Dosimetry impact of gating latency in cine magnetic resonance image guided breath-hold pancreatic cancer radiotherapy

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Keywords: breath hold, cine MRI, gating latency, pancreatic cancer, motion management

Abstract

\textbf{Objective.} We investigated dosimetry effect of gating latency in cine magnetic resonance image (cine MRI) guided breath-hold pancreatic cancer radiotherapy. \textbf{Approach.} The gating latency was calculated based on cine MRI obtained from 17 patients who received MRI guided radiotherapy. Because of the cine MRI-related latency, beam overshoot occurs when beam remains on while the tracking target already moves out of the target boundary. The number of beam on/off events was calculated from the cine MRI data. We generated both IMRT and VMAT plans for all 17 patients using 33 Gy prescription, and created motion plans by applying isocenter shift that corresponds to motion-induced tumor displacement. The GTV and PTV coverage and dose to nearby critical structures were compared between the motion and original plan to evaluate the dosimetry change caused by cine MRI latency. \textbf{Main results.} The time ratio of cine MRI imaging latency over the treatment duration is 6.6 ± 3.1%, the mean and median percentage of beam-on events < 4 s are 67.0 ± 14.3% and 66.6%. When a gating boundary of 4 mm and a target-out threshold of 5% is used, there is no significant difference for GTV V33Gy between the motion and original plan (\(p = 0.861\) and 0.397 for IMRT and VMAT planning techniques, respectively). However, the PTV V33Gy and stomach D\text{max} for the motion plans are significantly lower; duodenum V12.5 Gy and V18Gy are significantly higher when compared with the original plans, for both IMRT and VMAT planning techniques. \textbf{Significance}. The cine MRI gating latency can significantly decrease the dose delivered to the PTV, and increase the dose to the nearby critical structures. However, no significant difference is observed for the GTV coverage. The dosimetry impact can be mitigated by implementing additional beam-on control techniques which reduces unnecessary beam on events and/or by using faster cine MRI sequences which reduces the latency period.

1. Introduction

Respiratory motion is a major concern in radiotherapy treatment of tumors located in the thoracic or abdominal regions (Han \textit{et al} 2018). Therefore, motion management is critical for accurate delivery of radiation dose to the abdominal tumor target, particularly in the scenario of stereotactic radiotherapy (Caillet \textit{et al} 2017). Nowadays, image guided radiation therapy (IGRT) has become a standard, where cone beam computed tomography (CBCT) is commonly utilized to localize the tumor and assist patient positioning (Belshaw \textit{et al} 2019, Liang \textit{et al} 2019). This has substantially reduced the setup uncertainty caused by interfractional motion, and made intrafractional motion more of a concern, particularly in the treatment of thoracic and abdominal tumors.
Recently, with the development of magnetic resonance guided radiation therapy (MRgRT), cine magnetic resonance imaging (MRI) has been used to monitor intrafractional tumor motion (Steinmann et al. 2019). Compared with x-ray imaging, cine MRI has better soft tissue contrast, does not carry radiation dose, and can image any plane across the tumor, therefore represents a superior image modality for real-time tumor monitoring (Boldrini et al. 2019).

Different strategies have been implemented to manage respiratory tumor motion (McClelland et al. 2013, Tahmasebi et al. 2018, Mittauer et al. 2020). The easiest strategy is treating with free breathing. This, however, requires a big margin to sufficiently encompass the tumor trajectory when creating the planning target volume (PTV) (He et al. 2016). Free breathing treatment saves treatment time at the expense of irradiating more tumor-surrounding soft tissues. Breath hold, which temporally freezes the tumor at the end of inspiration or expiration, represents another motion management strategy (Chang et al. 2020). It restrains tumor motion, hence reduces PTV margin and irradiates less tumor-surrounding normal tissues. However, radiation beam is turned on only when patients are on breath hold (Pandeli et al. 2019). Therefore, the treatment time is typically longer than free breathing treatment. In the treatment of pancreatic tumors, it is of high priority to preserve duodenum and other nearby critical structures, so breath hold treatment is usually the treatment technique of choice (Tchelebi Leila et al. 2020).

