Original paper

A total EQD_2 greater than 85 Gy for trachea and main bronchus D_{2cc} being associated with severe late complications after definitive endobronchial brachytherapy

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Abstract

Purpose: The endobronchial brachytherapy (EBBT) is an established treatment method for tumors of the tracheobronchial system, however, little is known about the tolerance dose for organ at risk (OAR) in EBBT. The purpose of this study is to analyze patients with superficial bronchial carcinoma treated with definitive EBBT, and to investigate a relationship between late complications and dose for OAR.

Material and methods: Endobronchial brachytherapy was performed 6 Gy per fraction for three to four fractions with or without external beam radiation therapy (EBRT). For the purpose of dosimetric analysis, the wall of the lower respiratory tract (LRT: trachea, main bronchus, and lobar bronchiole), trachea, and main bronchus (TMB) was extracted. $D_{0.5cc}$, D_{1cc}, and D_{2cc} of LRT and TMB were calculated in each EBBT session and added together. V_{100}, V_{150}, and V_{200} of LRT were also calculated.

Results: Between March 2008 and April 2014, EBBT was performed in 14 patients for curative intent. The 2-year overall survival (OS), progression-free survival (PFS), and local recurrence free survival (LRFS) was 82.1%, 77.9%, and 91.7%, respectively. There was one patient with grade 5, one grade 4, and three grade 3 obstruction of trachea or bronchus. The mean EQD_2 of LRT D_{2cc}, TMB D_{2cc}, D_{1cc}, and $D_{0.5cc}$ of patients with or without late severe respiratory complications was significantly different between two groups (p = 0.018, 0.008, 0.009, and 0.013, respectively). The 2-year incidence rates of late severe complications in patients with TMB $D_{2cc} \leq 85$ Gy in EQD_2 and > 85 Gy were 0% and 83.3%, respectively with a statistically significance (p = 0.014).

Conclusions: It was discovered that TMB D_{2cc} > 85 Gy in EQD_2 is a strong risk factor for severe late respiratory complication after EBBT.

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Key words: bronchial cancer, DVH, endobronchial brachytherapy, main bronchus, severe late complications.

Purpose

Endobronchial brachytherapy (EBBT) is an established treatment method for patients with tumors of the tracheobronchial system either as a palliative [1, 2, 3, 4, 5] or a definitive treatment [6, 7, 8, 9]. Fatal hemoptysis, ulcer, necrosis, or stenosis of the bronchi have been reported as late severe respiratory complications related with EBBT [10, 11, 12]. However, little is known about the tolerance of dose for organ at risk (OAR) in EBBT presumably because EBBT is mainly applied as palliative intent and it is difficult to distinguish between treatment-related toxicities or symptoms caused by tumor progression, and most patients die of present disease before late complications develop. Starting from 2008, CT-based image-guided EBBT has been performed as a definitive therapy for patients with superficial carcinoma of trachea, bronchus, or bronchiole without extrabronchial spread, regional lymph node metastasis, nor distant metastasis in our institution. Since then, we experienced several late severe respiratory complications related with EBBT. The purpose of this study was to analyze patients with superficial bronchial carcinoma treated with CT-based high-dose-rate EBBT

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and to investigate relationship between late severe respiratory complications and dose for OAR.

Material and methods

Since March 2008, patients with superficial carcinoma of trachea, bronchus, or bronchiole without extrabronchial spread, regional lymph node metastasis, nor distant metastasis were treated with CT-based three-dimensional image-guided EBBT as curative intent.

Radiation therapy

The principles of EBBT procedure is described in the referred report [10]. Twelve French plastic catheters with two 15 mm diameter wings was used for all the EBBT sessions. Catheter insertion was performed under local anesthesia and sedation under bronchofiberscopic and fluoroscopic guidance. At each EBBT session, CT image of 1-2 mm slice was taken by a CT simulator (Aquilion™ LB, Toshiba Medical Systems, Tokyo, Japan) situated in a brachytherapy operating room. All EBBT was carried out by ^{192}Ir remote after loading system (RALS, MicroSelectron HDR™, Nucletron, Veennendaal, The Netherlands). Dwell time in each dwell position was calculated with brachytherapy planning system (Oncentra® Nucletron, Veenendaal, The Netherlands), so that homogenous dose to reference points set on 1 cm laterally from the source was achieved, and 6 Gy per fraction was prescribed to these reference points. When the applicator formed concave shape, reference points were set on inner surface of the catheter curvature in order to avoid creating hot spots. If possible, two catheters were inserted to sandwich tumors, which seated on the spur of the bronchi, so as to achieve better dose coverage.

