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A new normal portion of the esophagus (NPE) sparing technique for upper and middle esophagus cancer by SIB-IMRT automatic planning

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► ***Original article***

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ABSTRACT

Background: During upper and middle esophageal cancer patients' radiation therapy, dose hot spots located in the normal portion of the esophagus (NPE) may increase radiation esophagitis, so NPE may also needs sparing. Automatic planning may have an advantage on sparing NPE over conventional trial-and-error type planning. We compared radiation esophagitis predicted by two esophageal NTCP models between different optimization strategies. ***Materials and Methods***: 20 upper and middle esophagus cancer patients were reviewed and re-optimized by three strategies: autoplan in which NPE was not spared called A1 plan; trial-and-error type plan in which NPE was spared called T plan; autoplan in which NPE was spared called A2 plan.Dose volume parameters of four different esophagus structures were compared between three types of plans. Predicted radiation esophagitis between different optimization strategies were compared. ***Results:*** Target dose coverage of three types of plans all met clinical desires. Dose hot spots of ESOwhole-PGTV and ESOinfield-PGTV from A2 plans are lowest in 3 types of plans. While Dose hot spots of ESOwhole and ESOin field from T plans are highest.V60 and Dmax of four types of esophagus structures in A2 plans are lower than T plans. AET =2 probabilities predicted by Kwint modle for A2 plans are slightly lower than T plans, respectively 70.1±2.5%,76.9±3.2%,54.8±1.7% and 72.7±2.8%.AET=3 probabilities were also lowest for A2 plans. Standard deviation of dose volume parameters and AETs of four types of esophagus structures in automatic plans are significant less than T plans. ***Conclusion:*** Upper and middle esophagus cancer patients who received SIB-IMRT could benefited by a new NPE sparing technique by automatic planning. It may decrease patients' radiation esophagitis.

Keywords: *NPE sparing technique|NTCP model| SIB-IMRT|automatic planning.*

INTRODUCTION

Esophageal cancer is a high-incidence malignant disease in China, with 250 thousand new cases each year and high mortality rate. The main method of treating advanced esophageal cancer is concurrent chemoradiotherapy (CCRT). The main side effect of esophageal cancer radiotherapy is radiation esophagitis [1-3], severe acute esophagitis usually results in interruption of radiotherapy, poor nutrition status, and low tolerance of concurrent chemotherapy, which might have adverse effects on long term treatment outcome [4-6]. The risk of radiation esophagitis increases with the increase of esophagus V_{50} and V_{60} [7]. The main models at present to predict radiation esophagitis were separately proposed by Kwint and Kijsman, *et al.* [8, 9], both based on non-small cell lung cancer (NSCLC) patients' concurrent chemoradiotherapy treatment data. The esophagus is an important serial organ which should be severely

restricted maximum dose volume such as V_{50} and V_{60}. Several studies [10-12] have proposed esophagus-sparing technique to limit radiation esophagitis for lung cancer patients. During esophageal cancer patients' radiation therapy, the normal portion of the esophagus (NPE) itself may also need sparing.

With the continuous progress of the radiotherapy technology, it is possible to increase esophageal cancer patients' radiation dose while reducing the dose of NPE, and so to reduce the risk of radiation esophagitis [13]. For upper and middle esophagus cancer (UMEC), considering the risk of mediastinal and cervical lymph node metastases, the mainly adopted regimen at present [14, 15] is chemotherapy combined with SIB-IMRT (58.8~63 Gy and 50.4 Gy / 28 fractions). Huang BT, *et al.* [7] proposed that SIB-IMRT radiation therapy increases the risk of radiation esophagitis slightly while target dose coverage is higher.

Compared to 3DCRT or single dose-IMRT/VMAT (SD-IMRT/VMAT) planning, though the SIB-IMRT/VMAT radiotherapy planning has reduced mean esophageal dose, it hasn't taken full consideration of the high-dose volume of the portion of esophagus excluding tumor in the field, when target dose coverage is normalized. While the high-dose volume of NPE is further reduced, the risk of radiation esophagitis may be reduced.

