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Choosing the optimal gated window for defining target volume in lung stereotactic ablative radiotherapy

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► ***Original article***

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ABSTRACT

Background: This study aims to compare retrospectively generated gated internal target volumes (ITVs) and to evaluate whether gated ITVs can reduce planned target volumes (PTVs) compared with standard ITV expansions. ***Materials and Methods:*** In this study, we retrospectively generated respiratory-gated ITVs and PTVs for our cohort of patients who underwent four-dimensional computed tomography for thoracic radiotherapy in our department between August 2018 and February 2019. We calculated the standard ITVs and two gated ITVs to analyze the volumetric reduction. Further, we considered a PTV reduction of >10% to be significant, and we analyzed the role of the localization and the size of the gross tumor volumes. ***Results:*** We included 38 patients with a median age of 70 years (mean = 68, SD ± 13,4, range =43–89), of whom 18 (47%) were females and 20 (52%) were males. The two gated PTVs (PTV 30%–70% and PTV 80%–20%) were significantly smaller than the standard PTVs (p-value < 0,001 for both PTVs). Considering the volume of the gross target volume (GTV), we found a significant correlation between GTV30cc and ITV30%–70% (chi-square analysis, p:0,006) and between GTV5cc and ITV80%–20% (p:0,003). We also found a correlation between the localization of the target lesion (mediastinal/ central/peripheral lesion) for both the gated ITVs (p: 0,030 for ITV 30%–70% and p:0,018 for ITV 80%–20%). ***Conclusion:*** Gated ITV plans could be useful for the sparing of normal tissues. Our results show that this approach could be useful for small lesions and for certain localizations (island tumors).

Keywords: *Respiratory gating, SABR, radiotherapy, 4DCT.*

INTRODUCTION

The respiratory motion of the target volume, especially in the management of lung localization (either primary or metastatic), is crucial in modern radiotherapy [1].

The control of the respiratory motion can be accomplished with immobilization devices that include cradles that hold a polyurethane foam that conforms to the body of a patient [2], conformed cushions that become rigid as air is evacuated (e.g., BodyFIX®) [3], or abdominal compression techniques that constrict abdominal motion [4].

Other strategies have been developed to assess and measure the movements of the target, such as motion encompassing methods, respiratory gating, breath-hold control, forced compression approaches, and tumor tracking [5-7].

All these approaches employ four-dimensional computed tomography (4DCT),

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where the respiratory waveforms of patients are monitored during very low-pitch helical CT acquisitions [8, 9].

These waveforms are then used to retrospectively build a predetermined number of phases of the breathing cycle and to reconstruct the CT of a patient at each phase of the respiratory cycle.

4DCT is commonly used to define the motion of the gross target volume (GTV) in each phase of the breathing cycle to include its full range of movements within an internal target volume (ITV), [10]. The ITV is then expanded to the planning target volume (PTV) to calculate the treatment plan.

Additionally, other strategies have been developed to reduce the PTV further. Among them, respiratory gating implies the monitoring of a surrogate for the tumor motion, which can either be internal (implanted fiducial) or external (the abdominal or thoracic surface) [11, 12], and the beam can be activated only when the target lies within the predefined window of the waveform.

Theoretically, with this approach, we can reduce the treatment planning margins, and we can expect the reduced dose delivered to surrounding organs at risk (OARs).

At the same time, the workflow of this approach is time-consuming and entails the commissioning of the linear accelerator, as well as the complex phantom dosimetry, before applying it in a real clinical scenario.

In this study, we retrospectively generated standard and two gated ITVs, each one of whom includes half of the phases of the respiratory cycle (ITV30%–40%-50%-60%-70% and ITV80%–90%-100%-10%-20%, respectively) for our cohort of patients who underwent 4DCT for thoracic radiotherapy, to measure the reduction of PTVs for the gated approaches and to correlate this reduction to the volumes and to the localization of the target volume.

MATERIALS AND METHODS

Patient population

Thirty-eight patients underwent 4DCT at our unit of radiation therapy for thoracic localizations (either primary non-small cell lung cancer (NSCLC) or metastatic malignancies) between August 2018 and February 2019. The clinical and pathological data, collected before RT, of all the patients, were retrospectively recorded.

Ethics approval

All the patients gave written consent to the anonymous use of their examinations for the research scope. A study notification was submitted to the local ethical committee as established by national laws. All the procedures were undertaken in compliance with the ethical statements of the Helsinki Declaration (2008) of the World Medical Association.

