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RESEARCH ARTICLE

EVALUATION OF THE DOSIMETRIC DIFFERENCES IN ESOPHAGITIS INDUCED FROM RADIOTHERAPY OF LUNG CANCER PATIENTS USING THREE DIFFERENT RADIATION TECHNIQUES

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ABSTRACT

Objective: To evaluate the dosimetric differences in esophagitis induced from radiotherapy using three radiation techniques of lung cancer patients: "Low-Modulated" Intensity Modulated Radiation Therapy (LM-IMRT), Stereotactic Body Radiation Therapy (SBRT) and Three Dimensional Conformal Radiation Therapy (3DCRT).

Methods and Materials: In this retrospective study, treatment charts of 243 lung cancer patients treated with radiation therapy or combined with chemotherapy from year 2014 to 2017 at University of Mississippi Medical Center (UMMC) Radiation Oncology were reviewed. The dosimetric parameters such as mean esophagus dose (MED), D_{max}, D_{min}, V_5, V_{10}, V_{15}, V_{20}, V_{30}, V_{40}, V_{50}, and $V_{60}$from three treatment techniques are collected from the Pinnacle treatment planning system. One way ANOVA method was used to compare the dosimetric parameters, and Tukey multiple comparison tests were used for pairwise comparisons of the three treatment techniques.

Results: There were significant difference indosimetric parameters between SBRT and LM-IMRT, and between SBRT and 3DCRT. There were no significant difference between LM-IMRT and 3DCRT for mean esophagus dose, V_5, V_{10}, V_{15}, and V_{20}, but there were significant difference for V_{30} and V_{40} for treatment prescription of 3DCRT at 37.5Gy in 15 fractions(or 30 Gy in 10 fractions) and LM-IMRT at 60Gy in 30 fractions (or 59.4 Gy in 33 fractions) daily. However, after rescaling the prescription of the 3DCRT to the same level of LM-IMRT at 60Gy in 30 fractions daily, dosimetric difference of esophagus between 3DCRT and LM-IMRT turned out to be statistically significant ($p<0.05$).

Conclusions: The result of this study suggests that the Low-Modulated IMRT was superior compared to the 3DCRT technique in sparing the esophagus. Additionally, it is important to rescale the dose prescription to have apple to apple treatment technique comparison regarding the dosimetric parameters of esophagus from clinical application point of view. All treatment data for this research is from the single institute, therefore the variety of volumetric metrics of the esophagus from the different institute's published data are avoided. Findings from this study can help clinicians in making decisions about which treatment technique to choose and how dosimetric parameters can be optimized to avoid potential complication in esophagus.

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INTRODUCTION

In 1895 a German physicist, Wilhelm Conrad Roentgen, presented a remarkable lecture of “concerning a New Kind of ray.” Roentgen called it the “x-ray”, with “x” being the symbol for an unknown quantity (Hall, 2000).In 1898, Polish female physicist Marie Curie discovered the γ-ray from radium. Since then, the radiation therapy has gone through amazing evolution and developments of conceptual and technological innovations, and the basics of the safe and effective radiotherapies used today has been formed (Connell, 2009). Although radiation is beneficial at killing the tumor cells, it is harmful at detriment of the health organ (Emami, 2013). An ideal practice of radiotherapy involves optimization of treatment plans to maximize the radiation dose to the tumor and minimize the dose to the critical organs and structures around the tumor. Unfortunately, this is often impossible in radiotherapy due to the anatomic distribution and the limitation of the beam delivery. The aim of the radiation therapy is to deliver enough radiation dose to the tumor to destroy it without irradiating normal tissue to a radiation dose that will lead to serious complications (Johns, 1983). In other words, the goal of radiation therapy is to achieve an uncomplicated loco-regional control of cancer (Emami, 2013). In order to reach this goal, the precise knowledge of tumor control radiation dose and the tolerance dose (TD) of normal tissue to radiation is required (Werner-Wasik, 2010).Unfortunately, after over 100 years of practicing radiation oncology and besides muchrecent technology progresses, knowledge on radiation dose of normal tissue complication is kept very limited due to the basic complexity of the subject (Emami, 2013). The clinical practice of radiation therapy has far more influenced and changed by advanced technology developments than by biological and radiobiological insights (Connell, 2009).

