OPEN ACCESS

Journal of Oncology Research and Therapy

Research Article

Yue HC, et al. J Oncol Res Ther: JONT-151.
DOI: 10.29011/2574-710X. 000051

Optimal Dosimetry Study of Metal Stent with Three-Dimensional Conformal and Intensity Modulation Radiotherapy for Locally Advanced Esophageal Carcinoma

Hong Cheng Yue[1], Hong Ju Peng[1], Jian Wen Zhang[1*], Wei Liu[1], Bo Yang[1], Jing Pin Yang[2]

[1]Department of Oncology, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan Province, People's Republic of China

[2]Department of Oncology, First Hospital of Guangyuan, Guangyuan, Sichuan Province, People's Republic of China

[*]**Corresponding author:** Jian Wen Zhang, Department of Oncology, Affiliated Hospital of Southwest Medical University. No 25 of Taiping Street, Jiangyang District, Luzhou, Sichuan Province, People's Republic of China. Email: zhangjianwen66@126.com

Citation: Yue HC, Peng HJ, Zhang JW, Liu W, Yang B, et al. (2018) Optimal Dosimetry Study of Metal Stent with Three-Dimensional Conformal and Intensity Modulation Radiotherapy for Locally Advanced Esophageal Carcinoma. J Oncol Res Ther: JONT-151. DOI: 10.29011/2574-710X. 000051

Received Date: 10 March, 2018; **Accepted Date:** 03 April, 2018; **Published Date:** 11 April, 2018

Abstract

Aim: The purpose of this study was to analyze the differences of dose distribution for target areas and Organs at Risk (OARs) using Three-Dimensional Conformal (3DCRT) and Intensity Modulation Radiation Therapy (IMRT) for esophageal carcinoma inserted metal stent.

Methods: Target areas (the Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planned Treatment Volume (PTV)) and OARs were delineated for 5 patients with locally advanced esophageal carcinoma inserted esophageal stent by means of Simulation Computed Tomography (Sim-CT). 3DCRT and IMRT plans were designed respectively. Analyzed the differences of dose distribution for target areas and OARs.

Results: The doses of target areas using IMRT were higher compared to 3DCRT, but only dose of GTV had differences ($P<0.05$), there were no differences for CTV and PTV($P>0.05$). The doses of the spinal cord and lungs using IMRT were lower, and the dose of the heart was higher compared to 3DCRT ($P>0.05$).

Conclusion: IMRT would be more beneficial to increase GTV doses and protected preferably OARs compared to 3DCRT for locally advanced esophageal carcinoma inserted metal stent.

Keywords: Dosimerty; Esophageal Carcinoma; Intensity Modulation Radiation Therapy; Metal Stent; Three- Dimensional Conformal Radiation Therapy

Introduction

Esophageal Carcinoma (EC) is one of the most common cancers with the highest rates of cancer-related death [1]. In Korea, there were 2136 and 2245 persons diagnosed with EC, and 1406 and 1507 persons death at 2009 and 2011 respectively [2,3]. There were a higher morbidity and mortality rates of EC in China [4,5]. The morbidity and mortality rates of EC were 7.74% and 21.88%, and 9.29% and 15.85% in China at 2009 and 2010 respectively [6,7].

Dysphagia is the most common complaint of patients with EC, which not only impacts prognosis, but is also the main factor impacting health-related Quality of Life (QOL); therefore, the relief of dysphagia was an important method to improve the prognosis and QOL of locally advanced EC patients [7,8]. Esophageal stenting was the most commonly used and most effective method to relieve dysphagia compared to the other methods, because which can improve early dysphagia [8].

Radiation therapy played an important role in the comprehensive treatment of esophageal cancer [9], but many controversies existed on the treatment strategy and optimal radiation dose [10]. Three-Dimensional Conformal Radiation Therapy (3DCRT) and Intensity Modulation Radiation Therapy (IMRT) were the most common radiotherapy techniques for EC [11]. There are short of optimal dosimetry study of target areas and Organs at Risk (OARs) between 3DCRT and IMRT for locally advanced EC inserted metal stent. The purpose of this study was to analyze the optimal radiation dose distribution of the target areas and OARs received in patients inserted metal stent treated using 3DCRT and IMRT for locally advanced EC.

