

Mitigation on Bowel Loops Daily Variations by 1.5-T MR-guided Daily-adaptive SBRT for Abdomino-pelvic Lymph-nodal Oligometastases

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Abstract

Purpose

We report preliminary dosimetric data concerning the use of 1.5-T MR-guided daily-adaptive radiotherapy for abdomino-pelvic lymph-nodal oligometastases. We aimed to assess the impact of this technology on mitigating daily variations for both target coverage and organs-at-risk (OARs) sparing.

Methods

A total of 150 sessions for 30 oligometastases in 23 patients were analyzed. All patients were treated with MR-guided stereotactic body radiotherapy (SBRT) for a total dose of 35Gy in 5 fractions. For each fraction, a quantitative analysis was performed for PTV volume, V35Gy and Dmean. Similarly, for OARs we assessed daily variations of volume, Dmean, Dmax. Any potential statistically significant change between baseline planning and daily-adaptive sessions was assessed using the Wilcoxon signed-rank test, assuming a *p-value* < 0.05 as significant.

Results

Average baseline PTV, bowel, bladder and single intestinal loop volumes were respectively 8.9cc (range, 0.7-41.2cc), 1176cc (119-3654 cc), 95cc (39.7-202.9 cc), 18.3cc (9.1-37.7 cc). No significant volume variations were detected for PTV (*p*=0.21) bowel (*p*=0.36), bladder (*p*=0.47), except for single intestinal loops, which resulted smaller (*p*=0.026).

Average baseline V35Gy and Dmean for PTV were respectively 85.6% (72-98.8%) and 35.6 Gy (34.6-36.1 Gy). We recorded a slightly positive trend in favor of daily-adaptive strategy vs baseline planning for improved target coverage, although not reaching statistical significance. (*p*=0.11 and *p*=0.18 for PTV-V35Gy and PTV-Dmean).

Concerning OARs, a significant difference was observed in favor of daily-adapted treatments in terms of single intestinal loop Dmax [23.05 Gy (13.2-26.9 Gy) at baseline vs 20.5 Gy (12.1-24 Gy); *p*-value=0.0377] and Dmean [14.4 Gy (6.5-18 Gy) at baseline vs 13.0 Gy (6.7-17.6 Gy); *p*-value=0.0003].

Specifically for bladder, the average Dmax was 18.6 Gy (0.4-34.3 Gy) at baseline vs 18.3 Gy (0.7-34.3 Gy) for a *p*-value=0.28; the average Dmean was 7.0 Gy (0.2-16.6 Gy) at baseline vs 6.98 Gy (0.2-16.4 Gy) for a *p*-value=0.66. Concerning the bowel, no differences in terms of Dmean [4.78 Gy (1.3-10.9 Gy) vs 5.6 Gy (1.4-10.5 Gy); *p*-value=0.23] were observed between after daily-adapted sessions. A statistically significant difference was observed for bowel Dmax [26.4 Gy (7.7-34 Gy) vs 25.8 Gy (7.8-33.1 Gy); *p*-value=0.0086].

Conclusions

Daily-adaptive MR-guided SBRT reported a significantly improved single intestinal loop sparing for lymph-nodal oligometastases. Also bowel Dmax was significantly reduced with daily-adaptive strategy. A minor

advantage was also reported in terms of PTV coverage, although not statistically significant.

Introduction

The role of stereotactic body radiotherapy (SBRT) for the treatment of oligometastases is gaining a growing attractiveness in the oncological community. [1]

The use of SBRT represents a non-invasive ablative local treatment for both oligorecurrent or oligoprogressive disease in several anatomical sites, and its use is favorably reported in combination with novel systemic treatments such as immunotherapy. [2, 3]

SBRT allows clinicians to deliver high doses to small volumes in few sessions with a rapid dose fall-off outside the target, minimizing the involvement of the nearby healthy structures. Thus, SBRT represents an effective and safe treatment option with a minimal impact on toxicity or quality of life (QoL). All these favorable characteristics have led to a global widespread of this therapeutic approach. [4]

