.7%, respectively. Figure 7 shows the OS of patients who underwent SIB-IMRT and LCBGTV-IMRT group. For the SIB-IMRT group 1, 3 and 5 year OS rates and median survival time were 94.4%, 57.1%,52.4% and 62 months, whereas they were 81.1%, 52.8%, 37.7% and 49 months in LCBGTV-IMR group, respectively. The difference was not significant with a P value of more than 0.05. Figure 8 shows the PFS of patients in SIB-IMRT group and LCBGTV-IMRT group. The median PFS for the SIB-IMRT group and LCBGTV-IMRT

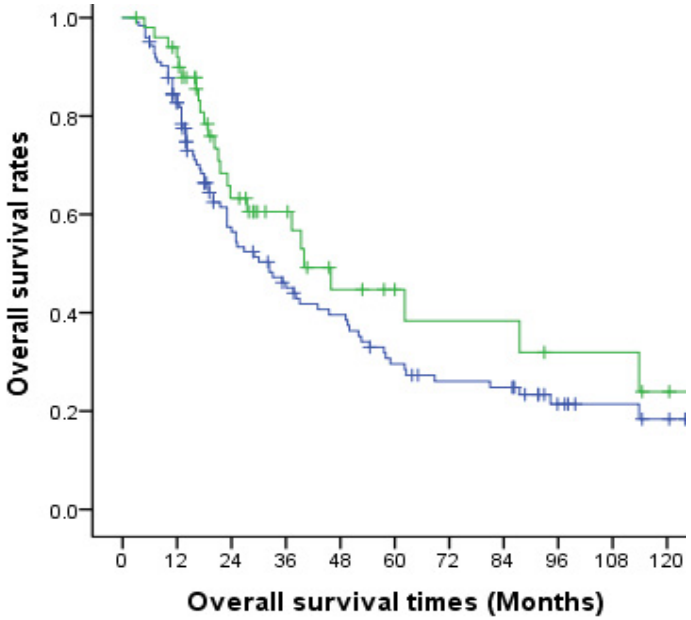

Figure 3: Kaplan Meier curves comparing overall survival rates by different radiotherapy techniques SIB-IMRT vs. LCBGTV-IMRT.

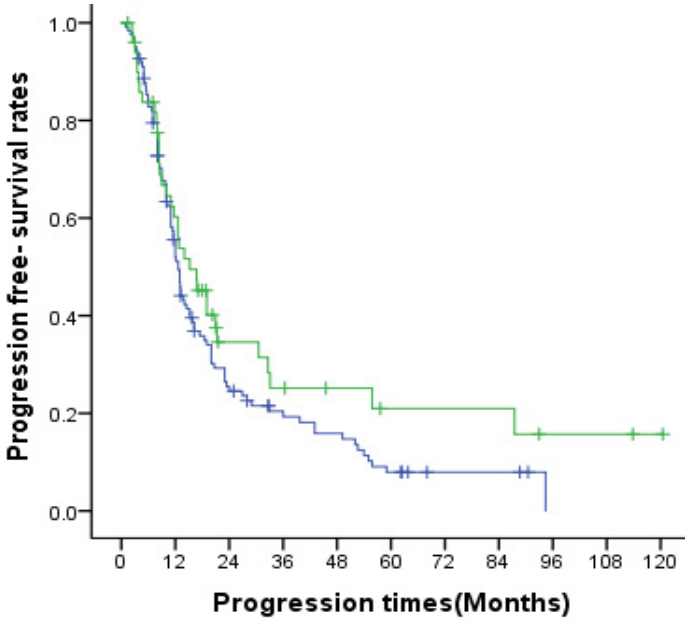

Figure 4: Kaplan Meier curves comparing progression- free survival rates by different radiotherapy techniques SIB-IMRT vs LCBGTV-IMRT.

Table 3: Clinicopathological characteristics of patients after matching.