Material and Methods

Patient Characteristics

A total of 5 adult cases (4 males, 1females, mean age 57 years, range 48~65 years) who were confirmed to have inoperable locally advanced EC by pathology and imageology from January to may 2016 (Table 1). A metal stent (MICRO-TECH Nanjing, China) made of Ni-Ti alloy (nitinol single reticulate metal stent with a diameter of 18 mm and a length of 100 mm) was inserted due to grade III/IV dysphagia. All patients underwent esophageal barium swallow examination, contrast-enhanced Computed Tomography (CT) of the thoracic region and 18-F-Fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) scans.

Number	Sex	Age (y)	Differentiation	Stage	Stent
1	Male	54	Moderate/SCC†	III	Yes
2	Male	57	Well/SCC	II b	Yes
3	Female	48	Well/SCC	II a	Yes
4	Male	62	Moderate/SCC	III	Yes
5	Male	65	Well/SCC	II a	Yes
† squamous cell carcinoma					

Table 1: Patient Characteristics.

Simulation CT Scanning

All cases were scanned by a contrast-enhanced simulation CT (Sim-CT, GE Corporation, America, scanning parameters 120 kV and 200 mA, 2.5 mm/layer) after intravenous injection of 98 ml Omnipaque (Schering AG, Germany, speed 3 ml/s). The region of Sim-CT scan was from the crico-thyroid membrane to the level of the adrenal gland, and the image of Sim-CT was transmitted to the CMS plan system (4.3, CMS Corporation, America).

Delineation of Target Areas

The target areas were delineated by a veteran radiotherapist according to the International Commission on Radiation Units and Measurements (ICRU)-62 report [12] and literature report [13] based on the results of the esophageal barium swallow examination in the CMS treatment plan system (CMS TPS). The target areas were affirmed by three persons, including two radiotherapists and a radio-physicist. For this study, the Gross Tumor Volume (GTV) was defined by the fusion of Sim-CT and PET and clinical information. The Clinical Target Volume (CTV) was defined as 3 cm proximal and distal to the GTV and 0.5 cm lateral to the GTV. The Planned Treatment Volume (PTV) was defined as 1 cm proximal and distal to the CTV and 0.5 cm lateral to the CTV (Figure 1).

Delineation of OARs

The delineation of the OARs included the whole lungs (right and left lung separately), heart, and spinal cord (extending 2 cm proximal and distal to the PTV).

Design of Radiation Plans

Both IMRT (0°/50°/100°/150°/210°/260°/310°, 6MV photons) and 3DCRT (0°/30°/130°/210°/330°, 6MV photons) plans were designed by means of the CMS TPS. The prescription doses of PTVs were 60Gy (30 fractions at 2 Gy per fraction). The requirements of the affirmation plan were the isodose curve of PTV D95% $\geq$ 56 Gy, a maximum dose of $\leq$ 110%, and a minimum dose of $\geq$ 93%. V20Gy $\leq$ 30% for both lungs, V30 Gy $\leq$ 40% for the heart, and D1cc $<$ 45 Gy for the spinal cord. The conformity index (CI, $\geq$ 0.70) and homogeneity index (HI, $\leq$ 1.20) were calculated in accordance with the literatures [14,15] (Figure 1).

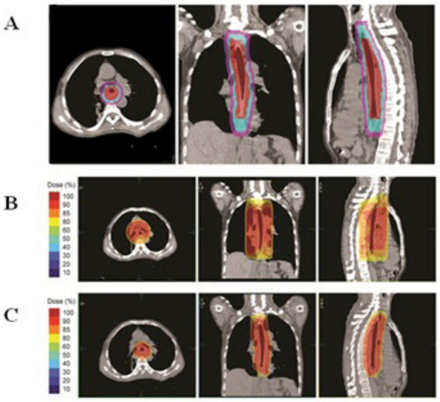

Figure 1: Delineation of target areas (transection, coronal and anteroposterior axes. Red (GTV). Sky-blue (CTV). Purple (PTV)) (A). The isodose curve distributions using 3DCRT(B) and IMRT(C).

Evaluation Parameters

The evaluation parameters of the target areas included minimum, maximum, mean dose, D95%, D90%, D85% and D80% for GTV, CTV and PTV, while OARs included minimum, maximum, mean dose, V5Gy, V10Gy, V20Gy and V30Gy for both lungs; V20Gy, V30Gy, V40Gy and V50Gy for heart, and minimum, maximum, mean dose, D1cc and D5cc for the spinal cord.

