Comparison of Simultaneous Integrated Boost and Late-course Boost Intensity-modulated Radiation Therapy in the Treatment of Esophageal Carcinoma

Yu Xiao
Affiliated Hospital of North Sichuan Medical College
Guobo Du
Affiliated Hospital of North Sichuan Medical College
Jianping Hu
Affiliated Hospital of North Sichuan Medical College
Tingting Wu
Affiliated Hospital of North Sichuan Medical College
Xue Meng
Affiliated Hospital of North Sichuan Medical College
Bangxian Tan (tbx_nsmc@126.com)
Affiliated Hospital of North Sichuan Medical College

Research Article

Keywords: esophageal neoplasm, simultaneous dose boost, late-course dose boost, intensity-modulated radiotherapy, curative effect, prognosis

Posted Date: August 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-835617/v1

Comparison of simultaneous integrated boost and late-course boost intensity-modulated radiation therapy in the treatment of esophageal carcinoma

Yu Xiao[a, b], Guobo Du[a], Jianping Hu[a], Tingting Wu[a], Xue Meng[a], Bangxian Tan[a]

[a] Department of Oncology, Affiliated Hospital of North Sichuan Medical College, Nanchong, People's Republic of China

[b] Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou , People's Republic of China.

Correspondence: BangXian Tan* Department of Oncology, Affiliated Hospital, North Sichuan Medical College, Maoyuan Road, Shunqing District, Nanchong City, Sichuan Province , 637000 , People's Republic of China

Tel +86 139 9077 0815

Email: tbx_nsmc@126.com

Comparison of simultaneous integrated boost and late-course boost intensity-modulated radiation therapy in the treatment of esophageal carcinoma

Abstract

This paper aimed to analyze and compare the outcomes of esophageal carcinoma treated with simultaneous integrated boost intensity-modulated radiation therapy (SIB-IMRT) and late-course boost intensity-modulated radiation therapy (LCB-IMRT). The retrospective study was designed to analyze the clinical data of 274 esophageal cancer patients who received radical radiotherapy in the Oncology Department of our hospital, from January 2014 to December 2017. Propensity score matching analysis was used to balance the variable differences in the two groups. Survival, toxicities, and target dose were observed and compared between the two groups. Statistical analysis was performed using SPSS 24.0 software. $P<0.05$ judged to be statistically significant. 200 patients were finally included after propensity scores matching , The 1-, 3-, and 5-year overall survival and local control rates of the entire group were 80.5% vs. 67.6%, 38.2% vs. 31.3%， and 22.2% vs. 20.4%, respectively. The 1-, 3-, and 5-year overall survival rates of the SIB-IMRT and LCB-IMRT group were 85.0% vs. 76.0%, 41.8% vs. 34.5%, and 25.5% vs. 21.3%, respectively ($P>0.05$). The 1-, 3-, and 5-year local control rates of the SIB-IMRT and LCB-IMRT group were 77.3% vs. 58.0%, 31.4% vs. 30.1%, and 20.0% vs. 20.7%, respectively ($P>0.05$). The recent total effective rates of the SIB-IMRT and LCB-IMRT group were 96.0% vs. 92.0% ($P>0.05$). There were statistically significant differences in the incidence of ≥2 grade acute radiation esophagitis and pneumonia

between the two groups（$P<0.05$）. The does of lung V5, lung V10, lung Dmean, and spinal cord Dmax in the SIB-IMRT group were significantly lower than those in LCB-IMRT group ($P < 0.05$). Patients age, tumor location, tumor length, gross tumor target volume, N stage were independent prognostic factors of overall survival and local control. Compared with the LCB-IMRT group, the survival prognosis of the SIB-IMRT group has benefit trend, patients in the SIB-IMRT group received less radiation dose to the normal organs around the target area, and the toxicities effects of radiotherapy were lighter, which is more conducive to the protection of normal tissues around the target area.

Keywords: esophageal neoplasm; simultaneous dose boost; late-course dose boost; intensity-modulated radiotherapy; curative effect; prognosis

Introduction

Esophageal cancer (Esophageal Cancer, EC) is one of the most common malignant tumors in the world. According to the data released by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) after the global epidemiological survey of malignant tumors in 2020, the incidence of esophageal cancer ranks seventh and the mortality ranks sixth in the world[1]. Its high morbidity and mortality pose a great threat to public health. In different countries or regions of the world, the incidence of esophageal cancer is different, and the pathological types are also significantly different due to regional diet, culture, race and other differences. The number of cases of esophageal cancer in China accounts for about half of the world, and the main pathological type is squamous cell carcinoma (SCC), while the incidence of esophageal cancer in Europe and the United States and other developed countries and regions is relatively low, the main pathological type is adenocarcinoma (Adenocarcinoma, AC), accounting for about 70%[2].

Due to insufficient promotion of annual endoscopic screening, more than half of the patients in the advanced stages of the disease when they were first diagnosed, often with difficulty in eating, poor nutritional status. For patients with inoperable esophageal cancer, definitive radiotherapy plus concurrent

chemotherapy were usually considered to be the standard treatments3,4. A radiation dose of 50.4 Gy was recommended 5,6. However, recent research showed that the dose of 50.4Gy cannot achieve satisfactory local control rate and survival rate7, the 5-year overall survival rate ranges from 15% to 35% 8,9.

In most Asian countries, 60 Gy was a more commonly used radiation dose10, it has been proved that the total dose exceeding 60Gy can be used safely. However, there is no clear evidence that increasing dose can bring survival benefit and improve local control rate[11,12]. Therefore, a practical clinical method to solve the problem of local failure and regional dose increase after treatment may be to change the mode of radiotherapy. A technique called “late course boost” was commonly used, which can achieve this dose without significantly increasing the incidence of toxicities. However, it requires re-simulation and re-planning in one treatment course. At the beginning of the 21st century, radiation oncologists created the SIB-IMRT technique, it can better protect the surrounding normal tissues and organs while increasing the radiation dose to the target area. Also, it can simultaneously make local tumors receive relatively higher radiation doses within the same radiotherapy plan, thereby shortening the treatment time and saving patients' economic costs[13,14]. SIB-IMRT radiotherapy technology has

achieved significant results in radiotherapy research on a variety of solid tumors[15-18]. Due to the potential risks of bleeding or perforation, SIB-IMRT has not been generally used for treatment of esophageal cancer, therefore there is no large number of comparative studies on the SIB-IMRT and LCB-IMRT.

The esophagus is a hollow organ and is surrounded by important organs of the human body, such as heart, spinal cord, lung and so on, more attention should be paid to avoid the risk of esophageal perforation and bleeding while increasing the dose of single radiotherapy for local lesions of esophageal tumors, and the protection of surrounding normal tissues and organs. At present, most studies on the efficacy and safety of SIB-IMRT technology in the treatment of esophageal cancer are positive. Several studies have proved that SIB-IMRT technology in the treatment of esophageal cancer is safe and feasible, and the toxicity is in the acceptable range [19-21]. However, most of the current studies are short-term efficacy observation, and the lack of large samples of clinical control studies. Therefore, the purpose of this study is to compare the short-term and long-term effects and toxicities of the two modes of radiotherapy for esophageal cancer, namely, SIB-IMRT and LCB-IMRT, and to provide individualized treatment strategies for patients with esophageal carcinoma.

Materials and methods

Inclusion and exclusion criteria. 1. patients with unoperated esophageal cancer confirmed by pathology; 2. patients with good general condition, Kps score ≥ 70; 3. patients who can eat general, soft, semi-liquid or liquid food; 4. imaging and clinical symptoms without signs of esophageal perforation or bleeding; 5. the first course of radiotherapy with SIB-IMRT or LCB-IMRT. 6. all patients received radical radiotherapy ±chemotherapy; 7. all patients knew about each treatment and operation, and signed the informed consent form.