At the discretion of the attending physician, external beam radiation therapy (EBRT) was delivered by three-dimensional conformal technique with linear accelerator (Clinac iX, Varian Medical System, Palo Alto, CA, USA) using 6 or 10 MV photon beam. Treatment planning was based on CT images of 3 mm slice thickness taken by another large bore computed tomography (CT) simulator (Aquilion™ LB, Toshiba Medical Systems, Tokyo, Japan). The common EBRT fields included primary tumor with adequate margin. Regional lymph node area was not included in the fields. There was a tendency that very superficial tumors were treated solely with EBBT.

Statistical analysis

To investigate the relationship between dose to OAR and late severe respiratory complications, wall of the lower respiratory tract (LRT: trachea, main bronchus, and lobar bronchiole), trachea, and main bronchus (TMB) was extracted with 2 mm thickness wall structures, which is the thinnest thickness in Oncentra®. Most exposed, 0.5 cc, 1 cc, and 2 cc of LRT and TMB were calculated in each EBBT session and added together. Volume of LRT, which receives 100%, 150%, and 200% of prescribed dose were also calculated in each EBBT session and a mean value of $V_{xx\%}$ through all the sessions was derived. Because no fatal hemoptysis was observed in this retrospective study, no vascular structures were contoured as an OAR. For adding dose of EBRT and EBBT, the equivalent dose in 2 Gy fractions (EQD_2) according to the Linear-Quadratic (LQ) model [13, 14] was calculated by following formula:

$$EQD_2 = \frac{Nd\,(1 + \frac{d}{\alpha/\beta})}{1 + \frac{2}{\alpha/\beta}}$$

The parameter N indicated the number of fractions and d the dose per fraction. For calculating normal tissue late complications, α/β value was assumed as 3 Gy. As dose calculation of EBBT was based on CT taken by each brachytherapy session, EQD_2 at every EBBT session could be calculated and added together. For patients who had past history of thoracic irradiation, dose of the thoracic radiation was also added to EQD_2 for OARs.

Late complications regarding to respiratory tract, which were obviously related with EBBT that occurred later than three months after the end of EBBT, were assessed by the National Cancer Institute common toxicity criteria ver. 4.0 (http//ctep.cancer.gov/forms/CTCAEv4.pdf), and late severe respiratory complications of grade 3 or higher (obstruction or stenosis of the air way) were counted. For the analysis of late severe respiratory complications, patients with local recurrence were excluded because it was difficult to distinguish the complication whether it was caused by EBBT or by tumor progression. Overall survival (OS) rate was estimated from the start of radiotherapy to the date of death or the last follow-up visit. Progression-free survival (PFS) rate was estimated from the start of radiotherapy to the date of any disease relapses were considered as an event. Patients without relapse who died of intercurrent disease or were alive were censored at the time of death or last follow-up. In calculating local relapse free survival rate (LRFS), only local relapse was counted as an event and regional lymph node or distant metastasis were not counted as an event. Overall survival, PFS, and LRFS were calculated by the Kaplan-Meier method. All of the statistical analyses were performed using SPSS Statistics (version 18.0; SPSS, Inc., Chicago, IL, USA). Student's unpaired t test was used to compare the continuous variables and Person's χ^2 test to compare categorical variables. A p value of < 0.05 was considered as statistically significant.

This retrospective study was approved by the institutional ethical review board of the National Cancer Center Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Between March 2008 and April 2014, 14 patients were treated as curative intent by EBBT. Patients characteristics was summarized in Table 1. Most of the patients were male, elderly, and had a histology of squamous cell carcinoma. Median thickness of the tumor assessed by pretreatment thin slice CT was 5.0 mm (range 1-8.8). No patients had regional lymph node involvement nor distant metastasis before EBBT. Most patients were treated

with EBBT because they were technically or medically inoperable.

Figure 1 shows distribution of the sites of the tumor in all the patients. The number shown in each small circle represents individual patient. Some patients had multiple diseases, so the total number of circles, which represent the location of the tumor exceeded the number of patients. Gray circles represent patients without grade 3 of greater late severe respiratory complications, black circles with complications mentioned above, and shaded circles with local recurrence.