Computed tomography imaging

We retrospectively analyzed the 4DCT that was used for simulation purposes before radiotherapy. All 4DCTs were performed using the same 16-detector row 4DCT scanner (Discovery CT580, GE Healthcare, and Milwaukee, WI, USA).

4DCT scans were performed in all the patients to finally reconstruct 10 respiratory phases using a phase-based binning software tool that used an external surrogate on the thoracic surface of the patients for the tumor motion (Sentinel 4D CT Software, C-Rad, Uppsala, Sweden) and a dedicated software tool for the live monitoring of the patients during the radiotherapy treatment (Catalyst Software, C-Rad, Uppsala, Sweden).

GTV contouring and ITV definition

For each patient, as in the RTOG 0915 trial, the gross tumor volume (GTV) was defined as the visible tumor within the CT pulmonary window, and the clinical target volume was identical to the GTV [13].

The CTV was deformably propagated across phases for the three defined ITVs using the MIM Maestro software, a commercially deformable image registration tool (MIM Software Inc., Cleveland, OH, US). The quality of contour propagation was also inspected visually by a clinician with 25 years of experience in lung

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radiotherapy, and modifications were made where required.

Two gated ITV were used, each one of whom includes half of the phases of the respiratory cycle: ITV30%–40%-50%-60%-70% (ITV30%-70%) and ITV80%–90%-100%-10%-20% (ITV80%-20%), respectively. The first one (ITV30%-70%) represent the gating around end -inspiration breathing cycle, whereas the second one (ITV80%-20%) represent the gating around the end-expiration breathing cycle.

The PTV used for treatment was generated by isotropically expanding the ITV by 5 mm.

Radiotherapy delivery and target localization

RT was delivered on a case-by-case basis, with stereotactic ablative radiotherapy, using a VersaHD linear accelerator (Elekta, Stockholm, Sweden).

The patients were immobilized using the BodyFix (Elekta, Stockholm, Sweden) immobilization system. An abdominal compression system was also used in patients with the target of the lower lobes.

The distribution of tumors was defined as central (within 2 cm of the proximal bronchial tree), mediastinal, or peripheral [13]. Peripheral lesions were further divided in "island" or lung wall-seated tumors [14].

The tumors were finally divided between the upper and lower lobes.

Endpoints and statistical analysis

We correlated the volumes of PTV for standard and gated ITVs with the Wilcoxon sign correlation test. A reduction of PTV>10% than the standard PTV was considered as significant.

Furthermore, we analyzed the ratio of patients who showed a significant reduction of PTVs according to the volume and with the localization of the GTV with chi-square analysis.

A p-value ≤ 0.05 was considered statistically significant.

All the statistical analyses were performed with the SPSS v. 23 software (IBM Corporation, New York, US) package for Windows and revised by a biomedical statistician.

RESULTS

Table 1 summarizes the main features of our cohort of patients. The median age was 70 years (mean = 68, 3 SD ± 13, 4, range = 43–89). Among the patients, 18 (47%) were females, and 20 (52%) were males.

All the patients underwent SABR, with various doses and fractionations, on a case-by-case basis.

Table 1. Characteristics of the patient cohort.

Parameters	Volume (mean and s.d.)	Univariate analysis (Wilcoxon test)
PTV standard **PTV 30-70**	82,16 +/- 92,90 cc 77,99 +/- 88,93 cc	p<0,001
PTV standard **PTV 80-20**	82,16 +/- 92,90 cc 79,74+/- 91,81 cc	p<0,001
PTV 30-70 **PTV 80-20**	77,99 +/- 88,93 cc 79,74+/- 91,81 cc	p:0,053

Analysis of PTV

The two gated PTVs were significantly smaller than the standard PTVs (Wilcoxon analysis, p-value < 0,001 for both the PTVs), whereas the difference between the two gated PTVs was insignificant (p-value: 0,053) (figure 1 and table 2).

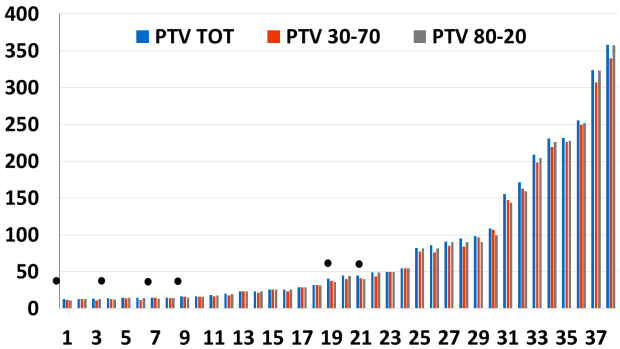


Figure 1. Volume of all the PTVs. Round Circle: significant reduction (>10%) of gated PTV 80-20; Star: significant reduction of gated PTV 30-70.