In the 1970s, computers were introduced into radiation therapy and the treatment planning process. Computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scans make it available to target the tumors precisely in three dimensions. The development of multi-leaf collimator in modern linear accelerator “LINAC” makes the beam being able to be modulated, so that the beam can be delivered with the dose of concave shaped to conform to the target and to limit the dose to normal tissues using Intensity Modulated Radiation Therapy (IMRT) and Imaging Guided Radiation Therapy (IGRT). Therefore, a new concept of “three dimensional treatment planning and dose delivery” has been developed, which have significantly improved conformation of radiotherapy and have greatly impacted the dose distribution, therefore, leading to escalated dose to the target volume and limited amount of normal tissue receiving a high dose (Bortfeld, 2002). Even though, the question “What radiation dose is best for cancer treatment?” has never been stopped being askedsince the onset of radiation therapy in the 19th century (Bentzen, 2016).

Since the late 1980s, radiation therapy was considered the standard care for patients with lung cancer (Rodriguez, 2009). Esophagus is one of the critical organs at risk (OAR) during lung cancer treatment by radiotherapy. Radiation induced acute esophageal toxicity (esophagitis) is seen as one of the main complications for lung cancer radiation treatment and it is known to be a significant dose-limiting factor (Werner-Wasik, 2010), as well as related to radiation treatment techniques (Werner-Wasik, 2010). Severe esophagitis can cause patient hospitalization, and treatment breaking, which will reduce the tumor control probabilities. (Werner-Wasik *et al*., 2010) The existing literature indicated that the dosimetric parameters are predictors of esophagitis; however, they are so many parameters that are too variable to be unified. It is prudent to understand and correlate the dosimetric parameters to esophagitis associated with different treatment techniques in order to prevent or reduce the incident of esophagitis.At radiation oncology department of UMMC, three radiation treatment techniques have been implemented for the lung cancer patients, namely “Low-Modulated” Intensity Modulated Radiation Therapy (LM-IMRT), Stereotactic Body Radiation Therapy (SBRT) and Three Dimensional Conformal Radiation Therapy (3DCRT). In this study, the dosimetric parameters of esophagus radiationdose was retrospectively reviewed and compared among these three treatment techniques.

MATERIALS AND METHODS

This research was approved by the Institutional Review Board of University of Mississippi Medical Center (UMMC). All patients with lung cancer treated in the department of Radiation Oncology at UMMC from January 01, 2014 to June 30, 2017 were included in this study. A total of 350 charts of lung patients, who underwent radiation therapy with concurrent chemotherapy or sequential chemotherapy in this period werecollected and reviewed. 107 patients either without on-treatment notes or metastasized from lung cancer, were excluded, leaving 243 evaluable patients. The dosimetric parameters such as mean esophagus dose (MED), D_{max}, D_{min}, V_5, V_{10}, V_{15}, V_{20}, V_{30}, V_{40}, V_{50}, andV_{60} ofesophagus, as well as, the treatment technique were collected from the treatment planning system (Pinnacle) and from the treatment record and verify system (Mosaiq). Definitions of treatment planning parameters in dosimetry and other terminologies used in this study are listed in Table 1.

Patients were placed in the supine and head first position on a wing board with both arms placed above the head for the treatment planning computed tomography (CT) scan on a Phillips Brilliance Big Bore CT with 16 multi-slice capabilities. Images were obtained using a helical scanning mode with 3 mm slice thickness. Gross tumor volume (GTV), clinical target volume (CTV), skin, lungs, esophagus, spinal cord, and heart, etc. were contoured by the radiation oncologists on the axial view of the 3Dimensional CT (3DCT) data set. Both LM-IMRT and SBRT require four dimensional CT (4DCT) techniques to manage the tumor motion. The internal target volume (ITV) was created based on the maximal intensity projection (MIP) from the 4DCT and expanded with a margin of normally 0.5 - 1.0 cm to create the planning target volume (PTV). The dosimetric parameters from three treatment techniques are compared and analyzed using the one way ANOVA method and Tukey multiple comparison tests. All the statistical analyses were performed using IBM SPSS software version 24. All statistical tests of significance were performed at the 5% significant level (α=0.05).

RESULTS

Table 2 illustratesfrequency distribution information for the three treatment techniques. Out of 243 lung patients, there were 139, 69 and 35 patients were treated usingLM-IMRT, SBRT and 3DCRT, respectively.