Exclusion criteria. 1. esophageal perforation and bleeding before radiotherapy; 2. esophageal cancer surgery; 3. distant organ metastasis; 4. combined with other organ malignant tumors confirmed by pathology; 5. the total dose of radiotherapy was less than 50Gy; 6. radiotherapy was interrupted more than 2 weeks.

Treatment. The patient was placed in supine position with head cushion and pillow, and the body/neck and shoulder were fixed with thermoplastic film. Simulated localization under CT machine, and enhanced scanning of chest + neck/lower neck and upper abdomen was performed according to the specific lesion site of the tumor, with a thickness of 3mm.The scanned images are transmitted to the Treatment Planning System (TPS). In

combination with CT localization images, esophageal X-ray imaging, esophagogastroscopy, esophageal ultrasound, PET-CT and other imaging data, the radiotherapy physicians delineated gross tumor target volume (GTV), clinical target volume (CTV), planned target volume (PTV) and organs at risk (OAR) in the treatment planning system. Esophageal lumen diameter without gas > 1.0cm and esophageal wall thickness > 0.5cm were considered as primary esophageal tumor lesions. Para-esophageal, para-esophageal airway and pericardial Angle lymph nodes with diameters > 0.5cm, para-aortic and left gastric lymph nodes with diameters > 0.5cm, clusters of ≥3 small lymph nodes in the same lymph node drainage area, PET-CT positive lymph nodes and mediastinal lymph nodes with diameters > LCM were all determined as metastatic lymph nodes. GTV included primary esophageal tumor lesion (GTV1) and metastatic lymph node (GTVnd). The clinical target volume (CTV1) was 0.5cm to 0.8cm before and after the primary tumor GTV, 3.0cm above and below, and adjusted according to the anatomical barriers. CTVnd was 0.5cm evenly expanded in all directions of GTVnd. All patients in the whole group were subjected to preventive irradiation in the lymph drainage area. The delineation range of CTV varied according to different lesion sites. CTV covers CTV1 and CTVnd. The planned target volume (PTV) is 0.5cm evenly

expanded to all sides based on CTV. In addition, the target area of radical radiotherapy for esophageal cancer should be delineated as spinal cord, lung, heart and other organs at risk. (Figure.1a, 1b, 1c and 1d)

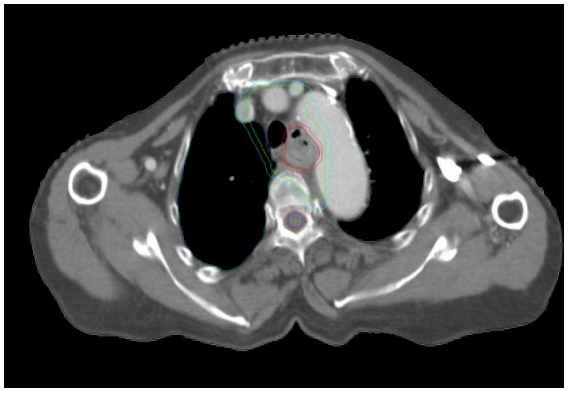

Figure 1a Schematic diagram of the target area of radical radiotherapy for esophageal cancer（SIB-IMRT）

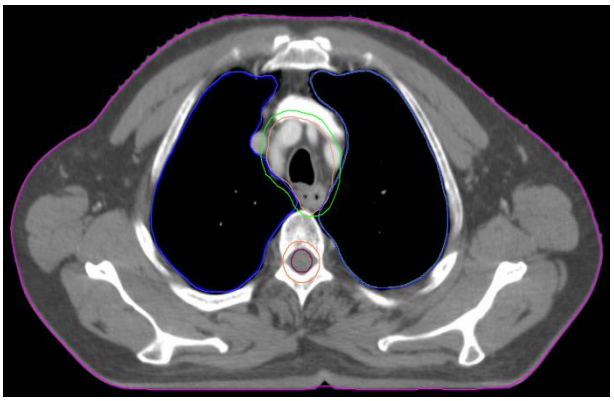

Figure 1b Schematic diagram of the target area of radical radiotherapy for esophageal cancer（LCB-IMRT——The first course）

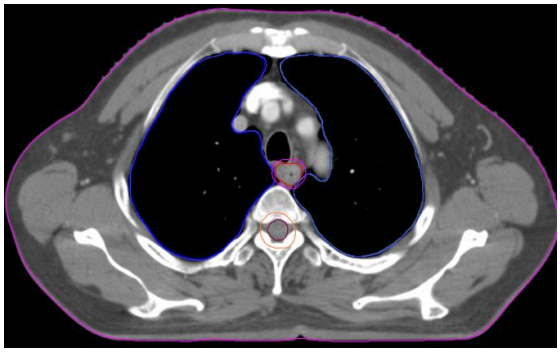

Figure 1c Schematic diagram of the target area of radical radiotherapy for esophageal cancer（LCB-IMRT——The second course）

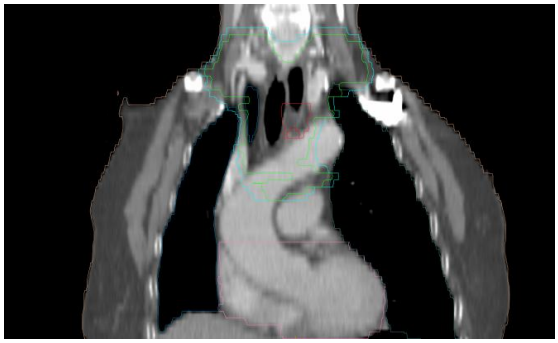

Figure 1d Schematic diagram of the target area of radical radiotherapy for esophageal cancer（Coronal position）

All patients in the group were treated with 6MV-X linear accelerator for IMRT, and the radiotherapy plan of SIB-IMRT group was as follows: The dose of 95%PTV was 50.4 ~ 54Gy/28 ~ 30 times (1.85～2.2Gy), and the

dose of 95%PGTV was 59.92 ~ 66Gy/28 ~ 30 times (1.95～2.2Gy), once a day, 5 times a week, and the whole radiotherapy time was 5.5 ~ 6.5 weeks. LCB-IMRT group: 95%PTV dose of 45 ~ 54Gy/23 ~ 28 times (single fractionation of 1.8 ~ 2.0Gy), after field reduction to PGTV dose of 58 ~ 66Gy/29 ~ 35 times (single fractionation of 1.8 ~ 2.0Gy), once a day, 5 times a week, the whole radiotherapy time was 6 ~ 7 weeks. Limits of organs at risk: V5<60%, V20<30%, V30<20% in both lungs, MLD<30Gy, V30<30% in heart, Dmax of spinal cord <45Gy, increase of lower esophageal cancer limited stomach V30≤40%, liver V30≤30%.

After the completion of the target sketch by radiotherapy center physics teacher to complete the design of treatment plan, and the physical teacher and check and above the level of radiation, deputy director of the physician radiotherapy plan, evaluate the isodose curve distribution, dose volume histogram (DVH), for the target area and the surrounding organs threatening to meet the prescribed dose limit, dose distribution as evenly as possible,95%PTV and 95%PGTV volume received the prescribed dose at the specified point.

Synchronous or sequential chemotherapy is adopted, the chemotherapy was often administered in combinations of platinum-based compounds. And the chemotherapy cycle is not less than four cycles. Elderly patients usually

use S-1 single-agent chemotherapy[22].

Evaluation criteria for efficacy and toxicity. This study was evaluated according to RECIST short-term efficacy evaluation criteria [23]. Acute and late toxicities were scored according to the Common Toxicity Criteria for Adverse Events, version 4.0. The total radiotherapy time from the beginning to the end of radiotherapy and the short-term curative effect after the first treatment, including complete response, partial response, disease stability and disease progression, were analyzed and compared between the two groups for statistical differences in the overall radiotherapy time and short-term curative effect. The incidence of acute adverse reactions, including acute radiation esophagitis, acute radiation pneumonia and bone marrow suppression, in all patients within 3 months after the end of treatment were counted, and the incidence of acute adverse reactions after radiotherapy was calculated and compared between the two groups.

