Technology in Cancer Research & Treatment
Volume 20: 1-9

DOI: 10.1177/15330338211016472
journals.sagepub.com/home/tct
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Evaluation of IGRT-Induced Imaging Doses and Secondary Cancer Risk for SBRT Early Lung Cancer Patients In Silico Study

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Abstract

Objectives: This study performed dosimetry studies and secondary cancer risk assessments on using electronic portal imaging device (EPID) and cone beam computed tomography (CBCT) as image guided tools for the early lung cancer patients treated with SBRT. **Methods:** The imaging doses from MV-EPID and kV-CBCT of the Edge accelerator were retrospectively added to sixty-one SBRT treatment plans of early lung cancer patients. The MV-EPID imaging dose (6MV Photon beam) was calculated in Pinnacle TPS, and the kV-CBCT imaging dose was simulated and calculated by modeling of the kV energy beam in TPS using Pinnacle automatic modeling program. Three types of plans, namely $Plan_{EPID}$, $Plan_{CBCT}$ and $Plan_{origin}$, were generated with incorporating doses of EPID, CBCT and no imaging, respectively, for analysis. The effects of imaging doses on dose-volume-histogram (DVH) and plan quality were analyzed, and the excess absolute risk (EAR) of secondary cancer for ipsilateral lung was evaluated. **Results:** The regions that received less than 50 cGy were significantly impacted by the imaging doses, while the isodose lines greater than 1000 cGy were barely changed. The DVH values of ipsilateral lung increased the most in $Plan_{EPID}$, followed by $Plan_{CBCT}$. Compared to $Plan_{origin}$ on the average, the estimated EAR of ipsilateral lung in $Plan_{EPID}$ increased by 3.43%, while the corresponding EAR increase in $Plan_{CBCT}$ was much smaller (about 0.4%). Considering only the contribution of the imaging dose, the EAR values for the ipsilateral lung due to the MV-EPID dose in 5 years,10 years and 15 years were 1.49 cases, 2.09 cases and 2.88 cases per 10^4PY respectively, and those due to the kV-CBCT dose were about 9 times lower, correspondingly. **Conclusions:** The imaging doses produced by MV-EPID and kV-CBCT had little effects on the target dose coverage. The secondary cancer risk caused by MV-EPID dose is more than 8.5 times that of kV-CBCT.

Keywords

imaging dose, MV-EPID, kV-CBCT, TPS, early-stage lung cancer, SBRT, secondary cancer risk

Abbreviations

EPID, electronic portal imaging device; CBCT, cone beam computed tomography; DVH, dose-volume-histogram; EAR, excess absolute risk; NSCLC, early non-small-cell lung cancer; SBRT, stereotactic body radiotherapy; IGRT, Image guided radiotherapy; OARs, organs at risk; TPS, treatment planning system; PTV, Plan target volume; ITV, internal target volume; RTOG, recommendations of radiation oncology working group; PDD, depth dose curves; V20, percent of total lung volume receiving 20 Gy or more;

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V10, percent of total lung volume receiving 10 Gy or more; V30, percent of total lung volume receiving 30 Gy or more; V5, percent of total lung volume receiving 5 Gy or more; AP, Auto-Planning; DMPO, direct machine parameter optimization; CCC, collapsed cone convolution; MLC, multi-leaf collimator; EAR, excess absolute risk; PY, person-year; ERR, excess relative risk; MC, Monte Carlo.

Received: September 03, 2020; Revised: March 23, 2021; Accepted: April 19, 2021.

Background

Developments in various diagnostic technologies have enabled early detection of neoplastic lesions, thus early-stage treatment across various malignancies, including lung cancer. Although lobectomy is the standard treatment for patients with early non-small-cell lung cancer (NSCLC), some patients are unsuitable or unwilling to undergo surgery. Chang *et al*[1] reported that the 3-year survival rate of early stage NSCLC patients treated with stereotactic body radiotherapy (SBRT) was as high as 95%, and therapeutic effect was similar to or even better than that of surgery. With the advantages of short treatment time, low toxicities and non-invasiveness, more and more clinicians and patients rank SBRT as the preferred choice of treatment for early stage NSCLC.[1-3] SBRT is conducted with large fractional doses and relatively small treatment margins, thus requires stringent treatment positioning accuracy. The high requirement of the position accuracy often demands the use various imaging technologies at treatment, which inevitably deliver additional imaging doses to patients.