Table 1. Abbreviations of Treatment Planning Parameters in Dosimetry

DVH	Dose volume histogram, commonly used cumulative DVH: relative volume (%) versus absolute dose (Gy)
D_v	Highest dose that encloses v% organ volume, e.g. D_5: dose to 5% of volume received
D_{max}	Maximum dose in an organ (Gy)
V_D	Volume (%) receiving ≥ dose D, e.g.V_{20}: volume in % receiving ≥ 20 Gy
D_{mean}	Mean dose (Gy)
$TD_{5/5}$	Tolerance dose (Gy) for 5% complication probability at year 5
$TD_{50/5}$	Tolerance dose (Gy) for 50% complication probability at year 5

Table 2. Frequency Distribution of Patients Treated with Three Different Techniques

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	IMRT	139	57.2	57.2	57.2
	SBRT	69	28.4	28.4	85.6
	3D	35	14.4	14.4	100.0
	Total	243	100.0	100.0	

The results (one way ANOVA) indicated that there were significant difference between the three different treatment techniques (p-value <0.0001). Furthermore, post hocTukey multiple comparisons tests of the mean of the dosimetric parameters for V_5, V_{10}, V_{15}, V_{20}, V_{30}, V_{40}, V_{50}, V_{60}, mean esophagus dose, and maximum dose among the three different treatment techniques indicated that there was a significant difference between SBRT and LM-IMRT ($p<0.05$), and between SBRT and 3DCRT ($p<0.05$) for V_5, V_{10}, V_{15}, V_{20}, V_{30}, V_{40}, V_{50}, and V_{60}, and mean esophagus dose. The difference between LM-IMRT and 3DCRT was not significant for V_5 (p=0.921), V_{10} (p=0.167), V_{20} (p=0.079), V_{40} (p=0.062), V_{50} (p=0.148), V_{60} (p=0.994), and mean dose of esophagus (p=0.664). While the difference for V_{15} (p=0.046) and V_{30} (p=0.026) and maximum esophagus dose (p=0.023) was statistically significant. Figures 1 and 2 display the comparison of dosimetricparameters of treatment planning chart data among the three treatment techniques: LM-IMRT, SBRT and 3DCRT. It is worth mentioningthat the treatment prescriptions were different according to the different treatment techniques. For example, the prescriptions for patients using LM-IMRT technique were 59.4 Gy or 60 Gy in 33 or 30 fractions. The prescriptions for patients using 3DCRT were 37.5 Gy or 30Gy in 15 or 10 fractions. In order to have an “apple to apple” treatment technique conclusive comparison, a new plan for 3DCRT was rescaled by changing prescription to 60 Gy in 30 fractions which was the prescription used in the LM- IMRT technique. Figure 3 and 4 show the comparisons based on the same level prescriptions for the two techniques (data rescaled). There was a significant difference of dosimetric parameters of esophagus for V_{40}, V_{50}, V_{60} and MED. It is very clear that LM-IMRT spared dose to esophagus compared to 3DCRT. This finding agreed withpreviously documented study by Christine Higby *et al*. (2016) and Ling *et al*. (2016)

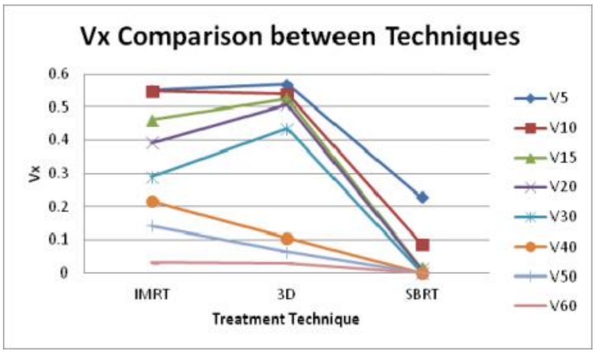

Figure 1. Comparison of different dosimeter parameters among the three treatment techniques: LM- IMRT, SBRT and 3DCRT from the Clinical Prescription