All enrolled patients were followed up from the end of treatment, and followed up by telephone, outpatient and inpatient review. According to the actual situation of the patients at the time of the review, imaging examinations and laboratory examinations were selected, such as chest enhanced CT scan, esophagography, gastroscopy, blood routine, etc., and the follow-up was up to December 31, 2020.

Statistical analysis. SPSS 24.0 statistical software was used for statistical analysis. PSM was used to adjust for unbalanced covariates. OS, LC rate, after PSM were estimated for each treatment group using Kaplan-Meier plots. COX regression model was used for multivariate analysis. Logrank method was used for univariate analysis. $P < 0.05$ was considered statistically significant.

Ethical approval. This study was approved by the Ethical Committee of Affiliated Hospital of North Sichuan Medical College.

Informed consent. Informed consent was obtained from all participants, and all methods were performed in accordance with the relevant guidelines and regulation.

Results

Patient Characteristics. A total of 274 pathologically confirmed esophageal carcinoma patients, including 270 cases of squamous cell carcinoma, 1 case of adenocarcinoma, and 3 cases of small-cell neuroendocrine carcinoma. There were 102 patients (37.2%) in the SIB-IMRT group and 172 patients (62.8%) in the LCB-IMRT group. There were 189 males (69.0%) and 85 females (31.0%), with a median age of 66 years, ranging from 39 to 85 years old. The whole group obtained 33 cases (12.0%) of cervical esophageal cancer, 73 cases (26.7%) of upper thoracic

esophageal cancer, 117 cases (42.7%) of middle thoracic esophageal cancer, 51 cases (18.6%) of lower thoracic esophageal cancer. Before radiotherapy, 46 cases (16.8%) could eat general diet, 56 cases (20.4%) could eat soft diet, 108 cases (39.4%) could eat semi-liquid diet, and 64 cases (23.4%) could eat liquid diet. Combined with gastroscopy and upper digestive tract angiography, the tumor length in the whole group was 1.2cm ~ 16.0cm, with a median tumor length of 5.5cm. There were 30 cases (11.0%) of T1 stage, 99 cases (36.1%) of T2 stage, 91 cases (33.2%) of T3 stage, and 54 cases (19.7%) of clinical T4 stage. There were 109 cases (39.8%) of clinical N0 stage, 111 cases (40.5%) of clinical N1 stage, and 54 cases (19.7%) of clinical N2 stage. There were 251 patients (91.6%) with clinical M0 stage, and 23 patients (8.4%) with clinical M1 stage (only supraclavicular lymph node and celiac trunk lymph node metastasis). Forty-eight patients (17.5%) were in stage I, 117 (42.7%) were in stage II, 87 (31.8%) were in stage III, and 22 (8.0%) were in stage IV. All patients were staged according to the 6th edition (2002) of the American Joint Committee on Cancer TNM staging. Among 274 cases of esophageal cancer patients, 88 cases (32.1%) received radiotherapy alone, and 186 cases (67.9%) received radiotherapy combined with chemotherapy.

In order to reduce the selection bias caused by the clinical data

imbalance between the two groups of patients and improve the accuracy of the study results, the enrolled patients were matched with propensity score (PSM). Age, gender, tumor length (cm), GTV volum (cm^3), diet, tumor location, disease stage and concurrent chemotherapy were included in the propensity score matching system since they were considered unbalanced between SIB-IMRT and LCB-IMRT groups. The SIB-IMRT group and the LCB-IMRT group were matched with a 1:1 propensity score using the least-adjacent method, and the caliper value was set to 0.1. After propensity score matching, a total of 200 patients were successfully matched, the SIB-IMRT group (n = 100) and the LCB-IMRT group (n = 100). There was no statistically significant difference in basic data between the two groups after matching. The comparison of basic data before and after matching was shown in Table 1.

Table 1 Comparison of clinical data after PSM between the two groups

Clinical data	Before matching		After matching		*P*	
	SIB-IMRT	LCB-IMRT	SIB-IMRT	LCB-IMRT	Before	After
Age（year）	66.7±8.2	64.7±8.1	66.6±8.3	65.9±8.1	0.058	0.531
Length（cm）	4.9±2.5	5.1±2.0	4.9±2.6	4.8±2.0	0.477	0.756
GTV（cm^3）	32.6±26.0	41.4±29.6	32.7±26.2	38.9±29.7	0.013	0.120
Sex					0.714	0.655
male	69	120	67	64		
female	33	52	33	36		
Location					0.871	0.928
Cervical	14	19	14	11		
Upper thoracic	27	46	26	28		
Middle thoracic	41	76	40	40		
Lower thoracic	20	31	20	21		
T stage					0.180	0.152
T1	16	14	15	6		
T2	38	61	37	44		
T3	32	59	32	29		
T4	16	38	16	21		
N stage					0.165	0.300
N0	48	61	47	37		
N1	36	75	36	46		
N2	18	36	17	17		
M stage					0.800	0.602
M0	94	157	93	91		

Table 1 (Continued)

Clinical data	Before matching		After matching		*P*	
	SIB-IMRT	LCB-IMRT	SIB-IMRT	LCB-IMRT	Before	After
M1	8	15	7	9		
Stage					0.256	0.354
I	25	23	26	20		
II	45	72	44	38		
III	25	62	23	33		
IV	7	15	7	9		
Chemotherapy					0.740	0.651
Yes	68	118	66	69		
No	34	54	34	31		
Diet					0.983	0.590
General	17	29	16	13		
Soft	22	34	21	15		
Semi-liquid	39	69	39	45		
Liquid	24	40	24	27		

Short-Term Efficacy

Patients in the whole group were followed up until December 30, 2020, with a follow-up rate of 97.5% and a median follow-up of 27 months. The total radiotherapy time was 29.54±1.158 days in the simultaneous push group and 32.87±1.535 days in the posterior field push group. The difference in the overall radiotherapy time between the two groups was statistically significant (t=-17.315, P=0.000), (Table 2). 1 to 3 months after the end of

radiotherapy, the short-term efficacy was evaluated according to esophagography and chest CT images. There were a total of 200 patients in the group, including 16 patients (8.0%) with complete response, 153 patients (76.5%) with partial response, 19 patients (9.5%) with stable disease, and 12 patients (6.0%) with disease progression. The total effective rate (CR+PR+SD) was 94.0%, among which the total effective rate was 96.0% in the simultaneous push group and 92.0% in the late field push group. There was no significant difference between the two groups (P > 0.05). (Table 3).

Table 2 Comparison of the treatment time between SIB-IMRT and LCB-IMRT group

Group	**Treatment time**（day）	*t*	*P*
SIB-IMRT	29.54±1.158	-17.315	0.000
LCB-IMRT	32.87±1.535		

Table 3 Comparison of the curative effects between SIB-IMRT and LCB-IMRT group

Group	**Curative effects**				Effective rate（%）	χ^2	*P*
	CR(n)	PR(n)	SD(n)	PD(n)			
SIB-IMRT	9	81	6	4	96.0	4.692	0.196
LCB-IMRT	7	72	13	8	92.0		

Toxicities

The incidence of acute radiation esophagitis after radiotherapy was 73.0%, including 8 cases of esophageal perforation, 3 cases of SIB-IMRT group and 5 cases of LCB-IMRT group. The incidence of acute radiation

pneumonia was 24.5%, and the incidence of myelosuppression was 58.0%, among which 18 cases of myelosuppression occurred in patients with concurrent chemoradiotherapy (Table 4). The incidence of grade 2 and above acute radiation esophagitis and acute radiation pneumonia in SIB-IMRT group was significantly lower than that in LCB-IMRT group (P = 0.037 and 0.030, respectively) (Table 5).