In particular, in the setting of oligometastatic lymph-nodal disease, the delivery of a metastasis-directed approach resulted in excellent local control and progression-free, with no relevant side effects. [5–8]

The main basis for lymph nodes SBRT relies on the possibility to deliver high doses to small volumes with increased accuracy, by using cone beam CT-based image guided radiotherapy (IGRT). The consequently increased precision for the delivery phase resulted in a significant reduction of inter-fraction variability due to physiological changes in position and volume of healthy structures. However, especially in the abdominal-pelvic region, target identification may be suboptimal with conventional cone beam CT-imaging due to the low soft tissue contrast.

In this scenario, the recent introduction of MR-Linacs represents a potential paradigm shift for the implementation of lymph-nodes SBRT. Based on a superior anatomy visualization, MR-Linacs are supposed to refine not only target volumes but also organs at risk (OARs) identification, with a consequently improved inter- and intra-fraction precision. This is a crucial issue especially in the case of targets very close to healthy structures, which are more influenced by daily anatomical variations, such as bowel loops. Furthermore, the MRI-based daily position verification minimizes the risk of target missing and the use of MR-guided online adaptive workflows allows a safe delivery of the treatment, which is calculated on real-time anatomy conditions. [9–12]

In October 2019, we started our clinical activity with the 1.5 T MR-Linac Unity Elekta (Elekta AB, Stockholm, Sweden). This device conjugates a 7 MV Flattening Filter Free (FFF) linear accelerator mounted on a rotating gantry system with a high quality magnetic-resonance imaging system.

Herein we report the preliminary dosimetric data concerning the first consecutive 23 patients who received MR-guided SBRT for lymph-nodal oligometastases. In the present series, we analyzed the daily variation of the nearby healthy structures and the role of MR-guided daily adaptive radiotherapy in mitigating the impact of daily anatomical variations on target volumes coverage.

Materials And Methods

Patient data characteristics

The following results are derived from the prospective observational study ongoing at our institution, which was approved on April 2019 by the Local Ethical Committee. Between October 2019 and October 2020, 50 oligometastatic patients were enrolled. Of these, our dosimetric analysis regards a total of 150 sessions for 30 lymph-nodes in the first 23 consecutive patients who were treated with MR-guided SBRT for abdominal-pelvic lymph nodes oligometastases.

Eligible patients had oligometastatic disease (≤ 5 sites of disease) from solid tumors, and aged ≥ 18 years. Exclusion criteria were general contraindications for 1.5T MRI and an inability to tolerate a 45-minute treatment. Re-treatment was not an exclusion criterion. Patients' characteristics are reported in Table 1.

Table 1
Patients' characteristics

<i>Characteristic</i>	<i>Value</i>
Median age	69 years (range, 58–74)
Primary Histology	Prostate (96%); Endometrium (4%)
Oligometastasis site	Lombo-aortic (n = 8; 26%); pelvic (n = 22; 74%)
Number of lymph-node oligometastes treated per patient	4 (n = 2; 8%); 2 (n = 1; 4%); 1 (n = 20; 88%)
Total dose delivered	35 Gy/5 fractions (n = 30; 100%)
Median treatment session time	37 minutes (range, 26–81)

Pre-treatment imaging

Pre-treatment imaging consisted of a planning CT-scan (Somatom AS, Siemens, Germany), with 3 mm slice thickness, and a 3D T2-weighted (T2w) MRI-scan (1.5T Philips Ingenia) with a 1 mm slice thickness, then the same MRI-scans were daily performed for treatment. All the scans were acquired in head-first supine treatment position with a knee support and arms on the chest in the case of pelvic or lower-abdominal lesions. The anterior coil was positioned over the patient body, in order to maximize the signal-to-noise ratio. The same patient and coil index position was reproduced for each treatment fraction.