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Table 2. Univariate analysis (Chi Square test) for gated PTVs, localization and volume of the GTV.

Parameters	PTV 30-70 reduction >10%	PTV 30-70 reduction <10%	PTV 80-20 reduction >10%	PTV 80-20 reduction <10%	Chi square analysis
Localization					
Mediastinum	4	6	0	10	**p:0,030**
Central	4	4	2	12	(PTV 30-70);
Peripherally					
Island	6	2	4	4	**p:0,018**
Lung Wall Tumors	0	6	0	6	(PTV 80-20)
Localization					p: 0,162
Higher (or central) lobes	8	14	4	18	(PTV 30-70)
Lower lobes	2	4	2	4	p: 0,423
					(PTV 80-20)
Volume					
GTV<5cc	6	6	5	7	**p:0,003**
GTV>5cc	8	18	1	25	(PTV 80-20) if GTV<5cc
GTV<30cc	13	12	6	19	**p:0,007**
GTV>30cc	12	1	0	13	(PTV 30-70) if GTV<30cc

Fourteen (36, 8%) patients showed a PTV reduction of >10% in ITV30%–70%, while only six (15, 8%) patients exhibited a significant reduction in ITV80%–20%.

Considering the volume of the GTV, we found a significant correlation between GTV30cc and ITV30%–70% (chi-square analysis, p: 0,006) and between GTV5cc and ITV80%–20% (p: 0,003) (table 3).

For gated ITV30%–70%, only one (7, 7%) patient showed a significant PTV reduction with GTV>30cc versus 13 (52%) patients in the subset with a lower GTV (figure 2).

Conversely, for gated ITV80%–20%, only one (3, 8%) patient exhibited a significant PTV reduction with GTV>5cc, while five (41, 7%) patients presented a significant reduction in the subset with GTV<5cc (figure 2).

We also found a correlation between the localizations of the target lesion (mediastinal/ central/peripheral lesion) for both the gated ITVs (p: 0,030 for ITV30%–70% and p: 0,018 for ITV80%–20%) (table 3).

None of the patients with wall-seated lung tumors showed a PTV reduction for the gated approaches, whereas the subset that showed the highest ratio of significant reduction with the gated ITVs comprised the patients with island tumors (6/8 patients, 75% with ITV30%–70% and 4/8 patients, 50% with ITV80%–20%) (figure 2).

Finally, we did not find any correlation between the target localizations in terms of lobes (higher versus lower lobes) for both the gated ITVs.

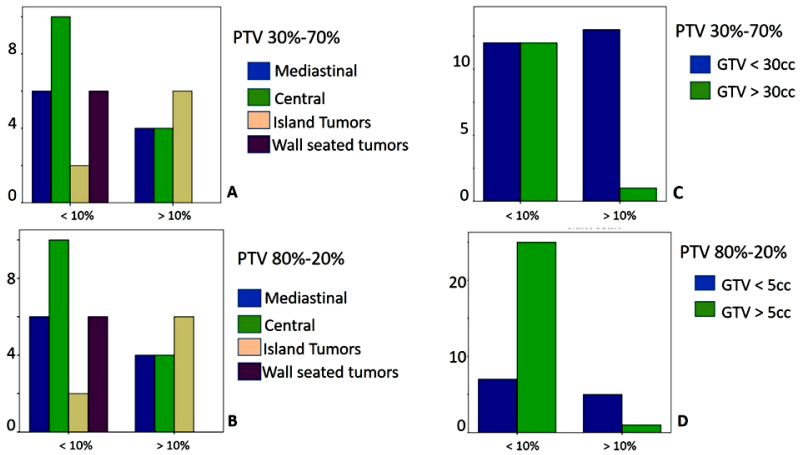


Figure 2. Histogram analysis of the different distribution of gated ITV that showed a significant reduction. In each histogram, on the left a PTV reduction <10%, on the right a PTV reduction >10% (significant reduction); The y-axis shows the count of the volumes.
A: localization for the PTV30-70; B: localization for the PTV80-20; C: PTV30-70 for a cut off of GTV:30cc; D: PTV 80-20 for a cut off of GTV: 5cc.

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DISCUSSION

Phase gating aims to reduce the respiratory motion treating only the GTV in a user-defined window by continuously monitoring the surface of the patients with a localization system that can turn the linac beam on only when the GTV is localized in the correct position (figure 3).