Image guided radiotherapy (IGRT) has become a routine procedure of position verification for patients treated with SBRT.[4] Most of IGRT relies on electronic portal imaging device (EPID) and cone beam computed tomography (CBCT) to improve the positioning accuracy during radiotherapy. Since the IGRT process delivers additional radiation dose to patients, it may cause organs at risk (OARs) complications, as well as increasing secondary cancer risk, especially for early lung cancer patients with long survival time.[5,6] However, the treatment planning system (TPS) generally does not take the imaging dose into account at the planning design stage, and the risks caused by the imaging dose is normally ignored and not thoroughly investigated.

In recent years, several studies on image-guided dose and its triggered secondary cancer have been conducted and reported. Dzierma *et al*[7] measured the abdominal imaging dose and assessed the associated secondary cancer risk. They also studied the imaging dose during radiotherapy for children with Hodgkin disease and established its corresponding secondary cancer prediction model.[8] Kim *et al*[9] assessed the secondary cancer risks of head and neck, chest and abdomen caused by the imaging dose using the simulation phantom as the measuring tool. Quinn *et al*[10] used the quadratic equation model of radiation-induced secondary cancer risk to calculate the contralateral breast secondary cancer risk after adding imaging dose to patients with breast cancer. However, since SBRT is relatively new, no study has been found to investigate the impacts of the IGRT imaging doses for early lung cancer patients treated with SBRT.

This study is aimed to calculate and analyze the imaging doses of clinically used megavoltage EPID and kilovoltage CBCT for early lung cancer patients treated with SBRT, and then superimposed imaging doses into the treatment plan to evaluate the secondary cancer risk. The results of this study can provide a data reference about IGRT-induced imaging doses and secondary lung cancer risk of early-stage lung cancer patients treated with SBRT.

Materials and Methods

Data Collection and Patient Characteristics

Sixty-one (31 men and 30 women) patients treated in our center from January 2016 to September 2018 were retrospectively selected and included in this study. The patients all had early stage inoperable NSCLC and were consulted with at least 2 radiation oncologists before being recommended for receiving SBRT treatment. The age of the patients ranged from 46 to 79 (median age 68 years and mean age 65 years) years. The volume of internal target volume (ITV) ranged from 3.91 cm^3 to 34.42 cm^3, and clinical stage was all $T_1N_0M_0$. The prescription dose was 5,000 cGy in 5 fractions. All the patients signed informed consents and completed their radiotherapy treatments. The study was approved by the native Ethics Committee (the committee's reference Number: KS1863).

Structure Delineation, Prescription, and Plan Design

All of the patients underwent 4DCT simulation. The internal target volume (ITV) and OARs were delineated by radiation oncologists on the 4DCT images, and the planning target volume (PTV) was obtained by extending 0.5 cm of ITV in 3 dimensions. All structures were reviewed and approved by an independent radiation oncologist before being used for planning design.

The treatment plan constraints recommended in RTOG 0915[11] were followed for the treatment plan design of the SBRT patients. Briefly, 100% prescription isodose was normalized to cover 95% of the PTV volume, and 99% of the PTV volume was encompassed by at least 90% of the prescribed dose. The maximum dose of PTV was between 111% and 167% of the prescribed dose. The dose constraints for OARs recommended by RTOG 0915[11] were also strictly followed to ensure that the percent of total lung volume receiving 20 Gy or more (V20) were less than 10%.

Table 1. Parameters in BEIR VII Model for Lung Secondary Cancer.[18]

Model parameter	Female	Male
β_s	3.4	2.3
γ	-0.41	-0.41
η	5.2	5.2

The treatment plans were generated using the Auto-Planning (AP) module in the Pinnacle 9.10 (Philips Radiation Oncology Systems, Fitchburg, WI, USA) system, with 10 or more coplanar 6 MV photon beams and the IMRT technology. The direct machine parameter optimization (DMPO) algorithm and the collapsed cone convolution (CCC) algorithm were used for plan optimization and dosed calculation, respectively. Considering that the target of SBRT is generally small, the dose calculation grid was set to 2 x 2 x 2 mm^3. The treatments were all delivered on Edge accelerator (Varian Medical Systems, Palo Alto, CA), which is equipped with a high-definition 120 multi leaf collimator system (HD MLC).

Image Guided Dose Calculation

The Edge accelerator is equipped with a 6MV Low Dose mode (hereinafter referred to as MV-EPID) and a kV CBCT imaging mode. The MV-EPID imaging mode can be used to take 2D orthogonal images for the purpose of treatment positioning during which a pair of anterior-posterior (AP) and Lateral images are usually taken. In our clinic, when used for treatment positioning, the MV-EPID images were taken with the double exposures which included 2 exposure fields of 10 x 10 cm^2 and 28.4 x 28.4 cm^2 at each of the imaging angles, and each of the exposures was turned on for 1.5 monitor unit (MU). The thorax kV-CBCT protocol was selected for CBCT scanning. The image acquisition parameters were 125 kV, 270 mAs, Half Fan Bow-Tie, and rotation angle of 360°.