Table 4 Comparison of acute toxicities between SIB-IMRT and LCB-IMRT group

Acute toxicities	Grade	SIB-IMRT		LCB-IMRT	
		Number (n)	Occurrence （%）	Number (n)	Occurrence （%）
Radiation esophagitis		69	69.0	77	77.0
	0	31	31.0	23	23.0
	1	49	49.0	54	54.0
	2	14	14.0	25	25.0
	≥3	6	6.0	8	8.0
Radiation pneumonia		17	17.0	32	32.0
	0	83	83.0	68	68.0
	1	12	12.0	18	18.0
	2	5	5.0	14	14.0
	≥3	0	0	0	0
Bone marrow suppression		50	50.0	66	66.0
	0	50	50.0	34	30.4
	1	36	36.0	42	42.0
	2	11	11.0	18	18.0
	≥3	3	3.0	6	6.0

Table 5 Comparison of⩾2 Grade acute toxicities between the SIB-IMRT and LCB-IMRT Group

Acute toxicities	SIB-IMRT	LCB-IMRT	χ^2	*P*
	≥2grade（n）	≥2grade（n）		
Radiation esophagitis	20	33	4.338	0.037
Radiation pneumonia	5	14	4.711	0.030
Bone Marrow suppression	14	24	3.249	0.071

Exposure dose to organs at risk

As shown in Table 6, there were statistical differences in lung V5, lung V10, lung Dmean and spinal cord Dmax between the simultaneous push group and the posterior field push group (*P* values were 0.000, 0.030, 0.000 and 0.003, respectively).

Table 6 Comparison of doses to organs at risk between SIB-IMRT and LCB-IMRT group

Observation index	SIB-IMRT	LCB-IMRT	*t*	*P*
Lung V5（%）	54.8±13.1	56.9±17.4	-5.868	0.000
Lung V10（%）	41.2±10.1	44.0±10.3	-2.178	0.030
Lung V20（%）	21.6±5.4	22.3±5.2	-1.036	0.301
Lung V30（%）	10.8±3.7	11.3±8.4	-0.605	0.546
MLD（Gy）	12.0±2.7	13.7±3.0	-4.829	0.000
Heart V30(%)	23.3±15.7	22.1±13.4	0.687	0.493
Heart V40(%)	12.3±9.2	10.6±7.4	1.676	0.095
Heart Dmean（Gy）	17.9±10.4	19.6±9.0	-1.423	0.156
Spinal cord Dmax（Gy）	40.56±4.1	42.3±4.8	-2.997	0.003

Survival analysis. In this study, in order to reduce selection bias and improve the accuracy of the results, the data of 274 patients were matched by 1:1 propensity score, and a total of 200 patients were successfully matched, including 100 patients in the SIB-IMRT group and 100 patients in the LCB-IMRT group. The follow-up time was up to December 31, 2020, and 5 cases were lost to follow-up, with a follow-up rate of 97.5%. Kaplan-meier analysis showed that the overall survival rate at 1, 3 and 5 years was 80.5%, 38.2% and 22.2%, respectively, and the median survival time was 27.0 months. The 1 -, 3 - and 5-year local control rate were 67.6%, 31.3% and 20.4%, respectively, and the median local control survival was 20.0 months. The 1-, 3- and 5- year overall survival rates of SIB-IMRT group and LCB-IMRT group were 85.0%, 41.8%, 25.5% and 76.0%, 34.5%, 21.3%, respectively, with no significant difference (χ^2=0.642, P =0.423). See Figure 2 and Table 7. The 1-, 3- and 5-year local control rates of SIB-IMRT group and LCB-IMRT group were 77.3%, 31.4%, 20.0% and 58.0%, 30.1%, 20.7%, respectively, and there was no significant difference (χ^2=2.102, P =0.147), (Figure 3, Table 8).

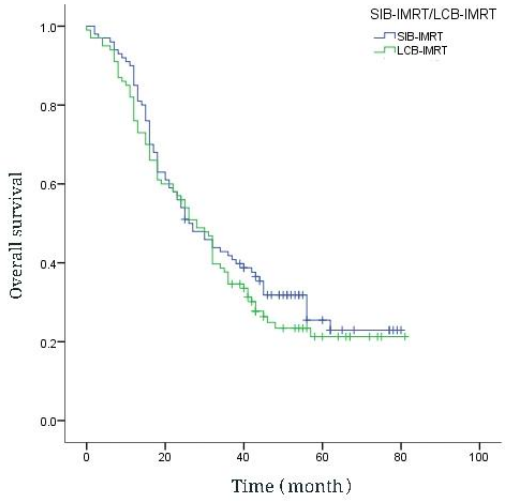

Figure 2 Comparison of overall survival between two groups

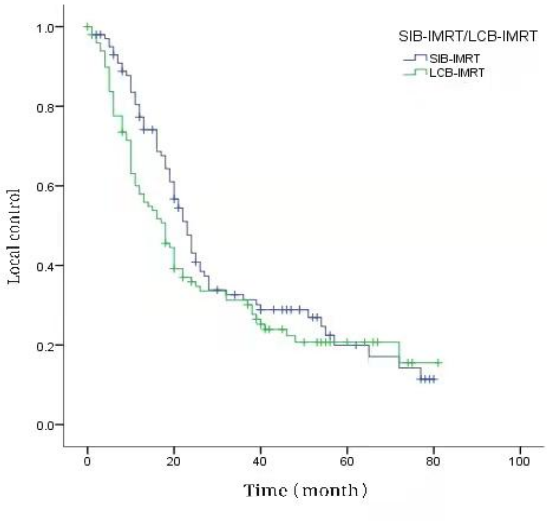

Figure 3 Comparison of local control between two groups

Table 7 Comparison of the overall survival between two groups

Group	Median time （m）	Overall survival（%）			95%*CI*	χ^2	*P*
		1year	3year	5year			
SIB-IMRT	28.0	85.0	41.8	25.5	18.732～33.268	0.642	0.423
LCB-IMRT	26.0	76.0	34.5	21.3	23.178～32.822		

Table 8 Comparison of the local control between two groups

Group	Median time（m）	Local control（%）			95%*CI*	χ^2	*P*
		1year	3year	5year			
SIB-IMRT	23.0	77.3	31.4	20.0	19.993～26.007	2.102	0.147
LCB-IMRT	18.0	58.0	30.1	20.7	12.789～23.211		

The clinical data of patients in the two groups were stratibly analyzed, and the results showed that age, tumor location, lesion length, GTV volume, T stage, N stage and TNM stage had no significant effect on the overall survival and local control rate of patients in the two groups. The local control rate of the simultaneous IMRT group was significantly higher than that of the late field IMRT group. The 1-year, 3-year and 5-year local control rate were 42.0%, 29.1%, 19.9% and 33.3%, 20.0%, 8.9%, respectively, with statistical significance (χ^2=3.077, P= 0.042). (Table 9 and Table 10).