Target delineation

The planning CT-scan and planning MRI-images were rigidly co-registered based on bony anatomy, mainly to obtain the bulk densities for each tissue. Lymph-node gross tumor volume (GTV) and OARs were contoured on the MRI-scan with the visual support of the registered CT-scan, and of the staging

diagnostic exams (i.e. PET-CT). Thus, GTV was delineated as the entire visible tumor and it was considered equal to the clinical target volume (CTV). OARs were contoured as avoidance structures depending on the proximity to the target. All volumes, including OARs, were delineated by a radiation oncologist experienced in MRI-imaging in accordance with consensus delineation guidelines, defining single loop as the portion of intestine in proximity to the target and cranio-caudally extended to 1 cm above and below the target. [13]

The GTV to planning target volume (PTV) margin was created in accordance with the margins employed for conventional linacs treatment ranging from 3 to 5 mm, based on the distance and on the motion between target and OARs. A dose inhomogeneity in the PTV overlapping with the OARs was allowed, in order to comply with the dose constraints for OARs.

Plan generation

The pre-treatment plan was generated using the Monaco 5.40.01 (Elekta AB, Stockholm, Sweden) treatment planning system. Intensity modulated radiotherapy (IMRT) offline plans were optimized on MRI-scan, generally with 10–11 fixed beam angles. An FFF photon beam is employed.

Treatment was typically prescribed in order to guarantee at least 95% of the PTV to receive at least 95% of the prescription dose. The maximum dose in the PTV should not exceed 107%. A lower PTV coverage was accepted only to comply with maximum dose constraints to surrounding OARs. All pre-treatment plans passed the standard QA procedure before the first treatment session.

Online adaptive workflow and dose delivery

In all sessions, treatment delivery was performed using the online adapt to shape workflow (ATS), consisting of a daily re-contouring of both target volumes and OARs prior to each session. [14]

This approach is the most robust because it allows a full contour adaptation (manually or by deformable registration) and re-planning, taking into account every motion or change in OARs shape or volume.

In fact, an important limitation of the adapt to position workflow (ATP), in which only the isocenter is updated, is that the exact dose received by OARs at every fraction is unknown, as the same contours are used as an avoidance structure for daily re-planning and the delineated OARs could not be the exact OARs on the daily image.

Consequently, despite ATS approach is more time consuming with a longer treatment time per fraction compared to ATP workflow, it enables a better assessment of the real dose received by the organs in proximity of the target. Thus, ATP workflow is usually adopted to speed up this procedure only in the case of no major differences in the daily anatomy compared to reference imaging.

Daily online workflow consists of an initial T2w 3D MRI-scan, rigidly registered to the pretreatment MRI-scan. The contours of target and OARs were automatically propagated to the scan of the day by a deformable registration and used for plan optimization.

Thereafter, when ATS workflow was used, a trained radiation oncologist adapted the deformed contours of the GTV and OARs. Meanwhile, a full plan re-optimization was performed, a verification MRI-scan was acquired in order to assess any target and OARs movements. [15]

Afterwards, the radiation oncologist and the physicist evaluated the new treatment plan and checked the absence of major movements by visual comparison (iso-to-iso) of the images and contours. In this case, the radiation treatment was delivered, otherwise a new ATP or ATS were started.

Prior to the delivery start, intra-fraction motion was monitored with a real-time 2D cine-MRI (T2/T1-weighted balanced steady-state free precession) acquired on two coronal and sagittal planes. Finally, another 3D scan was acquired after the treatment for offline re-computation purposes as assessment of intrafraction target coverage. The whole session time, defined as the time between the patient entrance and exit from the treatment room, was timed and registered by a radiotherapy technologist (RTT).

Data collection and statistical analysis

A total of 150 sessions for 30 lymph-nodes in 23 patients were analyzed. Descriptive statistics were collected for continuous variables. For each fraction, a quantitative analysis was performed for PTV coverage in terms of volume, V35Gy and Dmean. Similarly, for OARs the analysis assessed Dmean, Dmax, and daily variations in terms of volume for each session of treatment. Any potential statistically significant change between baseline treatment planning and daily-adaptive treatment sessions was assessed using the Wilcoxon signed-rank test and graphically displayed using box-plot diagrams. A p -value < 0.05 was considered to be statistically significant. All the statistical analyses were carried out using Graphpad Prism v.8.4.2 (Graphpad Software, San Diego, CA, USA).