Automatic planning now starts to be applied to intensity modulated planning and becomes a focus of research. Some studies [16, 17] have shown that auto planning has a significant effect on improving target dose coverage and further sparing organs at risk (OARs), while at the same time it improves the efficiency of completing plans and reduces the quality difference between plans completed by different planners. The conventional trial-and-error type planning depends largely on the experience of the planners. One of the important objectives of esophageal cancer radiotherapy planning is to reduce the high dose of NPE, and to improve the homogeneity in achieving the objective. The NPE of esophageal cancer include NPE outside of the field and that inside the field. NPE outside the field refers to the whole esophagus excluding planning clinical tumor volume (PCTV), while NPE inside the field refers to the part of esophagus in field excluding planning gross tumor volume (PGTV). In our study, we proposed an auto-planning-based esophagus sparing technique, which may be a better way to restrict the high-dose hot spots of NPE in the field. There have been very few reports about NPE dose hot spots restriction by automatic planning until now.

The study compared optimization method by automatic planning to trial-and-error-based optimization approach. With the target dose coverage of UMEC patients complied with the clinical requirements, the potentials of the two planning types to reduce the NPE dose hot spots in the field, as well as the difference in their consistency were compared. This study uses two kinds of radiation esophagitis prediction models to compare the level and difference of the risks of esophageal toxicity events based on the two types of planning. The results of this research can help further to find the proper planning optimization strategy for esophageal cancer, and also to present referable automatic planning optimization objectives to spare NPE.

MATERIALS AND METHODS

20 histologically or cytologically confirmed upper and middle esophagus cancer (UMEC) patients who were treated in our center during 2015-2016 were selected by this research. Among these patients: 17 male and 3 female, age 47~68, median age 58.6, squamous cell carcinoma (SCC) 20 cases. In accordance with American Joint Committee on Cancer (AJCC) 6th edition's TNM clinical staging systems on esophageal cancer, there were 14 cases IIIA and 6 cases IIIB. The patients were fixed with head and neck shoulder thermoplastic in supine position. CT scan was started from cervical vertebra C3 to the lower edge of the liver including the entire esophagus; the thickness of CT scan was 3 mm. The images were transferred to a Pinnacle 9.10 treatment planning system (Philips Medical System).

Table 1. Clinical characteristics of 20 patients.

Characteristic	Value
Mean age, years	(58.6, range 47~68)
Gender	
Male	17
Female	3
Tumor stage	
IIIa	14
IIIb	6
Pathology	
SCC	20
Adenocarcinoma	0
ESO_{whole}	26±2.5 cm
$ESO_{in\ field}$	17.5±1 cm
ESO_{whole}-PGTV	4±0.5 cm
$ESO_{in\ field}$-PGTV	4±0.5 cm

Each patient's simulation CT images were fused with functional images; then a physician with more than 5 years clinical experience would delineate the target volume. On the CT images, in accordance with imaging and clinical examination results, the physician would define primary lesions of the esophagus, the mediastinal lymph node of high standardized uptake values (SUVs) and the ipsilateral or contralateral supraclavicular lymph nodes as the gross tumor area (GTV). The range of clinical tumor volume (CTV) delineation includes the mediastinum and supraclavicular lymph nodes whose SUV values indicate low metabolism. The plan's PGTV was formed by expanding from GTV and PCTV formed by expanding from CTV. The expanding margins were based on the standard protocol of our center and adjusted accordingly to the patients' actual respiratory mobility. PGTV prescription dose was 215 cGy×28 fractions, and PCTV prescription dose was 180 cGy×28 fractions; the prescription dose for 95% PGTV volume was covered by 60.2 Gy.

OARs included several important adjacent organs such as the whole lung with GTV excluded, spinal cord and heart. There are 4 interesting dose-related esophagus areas, including ESO_{whole}, $ESO_{in\ field}$, $ESO_{whole\text{-}PGTV}$ and $ESO_{in\ field\text{-}PGTV}$. ESO_{whole}: the whole esophagus; $ESO_{in\ field}$: esophagus within the field; $ESO_{whole\text{-}PGTV}$: the whole esophagus minus PGTV; $ESO_{in\ field\text{-}PGTV}$: $ESO_{in\ field}$ minus PGTV.