Both of the above 2 modes in the Edge accelerator imaging system were simulated in Pinnacle 9.10 TPS so that the imaging dose could be calculated in conjunction with the treatment plan. The MV-EPID imaging dose could be directly calculated with 6MV photon beam used for treatment, while the simulation of kV-CBCT imaging dose required modeling of the kV energy in the TPS.[12-16] The image beam line was modeled using Pinnacle automatic modeling program, which provides a stable inversion related to the initial spectral selection.[13] In order to build the beam energy model of the kV-CBCT in the TPS, it is necessary to collect the characteristic data of the beam, including data such as percentage depth dose curves (PDD), beam profiles, output factors, energy spectrums, etc. These are similar to the standard commissioning of therapeutic energy beams.[14]

For each patient, the original treatment plan ($Plan_{origin}$) that did not include the imaging dose was compared to the following scenarios for dosimetry:

$Plan_{EPID}$: the plan after the dose superposition of $Plan_{origin}$ and the imaging dose contributions from the MV-EPID imaging for all the fractions.

$Plan_{CBCT}$: the plan after the dose superposition of $Plan_{origin}$ and the total kV-CBCT imaging doses from all the fractions.

Imaging dose calculations were performed using a CCC algorithm in Pinnacle 9.10 with a 2x2x2mm^3 dose calculation grid.[17] A comparative analysis of dosimetry was performed for both the MV-EPID and the kV-CBCT imaging modes. Dose-volume histogram (DVH) was used as an evaluation tool for OARs and target.

Secondary Cancer Risk Calculation Model

The calculation of secondary cancer risk was based on BEIR VII model.[18,19] The level of risk could be quantified by excess absolute risk (EAR), which characterizes the number of irradiated people who develop secondary cancer per 10000 person-year (PY). In this study, the age-dependent EAR values of lung cancer were calculated. EAR was defined as a function of attained age (a) in BEIR VII model, and the attained age was normalized to a reference age of 60 years. The specific formula is as follows:

$$\mathrm{EAR}(D, \mathrm{s}, e, a) = D \cdot \beta_s \cdot \exp(\gamma e^*) \left(\frac{a}{60}\right)^{\eta}.$$

Where D is the equivalent dose (unit: Sv), s is the gender, β_s is the excess relative risk per sievert (ERR/Sv), e is age at radiation therapy, e* = (e-30)/10(e <30), e*=0 (e $\geq$30), a is attained age, γ and η are the dependent parameters of ERR/Sv for e and a. The parameter values used in this study that are associated with the risk of second cancer after lung radiotherapy are presented in Table 1.

The BEIR VII model calculation software was developed using MATLAB R2016b (MathWorks, Natick, Massachusetts, USA). The software was introduced the equivalent biological dose of lung along with other corresponding parameters into it to make the calculation more convenient.

In this paper, the EARs caused by doses in $Plan_{EPID}$, $Plan_{CBCT}$ and $Plan_{origin}$ were calculated, and the results obtained from the 3 plans were compared and analyzed.

Statistical Analysis

Statistical analysis was performed in Origin Pro 9.0 (Origin Lab, Northampton, Massachusetts, USA). In order to evaluate the differences between different plans, the Wilcoxon signed-rank test was used to analyze the significance on different plans and imaging modes. When $P < 0.05$, it was considered that there was statistical difference between the 2 groups.

Results

Dose Distributions

The dose constraints to the targets and OARs met all clinical requirements in the original plans. For all the patients, and the imaging doses had major impacts to the low dose regions