MRgRT is a new radiotherapy modality and has two distinct advantages of better soft tissue contrast for image guidance and real-time imaging capability for motion management (Baumgartner et al. 2017, Corradini et al. 2019, Kiser Kendall et al. 2019, Winkel et al. 2019). However, MRgRT is still in an early phase, and its clinical utility should be rigorously evaluated, particularly in the aspect of cine MRI based motion management which is fundamentally different from conventional methods such as RPM and ABC (Wong et al. 2010, Kaplinsky et al. 2018). One key concern is that cine MRI gating causes beam on/off latency which could affect the actual dose delivery (Datta et al. 2018, Paganelli et al. 2018). Green et al. (2018) reported an overall gating latency period of 394 ms for the ViewRay MRgRT system. The gating latency accompanies the beam on/off event during cine MRI gating, and depending on the beam on/off switch frequency, may severely compromise the dose delivered to the tumor target and nearby critical structures. This study is to investigate the gating latency and its dose impact in cine MRI gated breath-hold pancreas cancer treatment.

2. Methods and materials

2.1. Cine MRI gating

The cine MRI videos used for tumor motion analysis and treatment planning were from 17 pancreatic cancer patients who received SBRT on an MR-guided 0.35 T MRgRT system (MRIdian, Viewray, Inc., Oakwood Village, Ohio, USA) with deep inspiration breath-hold. The patients were treated in the University of Miami from September 2016 to December 2018. Imaging for MRgRT included volumetric MRIs acquired using a steady-state precession pulse sequence (TrueFISP) for localizing treatment targets, and 2D TrueFISP cine MRIs acquired in a sagittal plane for target tracking (Green et al. 2018). The cine imaging frame rate was 4 Hz, field of view was 35 × 35 cm², spatial resolution was 3.5 × 3.5 mm², and scanning thickness was 5 mm. This study followed the protocol approved by the University of Miami (IRB # 20160817).

The MRIdian system adopts a target contour-based motion tracking strategy. The tracking target is real-time contoured based on deformable image registration. The tracking algorithm deformably registers images between a reference frame and a real-time motion frame (Mutic and Dempsey 2014). Radiation is delivered only when the target, most often the GTV, is located within a preset gating boundary. A target-out percentage is calculated as the percentage of the target volume exceeding the tracking boundary. Since targets and organs at risk (OARs) can have different degrees of structural deformation, specific tracking algorithms have been developed for particular applications, in addition to the tracking algorithm for general applications as used in this investigation (ViewRay 2020, Kim et al. 2021).

In this study, the GTV was set as the tracking target, and a tracking boundary of 3–5 mm was used. A beam-on event was triggered when the tracking target moved into the boundary. Beam was turned off when >5% of the tracking target moved out of the boundary. The cine MRI and target tracking are demonstrated in figure 1.

2.2. Beam-off gating latency

The fast cine MRI provides a mechanism of real-time motion monitoring. However, the finite imaging time causes gating latency, i.e. a delay between the moment that the tracking target moves out and that the beam is turned off. Figure 2 explains the beam-off gating latency mechanism. The beam remains on as long as no more than 5% of the tracking target is out of tracking boundary. We define the time point t1 as that exact 5% of the target is moving out of boundary, and the time point t2 as that the beam is being turned off. Around time point t1, the system starts acquiring an image frame to capture the target-out status. But the image frame is not...
rendered until after 0.25 s which is the image acquisition time. Ideally, the beam should be turned off immediately after $t_1$. However, the system detects the target-out status only after the image frame is rendered. Therefore, a beam-off latency exists which is the time delay from the point of target moving out of the tracking boundary by 5% to the point of system detecting the target-out status and beam being turned off. Beam overshoot occurs during beam-off latency, and potentially misses the target and over-irradiates nearby OARs. The beam overshoot time $\Delta t = t_2 - t_1$ includes the image acquisition time and the time taken to turn beam off. In this study, we specifically aim to investigate the effect of cine MRI gating on MRI guided Linac dose delivery. Therefore, the beam overshoot time is approximated as the cine image acquisition time and the beam turn-off time which is only a few milliseconds and much less than the image acquisition time, is negligible. Furthermore, the time for the algorithm to calculate the target-out percentage which varies depending on the specific MRgRT system used is also neglected in this study. The beam overshoot percentage, is defined as the proportion of the total beam overshoot time, i.e. the total beam latency, over the total beam on time. The total beam overshoot time is the multiplication of each beam overshoot time $\Delta t$ (0.25 s) and the number of beam-on events, where $\Delta t$ is approximated as the cine image acquisition time.