Statistical Analysis

SPSS 17.0 statistical analysis software was used for the statistical analysis. A paired t-test was used to count data in accordance with Gaussian distribution, or else by rank sum test. A significance of $p < 0.05$ was used.

Results

Dosimetry of Target Areas

The CI and HI of the target areas were slightly different between 3DCRT and IMRT (0.76±0.03 and 0.78±0.01, 1.24±0.02 and 1.18±0.01 respectively), but there were not significant differences ($P>0.05$). The doses of target areas using IMRT were generally higher compared to the doses using 3DCRT, but only the doses of GTV had differences ($P<0.05$) (Table 2).

Volume Doses	3DCRT (n = 5)	IMRT (n = 5)	T	P
Min dose †	37.5±2.44	47.47±2.83	2.1	0.1
Max dose‡	69.22±1.52	72.07±1.76	1	0.4
Mean dose	5.72±4.71	58.55±3.27	0.8	0.5
GTV				
$D_{95\%}$§	62.00±0.40	63.85±0.24	4.9	0
$D_{90\%}$	62.19±0.36	64.27±0.22	5.2	0
$D_{85\%}$	62.89±0.30	64.53±0.21	5.4	0
$D_{80\%}$	63.11±0.29	64.86±0.22	7.9	0
CTV				
$D_{95\%}$	59.30±0.94	60.78±0.57	1.1	0.3
$D_{90\%}$	60.07±0.77	61.41±0.63	2.2	0.9
$D_{85\%}$	60.93±0.53	62.21±0.59	1	0.4
$D_{80\%}$	61.77±0.40	62.48±0.49	0.9	0.4
PTV				
$D_{95\%}$	56.48±0.80	58.35±0.06	2.3	0.1
$D_{90\%}$	58.01±0.79	58.91±0.35	1.1	0.3
$D_{85\%}$	59.1±0.63	59.91±0.4	1.2	0.3
$D_{80\%}$	59.78±0.6	60.48±0.45	1.3	0.3

† minimum dose.
‡ maximum dose.
§ ncc of the target volume receiving radiation = Gy

Table 2: Comparison of dosiology features for target areas between 3DCRT and IMRT (n = 5, Gy. $\overline{x}$ ±s).

Dosimetry of OARs

For the lungs, in addition to minimum and mean doses, the other doses using IMRT were lower compared to the doses using 3DCRT, there were significant differences for the V5Gy, V10Gy and V20Gy of right lung and V5Gy and V10Gy of left lung($P<0.05$); the others had no significant differences ($P>0.05$) (Table 3).

Volume Doses	3 DCRT (n = 5)	IMRT (n = 5)	T	P
Right Lung				
Min Dose† (Gy)	0.64±0.14	1.22±0.42	1.7	0.2
Max Dose‡ (Gy)	63.32±0.75	62.56±0.57	0.8	0.5
Mean Dose(Gy)	13.69±2.14	18.66±1.36	2	0.1
$V_{5\ Gy}$(%)§	89.18±5.21	56.52±6.65	3.9	0
$V_{10\ Gy}$(%)	78.82±6.22	51.40±6.66	3.4	0
$V_{20\ Gy}$(%)	43.52±4.57	29.24±4.26	4.1	0
$V_{30\ Gy}$(%)	19.86±5.81	18.02±3.05	0.4	0.7
Left Lung				
Min Dose(Gy)	0.39±0.09	0.97±0.28	2.8	0.1
Max Dose(Gy)	66.37±1.34	63.57±0.28	2.1	0.1
Mean Dose(Gy)	16.37±2.48	22.02±0.57	2.4	0.1
$V_{5\ Gy}$(%)	95.94±2.31	63.96±5.89	4.2	0
$V_{10\ Gy}$(%)	85.82±1.99	57.37±6.00	3.7	0
$V_{20\ Gy}$(%)	45.06±3.72	27.66±1.79	0.5	0.6
$V_{30\ Gy}$(%)	23.59±4.18	19.02±2.82	1.1	0.3

† minimum dose.
‡ maximum dose.
§ percentage of the lungs volume receiving radiation = n Gy

Table 3: Comparison of lungs doses between 3DCRT and IMRT (n=5. $\overline{x}$ ±s).

The minimum and mean doses of the spinal cord using IMRT were higher compared to the doses using 3DCRT, but there were no significant differences (P>0.05). However, the other doses using IMRT were lower compared to the doses using 3DCRT, there were significant differences (P<0.05). (Table 4). For the heart, in addition to maximum doses, the other doses using IMRT were higher compared to the doses using 3DCRT; but there were no significant differences (P>0.05) (Table 4).