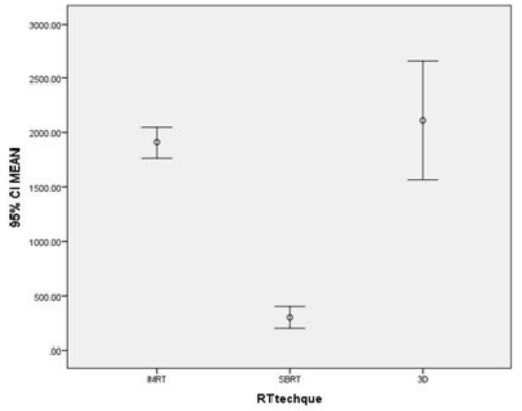

Figure 2. Comparison of mean esophagus dose among the three treatment techniquesLM-IMRT, SBRT and 3DCRT from the Clinical Prescription

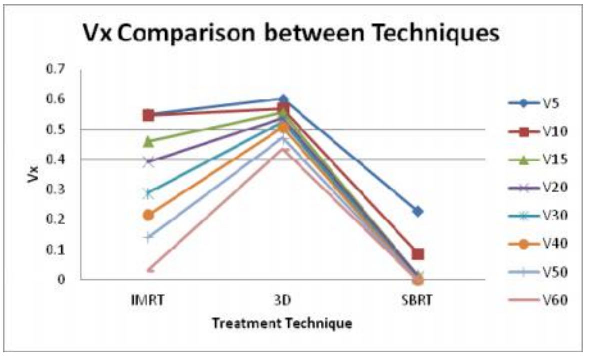

Figure 3. Comparison of dosimeter parameters between these three techniques: LM-IMRT, SBRT and 3DCRT from the rescaled clinical prescriptions

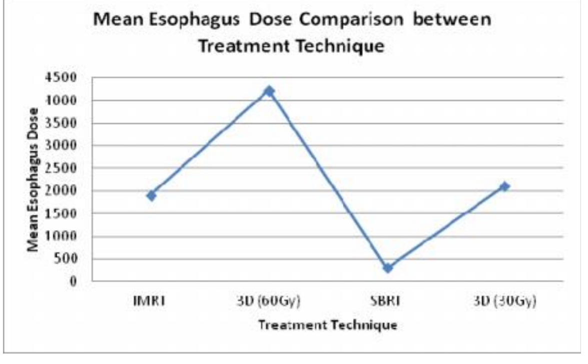

Figure 4. Comparison the mean of mean esophagus dose between techniques LM- IMRT, SBRT and 3DCRT from the rescaled clinical prescriptions

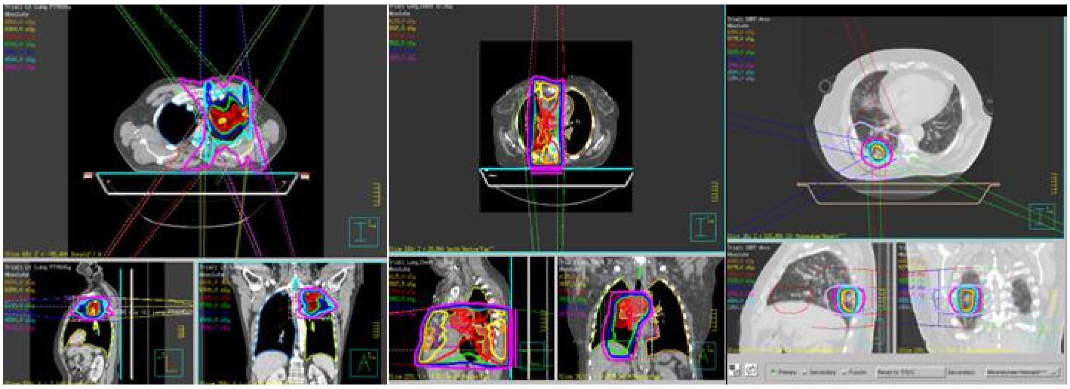

Figure 5A, 5B and 5C. Examples of comparisons of Isodose and beam arrangement of LM-IMRT, 3DCRT and SBRT from UMMC