Characteristics	Whole cohort (n=74)	SIB-IMRT (n=37)	LCBGTV-IMRT (n=37)	X^2	P
	n%	n%	n%		
Age (mean) years	65.5 ± 7.5	65.2 ± 8.4	65.8 ± 6.7	0.294	0.588
Min-Max	42-85	42-80	50-85		
≤60	18 (24.3)	8 (21.6)	10 (27.0)		
>60	56 (75.7)	29 (78.4)	27 (73.0)		
Sex (sex-ratio M/F)	1.2	1.2	1.3	0.055	0.815
Female	33 (44.6)	17 (45.9)	16 (43.2)		
Male	41 (55.4)	20 (54.1)	21 (56.8)		
cTNM stage				0.5	0.48
I-II	43 (58.1)	23 (62.2)	20 (54.1)		
III-IV	31 (41.9)	14 (37.8)	17 (45.9)		
Histology				0.126	0.722
Non-sq. carcinoma	9 (12.2)	5 (13.5)	4 (10.8)		
SCC	65 (90.6)	32 (86.5)	33 (89.2)		
T-location				0.897	0.344
CUT	44 (59.5)	20 (54.1)	24 (64.9)		
MLT	30 (40.5)	17 (45.9)	13 (35.1)		
T-length (mean) cm	5.6 ± 2.1	5.6 ± 2.1	5.6 ± 2.0	0.054	0.816
Min-Max	1.9-11.7	1.9-11.7	2.0-9.8		
≤5	35 (47.3)	17 (45.9)	18 (48.6)		
>5	39 (52.7)	20 (54.1)	19 (51.4)		
GTV-volume (mean) cm^3	38.2 ± 21.0	42.4 ± 22.7	34.0 ± 18.6	0.881	0.348
Min-Max	4.7-102.7	13.8-102.7	4.7-80.7		
≤30	32 (43.2)	4 (37.8)	18 (48.6)		
>30	42 (56.8)	23 (62.2)	19 (51.4)		
RT dose (mean) Gy	62.0 ± 2.5	61.6±2.4	62.0 ± 2.7	1.097	0.578
Min-Max	52.0-64.4	52.0-64.4	52.0-66.0		
50.4-60	20 (27.0)	12 (32.4)	8 (21.6)		
60.1-62.0	26 (35.1)	12 (32.4)	14 (37.8)		
>62	28 (37.8	13 (35.1	15 (40.5)		

OS					
Alive	34 (45.9)	19 (51.4%)	15 (40.5)	0.871	0.351
Death	40 (54.1)	18 (48.6%)	22 (59.5)		
LRC					
Yes	44 (59.5)	25 (67.6)	19 (51.4)	1.425	0.49
No	30 (40.5)	12 (32.4)	95 (48.6)		
*PD					
Yes	53 (71.6)	22 (59.5)	31 (83.8)	5.385	0.02
No	21 (28.4)	15 (40.5)	6 (16.2)		

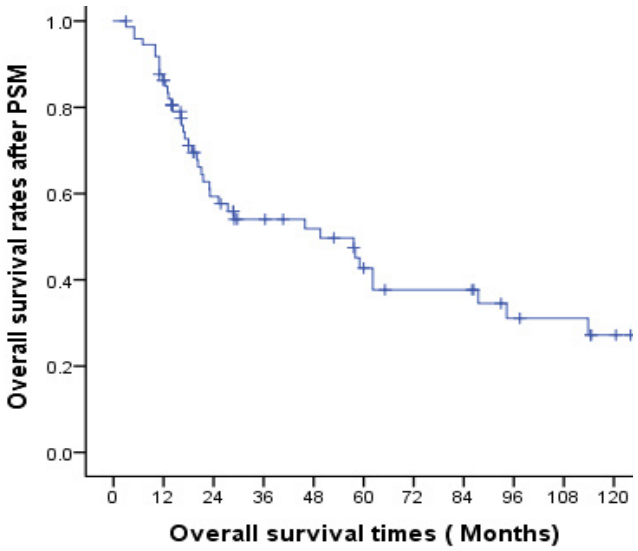

Figure 5: Propensity matched Kaplan Meier overall survival curve for all patients.