The 20 SIB-IMRT esophageal cancer radiotherapy plans was completed by Pinnacle 9.10 planning systems; the SIB-IMRT plans were designed by an auto-plan module and a conventional trial-and-error optimization module respectively. A medical electron linear accelerator EDGE (Varian, a U.S. based company) was used. It featured 6 MV X-ray, 600 MU / min dose rate and a 30-pair multileaf collimator (MLC), including 16 pairs of leaves in the middle at 2.5 mm width and 14 pairs outside at 5 mm width. Static intensity modulation technology was used for all IMRT plans. The following field settings were used for both automatic planning and trial-and-error-type planning: Because the length of PCTV exceeded 20 cm, and it exceeded the tolerance of jaws perpendicular to the MLC, so the collimator of the accelerator in both cases was set to 90°. Radiation to clavicular lymph nodes in the upper part would come from 5 fields (300°, 330°, 0°, 30°, 60°) in front of the patient, while that to mediastinal esophageal lesions at the back would come from 3 fields (210°, 0°, 145°). The location of immobilized jaws that divided the fields into front and back sections were close to the lung apices, and the isocenter of the fields were placed close to the center of the two lung apices, so that the jaws parallel to the MLC were ensured not to exceed opposite side 2 cm of central axis. Thus machine limits would not affect the design of planning.

The auto-plan optimization module of the Pinnacle 9.10 planning system and a conventional trial-and-error optimization module were used separately to complete the optimization of the 20 esophageal cancer patients' SIB-IMRT planning. Since $ESO_{in\ field}$ of the esophagus within the radiation area included target GTV and CTV, during optimization, $ESO_{in\ field}$ minus PGTV was used as an OAR called NPE to be involved in optimization where the maximum dose and maximum dose volume V_{52} were restricted. Three kinds of plans were made for each esophageal patient respectively, (a),auto plan in which NPE dose was not restricted, called A1 plan; (b),trial-and-error-type plan spared the NPE, called T plan; and (c), automatic plan spared the NPE, called A2 plan (figure 1 and2).

Figure 1. Target optimization goals in automatic plan module for esophageal cancer SIB-IMRT.

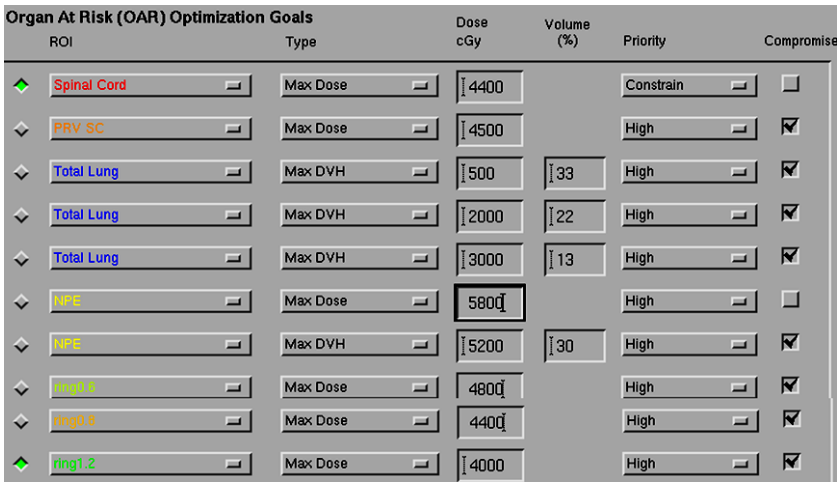

Figure 2. OARs optimization goals in automatic plan module for NPE sparing.

Dose-Volume Histogram (DVH) was used to evaluate the dose distribution of the target volumes and OARs. The dose-volume parameters used to evaluate the two types of planning included: 1) The PGTV target volume's D_2 and D_{98}; 2) PGTV's homogeneity index (HI): HI = $(D_2-D_{98})/D_{50}$, where a higher HI value means less homogenous dose distribution, target volume's conformity index (CI): CI = $(TV \cdot V_{RI})/ (TV_{RI} \cdot TV_{RI})$, a lower CI value means better conformity; 3) irradiation doses V_{50}, V_{60} and D_{max} of four types of esophagus (ESO_{whole}, $ESO_{in\ field}$, ESO_{whole}-PGTV and $ESO_{in\ field}$-PGTV); 4) for other OARs, dose-volume histogram (DVH) was used to evaluate the whole lung's D_2, V_5, V_{10}, V_{20}, V_{30} and mean dose.