Results

A total of 150 sessions for 30 lymph node metastases in 23 patients were treated and evaluated in the present analysis. Only in the case of one patient, the treatment was delivered as a re-irradiation. In 2 patients, MR-guided SBRT was performed to 4 oligometastases, in one patients to 2 lymph-node oligometastases. Median session time was 37 minutes (range, 26–81). All treatments were performed on consecutive days.

Globally, no constraints violations were recorded in all the treatment sessions, and all the dose criteria for target coverage were always met.

Average baseline PTV volume was 8.9 cc (range, 0.7–41.2 cc). No significant variations of the target volumes were detected during the five sessions ($p = 0.21$). Regarding OARs, average baseline bowel, bladder and single intestinal loop (in the case of targets very close to the bowel) volumes were respectively 1176 cc (119–3654 cc), 95 cc (39.7-202.9 cc), 18.3 cc (9.1–37.7 cc). Also in the case of the OARs structures, no statistically significant variations in terms of volume were detected for bowel (respectively 1176 cc [119–3654] at baseline vs 1177 cc [198.5-3660.5] in daily-adapted sessions $p =$

0.36) and bladder ($p = 0.47$), except for single bowel loops, where a significant difference was recorded ($p = 0.026$). (Table 2 and Figs. 1–4)

Table 2
Target and organs at risk volume variations

Target and OARs	Average volume at baseline planning MR (range)	Average volume during treatment sessions (range)	p-value
PTV	8.9 cc (0.7–41.2)	7.05 cc (2.1–44)	0.21
Bowel	1176 cc (119–3654)	1177 cc (198.5-3660.5)	0.36
Bladder	95 cc (39.7-202.9)	91 cc (32.8-207.4)	0.47
Single loop	18.3 cc (9.1–37.7)	15.3 cc (9.1–26.6)	0.026

Average baseline V35 Gy and Dmean for PTV were respectively 85.6% (72-98.8%) and 35.6 Gy (34.6–36.1 Gy). When compared to daily treatment sessions, no statistically significant differences were recorded, despite a minimum positive trend in favor of daily-adaptive strategy in terms of improved target coverage was observed ($p = 0.11$ and $p = 0.18$ respectively for PTV-V35 Gy and PTV-Dmean). (Table 3 and Fig. 1).

Table 3
Target and organs at risk dosimetric parameters variations

Target and OARs	Baseline Planning Dosimetric Criterion	Average Daily-adaptive Dosimetric Criterion	p-value
PTV V35Gy	85.6% (72-98.8)	86.8% (82.5–99.7)	0.11
PTV Dmean	35.6 Gy (34.6–36.1)	35.6 Gy (34.7–36)	0.18
Bladder Dmax	18.6 Gy (0.4–34.3)	18.3 Gy (0.7–34.3)	0.28
Bladder Dmean	7.0 Gy (0.2–16.6)	6.98 Gy (0.2–16.4)	0.66
Bowel Dmax	26.4 Gy (7.7–34)	25.8 (7.8–33.1)	0.0086
Bowel Dmean	4.7 Gy (1.3–10.9)	5.69 Gy (1.4–10.5)	0.23
Single Loop Dmax	23.05 Gy (13.2–26.9)	20.5 Gy (12.1–24)	0.0377
Single Loop Dmean	14.4 Gy (6.5–18)	13.0 Gy (6-17.6)	0.0003

As far as OARs, a statistically significant difference was observed in favor of daily-adapted treatments in terms of single intestinal loop Dmax [23.05 Gy (13.2–26.9 Gy) at baseline vs 20.5 Gy (12.1–24 Gy); p -value = 0.0377] and Dmean [14.4 Gy (6.5–18 Gy) at baseline vs 13.0 Gy (6.7–17.6 Gy); p -value = 0.0003] with a significantly improved sparing of the structure in the daily adapted sessions.