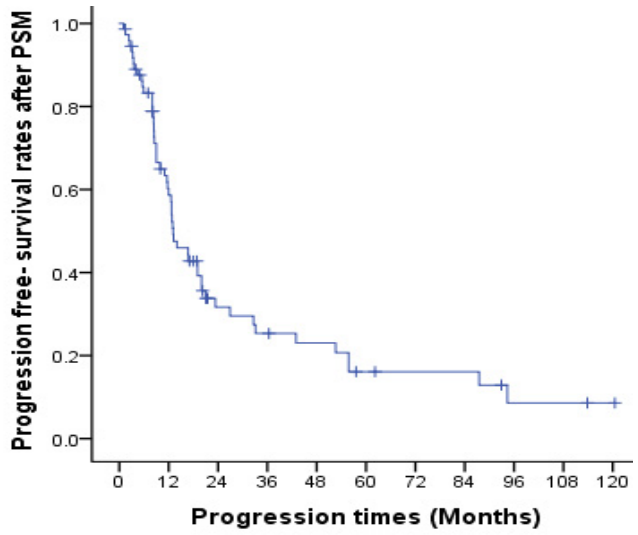

Figure 6: Propensity-matched Kaplan Meier progression-free survival curve for all patients.

group were 19 months and 12 months, respectively. The 1, 3 and 5 year PFS rates were 68.6%, 33.7%, and 27.6% in SIB-IMRT group, which were significant higher than that of 53.6%, 16.8%, and 6.7% in LCBGTV-IMRT group (χ^2=5.357, p=0.021).

Prognostic factors for OS and PFS in the whole group after propensity score matching

The univariate analysis for OS by the log-rank test was performed according to age, sex, initial stage (including T, N, and M stage), tumor location, histological subtype, dysphagia grade, tumor

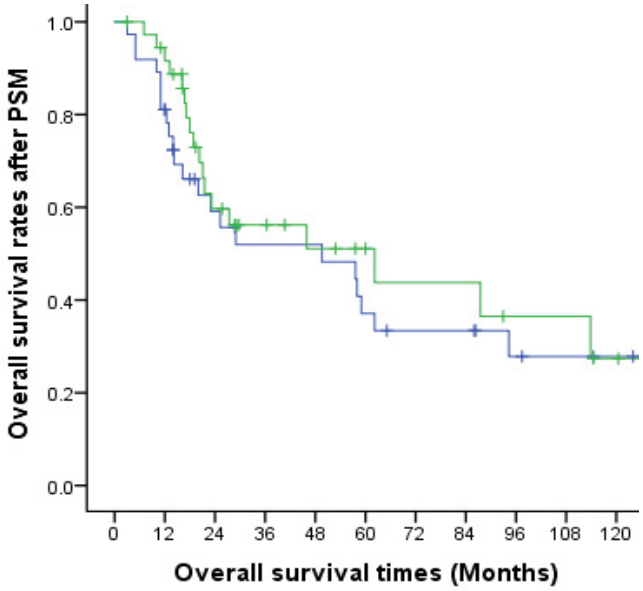

Figure 7: Propensity-matched Kaplan Meier curves comparing overall survival rates by treatment method SIB- IMRT vs. LCBGTV- IMRT.

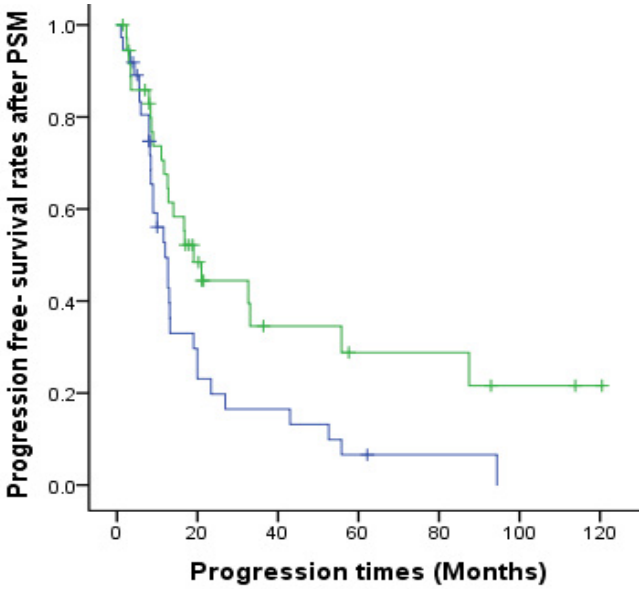

Figure 8: Propensity-matched Kaplan Meier curves comparing progression free - survival rates by treatment method SIB-IMRT vs. LCBGTV-IMRT.