Table 2 and Table 3 summarizes treatment detail and its associated grade of late respiratory complications for each patients. More than half of the patients received EBRT but some with very superficial lesion were treated by EBBT alone. Most patients received three or four fractions of EBBT except one patient who already had been treated by definitive EBRT of 60 Gy in 33 fractions and, therefore, treated by 2 Gy per fraction in total 46 Gy in 23 fractions of EBBT.

The median follow-up length of living patients was 24.8 months (10.1-77.9). There was one local recurrence and two regional lymph node recurrences observed. The patient with local recurrence received an additional 50 Gy in 25 fractions of EBRT but the disease could not

Table 1. Patients and tumor characteristics (n = 14)

Clinical data	Number, rate
Gender	
Male	13
Female	1
Age (median, range)	72 (58-87)
Histology	
SCC	13
Adenocarcinoma	1
Prior surgery	10
Prior EBRT	1
Prior PDT	3
Tumor depth (mm, range)	5.0 (1-8.8)
Indication of EBBT	
Technically inoperable	8
Medically inoperable	2
Positive margin after surgery	1
Post PDT residure/relapse	3

SCC – squamous cell carcinoma, EBRT – external beam radiation therapy, PDT – photodynamic therapy, EBBT – endobronchial brachytherapy

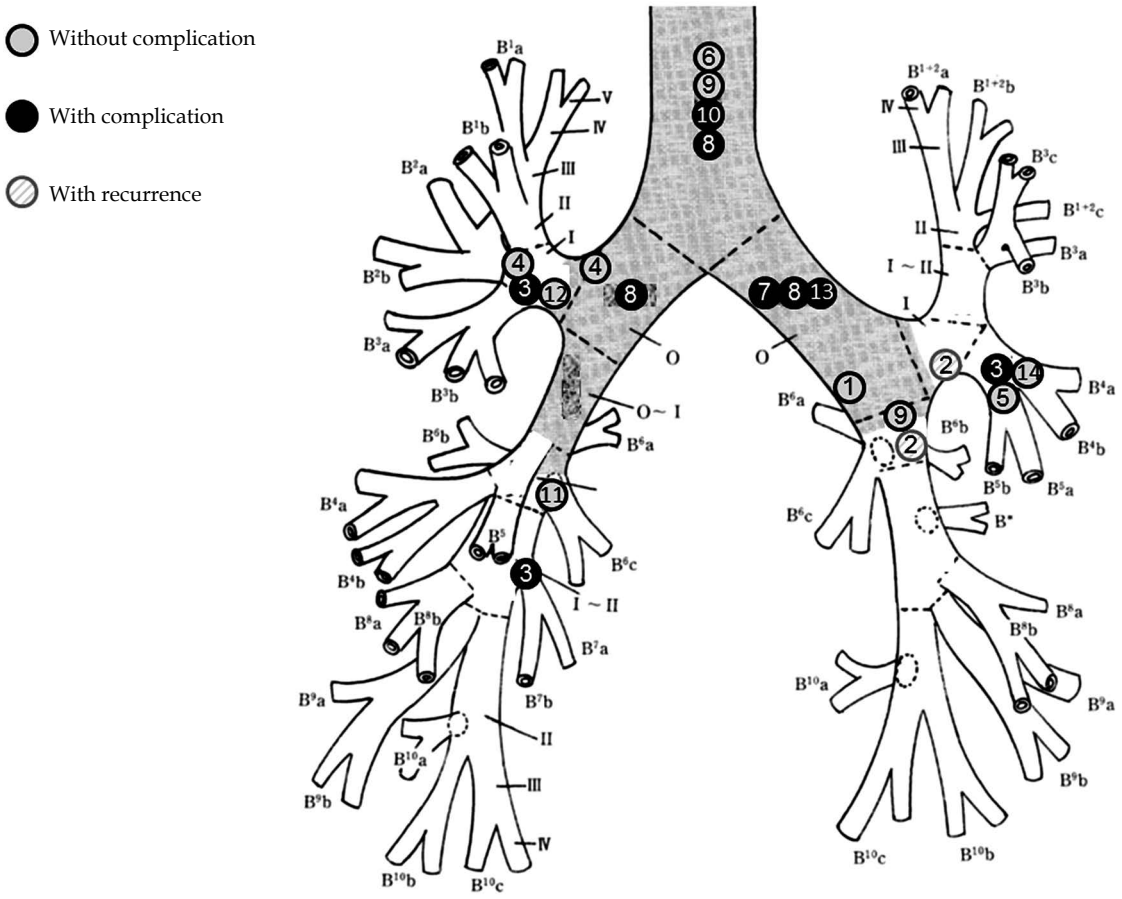

Fig. 1. Distribution of tumor sites. The number shown in each circle represents individual patient. Because some patients had disease more than one part of the lower respiratory tract, the total number of the circles exceeded the number of patients analyzed in this study. Gray circle represents patients without grade 3 of greater late complication, black circle with late complication, and shaded circle with local recurrence

Table 2. Treatment details

Median LRT V_{150} (cc)	1.5 (0.9-3.4)
Median LRT V_{200} (cc)	0.7 (0.2-1.8)
Median TMB D_{2cc} (EQD_2, Gy)	87.2 (6.6-156.3)
Median TMB D_{1cc} (EQD_2, Gy)	116.0 (21.5-191.4)
Median TMB $D_{0.5cc}$ (EQD_2, Gy)	153.8 (40.1-250.3)

LRT – lower respiratory tract (trachea, main bronchus, and lobar bronchiole), V_{xx} – volume of tissue which receives xx% of prescribed dose, TMB – trachea and main bronchus, D_{xxcc} – most exposed xx cm^3 of tissue, EQD_2 – equivalent dose in 2 Gy fractions