Radiobiological evaluation

We used the Kwint model to evaluate grade ≥ 2 and grade ≥ 3 acute esophageal toxicity (AET). The Kwint model was created based on the data of 139 lung cancer patients who received CCRT treatment. The model shows the incidence of grade ≥ 2 AET is related to V_{50} in a sigmoid shape. The Wijsman model was based on the approach proposed by Lyman-Kutcher-Burman (LKB) and derived from the data of 149 advanced stage NSCLC patients receiving CCRT treatment, which also can predict the incidence of grade ≥ 2 AET. All physical doses in this study are converted to a biologically effective dose (BED) delivered in fractions of 2 Gy (Equivalent Dose in 2 Gy/f, EQD_2), and based on which to compare the incidences as well as differences of the four types of different acute esophageal toxicity (AET) under two types of planning.

Formulas:
Kwint's AET model:
Risk of Grade ⩾3 AET: $\frac{1}{1+e^{-(-2.486+0.032V_{50})}}$ (1)

Risk of Grade ⩾ 2 AET: $\frac{1}{1+e^{-(-0.515+0.027V_{50})}}$ (2)

Kijsman's AET model:
Risk of Grade ⩾ 2 AET: $NTCP_{(x)} = \frac{1}{1+e^{-S(x)}}$ (3)

where,

$$S_{(x)} = \sum_{i=1}^{n} \beta_i . x_i \quad (4)$$

And β_i are the regression coefficients.

Statistical analysis:

SPSS 19.0 statistical software was used to perform statistical analysis of the data. The target volume, lung tissue dosimetry parameters and risk of radiation esophagitis of the two types of planning were used for paired t test, $P < 0.05$ is the statistically significant difference.

RESULTS

As a result of the three kinds of plans based on whether or not to spare NPE, three plans showed different dose distributions, as shown in figure3.

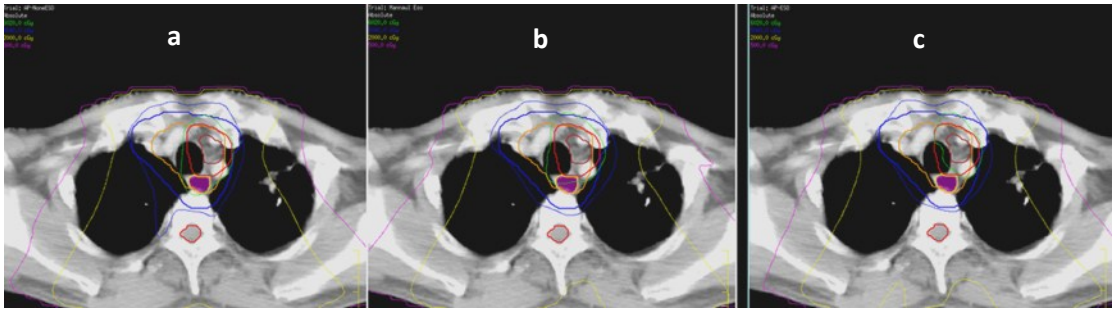

Figure 3. (a). auto plan not spared NPE, called A1 plan; **(b).** trial-and-error-type plan spared the NPE, called T plan; and **(c).** automatic plan spared the NPE, called A2 plan.

Figure 4 showed three kinds of plans target dose coverage and OARs sparing from one case of esophageal cancer. PGTV dose hot spots of trial-and-error-type plans were significantly higher than the other two automatic plans, lung tissue dose of two automatic plans were significantly lower than trial-and-error-type plans.

Figure 5 showed 4 types of esophagus structures dose volume histogram based on three kinds of plans from one case of esophageal cancer. Dose hot spots of ESO_{whole}-PGTV and $ESO_{in\ field}$-PGTV from A_2 plans were lowest in 3 types of plans, higher in T plans, and highest in A_1 plans. Dose hot spots of ESO_{whole} and $ESO_{in\ field}$ from T plans were highest.

