Original paper

Single fraction computed tomography-guided high-dose-rate brachytherapy or stereotactic body radiotherapy for primary and metastatic lung tumors?

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Abstract

Purpose: To provide a pilot dosimetric study of computed tomography (CT)-guided high-dose-rate (HDR) brachytherapy (BRT) and stereotactic body radiotherapy (SBRT) for primary and metastatic lung lesions.

Material and methods: For nine lung primary and metastasis patients, 3D image-based BRT plan using a single virtual catheter was planned for 34 Gy in single fraction to the gross tumor volume (GTV) + 3 mm margin to account for tumor deformation. These plans were compared to margin-based (MB-) and robustness optimized (RO-) SBRT, assuming the same tumor deformation under real-time tumor tracking. Consistent dose calculation was ensured for both BRT and SBRT plans using the same class of collapsed cone convolution superposition algorithm. Plan quality metrics were compared by Friedman tests and Wilcoxon t-tests.

Results and Conclusions: Brachytherapy plans showed significant higher GTV mean dose compared to MB- and RO-SBRT (122.2 Gy vs. 50.4 and 44.7 Gy, $p < 0.05$), and better dose gradient index (R_{50}) = 2.9 vs. 4.3 and 8.4 for MB- and RO-SBRT, respectively. Dose constraints per the RTOG 0915 protocol were achieved for all critical organs except chest wall in BRT. All other dose-volume histograms (DVH) metrics are comparable between BRT and SBRT. Treatment delivery time of BRT and SBRT plans significantly increased and decreased with increasing GTV size, respectively. SBRT using advanced MLC tracking technique and non-coplanar VMAT can achieve comparable dosimetric quality to HDR BRT. Whether or not, the significantly higher GTV dose can increase killing of radioresistant tumor cells and offset the effect of tumor reoxygenation in single fraction BRT, requires further clinical investigation.

Purpose

Computed tomography (CT-guided) minimally invasive Iridium-192 high-dose-rate (HDR) brachytherapy (BRT) has been introduced as a form of local radiation treatment for inoperable primary and metastatic lung cancer [1,2]. CT-HDRBRT is performed mostly through collaboration with interventional radiologists for insertion of brachytherapy catheters into the tumor [3]. This internal radioablative technique allows for the localized dose to be delivered in a single session with very rapid dose gradient within a few millimeters around the source to spare the adjacent normal tissues.

In a phase I prospective study, Ricke *et al*. [4] reported a local tumor control rate (LCR) of 97% for 15 patients with 30 lung lesions using a minimum dose of 20 Gy.

The follow-up period was, however, short at a median of 5+ months. The following phase II study included a larger cohort of 30 patients with 83 primary and secondary lung lesions, and they reported at a longer follow up of 12 months LCR of 91% with the same treatment dose level [5]. In another series comprising 60 lesions from 55 patients, the reported local control rates for metastatic tumors were 93%, 82%, and 82%, and for primary intrathoracic cancers were 86%, 79%, and 73% at 1, 2, and 3 years, respectively [6]. A recent phase I trial also investigated combined HDRBRT in single fraction of 30 Gy with ≥ 70 Gy intensity modulated radiotherapy (IMRT) in 2 to 2.2 Gy fractions for regional positive lymph node in locally advanced non-small cell carcinoma, showing 1- and 2-year overall survival rates (OS) of 90.9% and 67%, and median OS of 22.5 months [7]. Nonetheless, CT-HDRBRT is not

frequently used in clinical practice primarily due to necessary intervention, the limited reports of long-term outcomes, the difficulty in gaining expertise with CT-guided interstitial techniques, and the inadequate dosimetry formalism to obtain dose distribution in the low-density heterogeneous lung tissue [8].

The alternative treatment option that has gained widespread popularity is stereotactic body radiotherapy (SBRT). This treatment technique has been associated with mature treatment outcomes demonstrating acceptable toxicities with excellent long-term LCR and OS for both inoperable primary non-small cell lung carcinomas (NSCLC) and secondary metastases [9,10,11,12]. However, excessive grade 3 and 4 toxicities including decline pulmonary function tests, pneumonias, skin and pleural reaction were observed for the centrally located lesions from the early experience [13]. With a modified dose schedule of 50 Gy in 4 fractions, the toxicities of grade 3 and above were successfully reduced to 1% [14]. Lower normal tissue toxicities in treating these central lesions were also reported using active motion compensation such as robotic or multileaf collimator (MLC) tracking techniques to reduce the dose burden with smaller safety margin [10]. The recently closed Radiation Therapeutic Oncology Group (RTOG) protocol 0915 comparing two dose schedules of 34 Gy in single fraction and 48 Gy in 4 fractions further found median OS of 4.1 vs. 4.0 years, and primary tumor failure (PTF) rate of 7.9% vs. 6.8% with no excess in late-appearing toxicity observed in either arm [15].