be controlled and this patient eventually died of present disease. First patient with regional lymph node metastasis developed chronic myeloid leukemia (CML) and best supportive care was chosen, and finally died 9 months after lymph node metastasis. Another patient with regional lymph node metastasis received an additional 60 Gy in 30 fractions of EBRT. Although tumor was controlled after the additional EBRT, this patient died of respiratory failure and was counted as having grade 5 late radiation bronchial obstruction. The 2-year OS, PFS, and LRFS was 82.1%, 77.9%, and 91.7%, respectively (Figure 2).

For the analysis of the dose tolerance of OAR, patient with local recurrence was excluded because it was difficult to distinguish the complications whether to be caused by EBBT or by tumor progression; therefore, 13 patients entered the analysis. There was one patient with grade 5, one grade 4, and three grade 3 obstruction of trachea or bronchus. Patient with grade 4 trachea obstruction developed severe aspiration pneumonia 22.6 months after EBBT. This patient received antibiotics and underwent tracheotomy, which made it easier to aspire infective sputum and eventually pneumonia resolved. Median time of development of late severe respiratory complications was 15.3 months (10.6-22.6). Comparison of dose-volume parameters of the LRT and TMB was summarized in Table 4 for the patients with or without late severe respiratory complications. The mean EQD_2 of LRT D_{2cc}, TMB D_{2cc}, D_{1cc}, and $D_{0.5cc}$ of patients with or without late severe respiratory complications was significantly differ-

Table 3. Treatment details and associated grade of late respiratory complications for each patients

Patient's number	Tumor location	Past history of thoracic RT	Combination of EBRT	EBBT	Reference point	Grade of late respiratory complications
# 1	Main bronchus	None	40 Gy/20 fr	18 Gy/3 fr	5 mm from the source	1
# 2	Bronchiole*	None	46 Gy/23 fr	18 Gy/3 fr	1 cm from the source	N/A*
# 3	Bronchiole**	None	0	18 Gy/3 fr	1 cm from the source	5**
# 4	Main bronchus and bronchiole	None	20 Gy/10 fr	24 Gy/4 fr	1 cm from the source	0
# 5	Bronchiole	None	40 Gy/20 fr	24 Gy/4 fr	1 cm from the source	0
# 6	Trachea	None	40 Gy/20 fr	18 Gy/3 fr	1 cm from the source	0
# 7	Main bronchus	None	40 Gy/20 fr	24 Gy/4 fr	7 mm from the source	3
# 8	Trachea and main bronchus***	60 Gy/30 fr	0	46 Gy/23 fr	Surface	3
# 9	Trachea and main bronchus	None	50 Gy/25 fr	18 Gy/3 fr	1 cm from the source	0
# 10	Trachea	None	40 Gy/20 fr	24 Gy/4 fr	Surface	4
# 11	Bronchiole	None	0	24 Gy/4 fr	7 mm from the source	1
# 12	Bronchiole	None	0	24 Gy/4 fr	1 cm from the source	0
# 13	Main bronchus	None	40 Gy/20 fr	18 Gy/3 fr	1 cm from the source	3
# 14	Bronchiole	None	0	24 Gy/4 fr	1 cm from the source	0