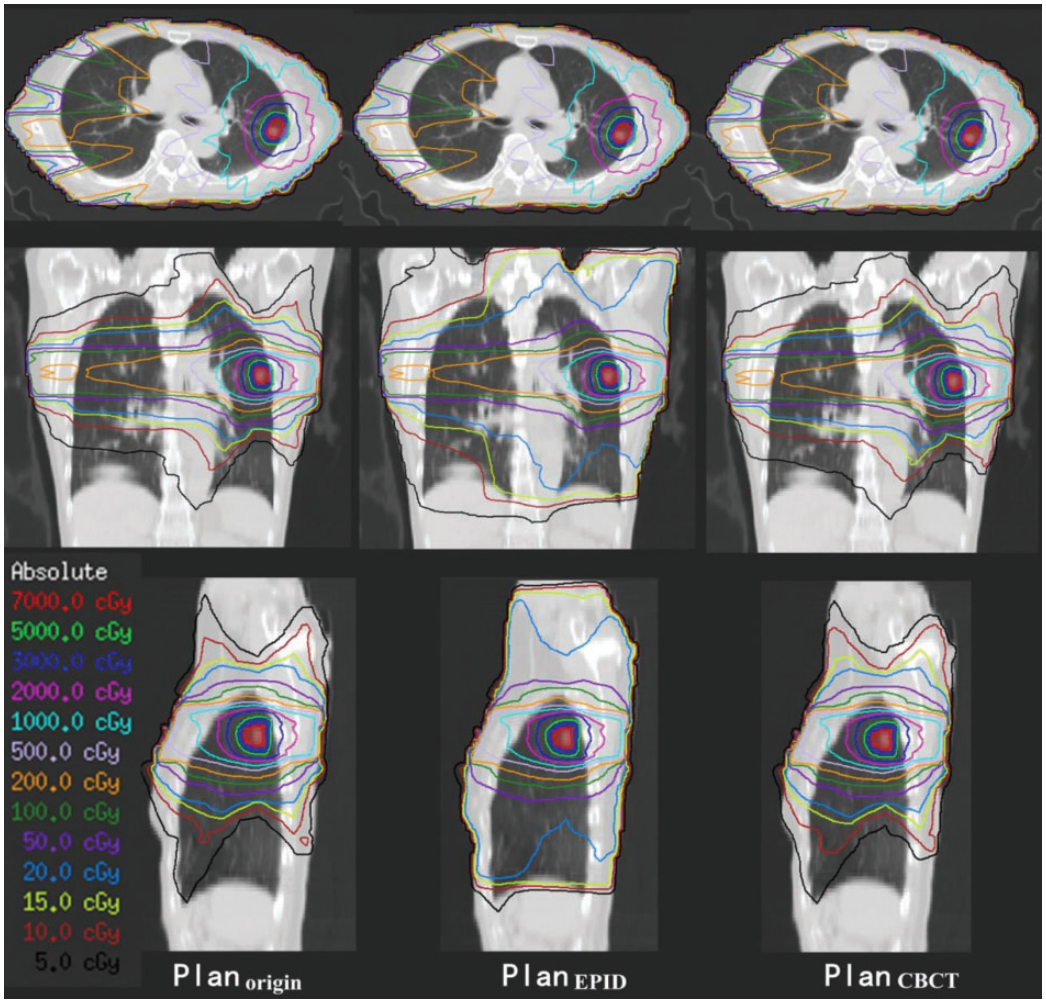

Figure 1. Dose distribution for 3 plans at the isocenter slice (taking case11 as an example). The red shadow area was ITV and the blue shadow area was PTV.

such as those receiving less than 50 cGy. There was no discernible difference among the 3 types of plan in the regions receiving more than 1000 cGy. Figure 1 shows the dose distributions at the isocenter slice for the 3 types of plan for one typical patient.

Figure 2 shows the imaging dose distributions contributed from the MV-EPID mode and the kV-CBCT imaging guidance, respectively, on the axial, sagittal and coronal planes passing through the isocenter for the same patient presented in Figure 1. Compared to the imaging doses contributed from the kV-CBCT, the regions covered by imaging doses less than 4 cGy increased significantly in the dose distributions contributed by the MV-EPID imaging, and dose area as high as 30 cGy appeared. However, no regions received imaging dose greater than 4 cGy from the kV-CBCT imaging.

DVH Analysis of OAR

The DVH data of the ipsilateral lung for all the patients are listed in Table 2. It is apparent that the values of $Plan_{EPID}$ for all DVH parameters were the highest, followed by $Plan_{CBCT}$. Compared with $Plan_{origin}$ on the average, D2% of PTV, V30, V20, V10 and V5 of the ipsilateral lung in $Plan_{EPID}$ increased by 0.35%, 1.39%, 1.74%, 1.86%, 2.48%, respectively, and the corresponding values in $Plan_{CBCT}$ increased by 0.03%, 0.13%, 0.16%, 0.19%, 0.27%, respectively. It is evident that the low-dose regions increased when imaging dose was added and the DVH parameters varied greatly from patient to patient, and there was a large variance in the data.

The results of statistical analysis on the relevant data using the Wilcoxon signed-rank test were listed in Table 3. For all the DVH parameters, P values obtained by comparisons of 2 different plans were less than 0.05, which was statistically significant.

Figure 3 displays the DVHs of the 3 types of plan. The yellow box displayed the locally enlarged curves of the ipsilateral lung around 20 Gy. It could be seen that the V20 of the ipsilateral lung was increased by the imaging doses and was the highest in $Plan_{EPID}$.