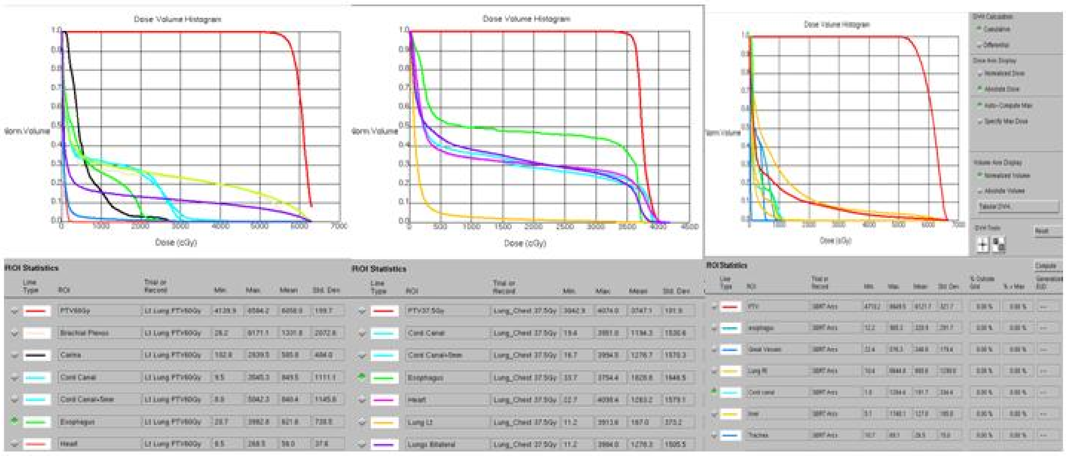

Figure 5D, 5E and 5F. Examples of DVH comparisons of LM- IMRT, 3DCRT and SBRT from UMMC

DISCUSSION

The 3DCRT technique is a conventional way using Anterior/ Posterior (AP/PA) beam arrangement to a target dose of 45 Gy with 1.8 Gy per fraction daily, then using “off spinal cord” beam arrangement (or oblique to avoid the cord) to boost the total target dose to 59.4 Gy. This technique has the advantage of easier patient set up and fast in treatment planning process. It is generally used for stage III and IV lung cancer treatment. Traditionally, AP/PA beam arrangement is applied for stage IV lung cancer patient for a palliative prescription dose of 37.5 Gy or 30 Gy in 15 or 10 fractions daily.

With the technology development, IMRT technique is increasingly implemented for conventional fractionated lung treatment because of its ability to generate concaved dose distribution to spare organs at risk (OAR) such as the spinal cord, heart, esophagus and healthy lungs (Jin, 2016). However, a fully intensity modulated IMRT possesses unique challenges for lung cancer treatment mainly due to the interplay between lung tumor motion and small segment multi-leaf collimator (MLC) movements (Diane*et al*., 2016).When the trajectory of the MLC and the target is not synchronous, uncertainty in dose delivery may occur around the target (Bortfeld*et al*., 2002). In contrast, LM-IMRT can be seen as a sparsely intensity modulated radiation therapy technique used by limiting both the degree of modulation, number of segments per beam and the IMRT segment size during the inverse planning process. The dosimetric criterion of the plan is $V_{95\%Rx} \geq 95\%$, which means that the 95% of the Planning Target Volume (PTV) should receive more than 95% of the prescription dose. Pinnacle treatment planning system (TPS) allows planners to set minimum segment size and number, which is not available in other TPSs. Our institution recommended guideline for LM-IMRT is to start the optimization with minimum segment size of 40 cm^2 and minimum monitor units (MU) of 20 per beam; however these values can be iteratively modified. LM-IMRT technique has been implemented uniquely at UMMCradiation oncology since 2010 and used mainly for stage IIor III lung cancer patients to generate a better conformal dose distribution around tumor and minimum radiation dose to the surrounding healthy tissues while most of other institutes ignore or debate the effects of interplay between lung tumor motion and small MLC segments movements. The selected effective dose prescription is normally 59.4 or 60 Gy with 1.8 Gy or 2 Gy per fraction daily with 6 MV photon beams.