length, GTV-volume, and radiation dose (Table 4). Among these factors, cT3- 4stage (p=0.008), cTNM- stage III-IV (p=0.000), SCC (p=0.024), and GTV-volume >30cm^3 (p=0.010) were found to be associated with significantly poor prognosis. Multivariate analysis showed that the cTNM-stage was an independent prognostic factor for OS (all p=0.000; Table 5). By contrast, there was no significant

Table 5: Univariate analysis of the effect of potential prognostic factors on PFS in patients with esophageal cancer treated by ENI using SIB-IMRT and LCBGTV-IMRT after PSM (n=74).

Prognostic factors	n	PFS (%)			χ^2	P
		1 yr	3 yr	5 yr		
Age						
≤ 60	18	47.1	20.9	0.0	1.112	0.292
>60	56	65.7	26.4	20.5		
Sex						
Male	41	55.3	25.3	10.8	0.204	0.651
Female	33	68.3	25.9	18.5		
cT-stage						
T1-2	28	60.0	28.5	18.7	0.376	0.540
T3-4	46	61.9	23.8	14.3		
N-status						
N0	33	56.3	18.3	14.6	0.383	0.536
N1+2	41	65.3	32.4	15.3		
cTNM-stage						
I-II	43	61.9	29.4	20.2	1.644	0.200
III-IV	31	60.0	18.3	0.0		
T-location						
CUT	44	58.5	18.2	11.2	2.919	0.088
MLT	30	64.9	36.5	23.2		
Histology						
Non-sq. carcinoma	9	52.9	38.0	37.8	0.338	0.561
SCC	65	62.3	23.6	13.2		
T-length (cm)						
≤ 5	35	60.6	25.5	16.2	0.093	0.760
>5	39	61.6	26.4	15.9		
Dysphagia (Grade)						
0-2	29	51.9	13.0	12.5	3.826	0.050
3-4	45	67.1	32.6	19.0		
GTV-volume (cm^3)						
≤ 30	32	70.5	26.6	22.5	1.726	0.189
>30	42	53.8	26.1	10.4		
RT-dose (Gy)						
50.4-60	20	48.7	35.7	16.1	0.299	0.861
60.1-62	26	70.2	23.2	15.4		
>62	28	62.3	20.8	15.6		

correlation between potential prognostic factors and PFS (p>0.05 for analysis, shown in Table 6).

Prognostic factors for OS and PFS in subgroup after propensity score matching

To identify patients who will benefit from SIB-IMRT using ENI, OS and PFS comparisons between SIB-IMRT group and LCBGTV-IMRT in subgroups of patients with different characteristics were conducted. Overall, patients were stratified by age, gender, cT-stage, N-status, cTNM-stage, tumor location, histology, GTV-volume and radiation dose. The PFS in SIB-IMRT group was significantly improved in patients who were male, age >60 years, middle and lower thoracic location, with cTNM- stage I-II, GTV (>30 cm^3) and radiation dose of >62Gy, compared with LCBGTV-IMRT (Table 7). In addition, patients with GTV (>30 cm^3) were also more likely to demonstrate an OS benefit from in SIB-IMRT from definitive radiotherapy (Table 8).