### 2.3. Treatment planning

We generated treatment plans for all 17 patients using both intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques on a Philips Pinnacle 9.10 treatment planning system (Likhacheva et al 2012) by adopting a SBRT prescription of 33 Gy delivered in 5 fractions (Pollom et al 2017). The IMRT plans were planned with 18 fields evenly distributed within 360°, and the VMAT plans were planned with one single arc from 0° to 360°. All contours were reviewed and approved by two experienced radiation oncologists. The GTV was expanded by 5 mm to create the PTV, and the duodenum expanded by 3 mm to create
the PRV. Then the PTV was modified by subtracting the PRV to create the final PTV structure. Patient information is listed in table 1. The dose constraints for OARs, including duodenum, stomach, small bowel, liver, kidneys, and spinal cord, are listed in table 2 (Benedict et al 2010).

The target moving distance was calculated when the GTV exceeded the boundary by 5% in cine MRI. The moving distance included two separate parts. The first part was the distance corresponding to the tracking boundary, typically 4 mm, and the second part was the distance beyond the boundary when the target-out volume was >5%. An iso-shift plan was created by shifting the radiation isocenter by a corresponding target moving distance. The motion plan was the composite of the original plan and iso-shift plan where the iso-shift plan had a weight equal to the beam-overshoot percentage. The workflow for motion plan generation was shown in figure 3. The motion plan was compared with the original plan to assess the dosimetry impact of tumor motion taking place during gating latency period.

### 2.4. Statistical analysis

Wilcoxon signed rank test was used to compare the motion and original plan. The significance was determined as $p$ value <0.05. The dose coverage of GTV and PTV and dose to OARs such as duodenum, stomach, small bowel, liver, kidneys and spinal cord were all evaluated. The data was reported with the format of mean ± standard deviation.
3. Results

3.1. Beam overshoot

Figure 4 shows the tumor motion patterns observed on cine MRI. The beam overshoot percentage averaged over all patients was $6.6 \pm 3.1\%$. This considerable beam overshoot was mainly caused by the surprisingly large number of short beam on events, i.e. the percentage of beam on events $<4$ s is as great as $67.0 \pm 14.3\%$. The mean target out percentage by volume was $5.9 \pm 0.8\%$, and the mean target moving distance $7.3 \pm 1.8$ mm.

3.2. Dose evaluation

3.2.1. Dose comparison for IMRT plans

Figure 5 shows the dose difference between the motion plan and original plan for one patient as an example. It can be seen from figure 5(A) that the maximum dose difference between the original plan and motion plan can reach as high as 200 cGy. The PTV coverage in the motion plan is lower than that of the original plan (94.42\% versus 99.51\%). But the difference for GTV coverage is smaller (97.05\% versus 98.71\%). The OAR dose is slightly higher for duodenum in the motion plan. The statistical comparison between the motion plans and original plans for IMRT is presented in table 3. The results show no significant difference for GTV V33Gy ($p = 0.861$), but significant difference for PTV V33Gy ($p < 0.001$), duodenum V12.5 Gy ($p = 0.002$), duodenum V18Gy ($p = 0.026$) and stomach Dmax ($p = 0.025$). There is no significant difference for other parameters. The relative deviations for PTV V33Gy, duodenum V12.5 Gy and duodenum V18Gy are $-3.7\%$, $8.4\%$ and $11.5\%$, respectively. For other OARs, the deviations are all within $3\%$, except the small bowel V25 Gy.

3.2.2. Dose comparison for VMAT plans

Figure 6 shows dose difference between the motion plan and original plan for the same patient. It can be seen from figure 6(A) that the maximum dose difference between the original plan and motion plan can reach as high
Figure 6. Dose difference between the VMAT original and motion plan of one patient. (A) The distribution of dose difference at a sagittal plane; (B) the DVH of the original plan and motion plan for VMAT.