Table 2 showed that V_{60} and D_{mean} of four types of esophagus structures in T plans were lower than A_1 plans. V_{50} of ESO_{whole} and ESO_{whole}-PGTV in T plans were lower than two automatic plans, V_{60} and D_{max} of four types of esophagus structures in A_2 plans were lower than T plans. Standard deviation of dose volume parameters of four types of esophagus structures in automatic plans were significant less than T plans.

Table 3 showed that for A_1 plans, the probabilities of the AET≥ 2 evaluated for four types of esophagus structures (ESO_{whole}, $ESO_{in\ field}$, ESO_{whole}-PGTV and $ESO_{in\ field}$-PGTV) based on Kwint model were respectively 72.8±2.3%, 80.4±3.5%, 56.3±1.9% and 77.5±3.2%, AET ≥2 probabilities for T plans were slightly lower than A_1 plans, respectively 70.5±2.9%,77.4 ±4.1%,55.2±3.2% and 74.3±3.9%, AET ≥2 probabilities for A_2 plans were slightly lower than T plans, respectively 70.1±2.5%, 76.9±3.2%, 54.8±1.7% and 72.7±2.8% (table 3). AET ≥3 probabilities were also lowest for A_2 plans respectively 39.1±2.7%, 59.2±3.5%, 16.4±1.2% and 43.8±3.2% (table 4). Standard deviations of AET ≥2 and AET ≥3 probabilities from automatic plans were less than T plans.

Table 5 showed that AET≥2 probabilities from 3 types of plans based on Kijsman model were lower than those based on Kwint model. The probabilities of AET ≥2 based on Kijsman model were similar to those based on Kwint model.

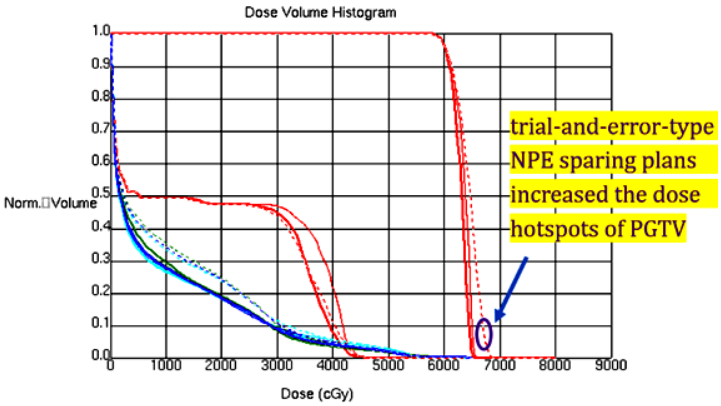

Figure 4. Three kinds of plans dose volume histogram from one case of esophageal cancer (thin solid lines: A_1 plan; the fine dashed line: T plan; thick solid lines: A_2 plan).

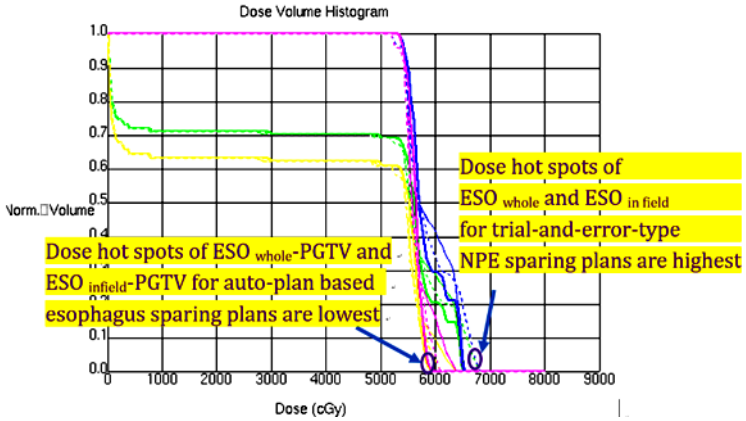

Figure 5. Four types of esophagus structures dose volume histogram from three kinds of plans(A1 plan (thin solid lines), T plan (thin dashed line), A2 plan (thick solid lines); ESO whole (green), the ESO in the field (blue), the ESO whole-PGTV (yellow), the ESO in field-PGTV (Magenta)).