Figure 4 shows the DVHs contributed only the imaging doses for the same patient as in Figure 1. The doses of almost all OARs from kV-CBCT were within 3 cGy, while MV-EPID exposed most OARs to doses above 10 cGy with the maximum dose of more than 30 cGy. The 2 imaging modes made the ipsilateral lung receive the highest imaging dose, where V3cGy >80% under the imaging dose of kV-CBCT, and V10 cGy = 100%, V15 cGy nearly 90%, V20 cGy >45% under the imaging dose of MV-CBCT.

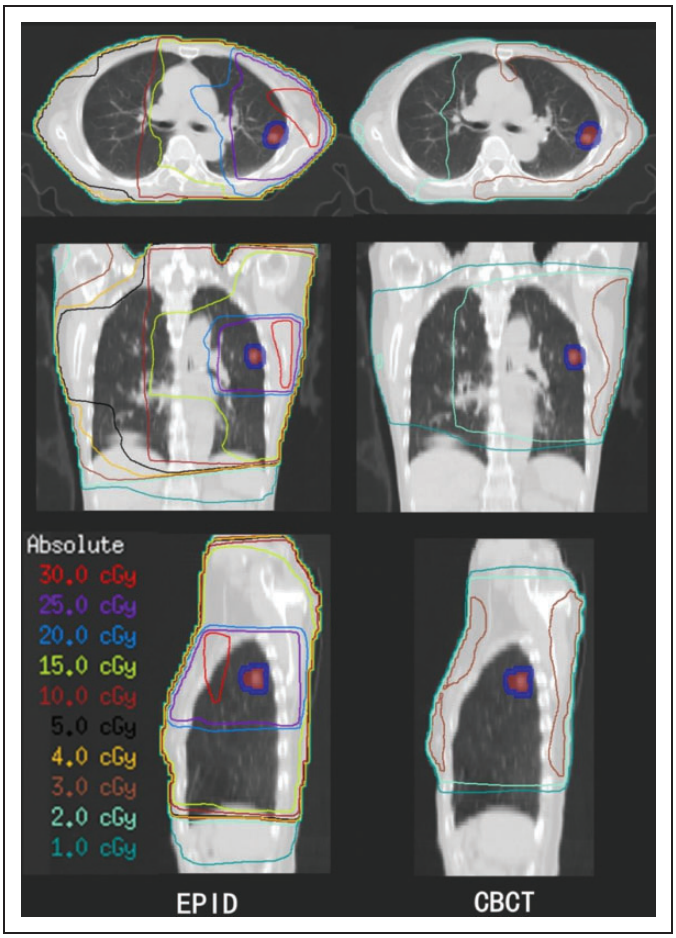

Figure 2. Dose distribution for different imaging modes at the isocenter slice (same patient as Figure 1). The dose distribution was generated by dose of total 5 fractions.

Imaging Dose-Induced Secondary Cancer Risk

Table 4 lists the EAR values of the ipsilateral lung in 5 years, 10 years, and 15 years after radiotherapy derived from the 3 types of plan for all the patients. The mean EAR values calculated from $Plan_{origin}$ in 5 years, 10 years, and 15 years after radiotherapy were 111.84 cases, 157.28 cases, and 216.74 cases per 10^4PY respectively. The corresponding values were 115.67 cases, 162.67 cases, and 224.17 cases, respectively, for $Plan_{EPID}$, and 112.28 cases, 157.90 cases, and 217.59 cases per 10^4PY, respectively, for $Plan_{CBCT}$. The results of the Wilcoxon signed-rank test (Table 3) shows that there were significant differences between the mean EAR values derived from different plans.

Table 4 also lists the EAR increased cases and increased rates after adding 2 imaging doses, respectively. Compared with $Plan_{origin}$, the mean EAR increase rate of $Plan_{EPID}$ in 5 years, 10 years, and 15 years after radiotherapy was 3.43% with the increased values of 3.83 cases, 5.39 cases, and 7.43 cases per 10^4 PY, respectively, while the corresponding increase rate of $Plan_{CBCT}$ was 0.44% with the increased values of 0.44 cases, 0.62 cases, and 0.85 cases per 10^4 PY respectively. The increase rate of secondary cancer risk caused by MV-EPID was about 8.79 times that of kV-CBCT. It is worth noting that the increase rate in EAR hardly varies with number of years after radiation therapy.