Volume doses	**3 DCRT (n = 5)**	**IMRT (n = 5)**	**T**	**P**
Spinal cord				
Min. dose†(Gy)	4.81±0.91	11.32±4.91	1.4	0.3
Max dose‡(Gy)	55.28±2.53	43.3±0.39	4.8	0
Mean dose(Gy)	26.27±2.92	33.78±0.74	2.2	0.1
D_{1CC}§(Gy)	53.07±3.74	40.82±0.35	3.5	0
D_{5CC}(Gy)	50.66±4.84	39.0±0.69	3	0
Heart				
Min Dose (Gy)	0.89±0.19	3.25±1.08	2	0.1
Max Dose (Gy)	60.62±2.51	58.62±3.89	0.4	0.7
Mean Dose(Gy)	16.29±4.16	22.31±5.00	0.7	0.5
V_{20Gy}(%)⍰	33.70±10.46	56.25±15.96	1	0.4
$V_{30\ Gy}$(%)	17.00±5.93	25.32±7.66	0.7	0.5
$V_{40\ Gy}$(%)	7.86±2.88	13.61±4.25	0.9	0.4
$V_{50\ Gy}$(%)	2.97±1.14	7.44±2.42	1.5	0.2

†Minimum dose.
‡ Maximum dose.
§ ncc of the spinal cord volume receiving radiation = Gy
¥ percentage V of the heart volume receiving radiation = n Gy .

Table 4: Comparison of spinal cord and heart doses between 3DCRT and IMRT (n =5. $\bar{x}$ ± s).

Discussion

Dysphagia induced by EC has many different treatments, such as alcohol injection, argon plasma coagulation, YAG laser, radiotherapy, chemotherapy, surgery, stent and so on [8], but t radiotherapy and stent are the most effective and most commonly used methods. Radiotherapy has a longer time lag to efficacy and needs patient good fitness. Disadvantage of stent is tumor ingrowth and pain. Effective combination of both may be the best way to relieve dysphagia. Median overall survival is significantly higher, and mean dysphagia-free survival time is longer with the combination of stenting and radiotherapy compared to stenting alone (118.6±55.8 vs. 96.8±43.0 days) [14].

Esophageal stent is widely applied in EC patients with grade III/IV dysphagia [15]. The dose of radiotherapy is a very important factor, which relates to the effective control rate of carcinoma. According to the literatures, the total radiation dose of chemoradiotherapy is usually in the range of 54-70 Gy, and the incidence of radiation pneumonitis increases when the total dose exceeds 60 Gy; therefore, the common radiation dose is in the range of 54-60 Gy, as a total dose of 60 Gy is feasible and safe and does not increase overall toxicity and side effects [16-18]. To compare the dose distributions of the target areas and OARs with different radiation plans, PTV is often the main factor for dose calculation [19]. In our study, the radiation target areas had GTV, CTV and PTV in the two plans consisting with the literatures [20,21].

In our study, CI and HI were very similar between the two groups with no significant differences (P>0.05), which indicated that the dose distributions of the target areas had high uniformity using 3DCRT and IMRT. The doses of target areas using IMRT were generally higher compared to the doses using 3DCRT, but there were differences only for GTV (P<0.05), the other doses were no difference between 3DCRT and IMRT (P>0.05). The results of our study indicated that IMRT had the benefit to increase the doses of target areas compared to 3DCRT.

OARs are a major consideration when performing radiotherapy for the treatment of cancer. The lungs are one of critical OARs in radiotherapy for EC, as impaired lung function impacts patient QOL and hinders completion of the radiotherapy plan [17,22]. Doses of >V20Gy and <V20 Gy are considered [23-25]. Fakhrian K et al compared the exposure dose of the lungs for five different radiation techniques (3D-45, 3D-54, HT-SIB, VMAT-SIB, and IMRT-SIB) with a radiotherapy plan based on 3DCRT in patients with locally advanced EC. The results showed that the mean lung doses were 13 Gy, 15 Gy, 12 Gy, 12 Gy and 13 Gy, V5 Gy doses were 71%, 74%, 79%, 75% and 73%, and V20 Gy doses were 20%, 25%, 16%, 18% and 19% for 3D-45, 3D-54, HT-SIB, VMAT-SIB, and IMRT-SIB, respectively [21]. When V20Gy ≥ 31%, the incidence of radiation pneumonitis was 85% [23]. In our study, for the left and right lungs, the mean doses were 13.69±2.14 Gy and 18.66±1.36 Gy, the V5 Gy doses were 89.18±5.21% and 56.52±6.65 %, and the V20Gy were 43.52±4.57% and 29.24±4.26% using 3DCRT and IMRT respectively. The results of our study indicated that IMRT had the benefit to decrease the doses of lungs compared to 3DCRT.