So far, there have been no clinical studies comparing CT-HDRBRT with SBRT for inoperable primary and metastatic lung tumors. In a recent dosimetric comparison, Milickovic et al. [16] showed equivalent target conformity with HDRBRT and sharper dose fall-off than historic SBRT plans based on nine to ten non-coplanar static beams. This study aimed to provide a pilot dosimetric analysis to understand the potential role of HDRBRT and the most state-of-the art SBRT technique realized by inversely optimized dynamic arc delivery through real-time MLC tracking. By using the same category of model-based collapse cone dose calculation engine, this study aimed to compare these two treatment modalities based on accurate estimation of the absorbed dose distributions.

Material and methods

Patient and treatment prescriptions

A total of 9 primary or metastatic lung lesions ≤ 5 cm in diameter were included in this planning study approved by the local ethics committee (NTWC/CREC/15140). Gross tumor volume (GTV) and various organs at risk (OAR) were defined on non-contrast computed tomography at mid-ventilation (MidV-CT). The prescription dose of 34 Gy in one single fraction chosen in this study was based on the RTOG protocol 0915 [17]. The dose constraint guideline as described in the protocol 0915 was also followed in the planning of CT-HDRBRT and SBRT. The principal planning objective was to achieve the prescription dose to 50% of the GTV (i.e., median GTV dose

= 34 Gy), where the tolerance dose to OAR could not be achieved. For each patient, the same set of planning MidV-CT together with the structure set was exported to the Oncentra® Brachy (OcB; Elekta, Stockholm, Sweden) treatment planning system (TPS) v.4.5 for CT-HDRBRT planning, and to the RayStation TPS v.5.0 (RaySearch Laboratories, Stockholm, Sweden) for SBRT planning. For consistency in dose specification, the same material assignment was used on both TPSs.

Treatment planning for brachytherapy

High-dose-rate brachytherapy was assumed to be delivered with an ^{192}Ir source of 41152.3 μGy m^2/h from a MicroSelectron® afterloader (Elekta Brachytherapy, Elekta AB, Stockholm, Sweden). For each lesion, a single virtual brachytherapy catheter was used. The route of the virtual needle insertion was defined by an interventional radiologist using the same principle of CT-guided biopsy at our institution. In general, the route was taken to be the shortest possible from where it entered to the tumor's center to minimize the trauma from the procedure. The placement of the brachytherapy catheter was assumed to follow the procedure described by Ricke et al. [4]. Furthermore, the virtual catheter path was such that it always passed through the tumor's center of mass (COM) and extended beyond the GTV surface by 3 mm corresponding to a uniform PTV margin. We assumed a coherent rigid movement of the brachytherapy catheter together with the tumor in presence of respiratory motion. Hence, the safety margin was needed to compensate only for the tumor deformation, which was measured from four-dimensional computed tomography (4D-CT) to be 2.7 mm at maximum in the craniocaudal direction [18].

Where necessary and technically feasible, the long axis of the source was oriented such that the dose to adjacent OAR was optimized by taking advantage of the anisotropic dose distribution. The source was manually loaded to one or multiple dwell positions, depending on the tumor size and the proximity of the tumor to the OAR. For small lesions, a single dwell position at the GTV's COM was generally sufficient, while for large lesion more than one source dwell positions were needed to yield better dosimetry. For all plans, dwell weights of the source were optimized in a manual manner.

Oncentra TPS offers two options for dose calculation: the TG-43 formalism and the model-based Advanced Collapsed cone Engine (ACE). The TG-43 formalism is the most clinically used method in brachytherapy treatment planning, but it is well known for its limitation of calculating absorbed dose to a semi-infinite water phantom only. It neglects the reduced attenuation and different scattering property of the lung tissue relative to water in the finite patient geometry. Hence, this study abandoned the TG-43 and used ACE in all dose calculations.

ACE models separated the dose depositions by primary and scatter photons by scaling the discretized point kernels according to the material type and density along each radiation transport line (i.e., the conical axis in the implementation of the collapsed cone algorithm). To enable the heterogeneity corrections with ACE, each contour

associated with the patient CT was assigned with a material of variable density according to the CT Hounsfield unit (HU). For this study, the lung contour was assigned as inflated lung whose elemental compositions were defined as in the TG 186 report [8]. For other hollow organs, which included the trachea, bronchi, and esophagus, the contours were segmented into air cavities and surrounding walls with assigned material types of air and water, respectively. The GTV and all other contours were also assigned as water. This yielded an absorbed dose distribution to media $D_{m,m}$.