Table 9 Comparison of the overall survival between SIB-IMRT and LCB-IMRT groups with different influence factors

Influence factors	Group	Number（n）	Overall survival（%）			χ^2	*P*
			1year	3year	5year		
Sex							
Female	SIB	33	90.9	39.4	27.6	0.382	0.537
	LCB	36	56.1	38.9	17.1		
Male	SIB	67	82.1	41.5	21.6	0.420	0.517
	LCB	64	70.3	32.2	10.1		
GTV (cm^3)							
≤35	SIB	63	95.2	60.0	31.1	1.846	0.174
	LCB	56	83.9	45.8	27.5		
>35	SIB	37	67.6	10.8	8.4	2.001	0.157
	LCB	44	65.9	20.5	12.1		
Age（y）							
≤65	SIB	47	91.5	46.5	32.3	0.032	0.858
	LCB	44	88.6	42.4	39.8		
>65	SIB	53	79.2	35.8	16.8	1.420	0.233
	LCB	56	66.1	28.6	9.6		
length（cm）							
≤5	SIB	57	94.7	55.8	31.0	0.412	0.521
	LCB	52	80.8	45.5	29.1		
>5	SIB	43	72.1	23.3	13.1	0.016	0.899
	LCB	48	70.8	22.9	10.1		
T stage							
T_1	SIB	15	93.3	49.4	26.2	1.947	0.205
	LCB	6	66.7	43.3	24.7		
T_2	SIB	37	94.6	45.9	14.6	1.151	0.283

Table 9 (Continued)

Influence factors	Group	Number （n）	Overall survival（%）			χ^2	*P*
			1year	3 year	5 year		
	LCB	44	90.9	51.5	32.1		
T_3	SIB	32	78.1	30.9	19.3	0.131	0.718
	LCB	29	65.5	24.1	15.11		
T_4	SIB	16	62.5	16.3	12.2	0.896	0.344
	LCB	21	61.9	14.3	9.5		
N stage							
N_0	SIB	47	85.1	55.3	30.1	0.011	0.917
	LCB	37	86.5	47.9	34.2		
N_1	SIB	36	91.7	32.4	15.1	0.273	0.601
	LCB	46	65.2	32.6	15.9		
N_2	SIB	17	64.7	17.6	8.6	0.147	0.702
	LCB	17	70.6	11.8	4.3		
M stage							
M_0	SIB	93	88.2	45.0	24.7	1.471	0.225
	LCB	91	79.1	34.7	20.3		
M_1	SIB	7	42.9	0	0	1.936	0.164
	LCB	9	44.4	0	0		
TNM stage							
I	SIB	26	96.2	73.1	39.0	0.086	0.769
	LCB	20	95.0	68.6	49.4		
II	SIB	44	90.9	40.3	17.9	0.955	0.328
	LCB	38	73.7	31.6	13.5		
III	SIB	23	69.6	17.4	10.38	0.122	0.727
	LCB	33	72.7	18.2	12.1		

Table 9 (Continued)

Influence factors	Group	Number （n）	Overall survival（%）			χ^2	*P*
			1year	3 year	5year		
IV	SIB	7	42.9	10.2	2.1	1.936	0.164
	LCB	9	44.4	8.4	2.6		
Dose（Gy）							
≤60	SIB	23	82.6	19.9	9.9	0.931	0.335
	LCB	16	62.5	43.8	27.3		
>60	SIB	77	85.7	48.1	26.7	2.350	0.125
	LCB	84	78.6	32.8	21.0		
Chemotherapy							
Yes	SIB	66	95.5	48.2	25.9	0.052	0.800
	LCB	69	87.0	41.5	28.4		
No	SIB	34	63.6	27.3	20.5	1.540	0.215
	LCB	31	51.6	19.4	8.1		

Table 10 Comparison of the local control between SIB-IMRT and LCB-IMRT groups with different influence factors

Influence factors	Group	Number （n）	Local control（%）			χ^2	*P*
			1year	3year	5year		
Sex							
Female	SIB	33	81.8	30.2	14.9	2.321	0.128
	LCB	36	47.2	24.4	17.1		
Male	SIB	67	70.8	28.4	21.5	0.197	0.657
	LCB	64	62.9	32.6	21.9		
GTV（cm^3）							
≤35	SIB	63	79.4	35.2	22.2	0.696	0.404
	LCB	56	60.0	36.1	25.7		

Table 10 (Continued)

Influence factors	Group	Number（n）	Local control（%）			χ^2	*P*
			1year	3year	5year		
>35	SIB	37	65.9	17.7	13.6	0.476	0.490
	LCB	44	53.5	20.9	12.5		
Age(y)							
≤65	SIB	47	84.4	46.9	29.4	1.429	0.232
	LCB	44	68.2	37.4	30.4		
>65	SIB	53	66.0	14.0	10.0	0.260	0.610
	LCB	56	48.2	23.2	11.9		
Length（cm）							
≤5	SIB	57	78.6	28.7	16.2	0.008	0.930
	LCB	52	59.6	38.2	24.4		
>5	SIB	43	69.1	29.6	23.3	3.062	0.080
	LCB	48	54.4	19.2	14.0		
T stage							
T_1	SIB	15	93.3	53.3	22.9	2.628	0.105
	LCB	6	50.0	16.7	15.8		
T_2	SIB	37	78.4	25.2	9.3	1.171	0.279
	LCB	44	63.6	42.8	16.0		
T_3	SIB	32	70.0	26.3	12.2	2.335	0.126
	LCB	29	50.1	17.9	6.7		
T_4	SIB	16	56.3	18.8	0	0.565	0.452
	LCB	21	55.0	13.2	0		
N stage							
N_0	SIB	47	73.9	34.1	27.3	0.011	0.918
	LCB	37	69.4	40.7	31.4		

Table 10 (Continued)

Influence factors	Group	Number（n）	Local control（%）			χ^2	*P*
			1year	3 year	5 year		
N_1	SIB	36	86.1	26.9	9.8	1.482	0.224
	LCB	46	57.8	24.7	10.6		
N_2	SIB	17	50.2	19.1	9.6	0.868	0.352
	LCB	17	29.4	17.6	8.7		
M stage							
M_0	SIB	93	75.8	30.2	20.5	2.858	0.091
	LCB	91	57.3	28.0	17.9		
M_1	SIB	7	57.1	14.3	0	0.961	0.327
	LCB	9	55.6	19.2	0		
TNM stage							
I	SIB	26	84.6	38.5	27.5	0.859	0.354
	LCB	20	85.0	60.0	21.9		
II	SIB	44	81.4	28.7	15.5	4.083	0.053
	LCB	38	54.1	17.9	8.9		
III	SIB	23	54.7	23.2	12.4	1.394	0.238
	LCB	33	37.5	15.6	10.8		
IV	SIB	7	57.1	14.3	8.2	0．961	0.327
	LCB	9	66.7	13.8	6.5		
Dose（Gy）							
<60	SIB	23	73.9	15.7	7.8	0.216	0.642
	LCB	16	50.0	37.5	23.4		
≥60	SIB	77	74.7	32.9	22.7	2.865	0.091
	LCB	84	58.6	27.9	19.4		
Chemotherapy							

Table 10 (Continued)

Influence factors	Group	Number（n）	Local control（%）			χ^2	*P*
			1year	3 year	5 year		
Yes	SIB	66	77.3	38.2	23.6	0.196	0.658
	LCB	69	75.0	36.3	29.8		
No	SIB	34	42.0	29.1	19.9	3.077	0.042
	LCB	31	33.3	20.0	8.9		

Survival Prognostic Factors Analysis

Logrank univariate analysis showed that age, GTV volume, lesion site, tumor length, clinical T stage, clinical N stage, clinical M stage, clinical TNM stage, radioactive esophagitis, and chemotherapy were all factors affecting the overall survival and local control of esophageal cancer patients in the whole group (Table 11, Table 12). COX multivariate regression model analysis showed that age, lesion site, lesion length, GTV volume and clinical N stage were independent factors affecting the overall survival of esophageal cancer patients treated with radical radiotherapy (Table 13). Age, tumor location, GTV volume, and clinical N stage were independent factors of local control rate (Table 14).