The spinal cord is another important OAR and is extensively considered in the planning of radiotherapy; the spinal cord exposure dose must be severely restricted to prevent severe radiation myelopathy [26,27]. The spinal cord dose is <45 Gy [28]. In our study, the spinal cord doses using IMRT were lower compared to the doses using 3DCRT, the D1cc and maximum dose were <45 Gy using IMRT, while > 45 Gy using 3DCRT, there were differences ($P<0.05$). The results of our study indicated that IMRT had the benefit to decrease the spinal cord doses compared to 3DCRT.

Radiation induced cardiac disease is a complication of radiotherapy and has a higher incidence when the heart receives a high exposed dose, and it is the main cause of morbidity and mortality for radiotherapy of cancer [29,30]. Evaluation of the heart exposure dose, mean dose and volume percentage receiving a high dose level are important indicators [31]. In our study, the doses of heart using IMRT were higher compared to the doses using 3DCRT, but there were no differences ($P>0.05$). Mean dose, V30Gy, V40Gy and V50Gy of the heart were less than 30%. The results of our study indicated that the risk of radiation-induced heart disease had no differences between IMRT and 3DCRT.

Conclusion

The results of our study indicated IMRT had the following dosimetry advantages compared to 3DCRT for locally advanced EC inserted metal stent:

- Target areas had higher doses, especially GTV, which were benefit to increase the local control rate.
- OARs had lower doses, which were benefit to protect preferably OARs. We suggested that IMRT would be the best option for locally advanced EC inserted metal stent, but the true results need to be further investigated.