Treatment planning of SBRT

Treatment plans were developed for a demonstration-purposed TrueBeam linac (Varian Inc., Palo Alto, CA, USA) to deliver volumetric-modulated arc radiotherapy (VMAT)-based SBRT in HDR flattening filter-free (FFF) mode. Two to three partial coplanar and non-coplanar arcs using either 10 MV or mixed 6 MV and 10 MV photon beams were used aiming to achieve the best possible sparing of the normal tissues [19,20]. The uniform 3 mm GTV-to-PTV margin for tumor deformation was the same as in CT-HDRBRT, assuming perfect image-guided real-time tumor tracking by multileaf collimator (MLC) as active motion management [21]. It is worthwhile noting that VMAT-based MLC-tracking SBRT in FFF mode has not been yet implemented clinically. Nonetheless, VMAT-based SBRT delivery in FFF mode was reported in a few clinical studies showing 1-year local control of 94% for primary and metastatic lung lesions [22], and 100% in early stage NSCLC [23]. The clinical implementation of real-time adaptive electromagnetic transponder-guided MLC tracking was also reported in SBRT of lung by Booth et al. [24], demonstrating great potential of this motion compensation technique to ensure the delivered dose to 95% (D_{95}) of GTV of 110 ±0.5% compared to 110% planned. A clinical trial for lung cancers using MLC tracking has been also registered by the same group recently [24].

This study compared two VMAT planning approaches with CT-HDRBRT, either using the conventional concept of PTV or based on the robust optimization method to explicitly accounts for the geometric tracking error, showing 3D root-mean square of 0.5 mm [25] and the tumor deformation of 2.7 mm. The total geometric error was rounded to 3 mm in this study. The resulting SBRT plans were abbreviated as MB-SBRT (margin-based SBRT) and RO-SBRT (robust optimized), respectively. The RayStation TPS achieves robustness by minimax optimization, in which optimization functions are considered in a worst-case scenario. The set of scenarios forms a discretization of the user-specified errors against, which the plan is robust from both the GTV' and the OARs' perspectives. Robustness was imposed to all dose-volume constraints of the serial organs and the GTV. This study further exploited the lateral electronic disequilibrium phenomenon to maximize the dose gradient at the lung-tumor interface [26], increasing the dose by as much as 40% (i.e., 60% isodose level relative to the maximum dose) to the PTV or GTV, depending on the optimization scenarios, to emulate brachytherapy. Higher PTV maximum dose was also reported to be asso-

ciated with improved local control [27]. For consistency in the dose reporting, the same tissue materials as defined for brachytherapy were used in all SBRT plans. The final dose distribution was calculated by a collapse-cone convolution superposition dose engine with a 2.0 mm grid. The dose specification was by default $D_{m,m}$.

For MB-SBRT, the prescription dose was normalized to the same level as for HDRBRT per case, which demanded that at least 95% of the PTV and 99% of the GTV received 34 Gy. For RO-SBRT, the dose normalization was based on the at least 99% GTV receiving 34 Gy.

Statistical comparisons of dosimetric metrics

HDRBRT and SBRT were compared following the dose constraints in the RTOG0915 protocol. Additionally, the absolute normal lung (bilateral lung minus GTV) and the ipsilateral lung volumes receiving at least 20 Gy, 10 Gy, and 5 Gy (i.e., V_{20}, V_{10}, and V_5) were compared. The plan quality was also quantified using the dose conformity index (CI) defined as

$$CI = TV_{PIV} \times TV_{PIV}/(TV \times PIV) \qquad \text{Eq. 1}$$

where TV_{PIV}, TV, and PIV are the volume of target covered by prescription dose, the target volume, and prescription dose volume, respectively [28]. The volume ratio of 17 Gy to 34 Gy (R_{50}) was used to assess the dose gradient achieved with the two treatment approaches. Comparisons of treatment length were based on the estimates from the Oncentra Brachy for HDRBRT and RayStation for SBRT, respectively.

For statistical comparisons of the above dose metrics and those in the RTOG 0915 protocol, Friedman tests were performed with further post hoc Wilcoxon t-tests comparison if significance were reached. For correlation of estimated treatment time with the PTV size, the Spearman correlations were used. All statistical tests were run using the Statistical toolbox in Matlab® R2014a (Math-Work, Natick, MA, USA).

Results

Table 1 summarizes the dosimetric and plan quality results over all patients. The GTV ranged from 0.6-20.3 cm^3, with a mean of 7.2 cm^3.