Table 11 Univariate analysis of the overall survival of 200 patients with esophageal cancer

Influence factors	Group	Number（n）	OS（%）			χ^2	*P*
			1-year	3-year	5-year		
Sex	Male	131	76.3	37.0	22.8	0.184	0.668
	Female	69	88.4	40.6	21.3		
Age（year）	≤65	91	90.1	44.5	35.8	9.033	0.003
	>65	109	72.5	33.0	13.1		
Diet	General	29	82.8	33.9	27.1	0.349	0.951
	Soft	36	83.3	35.2	16.5		
	Semi-liquid	84	79.8	44.0	19.3		
	Liquid	51	78.4	33.3	25.3		
Smoke	Yes	88	73.9	39.2	26.5	0.138	0.710
	No	112	85.7	37.5	18.5		
Alcohol	Yes	64	75.0	40.3	31.1	0.894	0.344
	No	136	83.1	37.3	17.9		
Tumor Location	Cervical	25	88.0	52.0	31.9	10.569	0.014
	Upper thoracic	54	88.9	45.8	30.5		
	Middle thoracic	80	76.3	32.1	13.4		
	Lower thoracic	41	70.7	29.3	21.5		
Length（cm）	≤5	109	88.1	50.9	30.2	21.989	0.000
	>5	91	71.4	23.1	15.4		
GTV（cm^3）	≤35	119	89.9	53.3	29.7	39.853	0.000
	>35	81	66.7	16.0	11.0		
T Stage	T_1	21	90.5	71.4	52.7	50.490	0.000
	T_2	81	92.6	48.9	24.1		
	T_3	61	72.1	29.1	16.8		
	T_4	37	62.2	8.1	3.2		
N Stage	N_0	84	88.1	52.1	32.1	20.003	0.000
	N_1	82	78.0	33.7	15.8		
	N_2	34	67.6	14.7	8.9		
M Stage	M_0	184	83.7	39.9	22.6	8.243	0.004

Influence factors	Group	Number（n）	OS（%）			χ^2	*P*
			1year	3year	5year		
T Stage	M_1	16	43.8	18.8	8.8	42.286	0.000
	I	46	97.8	71.2	43.4		
	II	82	84.1	37.4	17.2		
	III	56	71.4	17.9	14.9		
	IV	16	43.8	18.8	10.5		
Esophagitis	≤1 grade	147	83.7	41.8	26.7	4.299	0.038
	≥2 grade	53	71.7	28.3	15.1		
Pneumonia	≤1 grade	169	81.6	40.2	24.6	0.980	0.322
	≥2grade	31	75.7	29.7	18.0		
Chemotherapy	Yes	135	91.1	44.7	27.4	17.293	0.000
	No	65	57.8	23.4	14.0		
Radiotherapy dose（Gy）	<60	39	74.4	32.8	18.3	1.075	0.300
	≥60	161	82.0	39.6	25.3		

Table 12 Univariate analysis of the local control of 200 patients with esophageal cancer

Influence factors	Group	Number（n）	Local control（%）			χ^2	*P*
			1year	3year	5year		
Sex	Male	131	63.8	34.4	22.0	0.184	0.668
	Female	69	65.2	32.6	22.7		
Age（year）	≤65	91	69.7	43.0	33.1	9.439	0.002
	＞65	109	59.8	26.2	13.8		
Diet	General	29	62.1	30.7	25.5	1.428	0.699
	Soft	36	55.6	26.9	11.2		
	Semi-liquid	84	69.5	37.8	22.3		
	Liquid	51	79.7	33.8	28.9		
Smoke	Yes	88	65.1	36.8	25.2	0.257	0.612
	No	112	63.9	31.4	19.9		
Alcohol	Yes	64	62.0	29.9	19.6	1.333	0.248
	No	136	69.4	41.8	28.1		
Tumor location	Cervical	25	84.0	48.0	37.7	8.486	0.037
	Upper thoracic	54	72.8	36.4	23.2		
	Middle thoracic	80	54.8	30.3	18.2		

Table 12（Continued）

Influence factors	Group	Number（n）	Local control（%）			χ^2	*P*
			1year	3year	5year		
	Lower thoracic	41	52.5	27.5	19.3		
length（cm）	≤5	109	82.4	44.4	27.7	21.670	0.000
	>5	91	42.1	20.5	15.2		
GTV（cm^3）	≤35	119	84.7	45.7	28.2	34.624	0.000
	>35	81	33.4	15.4	12.8		
T Stage	T_1	21	90.5	66.7	56.7	49.977	0.000
	T_2	81	86.4	43.4	25.4		
	T_3	61	55.2	23.7	11.8		
	T_4	37	13.9	8.3	7.4		
N Stage	N_0	84	72.0	46.1	34.6	18.042	0.000
	N_1	82	67.9	28.0	11.1		
	N_2	34	36.5	16.6	12.4		
M Stage	M_0	184	67.8	35.0	22.6	7.657	0.006
	M_1	16	25.0	18.8	0		
TNM Stage	I	46	95.7	62.5	46.1	35.393	0.000
	II	82	75.0	30.9	13.4		
	III	56	33.4	17.7	6.5		
	IV	16	25.0	18.8	0		
Esophagitis	≤1grade	147	66.4	37.0	25.3	4.399	0.036
	≥2 grade	53	58.1	24.0	13.0		
Pneumonia	≤1 grade	163	65.8	34.8	22.1	0.336	0.562
	≥2 grade	37	57.2	28.6	22.9		
Chemotherapy	Yes	135	76.1	37.2	26.5	12.760	0.002
	No	65	37.8	24.7	14.7		

Table 12（Continued）

Influence factors	Group	Number（n）	Local control（%）			χ^2	*P*
			1year	3year	5year		
Does（Gy）	＜60	39	56.4	27.6	17.8	1.625	0.202
	≥60	161	66.3	35.2	23.3		

Table 13 Multivariate COX model overall survival analysis of the whole group

Influence factors	Overall survival			
	B	*SE*	*Sig*	*HR*(95%*CI*)
Age				
≤65/>65(y)	0.378	0.180	0.036	1.459（1.025～2.077）
Sex				
Male/Female	0.156	0.189	0.407	1.169（0.808～1.692）
Tuomr length			0.016	
Upper thoracic/ Cervical	0.075	0.319	0.813	1.078（0.577～2.015）
Middle thoracic / Cervical	0.694	0.300	0.021	2.001（1.112～3.601）
Lower thoracic / Cervical	0.569	0.334	0.089	1.766（0.918～3.400）
Tuomr length(cm)				
≤5/>5	0.408	0.203	0.045	1.504(1.010～2.240)
T stage			0.065	
T_2/T_1	0.280	0.370	0.448	1.324（0.641～2.732）
T_3/T_1	0.728	0.399	0.068	2.071（0.948～4.523）
T_4/T_1	0.979	0.465	0.035	2.662（1.070～6.624）
N stage			0.000	
N_1/N_0	0.562	0.196	0.004	1.754(1.195～2.576)
N_2/N_0	1.044	0.258	0.000	2.840(1.714～4.706)
M stage				

Table 13（Continued）

Influence factors	Overall survival			
	B	*SE*	*Sig*	*HR*(95%*CI*)
M_0/M_1	0.456	0.328	0.164	1.578(0.830～2.999)
GTV（cm^3）				
≤35/>35	0.549	0.225	0.015	1.731（1.114～2.690）
Dose(Gy)				
<60/≥60	0.333	0.214	0.120	0.717（0.471～1.090）

Table 14 Multivariate COX model local control analysis of the whole group

Influence factors	Local control			
	B	*SE*	*Sig*	*HR*（95%*CI*）
Age				
≤65/>65(y)	0.382	0.177	0.031	1.465（1.036～2.072）
Sex				
Male/female	0.232	0.184	0.207	1.261（0.880～1.808）
Tumor location			0.010	
Upper thoracic/ Cervical	-0.146	0.299	0.625	0.864（0.481～1.553）
Middle thoracic / Cervical	0.562	0.276	0.042	1.754（1.022～3.011）
Lower thoracic / Cervical	0.435	0.305	0.154	1.545（0.850～2.808）
Length(cm)				
≤5/>5	0.327	0.198	0.099	1.387(0.940～2.046)
T stage			0.115	
T_2/T_1	0.052	0.308	0.867	1.053（0.576～1.925）
T_3/T_1	0.503	0.342	0.142	1.654（0.845～3.234）
T_4/T_1	0.695	0.426	0.103	2.005（0.870～4.621）
N stage			0.000	