DISCUSSION AND CONCLUSION

Radiotherapy (RT) is widely recognized as one of the main treatment options for patients who have unrespectable EC, who decline surgery, or who are medically unfit for chemotherapy or surgery. The NCCN and European guidelines provide recommendations for RT planning, including radiation dose and target volume. However, although current therapies can be quite effective in some cases, local disease control, specifically within the GTV, remains a problem. This study was conducted to assess the prognostic factors for EC treated by ENI using LCBGTV-IMRT or SIB-IMRT, and to help us to choose treatment strategies appropriate for individual patients. Our results comparing the efficacy of LCBGTV-IMRT and SIB-IMRT confirmed that patients who underwent SIB-IMRT had significantly higher PFS rates than

Table 6: Multivariate analysis of the effect of potentials prognostic factors on OS and PFS in patients with esophageal cancer treated by ENI using SIB-IMRT and LCBGTV-IMRT (n=74).

Parameters	Prognosis factors	B	SE	Wald	Sig
OS	*cTNM-stage	1.327	0.352	14.253	0.000
	Histology	-1.716	1.017	2.845	0.092
PFS	T-location	-0.274	0.290	0.397	0.344
	Dysphagia	0.184	0.292	0.894	0.529

Table 7: Subgroup comparison of patients with different characteristics after PSM

Prognostic factors	RT-techniques	n	Overall survival (%)			χ^2	*P*
			1yr	3yrs	5yrs		
Age							
≤60	SIB-IMRT	8	87.5	34.0	33.6	1.612	0.204
	LCBGTV-IMRT	10	80.0	68.6	51.4		
>60	SIB-IMRT	29	96.4	63.9	57.6	2.090	0.148
	LCBGTV-IMRT	27	81.5	47.5	33.3		
Sex							
Male	SIB-IMRT	20	94.7	47.3	36.8	0.301	0.583
	LCBGTV- IMRT	21	80.9	54.3	42.3		
Female	SIB-IMRT	17	94.1	68.2	68.0	2.028	0.154
	LCBGTV- IMRT	16	81.3	51.7	31.0		

Ct-stage							
T1-2	SIB-IMRT	14	92.6	75.0	74.8	0.360	0.549
	LCBGTV- IMRT	14	100	68.4	51.3		
T3-4	SIB-IMRT	23	95.6	47.8	38.2	0.593	0.441
	LCBGTV-IMRT	23	69.6	43.1	28.7		
N-status							
N0	SIB-IMRT	17	94.1	66.4	56.1	0.257	0.612
	LCBGTV- IMRT	16	87.5	61.0	60.6		
N1+2	SIB-IMRT	20	94.7	49.0	48.8	1.644	0.200
	LCBGTV-IMRT	21	76.2	46.6	19.9		
cTNM-stage							
I-II	SIB-IMRT	23	95.6	66.0	65.9	0.368	0.544
	LCBGTV- IMRT	20	100	77.1	69.4		
III-IV	SIB-IMRT	14	92.6	42.1	25.3	1.017	0.313
	LCBGTV-IMRT	17	58.8	26.8	6.7		
T-location							
CUT	SIB-IMRT	20	89.7	65.6	54.7	0.904	0.342
	LCBGTV- IMRT	24	79.2	50.3	33.5		
MLT	SIB-IMRT	17	100	47.0	46.6	0.252	0.618
	LCBGTV-IMRT	13	84.6	57.3	45.8		
Histology							
Non-sq. carcinoma	SIB-IMRT	5	100	78.0	77.7	0.600	0.439
	LCBGTV- IMRT	4	100	100	100		
SCC	SIB-IMRT	32	93.5	53.9	48.5	0.735	0.391
	LCBGTV- IMRT	33	78.8	48.1	32.1		
T-length (cm)							
≤5	SIB-IMRT	17	87.5	63.2	63.0	0.681	0.409
	LCBGTV- IMRT	18	83.3	51.3	43.9		
>5	SIB-IMRT	20	100	53.8	44.9	0.206	0.650
	LCBGTV- IMRT	19	78.9	54.1	30.9		
GTV volume (cm^3)							
≤30	SIB-IMRT	14	85.2	68.0	68.0	0.009	0.923
	LCBGTV- IMRT	18	94.4	70.3	51.2		
>30	SIB-IMRT	23	100	51.2	42.7	2.985	0.084
	LCBGTV- IMRT	19	68.4	33.9	22.6		
RT dose (Gy)							
50.4-62	SIB-IMRT	12	50.0	39.0	38.8	0.014	0.907
	LCBGTV- IMRT	8	46.6	31.1	0.00		
60.1-62	SIB-IMRT	12	80.9	36.8	0.00	0.897	0.344
	LCBGTV- IMRT	14	61.5	18.0	17.6		
>62	SIB-IMRT	13	76.0	34.0	33.8	2.325	0.127
	LCBGTV- IMRT	15	50.0	8.3	0.00		