Organ at risks dose statistics

Dose constraints per the RTOG 0915 protocol were achieved for all OARs, except for the chest wall/ ribs. HDRBRT exceeded the volume maximum dose of 22 Gy limited to 1 cm^3 (V_{22Gy}) by 1.17 and 0.62 cm^3 in two plans, and maximum point dose of 30 Gy by 19.8 Gy in one plan. The ribs volume of 1 cm^3 limited to 22 Gy (V_{22Gy}) was exceeded in two HDRBRT plans by 1.17 and 0.62 cm^3, in two MB-SBRT plans by 1.5 and 1.4 cm^3, and in one RO-SBRT plan by 0.4 cm^3, respectively. The maximum ribs dose D_{max} was exceeded in the same patient by 19.8 Gy for HDRBRT, 10.5 Gy for MB-SBRT, and 8.8 Gy for RO-SBRT, respectively. The overall means of ribs V_{22Gy} and D_{max} were within the RTOG constraints. In Figure 1,

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Table 1. Dosimetric results from different treatment modalities

	HDRBRT	MB-SBRT	RO-SBRT
Normal total lung			
D_{1500cm^3} (Gy)	0.6 ±0.6	0.2 ±0.2	0.2 ±0.2
D_{1000cm^3} (Gy)	0.9 ±0.9	0.2 ±0.5	0.2 ±0.3
V_{5Gy} (cm^3)	239.0 ±136.9	237.7 ±92.7	230.2 ±115.0
V_{7Gy} (cm^3)	153.0 ±90.2	156.0 ±84.9	168.9 ±92.0
V_{10Gy} (cm^3)	97.3 ±59.9	109.4 ±51.9	114.5 ±68.5
V_{20Gy} (cm^3)	34.7 ±21.3	36.0 ±19.9	37.7 ±27.1
$V_{7.4Gy}$ (cm^3)	145.0 ±87.0	157.3 ±65.6	160.0 ±88.5
Ipsilateral normal lung			
V_{5Gy} (cm^3)	234.8 ±131.0	229.1 ±86.0	224.1 ±106.4
V_{10Gy} (cm^3)	91.1 ±60.0	106.2 ±47.6	110.9 ±63.7
V_{20Gy} (cm^3)	32.5 ±20.2	34.2 ±17.1	35.9 ±25.0
Trachea			
D_{4cm^3} (Gy)	1.6 ±2.1	1.9 ±3.4	1.3 ±2.6
$V_{10.5Gy}$ (cm^3)	0.0 ±0.0	0.3 ±0.9	0.0 ±0.0
D_{max} (Gy)	4.7 ±2.7	4.4 ±5.5	3.3 ±4.3
Bronchus			
D_{4cm^3} (Gy)	2.1 ±2.2	1.9 ±2.0	1.7 ±2.0
$V_{10.5Gy}$ (cm^3)	0.1 ±0.1	0.2 ±0.3	0.0 ±0.1
D_{max} (Gy)	7.8 ±4.5	9.9 ±6.3	8.0 ±6.1
Vessels			
D_{10cm^3} (Gy)	3.2 ±5.5	3.9 ±4.8	2.9 ±4.3
V_{31Gy} (cm^3)	0.1 ±0.3	0.0 ±0.0	0.1 ±0.2
D_{max} (Gy)	14.2 ±15.9	16.5 ±15.4	15.0 ±13.9
Heart			
V_{16Gy} (cm^3)	0.4 ±1.2	0.3 ±0.9	0.3 ±0.5
D_{15cm^3} (Gy)	3.4 ±3.2	3.9 ±3.8	3.6 ±4.1
D_{max} (Gy)	9.4 ±8.1	9.2 ±8.1	10.2 ±9.1
Esophagus			
$V_{11.9Gy}$ (cm^3)	0.0 ±0.1	0.0 ±0.0	0.0 ±0.0
D_{5cm^3} (Gy)	0.9 ±1.3	1.4 ±2.5	1.1 ±1.9
D_{max} (Gy)	3.7 ±2.0	4.9 ±2.8	3.6 ±2.2
Chest wall and ribs			
D_{1cm^3} (Gy)	15.2 ±7.8	18.4 ±5.4	17.5 ±4.8
V_{31Gy} (cm^3)	0.1 ±0.2	0.0 ±0.1	0.0 ±0.0
D_{max} (Gy)	22.6 ±12.8	25.0 ±8.9	22.9 ±8.5
V_{22Gy} (cm^3)	0.5 ±0.8	0.7 ±1.0	0.3 ±0.5
PTV			
V_{34Gy} (%)	96.2 ±0.7	96.2 ±0.7	N/A
$V_{30.6Gy}$ (%)	99.0 ±0.0	99.5 ±0.3	N/A
D_{mean} (Gy)	65.0 ±5.2	43.3 ±1.7	N/A
GTV			
V_{34Gy} (%)	100.0 ±0.0	100.0 ±0.0	99.0 ±0.1
D_{median} (Gy)	122.2 ±19.0	50.4 ±1.5	44.7 ±3.9
Spinal cord			
$D_{1.2cm^3}$ (Gy)	1.3 ±1.1	2.9 ±2.1	2.1 ±1.2
$D_{0.35cm^3}$ (Gy)	1.7 ±1.4	3.4 ±2.4	2.4 ±1.4
D_{max} (Gy)	3.1 ±2.0	4.0 ±2.6	3.0 ±1.8
Conformity index	0.7 ±0.1	0.9 ±0.0	0.7 ±0.1
R_{50}	2.9 ±0.0	4.3 ±1.4	8.4 ±4.1