Table 14（Continued）

Influence factors	Local control			
	B	*SE*	*Sig*	*HR*（95%*CI*）
N_1/N_0	0.610	0.193	0.002	1.841(1.260～2.689)
N_2/N_0	0.972	0.265	0.000	2.642(1.572～4.440)
M stage				
M_0/M_1	0.250	0.354	0.480	1.284(0.642～2.569)
GTV（cm^3）				
≤35/>35	0.478	0.225	0.034	1.613（1.037～2.509）
Dose (Gy)				
<60/≥60	-0.354	0.208	0.089	0.702（0.467～1.055）

Discussion

Esophageal cancer is one of the most common malignant tumors in the world, and its mortality rate ranks the 6th among malignant tumors [24]. Due to the hidden onset of the disease, most patients have lost the opportunity of surgery when seeking medical treatment. In recent years, with the continuous progress of radiotherapy technology, the application of intensity modulated radiotherapy technology for esophageal cancer is more and more widely, but the long-term survival rate is still not satisfactory results. The main mode of treatment failure is that the local tumor is not effectively controlled or the tumor relapse or even distant metastasis. Therefore, it is urgent to find an effective IMRT mode, which can increase the dose of tumor target area,

reduce the side effects of radiotherapy, and benefit the survival of patients without increasing the dose of the surrounding tissue.

Before the emergence of SIB-IMRT, the sequential boost technique was generally used to protect normal tissues adjacent to the primary tumor[10]. However, the use of sequential boost required simulation, delineation, and planning to be performed twice in one treatment course. Moreover, with sequential boost it was difficult to accurately evaluate treatment plans and the radiation dose to organs at risk. Inside the same treatment plan, SIB - IMRT can target tumor lesions and subclinical lesions target different single dose, in the prescription dose needed to meet the target at the same time, can reduce tumor adjacent tissues and organs by the exposure dose of target, shorten the treatment time, bring survival benefit for patients and local control rate of increase, reduce the economic burden on patients. However, there has been no large-scale report on the application of SIB-IMRT in esophageal cancer; most researches on this topic have been dosimetric studies[25-27] or small-sample phase I/II studies[19,27-29]. Few studies have investigated the safety or toxicity issues of SIB-IMRT in real-world clinical settings, and fewer studies have tried to compare the therapeutic effect of SIB-IMRT with LCB-IMRT.

This study attempted to provide reference for individualized and

accurate treatment of patients with radical radiotherapy for esophageal cancer by analyzing and comparing the short-term and long-term efficacy and toxic side effects of the two radiotherapy methods.

In order to reduce the bias of retrospective data, PSM was introduced in this study. After careful matching of baseline characteristics, we found that, SIB-IMRT program could significantly reduce the dose of both lungs and spinal cord, and significantly reduce the occurrence of grade 2 and above acute radiation esophagitis and acute radiation pneumonia while increasing the dose of the target area. The 1-, 3- and 5-year overall survival rates of SIB-IMRT group and LCB-IMRT group were 85.0% *vs.* 76.0%, 41.8% *vs.* 34.5%, 25.5% *vs.* 21.3%, respectively, with no significant difference (χ^2=0.642, P =0.423). The 1-, 3- and 5-year local control rates of SIB-IMRT group and LCB-IMRT group were 77.3% *vs.* 58.0%, 31.4% *vs.* 30.1%, 20.0% *vs.* 20.7%, respectively, and there was no significant difference (χ^2=2.102, P =0.147). However, compared with the LCB-IMRT group, the survival prognosis of the SIB-IMRT group tended to benefit, and the advantage of the SIB-IMRT group may become more significant after further expanding the sample size.

Studies have shown that in the radiotherapy of a variety of solid tumors, the use of SIB-IMRT technology to increase the target dose can greatly

improve the overall survival rate and local control rate of patients[30-34]. However, as the esophagus is a cavity organ, the risk of bleeding and perforation during radiotherapy is high, and the esophagus is adjacent to the heart, lung, spinal cord and other important organs. The upper bound of a single dose and its safety is one of the main concerns of clinicians. MD Anderson Cancer Center reported a study on the effects of different radiotherapy methods and radiotherapy doses on target dose for esophageal cancer[34]. A total of 10 patients with lower esophageal cancer were included, and different radiotherapy plans for esophageal cancer were analyzed and compared with target dose and after-treatment toxic reactions. In SIB-IMRT plan, the irradiation dose of 64.8Gy for primary esophageal tumor lesions was given, and the dose of PTV region was 50.4Gy. The results showed that the simultaneous thrust of the tumor focus could make the target area of the gross tumor receive higher dose while minimizing the exposure of the surrounding tissues and organs. Ishida et al.[35]retrospectively analyzed 21 cases of cervical esophageal squamous cell carcinoma without hypopharyngeal invasion treated with SIB-IMRT, and gave a dose of 60Gy to primary esophageal tumor lesions. It was also found that compared with 3D-CRT, SIB-IMRT resulted in a higher dose of tumor target coverage, but no significant increase in the dose of surrounding risk organs.

According to previous studies and clinical experience, the patient's age, tumor lesion length before treatment, tumor volume, clinical T, N, M stages, and whether chemotherapy are factors affecting the prognosis of patients with esophageal cancer. In this study, after further stratified analysis of these factors, the results showed that when patients received radical radiotherapy alone, the local control rate in the SIB-IMRT group was significantly higher than that in the LCB-IMRT group. The 1 -, 3 - and 5-year local control rates were 42.0% vs. 33.3%, 29.1% vs. 20.0%, 19.9% vs. 8.9%, respectively (χ^2=3.077, P=0.042). Guidelines recommend chemoradiation in the treatment of esophageal cancer at home and abroad, but most of the patients for the first time when the diagnosis is locally advanced, poor nutrition, and for the elderly, most patients are difficult to tolerate the chemoradiation, the adverse reaction of pure intensity modulated radiation therapy (IMRT) on the same period it has relatively low toxicity, its survival benefit compared with chemoradiation is more significant. Or perhaps the toxic side effects of systemic chemotherapy offset the potential survival benefit of concurrent IMRT. After stratified analysis of all influencing factors in this study, no statistical significance was found in the influence of other factors on the prognosis of the two groups of patients except whether chemotherapy was used or not. The analysis may be due to the small number of cases in each

subgroup. Further expanding the sample size or conducting a prospective randomized controlled study may make the research results more authentic and reliable.

Conclusion

Therefore, based on our studie, it can be initially concluded that SIB-IMRT has potential survival benefit value in radiotherapy for esophageal cancer, and SIB-IMRT technology can reduce the dose of radiation to organs at risk around the target area of radiotherapy for esophageal cancer, which is more conducive to the protection of normal tissues. However, it still needs to be supported by the evidence of large clinical prospective randomized controlled trials, and the appropriate upper bound of concurrent dose and possible benefit subgroups are still one of the hot topics for future exploration.

Author contributions

Yu Xiao designed the study and revised the article critically. Yu Xiao collected and analyzed the data, interpreted the results, and drafted the article. Bangxian Tan, Guobo Du helped in the collection of data. Jianping Hu, Xue Meng, Tingting Wu were involved in study implementation. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the North Sichuan Medical Collage Special Fund(18SXHZ0471).

Refernce

1 Sung, H. *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, doi:10.3322/caac.21660 (2021).

2 Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2019. *CA: a cancer journal for clinicians* **69**, 7-34, doi:10.3322/caac.21551 (2019).

3 Herskovic, A. *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *The New England journal of medicine* **326**, 1593-1598, doi:10.1056/nejm199206113262403 (1992).

4 Cooper, J. S. *et al.* Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *Jama* **281**, 1623-1627, doi:10.1001/jama.281.17.1623 (1999).

5 Ajani, J. A. *et al.* Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* **17**, 855-883, doi:10.6004/jnccn.2019.0033 (2019).