those who underwent LCBGTV-IMRT. In terms of local control, although the difference did not reach statistical significance, those patients who received LCBGTV-IMRT had less local control rates than those who received SIB-IMRT and is associated with a poor survival prognosis. Currently, the study showed that local relapse after nonsurgical treatment for unresectable EC mostly develops in the region of GTV that led radiation oncologist to increase dose in primary lesion [12]. However, although dose-escalation to the primary GTV has been shown to improve local control and survival in patients with tumors at other anatomic sites [13] caution is needed in applying this logic to EC. As the esophagus has a close connection to several critical structures, care must be taken to ensure that improvements in local control are not achieved at the cost of greater morbidity. Meanwhile, even though we found that GTV was the most common site of initial failure 15%-23%, most patients will eventually develop distant metastasis; thus, efforts to increase local control may not necessarily transform into improved survival. Of the 174 patients enrolled in this study, 51 patients (29.3%) had 50.4-60Gy, 51 patients (29.3%) had 60.1-62Gy and 72 patients (41.4%) had more than 62Gy. The 3-year OS and PFS rates were 58.3% and 30.7% for the standard dose levels of 50.4-60Gy; 47.1%, and 20.1% and 46.9%, and 12.8% for the doses levels of 60.1- 62Gy and >62Gy, respectively (all p>0.05,

Table 8: Subgroup comparison of patients with different characteristics after PSM.

Prognostic factors	RT-techniques	n	Progression free- survival (%)			χ^2	*P*
			1yr	3yrs	5yrs		
*Age							
≤60	SIB-IMRT	8	60.0	30.0	0.00	1.584	0.280
	LCBGTV- IMRT	10	36.8	12.3	0.00		
>60	SIB-IMRT	29	70.9	34.2	34.0	3.336	0.067
	LCBGTV- IMRT	27	60.0	18.5	9.2		
*Sex							
Male	SIB-IMRT	20	67.6	38.8	12.9	4.160	0.041
	LCBGTV- IMRT	21	43.6	12.5	6.2		
Female	SIB-IMRT	17	69.7	29.2	29.0	1.147	0.284
	LCBGTV- IMRT	16	66.7	22.2	7.4		
*cT-stage							
T1-2	SIB-IMRT	14	70.4	35.9	31.5	1.582	0.209
	LCBGTV- IMRT	14	50.0	21.4	14.3		
T3-4	SIB-IMRT	23	67.4	35.3	35.0	3.260	0.071
	LCBGTV- IMRT	23	56.1	12.5	0.00		
*N-status							
N0	SIB-IMRT	17	69.7	19.2	21.9	2.750	0.097
	LCBGTV- IMRT	16	41.9	7.0	6.9		
N1+2	SIB-IMRT	20	67.6	39.0	38.7	2.260	0.133
	LCBGTV- IMRT	21	63.2	25.3	6.3		
*cTNM-stage							
I-II	SIB-IMRT	23	73.3	36.0	29.5	3.815	0.051
	LCBGTV- IMRT	20	48.7	21.7	10.8		
III-IV	SIB-IMRT	14	60.0	33.3	-	0.587	0.443
	LCBGTV- IMRT	17	60.0	8.6	0.00		
*T-location							
CUT	SIB-IMRT	20	62.2	15.0	14.7	0.031	0.860
	LCBGTV- IMRT	24	55.6	20.2	10.2		
MLT	SIB-IMRT	17	75.8	59.8	46.5	6.485	0.011
	LCBGTV- IMRT	13	50.0	10.0	0.00		
*Histology							
Non- sq. carcinoma	SIB-IMRT	5	100	71.4	71.0	7.658	0.006
	LCBGTV- IMRT	4	-	-	-		
SCC	SIB-IMRT	32	63.9	27.9	20.9	1.678	0.195
	LCBGTV- IMRT	33	60.7	18.9	7.5		
*T-length (cm)							
≤5	SIB-IMRT	17	67.7	34.5	20.7	1.276	0.259
	LCBGTV- IMRT	18	54.3	18.1	12.1		
>5	SIB-IMRT	20	69.2	36.3	36.0	5.293	0.021
	LCBGTV- IMRT	19	52.9	15.1	0.00		
*GTV volume (cm^3)							
≤30	SIB-IMRT	14	84.6	39.0	38.5	4.978	0.026
	LCBGTV- IMRT	18	60.0	18.0	12.0		
>30	SIB-IMRT	23	59.1	34.2	22.8	1.859	0.173
	LCBGTV- IMRT	19	47.1	15.7	0.00		
*RT dose (Gy)							
50.4-62	SIB-IMRT	12	50.0	39.0	38.8	0.784	0.376
	LCBGTV-IMRT	8	46.7	31.1	0.00		
60.1-62	SIB-IMRT	12	80.9	36.8	0.00	0.305	0.581
	LCBGTV- IMRT	14	61.5	17.6	18.0		
>62	SIB-IMRT	13	76.0	34.0	33.7	6.624	0.010
	LCBGTV- IMRT	15	50.0	8.3	0.00		