Table 3. IMRT plan comparison.

| Parameter       | Original plan | Motion plan for IMRT |
|-----------------|---------------|----------------------|
|                 | Mean ± SD     | Median               | Mean ± SD     | Median | Relative deviation | p value |
| GTV  V33Gy (%)  | 89.78 ± 11.60 | 95.03                | 89.93 ± 10.94 | 94.41   | 0.2%                | 0.861   |
| PTV  V33Gy (%)  | 97.67 ± 1.40  | 97.03                | 94.04 ± 2.18  | 94.20   | −3.7%               | <0.001  |
| Duodenum Dmax  (cGy) | 2935 ± 730  | 3139                | 2981 ± 748   | 3166    | 1.6%                | 0.107   |
| V12.5Gy (cc)   | 9.04 ± 0.72   | 9.18                 | 9.80 ± 1.42  | 9.61    | 8.4%                | 0.002   |
| V18Gy (cc)     | 3.38 ± 0.77   | 3.29                 | 3.77 ± 1.40  | 3.42    | 11.5%               | 0.026   |
| Stomach Dmax  (cGy) | 2639 ± 581  | 2749                | 2621 ± 583   | 2745    | −1.4%               | 0.025   |
| V18Gy (cc)     | 4.83 ± 3.24   | 5.25                 | 4.72 ± 3.57  | 5.17    | −2.3%               | 0.698   |
| Liver V21Gy (cc) | 1548 ± 488  | 1458                | 1549 ± 487   | 1458    | 0.0%                | 0.066   |
| Small bowel Dmax (cGy) | 2451 ± 666 | 2875                | 2468 ± 678   | 2883    | 0.7%                | 0.868   |
| V25Gy (cc)     | 0.54 ± 0.62   | 0.16                 | 0.57 ± 0.67  | 0.15    | 5.6%                | 0.541   |
| Right kidney Dmean (cGy) | 368 ± 162 | 381                | 370 ± 161    | 388     | 0.5%                | 0.232   |
| Spinal cord Dmax (cGy) | 1079 ± 268 | 987                | 1076 ± 267   | 990     | −0.3%               | 0.073   |

Note: SD is short for standard deviation.

Table 4. VMAT plan comparison.

| Parameter       | Original plan | Motion plan for VMAT |
|-----------------|---------------|----------------------|
|                 | Mean ± SD     | Median               | Mean ± SD     | Median | Relative deviation | p value |
| GTV  V33Gy (%)  | 89.39 ± 12.12 | 94.56                | 89.15 ± 11.46 | 91.89   | −0.3%               | 0.397   |
| PTV  V33Gy (%)  | 97.59 ± 1.30  | 97.27                | 93.68 ± 1.81  | 93.22   | −4.0%               | <0.001  |
| Duodenum Dmax  (cGy) | 3118 ± 89  | 3144                | 3112 ± 99    | 3121    | −0.2%               | 0.795   |
| V12.5Gy (cc)   | 8.97 ± 0.71   | 9.13                 | 9.51 ± 1.00  | 9.84    | 6.0%                | 0.002   |
| V18Gy (cc)     | 3.10 ± 0.70   | 3.24                 | 3.32 ± 0.78  | 3.36    | 7.1%                | 0.003   |
| Stomach Dmax  (cGy) | 2642 ± 637 | 2828                | 2613 ± 630   | 2822    | −1.1%               | 0.009   |
| V18Gy (cc)     | 4.66 ± 3.35   | 3.83                 | 4.66 ± 3.53  | 3.66    | −0.1%               | 0.910   |
| Liver V21Gy (cc) | 1549 ± 487  | 1458                | 1550 ± 487   | 1458    | 0.0%                | 0.201   |
| Small bowel Dmax (cGy) | 2462 ± 649 | 2928                | 2447 ± 636   | 2873    | −0.6%               | 0.246   |
| V25Gy (cc)     | 0.51 ± 0.57   | 0.21                 | 0.52 ± 0.59  | 0.20    | 2.9%                | 0.241   |
| Left kidney Dmean (cGy) | 369 ± 170 | 362                | 368 ± 167    | 362     | −0.1%               | 0.248   |
| Right kidney Dmean (cGy) | 441 ± 183 | 381                | 442 ± 182    | 381     | 0.3%                | 0.151   |
| Spinal cord Dmax (cGy) | 1027 ± 269 | 881                | 1024 ± 268   | 877     | −0.2%               | 0.063   |