Table 5 lists the EAR for the ipsilateral lung caused by imaging dose only. The mean EAR in 5 years, 10 years and 15 years after radiotherapy from MV-EPID imaging dose were 1.49 cases, 2.09 cases and 2.88 cases per 10^4PY, respectively. The corresponding values obtained from the kV-CBCT imaging dose were 0.17 cases, 0.23 cases, and 0.32 cases, respectively. The results of Wilcoxon signed-rank test lists in Table 3 shows a statistically significant difference between EAR values from MV-EPID and kV-CBCT. As we expected, considering only the imaging dose, the MV-EPID imaging modality caused much higher cancer risk than kV-CBCT. The increases was 8.95 (8.76-9.09) times.

Table 2. Dose Criteria for the Ipsilateral Lung in Different Plans.

	$Plan_{origin}$		$Plan_{EPID}$		$Plan_{CBCT}$	
Criteria	Mean ± SD	Rate*	Mean ± SD	Rate*	Mean ± SD	Rate*
Dmean[cGy]	570.57 ± 157.22	-	589.82 ± 157.96	3.37	572.76 ± 157.18	0.38
PTV D2%[cGy]	7352.54 ± 289.27	-	7378.18 ± 289.33	0.35	7354.90 ± 289.18	0.03
V30[%]	4.63 ± 1.89	-	4.70 ± 1.91	1.39	4.64 ± 1.89	0.13
V20[%]	8.50 ± 3.19	-	8.65 ± 3.24	1.74	8.51 ± 3.19	0.16
V10[%]	17.65 ± 5.44	-	17.98 ± 5.50	1.86	17.68 ± 5.45	0.19
V5[%]	27.47 ± 6.97	-	28.15 ± 7.20	2.48	27.55 ± 6.97	0.27

Abbreviations: Dmean, mean dose; PTV D2, the dose received by 2% of the PTV; V30/20/10/5, volume receiving ≥30/20/10/5 Gy.
*The rate is increasing rate (%) compared to $Plan_{origin}$.

Table 3. *P*-Values of Wilcoxon Signed-Rank Test for the Ipsilateral Lung in Different Criteria.

Criteria	$Plan_{origin}$ vs. $Plan_{EPID}$	$Plan_{origin}$ vs. $Plan_{CBCT}$	$Plan_{EPID}$ vs. $Plan_{CBCT}$	CBCT vs. EPID
Dmean[cGy]	<0.001	<0.001	<0.001	<0.001
PTV D2%[cGy]	<0.001	<0.001	<0.001	-
V30[%]	<0.001	<0.001	<0.001	-
V20[%]	<0.001	<0.001	<0.001	-
V10[%]	<0.001	<0.001	<0.001	-
V5[%]	<0.001	<0.001	<0.001	-
EAR(5years)	<0.001	<0.001	<0.001	<0.001
EAR(10years)	<0.001	<0.001	<0.001	<0.001
EAR(15years)	<0.001	<0.001	<0.001	<0.001

Abbreviations: Dmean, mean dose; PTV D2, the dose received by 2% of the PTV; V30/20/10/5, volume receiving ≥30/20/10/5 Gy; EAR, excess absolute risk; EPID, electronic portal imaging device; CBCT, cone beam computed tomography.

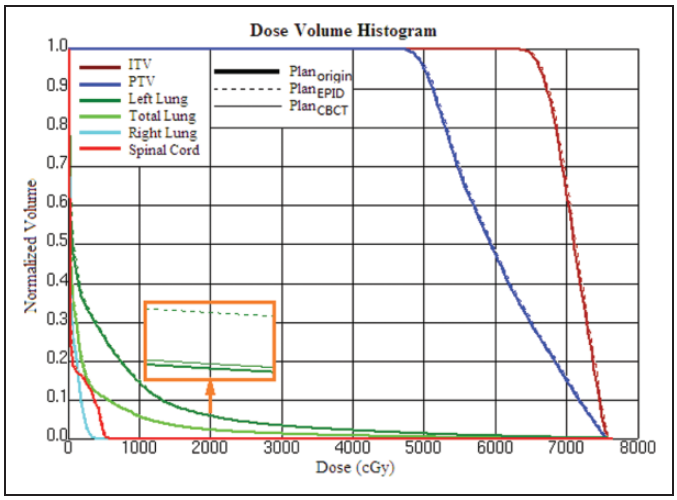

Figure 3. An example of DVH for 3 plans (same patient as Figure 1).