PTV – planning target volume; GTV – gross tumor volume; HDRBRT – high-dose-rate brachytherapy plan; MB-SBRT – margin-base stereotactic radiotherapy plan; RO-SBRT – robustness optimized stereotactic radiotherapy plan; $D_{0.35cm^3}$, D_{1cm^3}, $D_{1.2cm^3}$, D_{4cm^3}, D_{5cm^3}, D_{10cm^3}, D_{15cm^3}, D_{1000cm^3}, D_{1500cm^3} – dose received by 0.35 cm^3, 1 cm^3, 1.2 cm^3, 4 cm^3, 5 cm^3, 10 cm^3, 15 cm^3, 1000 cm^3, 1500 cm^3 of volume respectively; D_{max} – maximum dose; V_{5Gy}, V_{7Gy}, $V_{7.4Gy}$, V_{10Gy}, $V_{10.5Gy}$, $V_{11.9Gy}$, V_{16Gy}, V_{20Gy}, V_{22Gy}, $V_{30.6Gy}$, V_{31Gy}, and V_{34Gy} – volume received by 5 Gy, 7 Gy, 7.4 Gy, 10 Gy, 10.5 Gy, 11.9 Gy, 16 Gy, 20 Gy, 22 Gy, 30.6 Gy, 31 Gy, and 34 Gy respectively; R_{50} – gradient index, which defined as a ratio of the 50% prescription isodose line to PTV volume
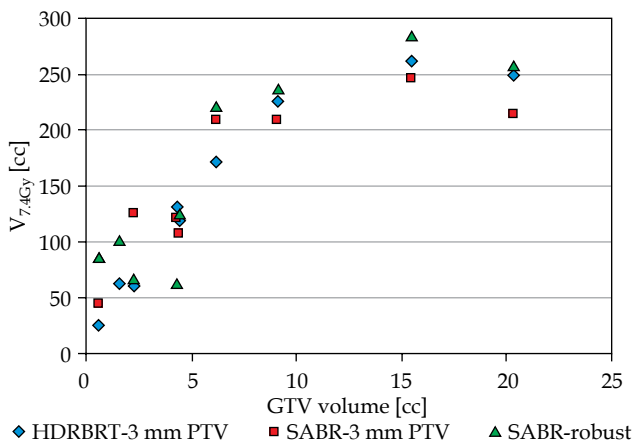
Fig. 1. Total lung volume receiving at least 7.4 Gy of individual lesions in order of increasing size

the normal total lung volume receiving no more than 7.4 Gy, which is associated with the risk of pneumonitis, is shown. The low (5 Gy) to high (20 Gy) dose volumes to the ipsilateral lung are also included in Figure 1. Statistically, all studied DVH metrics related to normal tissue showed no differences among treatment methods. Figure 2 shows the dose distributions obtained with HDRBRT, MB-, and RO-SBRT for an anterior and the other peripheral lesions.

GTV and PTV dose statistics

The prescription dose coverage (V_{34Gy}) to the PTV was normalized to ≥ 95%, and V_{34Gy} for GTV = 100% for all lesions in HDRBRT and MB-SBRT (Table 1). Figure 3 presents the GTV median dose for individual patients.

The averaged GTV mean dose is 122.19 ±19.0 Gy (one standard deviation: SD) for HDRBRT, 50.4 ±1.5 Gy for MB-SBRT, and 44.7 ±3.9 Gy for RO-SBRT. Pair-wise comparisons showed significant higher GTV mean dose with HDRBRT than MB- and RO-SBRT ($p < 0.01$). Mean doses to the PTV for HDRBRT and MB-SBRT were 65.1 ±5.2 Gy and 43.4 ±1.7 Gy, respectively ($p < 0.01$). Likewise, mean doses to the PTV border zone (i.e., PTV minus GTV) were also significantly higher ($p < 0.01$) for HDRBRT (51.5 ±3.8 Gy) than for MB-SBRT (39.6 ±0.8 Gy).

Plan quality index and treatment delivery efficiency

Other plan quality metrics of CI and the dose gradient index (R_{50}) are summarized in Figure 4. The mean CI for the HDRBRT plans was 0.7 (range: 0.6-0.8), for MB-SBRT plans 0.9 (range: 0.8-0.9), and for the RO-SBRT plans 0.7 (range: 0.4-0.8). Statistical tests showed significantly better CI with MB-SBRT than HDRBRT and RO-SBRT ($p < 0.01$). The dose fall gradient in terms of R_{50} showed means of 2.9 ±0.0 for HDRBRT, 4.3 ±1.4 for MB-SBRT, and 8.4 ±4.1 RO-SBRT, respectively. They were statistically different between HDRBRT and MB- ($p < 0.05$) and RO-SBRT ($p < 0.01$).