**Patient # 2 had two bronchiole lesions and was not assessed for late complications because this patient developed local recurrence.*
***Patient # 3 had three bronchiole lesions. After having regional node metastasis, this patient received additional 60 Gy/30 fr of EBRT. Although tumor was controlled after additional EBRT, this patient died of respiratory failure.*
****Patients # 8 had bilateral main bronchus lesions.*
RT – radiotherapy, EBRT – external beam radiation therapy, EBBT – endobronchial brachytherapy

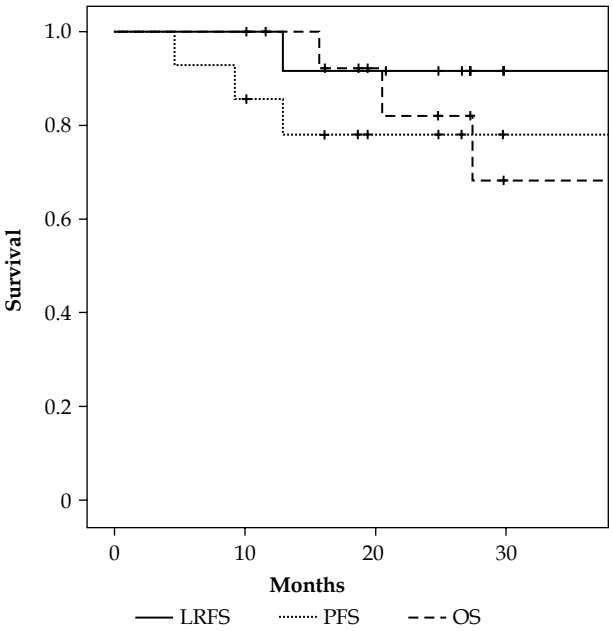

Fig. 2. Kaplan-Meier survival curves of local recurrence free survival (LRFS), progression free survival (PFS), and overall survival (OS)

Table 4. Predictors of grade 3 or higher late complication after EBBT

	With grade ≥ 3 late complication (n = 5)	Without grade ≥ 3 late complication (n = 9)	p value
Combined with EBRT	3	5	0.685
LRT D_{2cc} (EQD_2, Gy)	119.5	71.5	0.018*
LRT D_{1cc} (EQD_2, Gy)	200.6	145.9	0.201
LRT $D_{0.5cc}$ (EQD_2, Gy)	251.8	209.8	0.43
LRT V_{100} (cc)	4.6	3	0.06
LRT V_{150} (cc)	2.3	1.4	0.051
LRT V_{200} (cc)	1.1	0.7	0.183
TMB D_{2cc} (EQD_2, Gy)	124	54.1	0.008*
TMB D_{1cc} (EQD_2, Gy)	158.4	79.1	0.009*
TMB $D_{0.5cc}$ (EQD_2, Gy)	198.8	108.7	0.013*

EBRT – external beam radiation therapy, LRT – lower respiratory tract (trachea, main bronchus, and lobar bronchiole), TMB – trachea and main bronchus, EQD_2 – equivalent dose in 2 Gy fractions, D_{xxcc} – most exposed xx cm^3 of tissue, V_{xx} – volume of tissue which receives xx% of prescribed dose

ent between two groups (p = 0.018, 0.008, 0.009, and 0.013, respectively). Patients with late severe respiratory complications showed a trend toward having larger LRT V_{100} and V_{150} (p = 0.06 and 0.051). The 2-year incidence rates of late severe respiratory complications in patients with TMB D_{2cc} equal to or less than 85 Gy in EQD_2, and over 85 Gy were 0% and 83.3%, respectively with a statistically significant difference (Figure 3, p = 0.014).

Discussion

Fatal hemoptysis, ulcer, necrosis, or stenosis of the bronchi have been reported as late severe respiratory complications related with EBBT [10, 11, 12]. Direct contact of EBBT applicator to the tracheobronchial wall [10] or large V_{100} [12] was reported to be a risk factor of massive hemoptysis in EBBT. However, due to rarity of EBBT applied as a curative intent, there have been no report concerned the tolerance dose of OAR in EBBT and so far, the current report is the first report relating to DVH (dose-volume histogram) parameter of OAR and severe late respiratory complications in EBBT using modern three-dimensional image-guided brachytherapy.