Table 2. Four types of esophagus structure dose volume parameters comparison.

Strategy	Parameters	ESO_{whole}	$ESO_{in\ field}$	ESO_{whole}-PGTV	$ESO_{in\ field}$-PGTV
A1 plan	V_{30}(%)	70.1±12.2	100	62.2±9.3	100
	V_{40}(%)	70.1±12.2	100	62.2±9.3	100
	V_{50}(%)	69±11.8	100	60.8±8.6	100
	V_{60}(%)	28.7±3.6	41.6±8.7	9.7±0.5	16±1.3
	D_{mean}	4174.2±50.3	5898.6±61.2	3574±28.4	5665.1±60.7
	Dmax	6555.9±56.4	6555.9±70.5	6400.5±68.7	6400.5±68.7
T plan	V30(%)	69.7±13.1	100	61.8±8.7*	100
	V40(%)	69.7±13.1	100	61.8±8.7*	100
	V50(%)	67.8±10.6*	100	58.5±7.6*	100
	V60(%)	23.4±2.8*	33.9±6.5*	3±0.4*	4.9±0.7*
	Dmean	4172.9±49.8*	5892.7±60.9*	3543±26.6*	5608.2±59.7*
	Dmax	6836.9±58.7*	6836.9±73.1	6138.3±60.8*	6138.3±65.4*
A2 plan	V30(%)	70.5±10.2*	100	62.6±5.4**	100
	V40(%)	70.1±9.7*	100	62.2±4.8**	100
	V50(%)	69.5±5.9**	100	61.4±6.1**	100
	V60(%)	20.3±1.2**	29.4±3.6**	0**	0**
	Dmean	4142±38.9**	5848.7±44.2**	3556.9±23.1**	5632.3±45.7**
	Dmax	6519.9±48.6**	6519.9±56.1**	5919.5±48.6**	5919.5±46.3**

*: A significant difference existed between T plans and A1 plans;
**: A significant difference existed between A2 plans and T plans

Table 3. AET ≥2 probabilities from three types of plans based on Kwint model.

Strategy	AET ≥ 2	ESO_{whole}	$ESO_{in\ field}$	ESO_{whole}-PGTV	$ESO_{infield}$-PGTV
A_1 plan	Kwint(%)	72.8±2.3	80.4±3.5	56.3±1.9	77.5±3.2
T plan	Kwint(%)	70.5±2.9	77.4±4.1	55.2±3.2	74.3±3.9
A_2 plan	Kwint(%)	70.1±2.5	76.9±3.2	54.8±1.7	72.7±2.8
P_{21} *value*		0.023	0.004	0.035	0.017
P_{32} *value*		0.000	0.000	0.000	0.000

Table 4. AET ≥3 probabilities from three types of plans based on Kwint model.

Strategy	AET≥3	ESO_{whole}	$ESO_{in\ field}$	ESO_{whole}-PGTV	$ESO_{infield}$-PGTV
A_1 plan	Kwint(%)	40.7±3.2	62.7±3.8	17.4±0.9	46.8±3.5
T plan	Kwint(%)	39.5±3.6	60.9±4.1	16.8±1.7	44.5±4.2
A_2 plan	Kwint(%)	39.1±2.7	59.2±3.5	16.4±1.2	43.8±3.2
P_{21} *value*		0.035	0.015	0.022	0.019
P_{32} *value*		0.000	0.000	0.000	0.000

Table 5. AET≥2 probabilities from three types of plans based on Kijsman model.