The averaged treatment lengths varied from 12.3 minutes (range: 3.5-24.3 minutes) for HDRBRT, 5.4 minutes (range: 2.8-10.4 minutes) for RO-SBRT, to 4.7 minutes (range: 3.2-7.0 minutes) for MB-SBRT.

Correlation of plan quality parameters with GTV size

Table 2 presents the results of correlations between the GTV size and selected plan evaluation metrics. HDRBRT
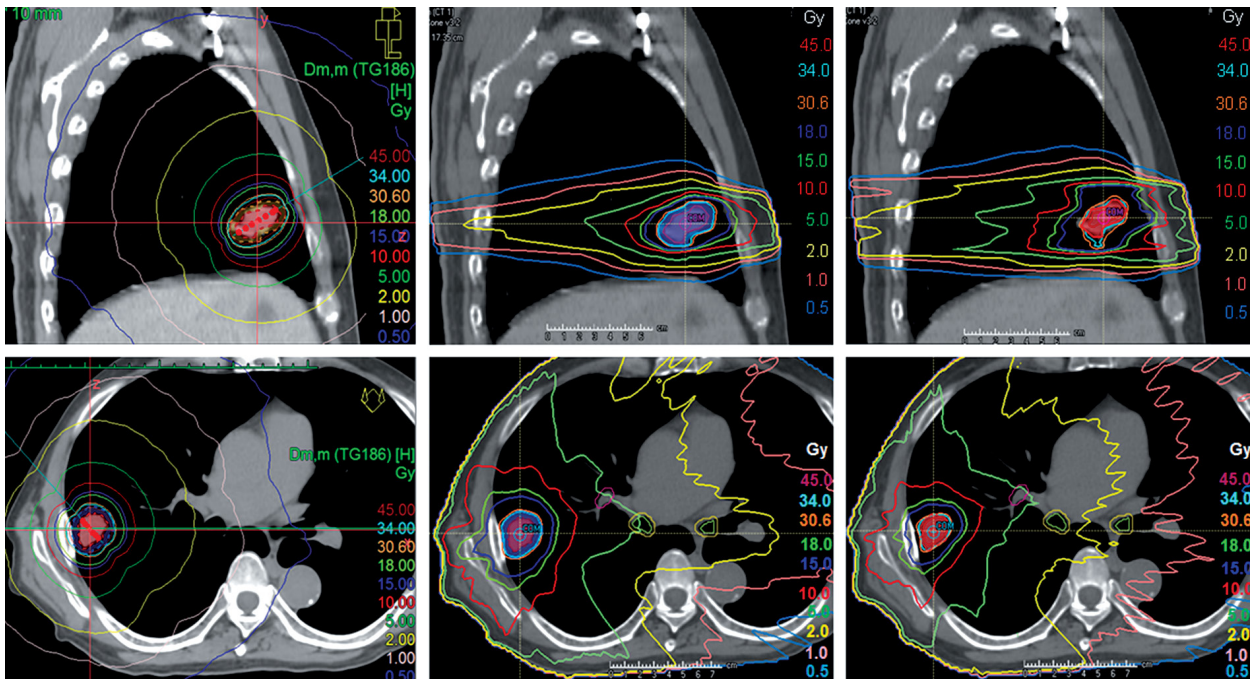
Fig. 2. Top row (from left to right) shows dose distributions of HDRBRT, MB-SBRT, and RO-SBRT for an anterior lesion, and bottom row for a peripheral lesion. For the anterior lesion, the needle path was angled to align with the long axis of the lesion in HDRBRT

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shows a trend of increasing GTV mean dose with decreasing GTV size. Similar trend was observed for RO-SBRT but not as obvious as for MB-SBRT. Correlations between treatment delivery time and GTV size were significant and were reciprocal for HDRBRT and MB-/RO-SBRT.

Discussion

Brachytherapy offers the potential of highly localized dose deposition with very sharp fall-off. This dosimetric characteristic makes it the ideal option as monotherapy and/or additive therapy for prostate and cervix cancers. However, its role in inoperable early stage NSCLC is not clearly defined as SBRT remains the preferred option due to its evidenced safety and efficacy through large scale clinical trials [9,15].