Tables 4 and 5). In the literature, data concerning the efficacy of dose escalation in unresectable EC patients have also confirmed the lack of survival benefit when comparing various dose levels to 50-50.4Gy, specifically the dose range encompassing 64.8Gy [6]. This implies that the improvement of dose escalation to GTV for OS might be limited. A potential explanation from our study might be the high proportion of death attributed to the PD. Indeed, we found that among 71.6% (53/74) of patients with PD, 83.8% (31/37) were allocated in LCBGTV-IMRT group, while this rate was lower 59.5% (22/37) in SIB-IMRT group (χ^2=5.385, p=0.020, Table 3). Besides, a retrospective study reported by James et al. suggested that the 64.8Gy SIB-IMRT led to increased radiation dose by 28% to the primary GTV-volume while simultaneously achieving substantial reductions in cardiac and pulmonary dose [6]. From the radiobiological standpoint, Fu W [14] also demonstrated that SIB-IMRT significantly reduced normal organs doses compared with a sequential boost using 3D-CRT. In the present study, we first applied SIB-IMRT that delivered GTV/GTV-nd at 58.05-65.1Gy/28-31 fractions of 1.95-2.15Gy, with the requirement that 95% PTV/PTV-nd receive the prescribed dose, and 95% PTV1 receive 48.6-57.6Gy/28-31 fractions with a single dose of 1.75-1.8Gy.The dose could be escalated in a single plan for the whole treatment plan, but still met dose constraints to critical normal structures such as the lung, spinal cord, and heart. With this approach, we observed that patients who underwent SIB-IMRT had both better PFS and OS compared to those treated by LCBGTV-IMRT (Figures 7 and 8). We used propensity score-matched analysis to reduce bias introduced by the non-random assignment of the two regimens being compared. Further studies are warranted to confirm these results.