References

1. Tan C, Qian X, Guan Z, Yang B, Ge Y, et al. (2016) Potential biomarkers for esophageal cancer. Springer plus 5: 467.
2. Jung KW, Park S, Kong HJ, Won YJ, Lee JY, et al. (2012) Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2009. Cancer Res Treat 44: 11-24.
3. Jung KW, Won YJ, Kong HJ, Oh CM, Lee DH, et al. (2014) Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2011. Cancer Res Treat 46: 109-123.
4. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67: 7-30.
5. Chen W, Zheng R, Zhang SW, Zeng HM, Zou XN (2013) The incidences and mortalities of major cancers in China. Chin J Cancer 106-112.
6. Chen W, Zheng R, Zhang S, Zhao P, Zeng H, et al. (2014) Annual report on status of cancer in China, 2010. Chin J Cancer Res 26: 48-58.
7. Mami Yamashita, Hideomi Yamashita, Shino Shibata, et al. (2015) Symptom relief effect of palliative high dose rate intracavitary radiotherapy for advanced esophageal cancer with dysphagia. Oncol Lett 9: 1747-1752.
8. Ramakrishnaiah VPN, Malage S, Sreenath GS, Kotlapati S, Cyriac S (2016) Palliation of Dysphagia in Carcinoma Esophagus. Clin Med Insights Gastroenterol 9: 11-23.
9. Lin SH, Hallemeier CL, Chuong M (2016) Proton beam therapy for the treatment of esophageal cancer. Chin Clin Oncol 5: 53.
10. Tai P, Yu E (2014) Esophageal cancer management controversies: Radiation oncology point of view. World J Gastrointest Oncol 6: 263-274.
11. Yang H, Feng C, Cai BN, Yang J, Liu HX, et al. (2017) Comparison of three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, and volumetric-modulated arc therapy in the treatment of cervical esophageal carcinoma. Dis Esophagus 30: 1-8.
12. Stroom JC, Heijmen BJ (2002) Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. Radiother Oncol 64: 75-83.
13. Zhang Y, Liu J, Zhang W, Deng W, Yue J (2017) Treatment of esophageal cancer with radiation therapy: a pan-Chinese survey of radiation oncologists. Oncotarget 8: 34946-34953.
14. Javed A, Pal S, Dash NR, Ahuja V, Mohanti BK, et al. (2012) Palliative stenting with or without radiotherapy for inoperable esophageal carcinoma: a randomized trial. J Gastrointest Cancer 43: 63-69.
15. Han X, Zhao YS, Fang Y, Qi Y, Li X, et al. (2016) Placement of transnasal drainage catheter and covered esophageal stent for the treatment of perforated esophageal carcinoma with mediastinal abscess. J Surg Oncol 114: 725-730.
16. Roeder F, Nicolay NH, Nguyen T, Saleh-Ebrahimi L, Askoxylakis V, et al. (2014) Intensity modulated radiotherapy (IMRT) with concurrent chemotherapy as definitive treatment of locally advanced esophageal cancer. Radiat Oncol 9: 191.
17. He J, Zeng ZC, Shi SM, Yang P (2014) Clinical features, outcomes and treatment-related pneumonitis in elderly patients with esophageal carcinoma. World J Gastroenterol 20: 13185-13190.
18. Pöttgen C, Stuschke M. (2012) Radiotherapy versus surgery within multimodality protocols for esophageal cancer--a meta-analysis of the randomized trials. Cancer Treat Rev 38: 599- 604.
19. Fakhrian K, Oechsner M, Kampfer S, Schuster T, Molls M, et al. (2013) Advanced techniques in neoadjuvant radiotherapy allow dose escalation without increased dose to the organs at risk: Planning study in esophageal carcinoma. Strahlenther Onkol 189: 293 -300.
20. Chen HY, Ma XM, Ye M, Hou YL, Xie HY, et al. (2014) Esophageal perforation during or after conformal radiotherapy for esophageal carcinoma. J Radiat Res 55: 940-947.
21. Kim DE, Kim UJ, Choi WY, Kim MY, Kim SH, et al. (2013) Clinical prognostic factors for locally advanced esophageal squamous carcinoma treated after definitive Chemoradiotherapy. Cancer Res Treat 45: 276-228.
22. Kangpyo Kim, Jeongshim Lee, Yeona Cho, Chung SY, Lee JJB, et al. (2017) Predictive factors of symptomatic radiation pneumonitis in primary and metastatic lung tumors treated with stereotactic ablative body radiotherapy. Radiat Oncol J 35: 163-171.
23. Tsujino K, Hirota S, Endo M, Obayashi K, Kotani Y, et al. (2003) Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 55: 110-115.
24. Pinnix CC, Smith GL, Milgrom S, Osborne EM, Reddy JP, et al. (2015) Predictors of Radiation Pneumonitis in Patients Receiving Intensity-Modulated Radiation Therapy for Hodgkin and Non-Hodgkin Lymphoma. Int J Radiat Oncol Biol Phys 92: 175-182.

25. Ozawa Y, Abe T, Omae M, Matsui T, Kato M, et al. (2015) Impact of Preexisting Interstitial Lung Disease on Acute, Extensive Radiation Pneumonitis: Retrospective Analysis of Patients with Lung Cancer. PLoS One 10: e0140437.

26. Pedicini P, Strigari L, Benassi M, Caivano R, Fiorentino A, et al. (2014) Critical dose and toxicity index of organs at risk in radiotherapy: analyzing the calculated effects of modified dose fractionation in non-small cell lung cancer. Med Dosim 39: 23-30.

27. Lievens Y, Nulens A, Gaber MA, Defraene G, Wever WD, et al. (2011) Lung Cancer Group. Intensity-modulated radiotherapy for locally advanced non-small-cell lung cancer: a dose-escalation planning study. Int J Radiat Oncol Biol Phys 80: 306-313.

28. Zhang X, Li Y, Pan X, Xiaoqiang L, Mohan R, et al. (2010) Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. Int J Radiat Oncol Biol Phys 77: 357-366.

29. Onwudiwe NC1, Kwok Y, Onukwugha E, Sorkin JD, Zuckerman IH, et al. (2014) Cardiovascular event-free survival after adjuvant radiation therapy in breast cancer patients stratified by cardiovascular risk. Cancer Med 3: 1342-1352.

30. Finch W, Shamsa K, Lee MS (2014) Cardiovascular complications of radiation exposure. Rev Cardiovasc Med 15: 232-244.

31. D'Errico MP, Grimaldi L, Petruzzelli MF, Gianicolo EA, Tramacere F, et al. (2012) N-terminal pro-B-type natriuretic peptide plasma levels as a potential biomarker for cardiac damage after radiotherapy in patients with left-sided breast cancer. Int J Radiat Oncol Biol Phys 82: e239-e246.