Unlike previous *in silico* study comparing HDRBRT to relatively obsolete SBRT techniques with unclear definition of safety margin [16], this study assessed the dosimetric quality in a more objective setting by assuming the most advanced technologies available to both SBRT and HDRBRT. Whilst real-time MLC tracking is far from a standard technique in clinical routine of SBRT and is exclusively trialed for lung SBRT [24], its realization made it possible to reduce or completely remove the safety margin by robustness augmentation [21]. The resulting lung doses to the ipsilateral lung in the low to high range were found to have negligible difference from those of HDRBRT. Interestingly, at low-dose of 5 Gy, the lung volume showed highest V_{5Gy} for HDRBRT, differing from MB-SBRT by 1.3 and 5.7 cm^3, and RO-SBRT by 8.8 and 10.7 cm^3 on average for the bilateral and ipsilateral lungs, respectively. From V_{7Gy} onward to V_{20Gy}, the trend was reversed with HDR BRT showing the lowest averages, which differed from the highest for RO-SBRT by 17.2 and 19.8 cm^3 (10 Gy), and 3.0 and 3.4 cm^3 (20 Gy) in bilateral and ipsilateral lungs. The significance of reduced contralateral lung dose can be seen in Figure 2. By contrast, SBRT was distinctively associated with smaller low-dose volume in the axial direction even by non-coplanar delivery, as demonstrated for the anterior lesion in Figure 2. From Table 2, significant and positive correlations between the GTV size and the lung dose volume metrics from V_{5Gy} to V_{20Gy} were observed in all treatment modali-

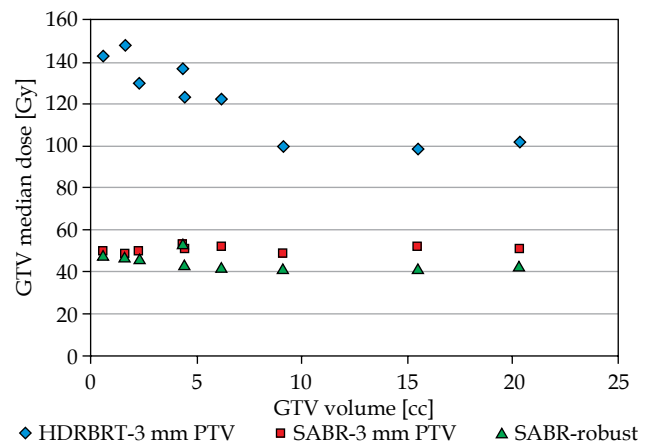**Fig. 3.** GTV median dose as a function of GTV size

ties. These results were the combined consequences of the shorter range of the ^{192}Ir γ rays (average photon energy of 397 keV vs. 6-10 MeV in SBRT) and internal irradiation, producing faster dose fall-off, and hence much better R_{50} for HDRBRT than MB- and RO-SBRT.

HDRBRT and SBRT showed reciprocal correlations between treatment length and GTV size. The treatment length increased for HDRBRT with increasing tumor size because more dwell positions and dwell times per unit source strength is required for the prescribed dose, and for SBRT, it decreased with increasing tumor size and hence, increasing output factor. Note that the length for the HDRBRT treatment was calculated based on the assumption of a source strength of 41152.3 μGym^2/h. As the ^{192}Ir source decays, the treatment length would be even more. According to the linear fits, HDRBRT would take longer treatment durations than MB- and RO-SBRT, when the GTV is larger than 1.5 and 0.2 cm^3 with corresponding diameter of 14 and 8 mm, respectively.

With the limitation of minimized needle insertion path through the lung tissue, the source path may not always be in the optimal orientation. Together with the limitation of single catheter versus multiple catheters, may not often produce very conformal dose distribution even by optimized source dwell position and time (Figure 4). The dose conformity index (CI) was HDRBRT, therefore worse for HDRBRT than MB-SBRT but better than
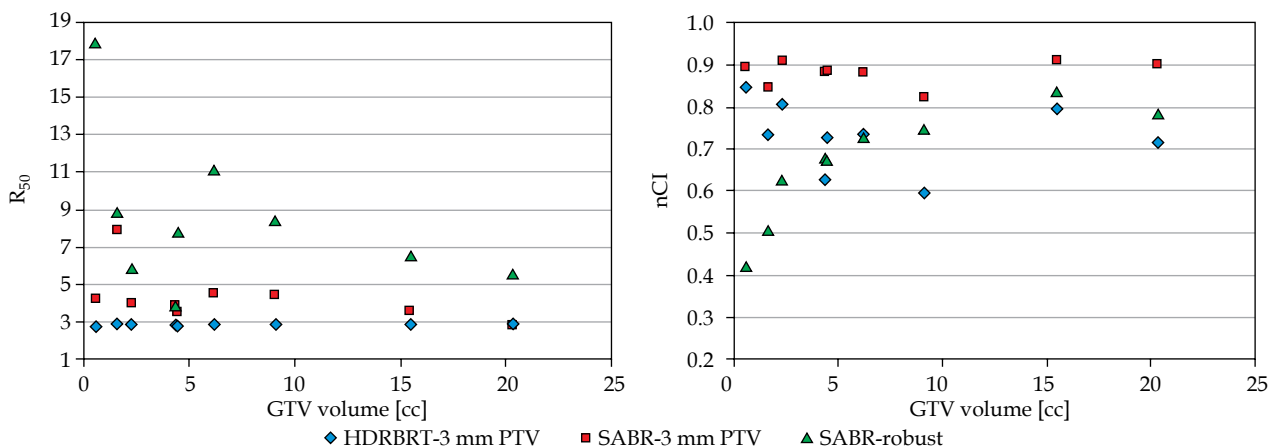