On the other hand, Wei Wei Y in phase III clinical study using SIB-IMRT indicated that the 1 and 3 year OS rate were 75.6% and 42.2%, the median of follow-up was 21 months, with the 1 year and 3 years PFS rate of 59.8% and 40.7%, respectively [15]. Our results showed a median survival of 40.0 months' range (28.0-51.9 months), with the 1, 3 and 5 year OS rate of 94.4%, 57.1%, and 52.4% in SIB-IMRT group, respectively. The 1, 3 and 5 year PFS was 68.6% 33.7%, and 27.6% corresponding PFS rates for LCBGTV-IMRT group of 53.6%, 16,8%, and 6.7% (χ^2=5.357, p=0.021, Figure 8). Growing evidence has now accrued that ENI using SIB-IMRT might not only improve patient's locoregional control but also allow substantial improvement patient's PFS and OS thus, ultimately improving clinical outcomes. Therefore, we believe that SIB-IMRT may be beneficial to EC patients with strict normal structure limits are applied to alleviate excess toxicity. By contrast, it was impossible to compare treatment-related late toxicity between the groups due to the lack of information in this study, making it difficult to prove the feasibility of ENI using SIB-IMRT after long-term follow-up. The mean radiation dose delivered with SIB-IMRT was 61.6Gy (95% CI: 52.0-64.4Gy), whereas 62.0Gy (95% CI: 52.0-66.0Gy) was for LCBGTV-IMRT. There was no significant difference between patients treated by LCBGTV-IMRT and those treated by SIB-IMRT who experienced acute grade 3-4 esophagitis, anemia, and pneumonitis radiation-related toxicities (p>0.05 for all analysis, Table 2). Of note, the sample size of SIB-IMRT group in our study was still small (n=51).

As many variables could potentially be responsible for the observed lack of survival benefit, independent of potential confounding variables, Urba SG reported that female sex, Charlson-Deyo score 0 and 1, cervical/upper esophagus location, squamous cell histology, lower T-stage, and node negative were independent and predictive for improved OS [6] In the current study, although cTNM stage, histology, and GTV-volume were of significant prognostic relevance for OS, multivariate analysis after the PSM confirmed that cTNM-stage was a significant and independent prognostic factor for OS (p<0.05, Table 6). Furthermore, an additional group analysis was performed examining the effect of RT on PFS based upon the patient's age, gender, cTNM-stage, histology, T-location, T-length, GTV-volume, and radiation dose. In this setting, there was no positive correlation between PFS and potential prognostic factors (all p>0.05; Table 6). Previous studies reported that tumor stage is one of the most meaningful prognostic factors in estimating survival rates including depth of tumor invasion, nodal involvement, and distant metastases [16]. Data from Boggs's [17] study indicated that GTV was a significant predictor for improved PFS (p=0.030), and OS (p=0.0012) in EC. Additionally, they concluded that GTV was a more powerful predictor of patient outcome than traditional TNM staging. Our results are consistent with their conclusion. Overall, in the present study, cTNM-stage III-IV and GTV (>30 cm^3) were unfavorable survival prognosis in the two groups (Tables 4-6). We thought with the best of our knowledge that the GTV-volume and the traditional cTNM staging are both a somewhat subjective measure because they rely on the physician's judgment. Inter-observer variability in the GTV-volume and TNM definition are well known, which could limit the universality of the results. Besides, the significant histology effect under univariate analysis in the present study appears to be primarily due to the small size of non-squamous cell carcinoma subtype (n=16/174) and probably to the confounding effect of radiation dose. Studies with a larger number of patients with a wide range non- squamous cell carcinoma in SIB-IMRT group will be needed to confirm the reported association. To evaluate the role of definitive RT using ENI in patients with different characteristics and the influence of different prognostic factors, we performed the subgroup analysis. The results showed that compared to SIB-IMRT, LCBGTV-IMRT tends to be associated with poor PFS in the following subgroups: male, aged >60 years, cT3-4 stage, No-1 status, middle and lower thoracic location, with cTNM-stage I-II, GTV (≤ 30 cm^3), and in those patients who received more than 62Gy (Table 8). These findings are consistent with a report that small-sized or hypervascularized tumors are easier to eradicate than larger or hypo vascularized tumors when treated with the same amount of radiation. Our data also suggested that SIB-IMRT improves survival in the subgroup of patients with GTV-volume 30 cm^3 (42.7% vs 22.6% if LCBGTV- IMRT) (Table 7). These findings led us to conclude that: 1different treatment modalities may lead to the different results and the used of ENI and SIB-IMRT may be superior to a sequential boost in GTV (LCBGTV- IMRT); 2 the addition of ENI to simultaneous integrated boost may also play a role in locoregional control and systemic cancer progression.

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