Discussion

On many occasions, SBRT has become the preferred choice of treatment for early stage lung cancer because of its advantages of short treatment time, mild toxicity, non-invasiveness, and therapeutic effect of similar to or even better than surgery.[1-3] SBRT is a high-precision irradiation that required position verification before each fractional treatment. However, the additional imaging dose will increase the probability of the secondary cancer. The survival time of lung cancer patients treated with conventional radiotherapy is relatively short, so the research of their secondary cancer had little significance. However, early stage lung cancer patients treated with SBRT can have long survival time, therefore knowing the amount of imaging dose and the induced secondary cancer risk is important. In this study, dosimetry studies and secondary cancer risk assessments on 2 position verification imaging guidance modalities of MV-EPID and kV-CBCT on an Edge accelerator were performed for early stage lung patients treated with SBRT.

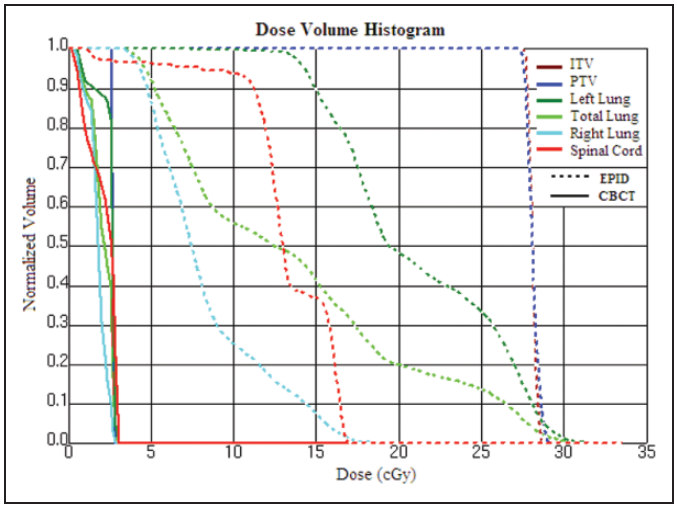

Figure 4. An example of DVH for different imaging modes (same patient as Figure 1).

The CBCT is the standard position verification method of SBRT.[20] The research of MV-EPID was to provide data reference for the radiation centers that had not yet equipped with kV device and had to use MV verification mode.

The differences of dose distributions among the 3 types of $Plan_{origin}$, $Plan_{EPID}$ and $Plan_{CBCT}$ (see Figure 1 for example) were mainly reflected in the low dose areas receiving less than 50 cGy, and there was almost no difference for the areas receiving greater than 1000 cGy. Since the prescription dose of the target was 5000 cGy in this study, it could be inferred that the imaging dose has little effect on the coverage of PTV.

Since the imaging dose was much smaller than the prescription dose, the DVHs incorporating the imaging dose had no apparent visual differences from those of $Plan_{origin}$ (Figure 3). However, when the imaging dose was added, the volume of OAR receiving a specific dose would inevitably increase. The actual dose of all OARs in this study was lower than the dose constraints of RTOG 0915. Even if the imaging dose was added, the OARs were still within the limits. Specifically, the acceptability of the plans in this study was not impaired by the imaging dose.

The lung imaging dose of kV-CBCT calculated by TPS in this study was consistent with the results obtained by Monte Carlo (MC) algorithm (0.8-3 cGy) in literature,[16,21-24] and also consistent with the dose measured by simulation model in literature.[25] MC was the gold standard for calculating kV dose,[21] and MC code BEAMnrc[22] could be used to simulate the source of kV X-ray in True-Beam system. Therefore, the dose calculation results of kV-CBCT in this study are reliable. For MV beams, several studies[26,27] confirmed that there was no significant difference between the lung dose distribution calculated by CCC algorithm and that simulated by MC code.

The mean EAR values in 5 years, 10 years and 15 years after radiotherapy presented in this study (Table 4) were greater than 100 cases (111.84-224.17 cases) per 10^4 PY. The median age

Table 4. EAR (in Cases per 10^4 PY) for the Ipsilateral Lung in Different Plans.

	EAR of 5 years			EAR of 10 years			EAR of 15 years		
	$Plan_{origin}$	$Plan_{EPID}$	$Plan_{CBCT}$	$Plan_{origin}$	$Plan_{EPID}$	$Plan_{CBCT}$	$Plan_{origin}$	$Plan_{EPID}$	$Plan_{CBCT}$
Mean	111.84	115.67	112.28	157.28	162.67	157.90	216.74	224.17	217.59
Case†	-	3.83	0.44	-	5.39	0.62	-	7.43	0.85
Rate*	-	3.43	0.39	-	3.43	0.39	-	3.43	0.39

Abbreviation: EAR, excess absolute risk (in cases per 104 PY).
†Increased cases of EAR (per 104 PY) for the ipsilateral lung for imaging added plans compared to Planorigin.
* Increased rate of EAR (%) for the ipsilateral lung for imaging added plans compared to Planorigin.