Fig. 4. Dose gradient index R_{50} and dose conformity index CI of individual lesions

Table 2. Correlation between size of gross tumor volume and plan quality metrics

	HDRBRT		MB-SBRT		RO-SBRT	
	r_0	*p*-value	r_0	*p*-value	r_0	*p*-value
Normal total lung						
D_{1500cm^3} (Gy)	0.69	0.04	0.10	0.80	0.06	0.88
D_{1000cm^3} (Gy)	0.71	0.03	−0.08	0.83	0.63	0.07
V_{5Gy} (cm³)	0.97	0.00	0.85	0.00	0.92	0.00
V_{10Gy} (cm³)	0.95	0.00	0.80	0.01	0.83	0.01
V_{20Gy} (cm³)	0.98	0.00	0.88	0.00	0.85	0.00
$V_{7.4Gy}$ (cm³)	0.95	0.00	0.82	0.01	0.83	0.01
Ipsilateral normal lung						
V_{5Gy} (cm³)	0.98	0.00	0.85	0.00	0.93	0.00
V_{10Gy} (cm³)	0.93	0.00	0.78	0.01	0.83	0.01
V_{20Gy} (cm³)	0.95	0.00	0.90	0.00	0.83	0.01
GTV						
D_{mean} (Gy)	−0.92	0.01	0.27	0.49	−0.80	0.01
PTV-GTV ring						
D_{mean} (Gy)	−0.42	0.27	−0.18	0.64		.
Conformity index	0.50	0.17	−0.03	0.93	−0.97	0.00
Delivery time (seconds)	0.93	0.00	−0.78	0.01	−0.72	0.03

GTV – gross tumor volume; PTV – planning target volume; HDRBRT – high-dose-rate brachytherapy plan; MB-SBRT – the margin-base stereotactic radiotherapy plan; RO-SBRT – robustness optimized stereotactic radiotherapy plan; D_{mean} – mean dose received by the target volume; D_{1000cm^3}, D_{1500cm^3} – dose received by 1000 cm³, 1500 cm³ of volume, respectively; V_{5Gy}, $V_{7.4Gy}$, V_{10Gy}, V_{20Gy} – volume received by 5 Gy, 7.4 Gy, 10 Gy, 20 Gy, respectively

RO-SBRT. These results disagreed with the previous study, where insignificant but better CI was achieved with HDRBRT than SBRT. These contradicting results were likely because the difference in number of catheters used (6-10 in Milickovic *et al*. [16] vs. one in the present study). Yet, the average CI in the present study was still better than that achieved by Yang *et al*. [1] with ideal needle configuration in terms of number of needles and placement (0.6 vs. 0.4), indicating that inter-center variability can be significant and limits the generalization of results from different dosimetric studies.

Due to the same limitations, doses to organs at risk, ribs, and chest walls in particular, may in some cases not be well controlled in order to achieve the primary objective of prescription dose coverage for the PTV and GTV. Although the RTOG 0915 protocol does allow some leeway to chest wall dose constraints, maximum dose to the ribs as high as 49.8 Gy in single fraction has never been reported, and its clinical implication on ribs fracture and chest wall pain remains a genuine concern. In contrast, the large degree of freedom offered by non-coplanar VMAT enables better dose control in certain preferential directions. This directly resulted in lower maximum ribs/chest wall dose (despite very limited arc range to minimize the radiation path through the healthy lung tissues). Doses to the other critical organs were found to be minimal for either HDRBRT or SBRT because the tumors were generally located at a distance by selection.

Although CT-guided percutaneous single catheter insertion is a minimally invasive procedure, pneumothorax and hemothorax remains a serious concern. The uncertainty of needle and needle displacement due to motion is largely unknown despite promising outcomes. On the other hand, almost all real time tumor tracking technologies today require the implantation of 3 to 4 fiducial markers to allow six degrees of freedom for motion correction [11,24]. The incident rate of pneumothorax associated with fiducial implantation was reported in the range of 26.7% to 33% [29,30], which was slightly higher than the 11.5% to 23.3% for single or multiple needle insertion in HDRBRT [4,7]. For this possible reason, most clinical studies reported HDRBRT by once or twice daily fractions on a single day. Such limitation may negate the tumor cell killing by tumor re-oxygenation and SBRT treatment should be fractionated [31,32]. Nonetheless, the GTV median dose in HDRBRT was over 70 Gy higher than that in SBRT ($p < 0.01$). Whether this significant higher dose is needed to increase killing of the radioresistant tumors and potentially offset the effect of the tumor re-oxygenation, remains the focal point of clinical investigation, as it will offer important insight into the results of RTOG 0915 trial comparing two arms of single versus multiple fractions.

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Disclosure

Authors report no conflict of interest.

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