Note: SD is short for standard deviation.

as 200 cGy. The PTV coverage in the motion plan is lower than that of the original plan (94.59% versus 98.49%). But the difference for GTV coverage is smaller (95.83% versus 97.37%). The OAR dose is slightly higher for duodenum in the motion plan.
The statistical comparison between the motion plans for VMAT and original plans is presented in table 4. The results show no significant difference for GTV V33Gy ($p \approx 0.397$), but significant difference for PTV V33Gy ($p < 0.001$), duodenum V12.5 Gy ($p = 0.002$), duodenum V18 Gy ($p = 0.003$) and stomach $\text{D}_{\text{max}}$ ($p = 0.009$). There is no significant difference for other parameters. The relative deviations for PTV V33Gy, duodenum V12.5 Gy and duodenum V18 Gy are $-4.0\%$, 6.0\% and 7.1\%, respectively. For other OARs, the deviations are all within 3\%.

4. Discussion

The study results suggest that cine MRI associated gating latency could undermine the dose coverage to the PTV and the dose sparing to the OARs surrounding the tumor. The under-dose to the PTV may increase the chance of local recurrence, metastasis and decrease the overall patient survival and the dose sparing to the OARs surrounding the tumor. The under-dose to the PTV could significantly decrease the dose to the PTV and increase the dose to the nearby critical structures. Of particular note, the short-term beam on events accounted for as high as 67.0\% of the total beam on events. These short-term events could cause considerable dose delivery uncertainties, and hence their trigger should be mitigated by implementing additional beam-on control techniques. For example, a time delay can be set so that the beam won’t be turned on until the GTV falls within and remains inside the tracking boundary for an appropriate period. Since the beam overshoot was determined by multiplication of the system latency and the number of beam on events, the cine MRI acquisition time, another way to mitigate the beam overshoot time is to increase the speed of cine MRI imaging via developing fast MRI imaging sequences. In addition, additional motion control techniques such as visual feedback (Mancosu et al. 2016) and active breath coordinator (Kunheri et al. 2017) can be used in combination with cine MRI to further reduce the unnecessary beam on/off switching events.

In cine MRI guided radiation delivery, the gating latency that triggers the beam overshoot typically includes time delay caused by MR image acquisition, target tracking algorithm and radiation beam turning off (Kim et al. 2020). Kim et al. (2021) reported an overall gating latency period of 302 ± 20 ms in a ViewRay 0.35 T MR-LINAC system on which the cine imaging frequency was also 4 Hz. Green et al. (2018) reported that the average system latency was about 394 ms on a ViewRay 0.35 T MR-Cobalt system. While Viewray's image guidance is based on sagittal-plane cine MR images (Kim et al. 2020), the other MR-LINAC system, Elekta Unity's image guidance is based on cine MR images acquired from three-orthogonal planes (Liu et al. 2020). Studies on Elekta Unity found that the overall latency was 347.45 ms at 4 Hz imaging speed and 204 ms at 8 Hz, roughly at the same magnitude as on the ViewRay system (Kim et al. 2020). In this study, we only analyzed the dose error caused by image acquisition latency which is largely determined by the imaging frame rate. The beam turning time is in the order of a few milliseconds and is much less than the imaging latency (Mancosu et al. 2016). The latency associated with the target tracking algorithm (Rose et al. 2013), on the other hand, can be reduced to the order of a few milliseconds or less with the development of fast tracking algorithms and continuous improvement in computing hardware (Borman et al. 2019, Roberts et al. 2021). The MLC motion latency could also cause beam overshoot, but may only occur in the dynamic MLC radiation delivery. In the step-and-shoot mode, the radiation beam will be immediately turned off without residual leaf motion once the target out signal was triggered. Even if in the dynamic MLC mode, the additional beam overshoot caused by MLC motion latency should also be negligible, because the radiation beam can be turned off before the residual MLC motion causes any dose delivery error, as long as the electronic beam turning-off time is less than the MLC motion latency (Jeremy et al. 2016, Glitzner et al. 1999).