6 Lordick, F., Mariette, C., Haustermans, K., Obermannová, R. &

Arnold, D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology* **27**, v50-v57, doi:10.1093/annonc/mdw329 (2016).

7 Huang, T. T. *et al.* Definitive chemoradiotherapy for clinical T4b esophageal cancer - Treatment outcomes, failure patterns, and prognostic factors. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **157**, 56-62, doi:10.1016/j.radonc.2021.01.007 (2021).

8 Karran, A. *et al.* Propensity score analysis of oesophageal cancer treatment with surgery or definitive chemoradiotherapy. *The British journal of surgery* **101**, 502-510, doi:10.1002/bjs.9437 (2014).

9 Chang, D. T., Chapman, C., Shen, J., Su, Z. & Koong, A. C. Treatment of esophageal cancer based on histology: a surveillance epidemiology and end results analysis. *American journal of clinical oncology* **32**, 405-410, doi:10.1097/COC.0b013e3181917158 (2009).

10 Kuwano, H. *et al.* Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. *Esophagus : official journal of the Japan Esophageal Society* **12**, 1-30, doi:10.1007/s10388-014-0465-1 (2015).

11 Minsky, B. D. *et al.* INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **20**, 1167-1174, doi:10.1200/jco.2002.20.5.1167 (2002).

12 Xu, Y. *et al.* The efficacy and safety of simultaneous integrated boost intensity-modulated radiation therapy for esophageal squamous cell carcinoma in Chinese population: A single institution experience. *Journal of cancer research and therapeutics* **12**, 82-88, doi:10.4103/0973-1482.191640 (2016).

13 Dogan, N. *et al.* Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. *International journal of radiation oncology, biology, physics* **57**, 1480-1491, doi:10.1016/s0360-3016(03)01569-4 (2003).

14 Fogliata, A., Bolsi, A., Cozzi, L. & Bernier, J. Comparative dosimetric evaluation of the simultaneous integrated boost with photon intensity modulation in head and neck cancer patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **69**, 267-275, doi:10.1016/j.radonc.2003.10.003 (2003).

15 Wong, F. C. *et al.* Whole-field simultaneous integrated-boost

intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. *International journal of radiation oncology, biology, physics* **76**, 138-145, doi:10.1016/j.ijrobp.2009.01.084 (2010).

16 Leclerc, M. *et al.* A dose escalation study with intensity modulated radiation therapy (IMRT) in T2N0, T2N1, T3N0 squamous cell carcinomas (SCC) of the oropharynx, larynx and hypopharynx using a simultaneous integrated boost (SIB) approach. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **106**, 333-340, doi:10.1016/j.radonc.2013.03.002 (2013).

17 Meng, Y. *et al.* Adaptive intensity-modulated radiotherapy with simultaneous integrated boost for stage III non-small cell lung cancer: Is a routine adaptation beneficial? *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **158**, 118-124, doi:10.1016/j.radonc.2021.02.019 (2021).

18 Dragan, T. *et al.* Clinical outcome and toxicity after simultaneous integrated boost IMRT in head and neck squamous cell cancer patients. *Oral oncology* **98**, 132-140, doi:10.1016/j.oraloncology.2019.09.012 (2019).

19 Yu, W. W. *et al.* Simultaneous integrated boost intensity-modulated radiotherapy in esophageal carcinoma: early results of a phase II

study. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al]* **190**, 979-986, doi:10.1007/s00066-014-0636-y (2014).

20 Li, C. *et al.* A phase I/II radiation dose escalation trial using simultaneous integrated boost technique with elective nodal irradiation and concurrent chemotherapy for unresectable esophageal Cancer. *Radiation oncology (London, England)* **14**, 48, doi:10.1186/s13014-019-1249-5 (2019).

21 Ristau, J. *et al.* Simultaneous integrated boost concepts in definitive radiation therapy for esophageal cancer: outcomes and toxicity. *Radiation oncology (London, England)* **16**, 23, doi:10.1186/s13014-021-01749-x (2021).

22 Li, C. *et al.* Definitive Simultaneous Integrated Boost Versus Conventional-Fractionated Intensity Modulated Radiotherapy for Patients With Advanced Esophageal Squamous Cell Carcinoma: A Propensity Score-Matched Analysis. *Frontiers in oncology* **11**, 618776, doi:10.3389/fonc.2021.618776 (2021).

23 Litière, S., Collette, S., de Vries, E. G., Seymour, L. & Bogaerts, J. RECIST - learning from the past to build the future. *Nature reviews. Clinical oncology* **14**, 187-192, doi:10.1038/nrclinonc.2016.195 (2017).

24 Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN

estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* **68**, 394-424, doi:10.3322/caac.21492 (2018).

25 Fu, W. H. *et al.* Comparison of conformal and intensity-modulated techniques for simultaneous integrated boost radiotherapy of upper esophageal carcinoma. *World journal of gastroenterology* **10**, 1098-1102, doi:10.3748/wjg.v10.i8.1098 (2004).

26 Wang, S. L. *et al.* Intensity-modulated radiation therapy with concurrent chemotherapy for locally advanced cervical and upper thoracic esophageal cancer. *World journal of gastroenterology* **12**, 5501-5508, doi:10.3748/wjg.v12.i34.5501 (2006).

27 Chen, J. *et al.* Radiation dose escalation by simultaneous modulated accelerated radiotherapy combined with chemotherapy for esophageal cancer: a phase II study. *Oncotarget* **7**, 22711-22719, doi:10.18632/oncotarget.8050 (2016).

28 Yu, W. *et al.* Safety of dose escalation by simultaneous integrated boosting radiation dose within the primary tumor guided by (18)FDG-PET/CT for esophageal cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **114**, 195-200, doi:10.1016/j.radonc.2014.12.007 (2015).

29 Welsh, J. W. *et al.* Local Control and Toxicity of a Simultaneous

Integrated Boost for Dose Escalation in Locally Advanced Esophageal Cancer: Interim Results from a Prospective Phase I/II Trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* **12**, 375-382, doi:10.1016/j.jtho.2016.10.013 (2017).

30 Lin, Y. H. *et al.* Pretreatment prognostic factors of survival and late toxicities for patients with nasopharyngeal carcinoma treated by simultaneous integrated boost intensity-modulated radiotherapy. *Radiation oncology (London, England)* **13**, 45, doi:10.1186/s13014-018-0990-5 (2018).

31 Wang, D. *et al.* Comparison of efficacy and safety between simultaneous integrated boost intensity-modulated radiotherapy and conventional intensity-modulated radiotherapy in locally advanced non-small-cell lung cancer: a retrospective study. *Radiation oncology (London, England)* **14**, 106, doi:10.1186/s13014-019-1259-3 (2019).

32 Franco, P. *et al.* Comparing simultaneous integrated boost vs sequential boost in anal cancer patients: results of a retrospective observational study. *Radiation oncology (London, England)* **13**, 172, doi:10.1186/s13014-018-1124-9 (2018).

33 Magli, A. *et al.* Hypofractionated simultaneous integrated boost (IMRT-SIB) with pelvic nodal irradiation and concurrent androgen

deprivation therapy for high-risk prostate cancer: results of a prospective phase II trial. *Prostate cancer and prostatic diseases* **21**, 269-276, doi:10.1038/s41391-018-0034-0 (2018).

34 Welsh, J. *et al.* Esophageal cancer dose escalation using a simultaneous integrated boost technique. *International journal of radiation oncology, biology, physics* **82**, 468-474, doi:10.1016/j.ijrobp.2010.10.023 (2012).

35 Ishida, Y., Sakanaka, K., Fujii, K., Itasaka, S. & Mizowaki, T. Intensity-modulated radiotherapy for cervical esophageal squamous cell carcinoma without hypopharyngeal invasion: dose distribution and clinical outcome. *Journal of radiation research* **60**, 517-526, doi:10.1093/jrr/rrz019 (2019).