Table 5. EAR (in Cases per 10^4 PY) for the Ipsilateral Lung Caused by Imaging Dose Only.

	EAR of 5 years		EAR of 10 years		EAR of 15 years	
	EPID	CBCT	EPID	CBCT	EPID	CBCT
Mean	1.49	0.17	2.09	0.23	2.88	0.32

Abbreviation: EAR, excess absolute risk (in cases per 10^4 PY).

and mean age of patients were 68 years and 65 years in this study. It could be estimated from the calculation formula of the secondary cancer risk that the EAR of 10 years after radiotherapy for 60-year-old patients was about 20 times higher than that of 30-year-old patients. This shows that the high risk presented in this study was largely due to the older age of the enrolled patients.

Compared to $Plan_{origin}$, the EAR of $Plan_{EPID}$ increased by 3.43%, and the EAR of $Plan_{CBCT}$ increased by 0.39% (Table 4). Obviously, kV imaging could significantly reduce the increase of the secondary cancer risk. Each radiotherapy center should combine the clinical requirements for SBRT imaging quality and dose limits of OARs to prioritize kV X-ray verification mode. For those centers without kV position verification equipment, a lower MV energy could be chosen to reduce the imaging dose and the risk caused by it.

It should be noted that data such as genetics and translational medicine are closely related to secondary cancer risk. The BEIR VII model used for the calculation of secondary cancer risk in this study is a mathematical model based on big data. Many factors have been taken into consideration during the mathematical formula modeling stage, including benign disease and genetic effects, the effect of modifying factors, including host (such as individual susceptibility and variability, age, and sex), environment (such as altitude and ultraviolet radiation), and lifestyle (such as smoking history and alcohol consumption) factors.[18] For ease of use, the model was finally presented in the form of dependent dosimetry input and related dependent parameters.

Although many studies had reported the imaging doses of kV or MV X-ray, only a few had focused on imaging doses-induced secondary cancer risk, and few reports on secondary cancer risk induced by 2 imaging modes of Edge accelerator for early stage lung cancer patients treated with SBRT.

This study also has some limitations. Firstly, the 2.5MV of the Varian Edge accelerator is also widely used in EPID verification, but this energy was not investigated within the study. Secondly, because of the lack of patients younger than 45 years old, we only calculated the EAR within 15 years, without calculating the secondary cancer risk of longer years after radiation. Thirdly, since commercially available model-based algorithms in TPS are optimized just for energy range dominated by Compton scattering, without taking into account the inherent photoelectric effect in low energy, the accuracy of calculation of kV energy in TPS was reduced.[28-31] It had been reported that the measurement deviation of kV beam commissioning for lung was less than 10%.[14] This study was conducted on the ipsilateral lung that had the highest risk of secondary cancer, but this did not mean that other tissues were safe. Considering that the contralateral lung and other OARs received much smaller treatment and imaging doses than ipsilateral lung, and the secondary cancer risk would be much smaller. The study for ipsilateral lung will be of greater clinical significance. Therefore, we have not conducted further studies on other tissues except for ipsilateral lung, and the follow-up studies can be conducted for more OARs research. In addition, this paper only draws the theoretical results of the TPS simulation. In future studies, a larger sample size and regular follow-up of patients are needed combined with the specific performance of the imaging dose in the clinic to obtain more evidence and support for data in this paper.

Conclusions

After the addition of the imaging dose, the low-dose area was different from the original plan, with little impact on target coverage and high dose. The implementation of MV-EPID increased the patient's secondary cancer risk by about 3.43%, which was 8.79 times that of kV-CBCT. If only the imaging dose is considered, the risk caused by MV-EPID is 8.95 times that of kV-CBCT.

Authors' Note

DYH: data collection, statistical analysis, writing and revising the manuscript. DB, SG, ZX, TH: statistical analysis and revising the manuscript. GHL: modeling of the kV energy in TPS.CH, WH, SY, FAH, YYC: patient administration, and critical revision of the manuscript. FXL, XZY: study design, critical revision of the manuscript and

funds collection. All authors gave final approval of the version to be published. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The study is a retrospective study. When the study began, all selected patients signed informed consents and completed radiotherapy. Ethical standards and patients' confidentiality were ensured and in line with regulations of the local institutional review board and data safety laws. This study was approved by the Ethics Committee of Shanghai Chest Hospital (the committee's reference Number: KS1863). Yan-Hua Duan and Heng-Le Gu made equal contributions to this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Nurture projects for basic research of Shanghai Chest Hospital (No.2019YNJCM05). The funding bodies provided the modeling of the energy in TPS, but had no role in design of the study, or collecting, analyzing or interpretation of the data and writing of the manuscript.

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