This window must be chosen accurately as it must be short enough to reduce the ITV effectively and long enough to permit efficient treatment times [15].

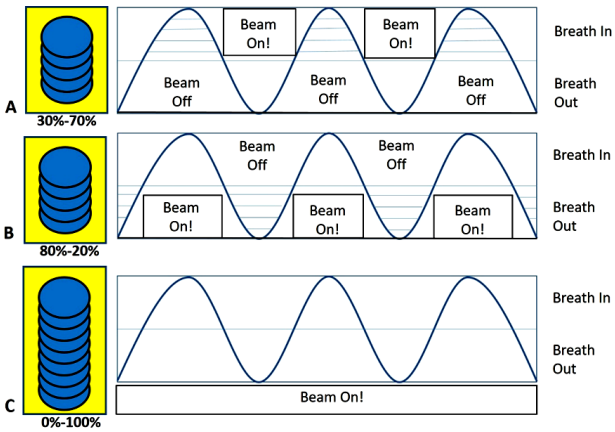


Figure 3. Method of gated radiotherapy for ITV 30%-70% **(A)** and ITV 80%-20% **(B)**. Normal ITV delineation and RT delivery **(C)**.

Conversely, another potential benefit of gated SABR is the interplay effect reduction due to the movement reduction of the GTV, especially when delivering SABR with volumetric-modulated arc therapy (VMAT) that can create inhomogeneous dose distributions across the target [16].

The linear accelerator must be characterized before the application of this complex technique to reduce the beam-on delay, to study the efficiency of the delivery, and to investigate the influence of frequent beam interruptions on the dosimetric accuracy of gated deliveries [17-21]. This technique is time-consuming, and its benefits must be further validated before its application in a clinical scenario.

Several studies have investigated the role of gated radiotherapy in lung SABR, which generally compares retrospectively generated plans to analyze the dosimetric improvements of OARs [22-24]. Unfortunately, these studies have not found a clinically relevant benefit for the majority of the patients, although the major pitfall of these studies is that they have only analyzed the dosimetric reduction to the OARs in the whole population. By contrast, we believe that the selection of patients whose ITV is effectively reduced with this technique could be useful to reduce the doses to OARs effectively or to deliver a higher dose to the targets.

Free breathing gating about the end-exhalation (50%) phase is commonly the most common choice in the previous works due to the reduced motion during end-exhalation [25, 26].

A recent work by Modiri *et al.* has analyzed the role of a personalized respiratory-gating technique using an inverse planning optimization approach that can significantly reduce the doses to OARs by an average of 15% to 26% [27].

We decided to divide the breathing cycle in two phases, with each one including half of the complete cycle (30%–70% (end-exhalation) and 80%–20% (end-inhalation), respectively, to effectively study the optimal volume reduction of the ITVs).

We also decided to consider a gated IT reduction of >10% to be significant to identify the subsets of patients that could benefit from this approach.

Our results corroborated that the volume of the GTV is the major determinant of the ITV reduction as the percentages of the patients who showed a significant PTV reduction are 52% with GTV<30cc in the gated phase 30%–70% and 40% with GTV<5cc in the gated phase 80%–20%.

In this regard, the volume of the target appears to be highly important as small volumes show high movements within the ITV and thus can benefit from a gated approach.

We found a significant correlation between the localization of the targets (mediastinal/central/island/wall seated) as the best results were seen in the subset of patients with island cancers, whereas no benefit was seen in patients with wall-seated tumors.

This finding can be explained as island tumors show higher movements than wall

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seated tumors, as the last ones are anchored to the surrounding structures.

With regard to mediastinal or central lesions, a gated approach appears to be useful in a significant subset of patients, and underlining that the central GTVs are closer to important OARs is noteworthy.

Finally, we did not find any correlation between the localization of the target in terms of lobes (lower versus higher lobe lesions).

We believe that our results are promising as in these subsets of patients, nearly 50% show a significant PTV reduction, and they must be further investigated to understand whether a gated approach could effectively allow the delivery of high doses or to spare the OARs in a significant percentage of patients significantly.

Limitations

Our work suffers from the limitations of a retrospective mono-institutional analysis and low patient numerosity.

CONCLUSIONS

A high percentage of patients with a low volume of GTV, as well as patients with some particular localization, especially island tumors, show a significant PTV reduction with a gated approach. These subsets of patients must be further analyzed to understand whether a gated radiotherapy approach could significantly reduce the doses to the OARs or to deliver high doses to the targets.

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Conflicts of interest**:** *Declared none.*

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