The third technique is SBRT, which utilizes high fractional doses of radiation in 5 or fewer treatments. Normal tissue risk is highly decreased due to the substantial steep dose fall off and tumor dose prescription is escalated due to the tumor conformal dose plans in SBRT technique. SBRT requires highly accurate and precise radiation delivery because of the high fractional dose of the treatment, as well as, the rapid radiation dose drop-off (Weintraub, 2012). The prescription can be 50 Gy or 55 Gy in 5 fractions delivered on every other day. SBRT is typically used to treat small, early-stage non-small cell lung tumors (Weintraub *et al*., 2012).It is used at UMMC for stage I lung cancer patients. Esophageal exposure dose varied depending on the tumor location, its proximity to the esophagus, the beam orientation selected, treatment techniques, and the protocol used. Figure 5A, 5B and 5C demonstrates the typicalisodose distributions and beam arrangements using these three treatment techniques of LM-IMRT, 3DCRT, and SBRTrespectively.The orange, yellow, red, green and pink isodose lines present the 110%, 105%, 100%, 95% and 90% of the prescription. It can be seen that in AP/PA technique, not only the tumor got the prescription dose, but also the partial healthy tissues outside the tumor received as high as prescription dose since the beam passes through the healthy tissues. LM-IMRT offered better dose conformation to the tumor, however, healthy tissues received split low dose, that was reported as one of the reasons to induce the esophagitis or healthy organ toxicities (Robin Wijsman*et al*., 2017). Figure 5D, 5E and 5F display the dose volume histogram (DVH) of LM-IMRT, 3DCRT and SBRT respectively. The green line represents the DVH of esophagus. The red line represents the PTV coverage. The rests of the different colored lines represent the DVHs of different organs at risk (OAR). It can be seen that the shape of DVH of esophagus were different among these three techniques. The dosimetric parameters are the highest for 3DCRT technique and the least for SBRT technique. SBRT provides the most conformal dose distribution around the tumor and the least dose to OARs, while 3DCRT offered the least conformal dose distribution and more dose to the OARs. LM-IMRT stays in the middle between SBRT and 3DCRT in regard to the conformal dose distribution of the tumor and dosimetric parameters of esophagus. LM-IMRT is superior compare to 3DCRT in tumor dose conformation and esophagus sparing.

In current clinical treatment practice for lung cancer, the esophagus dose constraint is set as mean dose less than 34 Gy (Emami *et al*., 1991). The previously reported dosimetric predictors for acute radiation-induced esophagitis were percentage of esophageal volume receiving larger than 45 Gy (V_{45}), V_{50}, V_{60}, maximal esophageal point dose (D_{max}), mean esophageal dose (MED), and esophageal surface area receiving 55 Gy (Takeda *et al*., 2005). The results of total 12 studies published between 1999 and 2009 in which assessed the dose-volume outcome in more than 90 patients treated for non-small cell lung cancer indicated a correlation between esophagitis for a variety of dose-volume factors, such as V_{20}, V_{35}, V_{60} and V_{70}. They found a variety of clinical and dosimetric parameters to have been associated with acute and late esophagitis although the inter-study variations have been large (Werner-Wasik *et al*., 2010). The predictors are too varied to unify them (Werner-Wasik *et al*., 2010).

The main difficulties to determine definitive dosimetric predictors from the published data werethe variety of volumetric metrics of the esophagus, some used absolute volume and some used relative volume (Werner-Wasik *et al*., 2010). To overcome this shortcoming, an owninstitute outcome analysis is recommended by “the Quantitative Analysis of Normal Tissue Effects in the Clinic” (QUANTEC). This current research dealt with a single institution treatment outcome data (UMMC), where the target delineation was standardized, treatment were uniformed, treatment planning were peer-reviewed, and toxicity recording is consistent, thus the data was under-control and meaningful.

Conclusion

In this study, the dosimetric parameters of esophagus of lung cancer patients treated with radiation therapy among three different treatment techniques: LM-IMRT, 3DCRT, andSBRT were retrospectively compared. We found that there are significant dosimetric parameter differencesamong these three techniques. Treatment techniques do play an important role in delivering dose to esophagus from lung cancer radiotherapy treatment. The uniquely implemented LM-IMRT techniqueat UMMC for lung cancer radiotherapy is superior to 3DCRT in sparing dose to esophagus while delivering conformal dose to the tumors. This technique avoids the interplay effects between lung tumor motion and MLC segmentation movements. As an extension of this work, which will be reported in the near future, the correlation between dosimetric parameters and probability of incidence of esophagitis wereperformed. Also, the dosimetric predictors and models were established with fitting the Lyman-Kutcher-Burman (LKB) model parameters using UMMC local treatment outcome data for lung cancer treatment group using LM-IMRT technique. Findings from this study can help clinicians in making decisions about which treatment technique to choose and how dosimetric parameters can be optimized to avoid potential complication in esophagus.

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