2D cine MRI offers natural advantages in imaging speed while still maintaining soft tissue contrast. However, it suffers from complications arising from through-plane motion which can render the detected target shift not consistent with the real 3D motion. Keiper et al. (2020) noticed the dependence of the tracking accuracy on the acquisition plane and the motion pattern, and suggested that choosing an appropriate tracking section is very important. In the current study, the tracking section located in the middle of the tumor where the target tracking variation caused by the through-plane effect was relatively small. Despite the consistent tracking section...
selection, the extent of the through-plane changes and their effect on target tracking accuracy still warrants careful investigation once fast 3D image tracking becomes available in the future.

It is worth to note that the current approach that completely shift the isocenter by a fixed distance to create the motion plan likely exaggerated the dosimetric impact and probably is a conservative evaluation. In reality, the moving parts are essentially the target and nearby OARs while most of the rest of body, especially the bony anatomy remain stationary. Instead, one can calculate the dose on the real-time 3D motion anatomy acquired during radiation delivery and then accumulate the dose using deformable registration. Generally, it is a consensus that in dose calculation and dose accumulation the results obtained by using deformation registration usually are more reliable and accurate than rigid registration (Kainz et al 2022). In the current investigation, however, we did not take tissue deformation into dose accumulation, due to the lack of sufficient anatomical information, particularly, the real-time 3D motion MRI images acquired during beam delivery, to perform deformable image registration. Better evaluation can be obtained once the real-time 3D motion MRI becomes available in the future.

Currently, step-and-shoot delivery technique is a more practical treatment option in MRI-Linac for now and that the investigation on VMAT planning is a little forward-looking. One major difference between IMRT and VMAT techniques probably is the gantry and MLC motion during radiation delivery. There may be cross-interference between the gantry motion and target/OAR motion for the VMAT delivery technique. The interference, either during VMAT or IMRT delivery, however, could not be fully modeled and considered in the current study due to lack of real-time patient 3D motion data. Regarding the planning technique itself, studies have investigated the difference in the dosimetry outcome between IMRT and VMAT plans. Redler et al (2019) re-planned eight SBRT patients who were previously treated with VMAT on TrueBeam using fixed-field IMRT on MR-Linac, and demonstrated a consistent dosimetry outcome between the two. This study also presented consistent effect on dosimetry outcome by cine MRI latency between the VMAT and IMRT planning techniques. Nevertheless, the interaction between different radiation delivery techniques and the respiratory motion on MRgRT systems may warrant careful investigations once the real-time 3D motion MRI becomes available in the future.

One limitation of this study is the relatively small patient sample size, because the number of enrolled patients who received MR guided pancreas SBRT was very limited. We used the PTV coverage data to calculate the statistical power for the sample size of 17 patients. The mean and standard deviation of paired differences between the original and motion plan calculated using PASS software are 3.9 and 1.4. The effect size is equal to 2.758 which is greater than 0.8, indicating that the number of 17 samples is statistically sufficient (Foley 2002). Another limitation was that the cine-MRI data was acquired from an MR-guided cobalt radiotherapy system, the treatment duration, breathing amplitude and frequency may change if the treatment is implemented in LINAC radiotherapy system. But, because the critical information used to create the motion plan was the ratio of beam overshoot time over the total beam on time, instead of the absolute beam overshoot time, it should not make a big difference in the study outcome. Therefore, this study can still provide essential insights about the impact of cine MRI imaging latency on dose delivery uncertainties.

5. Conclusions

In cine MRI gated breath hold pancreatic cancer radiotherapy, when a gating boundary of 4 mm and a target-out threshold of 5% is used, the cine MRI gating latency does not alter the GTV dose coverage, but significantly decreases the dose delivered to the PTV and increases the dose delivered to the critical structures surrounding the target. The dose compromise should be mitigated by implementing additional beam on control techniques to reduce the number of unnecessary beam on events and/or by using faster cine MRI sequences to reduce the image acquisition period.

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