Specifically for bladder, the average Dmax was 18.6 Gy (0.4–34.3 Gy) at baseline vs 18.3 Gy (0.7–34.3 Gy) for a p-value = 0.28. Similarly, the average Dmean was 7.0 Gy (0.2–16.6 Gy) at baseline vs 6.98 Gy (0.2–16.4 Gy) for a p-value = 0.66. Concerning the bowel, in agreement, no differences in terms of Dmean [4.78 Gy (1.3–10.9 Gy) vs 5.6 Gy (1.4–10.5 Gy); p-value = 0.23] were observed between baseline treatment planning and daily-adapted sessions. On the contrary, a statistically significant difference was observed for bowel Dmax [26.4 Gy (7.7–34 Gy) vs 25.8 Gy (7.8–33.1 Gy); p-value = 0.0086]. (Table 3 and **Figs. 2–4**)

Discussion

The present experience reports preliminary dosimetric data concerning the use of MR-guided SBRT for lymph node oligometastases in the case of tight proximity to OARs very close to the target. This setting is very challenging due to the need to guarantee an optimal target coverage still complying with the OARs dose constraints.

Consequently, the recent availability of MRI-linac allows clinicians to refine the accuracy for the identification of the daily exact mutual position of OARs and PTV, and the daily re-planning permits a real-time calculation of the treatment plan, with a lower risk of the so-called “geographical missing. [16–18]

This risk can be increased in the case of targets very close to healthy structures, such as bowel loops.

Thus, MR-Linac might have the possibility to account for intra-fraction anatomical variations during treatment delivery using Cine-MR sequences without adding ionizing radiations. The dosimetric advantages provided by MR-guided radiotherapy have also been reported by Dunlop et al. who underline the superior accuracy for image guidance. [19]

This advantage combined with the daily adaptive planning tool lies the foundations for a margin reduction policy that can be considered as another way to optimize PTV coverage without compromising OARs constraints. [20, 21]

Some experiences already described the use of reduced PTV margins of 1 or 2 mm on the CyberKnife system, but this would often require the use of implanted fiducial markers. [22, 23]

This invasive procedure may not be necessary for MR-linacs, since MR-guided online adaptive radiotherapy itself allows to correct for inter-fraction motion of the PTV without the need of implanted fiducial markers as a reference point.

Specifically in the context of SBRT lymph nodes oligometastases, Winkel et al. reported MR-guided SBRT as an attractive option due to the possibility to yield the most favorable dosimetric results by combining daily re-segmentation of the structures with the re-calculation of the plan. In fact, the authors in a comparison study of multiple adaptation methods, recorded superior outcomes in terms of target coverage and constraints violations when a full re-optimization of the plan was performed. [24]

In agreement, in our experience, all the treatment sessions were performed with the ATS workflow, since it represents the most reliable strategy to take into account both OARs and target daily variations.

Our dosimetric analysis reflects the favorable impact of the adoption of this workflow, as we have revealed a statistically significant advantage in terms of intestinal loop dose exposure in a dosimetric comparison between baseline treatment planning and daily-adapted recalculation. Interestingly, specifically in the case of single intestinal loop, a significant volume variation was recorded ($p = 0.026$), while for the other OARs, no relevant variations were observed, highlighting the larger magnitude of variations of this substructure. A significant variation in terms of Dmax was also detected for the bowel structure, in favor of daily-adaptive sessions, compared to baseline treatment planning.

We have also reported a favorable impact of daily-adapted strategy in terms of target coverage, with slightly improved data for PTV-V35Gy and PTV-Dmean, although not reaching a statistical significance (respectively $p = 0.11$ and $p = 0.18$).