Strategy	AET≥2	ESO_{whole}	$ESO_{in\ field}$	ESO_{whole}-PGTV	$ESO_{in\ field}$-PGTV
A_1 plan	Wijsman(%)	63.4±2.1	72.5±3.2	49.6±1.5	65.2±2.9
T plan	Wijsman(%)	62.9±2.4	72.1±3.5	49.2±1.7	64.7±3.3
A_2 plan	Wijsman(%)	62.7±1.9	71.8±2.7	48.8±1.6	64.1±2.3
P_{21} *value*		0.017	0.011	0.023	0.020
P_{32} *value*		0.000	0.000	0.000	0.000

DISCUSSION

Esophageal cancer is a high-incidence malignant disease. Simultaneous-integrated boost intensity-modulated radiation therapy (SIB-IMRT) has become one of the standard treatments for the esophageal cancer patients, the main side effect of radiation therapy is radiation esophagitis [1-3]. Xia Y, etc. [18] reported in a phase 2 chemotherapy clinical study 9.4% patients were observed to occur more than grade 3 radiation esophagitis among 53 local advanced esophageal cancer patients. Acute esophagitis is common and affects patient quality of life [1-6].

Esophagus is a special kind of serial organ. Kwint [8] reported that normal portion of the esophagus (NPE) V_{50}, V_{60} dose volume parameters and radiation esophagitis had a significant correlation. As esophageal cancer radiotherapy clinical, there may be a problem that NPE doses were neglected, restriction of NPE dose hot spots within the fields may decrease the risk of radiation esophagitis. During esophageal cancer patients' radiation therapy, the normal portion of the esophagus (NPE) itself may also need sparing.

Recently, OARs sparing technique based on IMRT were introduced to reduce the incidence of radiation esophagitis [10-12]. They proposed a contralateral esophagus-sparing technique (CEST) for lung cancer patients, the results showed that CEST can significantly reduce risks of grade≥3 esophagitis. We tried to propose a SIB-IMRT-based esophagus sparing technique, which may be a way to spare NPE in the field.

Which is the most appropriate plan optimization strategy to reduce the NPE dose hotspots hasn't been very clear until now, and this research was presented for the first time in automatic planning approach to reduce the NPE dose hot spots.

Automatic planning is one of the recently proposed optimization strategies as compared to conventional trial-and-error-type scheme [16-17], which improves the quality and homogeneity of the plan, while improving the efficiency of the plan completion. In this study, compared to the conventional trial-and-error-type program, the automatic plans could ensure the target dose coverage to meet the clinical requirements, reduce the NPE dose hot spots, and enhance the homogeneity in achievement of objectives.

This study compared the difference of acute esophageal toxicity based on Kwint and Kijsman models for different optimization programs. Xia Y [18] reported that esophagus cancer patients received chemotherapy with SIB-IMRT occurred grade≥2 and grade≥3 radiation esophagitis 63.8% and 14.5%, whose results were close to our NPE sparing predictive results based on Kwint model. Especially for AET ≥2, NPE sparing predictive results based on Kwint model were

lower than Xia's results. AET ≥2 and AET ≥3 probabilities predicted by Kwint model benefited from automatic plans were more homogenous than conventional trial-and-error-type plans. AET probabilities predicted by Kijsman model were similar to the Kwint model between two types of plans.

This study indicated that the automatic plans had a clear advantage in NPE sparing. From the ethical point of view, it's difficult to carry out a forward-looking clinical research on the basis of two optimization strategies within the field of NPE sparing. Esophageal cancer plans have been completed by conventional trial-and-error-type method in our center, and NPE dose hot spots were not restricted. After this conclusion was obtained, restrictions of NPE dose hot spots may be applied by automatic planning.

The delineation accuracy of the normal portion of the esophagus (NPE) in the field needs to be further improved. The dose volume parameters V_{50} and V_{60} proposed by Kwint and Kijsman for predicting radiation esophagitis need further clinical confirmation. This study used the radiation esophagitis prediction model to evaluate the significance of sparing normal esophagus based on automatic planning, but the new method did not carry out relevant clinical trial. Real clinical benefits have not yet been validated and supported by clinical follow-up data.

Based on the above, automatic plans which spare NPE can ensure the target dose coverage, at the same time reducing the esophagus dose hot spots, and improve the quality and homogeneity of the plans. The automatic plans have an advantage in reducing NPE dose hot spots over the trial-and-error-type program. It is recommended that treatment centers equipped with automatic planning module should apply proper optimization strategy to improve the quality of the plans for esophageal cancer SIB-IMRT radiotherapy.

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***Conflicts of interest*:** *Declared none.*

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