We experienced as many as five late severe respiratory complications out of 13 patients in this study. On the other hand, Kawamura *et al.* reported no patient with greater than grade 2 late complications treated either with the combination of EBRT and EBBT or with EBBT alone as a curative intent with 2-year local control rate of 86.2% [7]. They prescribed 5 Gy per fraction at mucosal surface with 4-5 fractions, which is shallower than our prescription point of 1 cm from the source. Although their local control rate was somewhat worse than our result of 91.7% but the complication rate was better. Therefore, modification of reference point setting or dose fractionation should be taken into consideration.

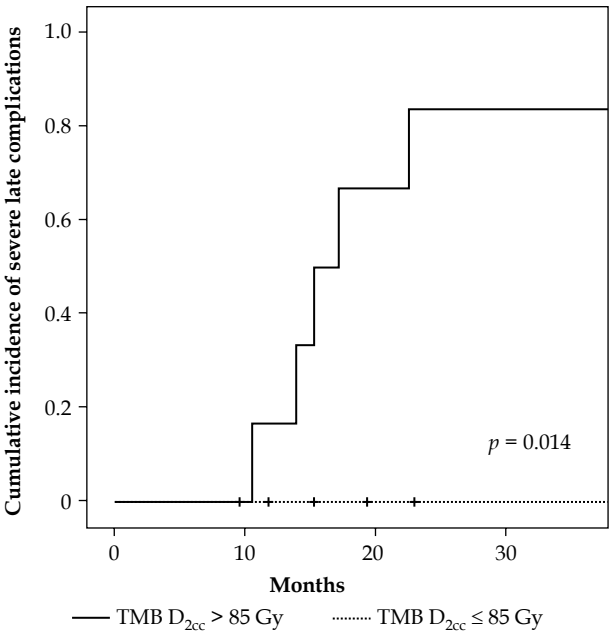

Fig. 3. Cumulative incidence of grade 3 or greater late respiratory complication stratified by trachea and main bronchus (TMB) D_{2cc} 85 Gy in EQD_2

Figure 1 shows, that most of the patients with severe late respiratory complications had their disease in trachea or main bronchus. Therefore, in addition to LRT, dose of TMB was also investigated and TMB D_{2cc} greater than 85 Gy in EQD_2 was found to be an adverse risk factor for severe late respiratory complications. This finding was in

line with Hennequin *et al*. who reported that tumor location in trachea and/or main bronchus was associated with severe late respiratory complications after EBBT [15], suggesting that severe reactions were more problematic in central region than in distal area.

In current study, control rate of EBBT for superficial bronchial carcinoma was excellent and if EBBT can be performed safely, EBBT could be an attractive alternative option for patients with superficial bronchial carcinoma because surgical resection often demands patients with severe loss of function.

Knowing what was demonstrated, that TMB D_{2cc} greater than 85 Gy in EQD_2 is a strong risk factor for severe late respiratory complications after EBBT, we can modify the total dose so that TMB D_{2cc} should not exceed 85 Gy.

There were four limitations in this study: 1. This was a single institutional retrospective study with limited number of patients because of rarity of patients treated by EBBT. To elicit more reliable result, more patients should have needed. Therefore, this study was nothing short of preliminary study and further investigation is warranted. 2. In the calculation of OAR, most heavily irradiated part of each OAR in each EBBT session was simply cumulated; however, this might be an overestimation because applicators haven't been always set at the same position and the hotspots did not always be at the same portion of individual OAR. 3. There is an argument that LQ model does not fit well when dose per fraction is larger than 8-10 Gy and should not be applied in such big single fraction [16]. 4. Inhomogeneity correction was not considered in the current treatment planning system because airways are filled with air and real dose distributions could be different from what dose planning system showed us.

Conclusions

It was discovered that TMB D_{2cc} greater than 85 Gy in EQD_2 is a strong risk factor for severe late respiratory complication after EBBT. Three-dimensional image-guided treatment planning should be performed to reduce the rate of late severe respiratory complications after EBBT. Because current study is a preliminary one with limited number of patients, further investigation is required with more patients involved.

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Disclosure

Authors report no conflict of interest.

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