These data reinforce the role of MR-guided daily adaptive radiotherapy in compensating the daily variations and motion of single targets and OARs. [25]

Nonetheless, as also stated by Winkel et al., uncertainties for lymph nodes MR-guided SBRT still remain, but since most of the treatments apply margins based on Cone-Beam CT-guided experiences, is reasonable to hypothesize that more mature data will provide further evidence in support of a tighter margins strategy or fewer fractions schedules. [26]

Compared to the previous mentioned study, in which a higher PTV-V35 Gy is reported, it is worthy to mention that our dosimetric analysis refers to a subgroup of target very close to critical structures in which the relatively lower value of PTV-V35 Gy may be influenced by the constraints of the healthy organs. Nevertheless, we have always guaranteed at least 95% of the PTV to receive at least 95% of the prescription dose.

The real challenge for MR-guided radiotherapy is represented by intra-fraction motion, given the need to take into account the longer delivery times compared to standard linacs.

In a previous study of our department, the favorable impact of this technology was favorably recorded in the context of prostate SBRT where the use of MR-linacs resulted in a minor rate of constraints violations compared to conventional linac treatments without fiducials. This suggests that MR-linac might achieve a level of accuracy comparable to linac-based SBRT with intraprostatic fiducials. [27]

To date, a tracking or gating system is not yet available for this technology. Future developments may include artificial intelligence and deep machine learning for automated detection and OARs and lesions contouring, intra-fraction plan adaptation and continuous re-optimization during beam-on-time aiming to shorten treatment session length. In our experience, MR-guided SBRT with daily planning adaptation for lymph nodal oligometastatic disease was delivered with excellent results in terms of dosimetric data, both for target coverage and OARs sparing. This is also confirmed by our previous studies that report

excellent results in terms of PROMs evaluation, regardless of the potential detrimental effect of longer treatment sessions on patient's compliance. [28–30]

The higher accuracy of this workflow certainly increases clinicians' confidence in proposing dose-escalated or single-session schedules. [31, 32]

Based on this background, we hypothesized to investigate a dose escalated SBRT schedule which is currently ongoing at our department, aiming also to reduce the sessions, in agreement with the growing literature in support of the single-fraction treatment of oligometastases. [33, 34]

Conclusions

To the best of our knowledge, this is one of the first studies exploring the dosimetric variability of target and OARs during daily-adaptive MR-guided SBRT for lymph-nodes oligometastases. Despite lacking of a comparison cohort, our study reports a substantial benefit from the adoption of this technique in order to gain a dosimetric advantage in terms of intestinal loops sparing. More mature data will clarify if the improved sparing of the OARs relates to a clinical benefit in terms of lowering toxicity incidence.

Declarations

Conflict of interest:

Filippo Alongi is a consultant and speaker honoraria for Elekta; Ruggero Ruggieri is a consultant and speaker honoraria for Elekta.

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Figures

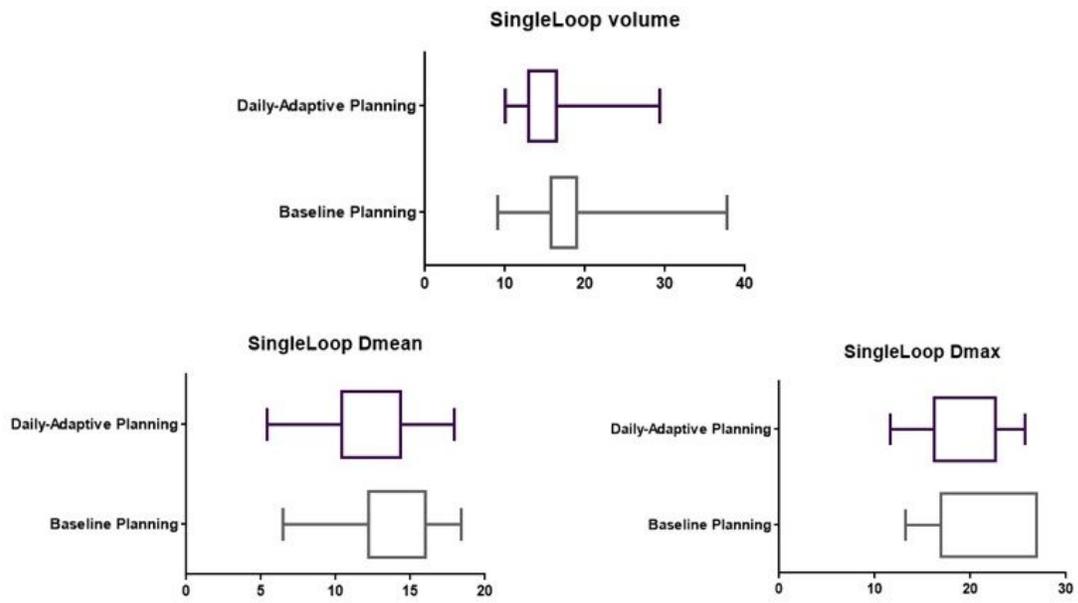


Figure 1

Single intestinal loop daily dosimetric variations

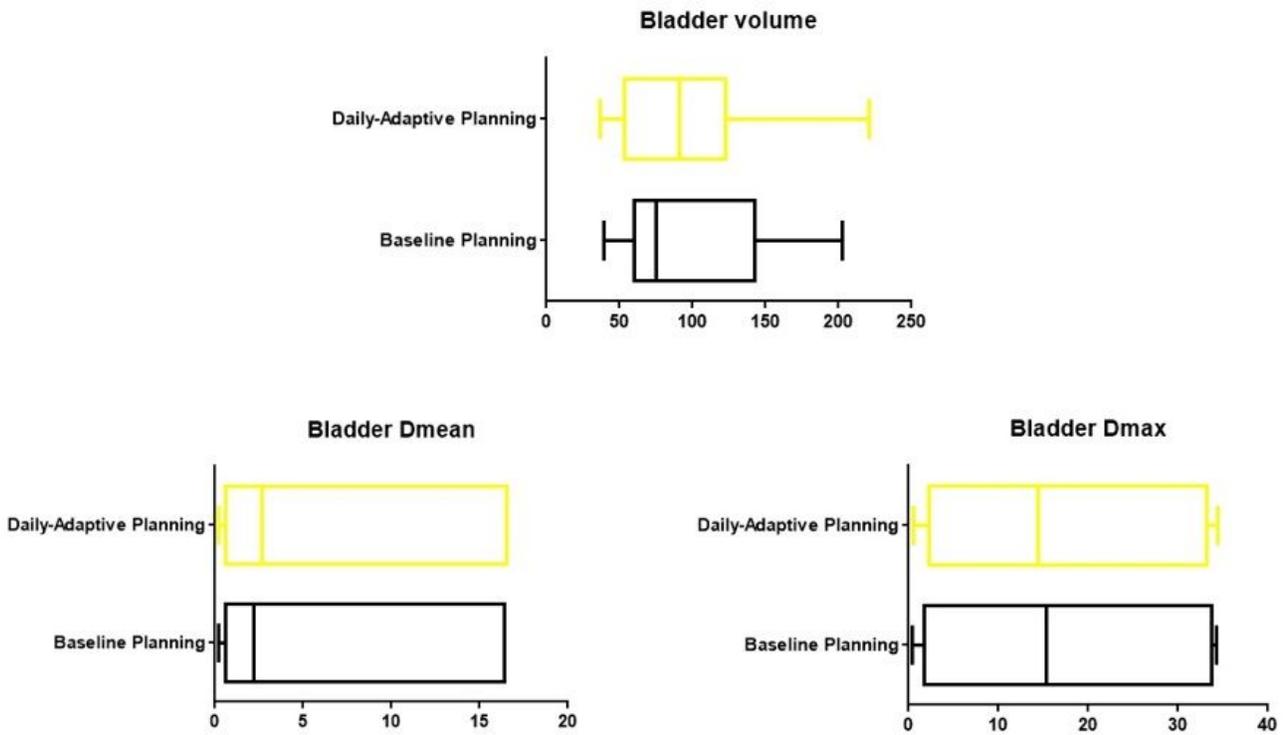


Figure 2

Bladder daily dosimetric variations

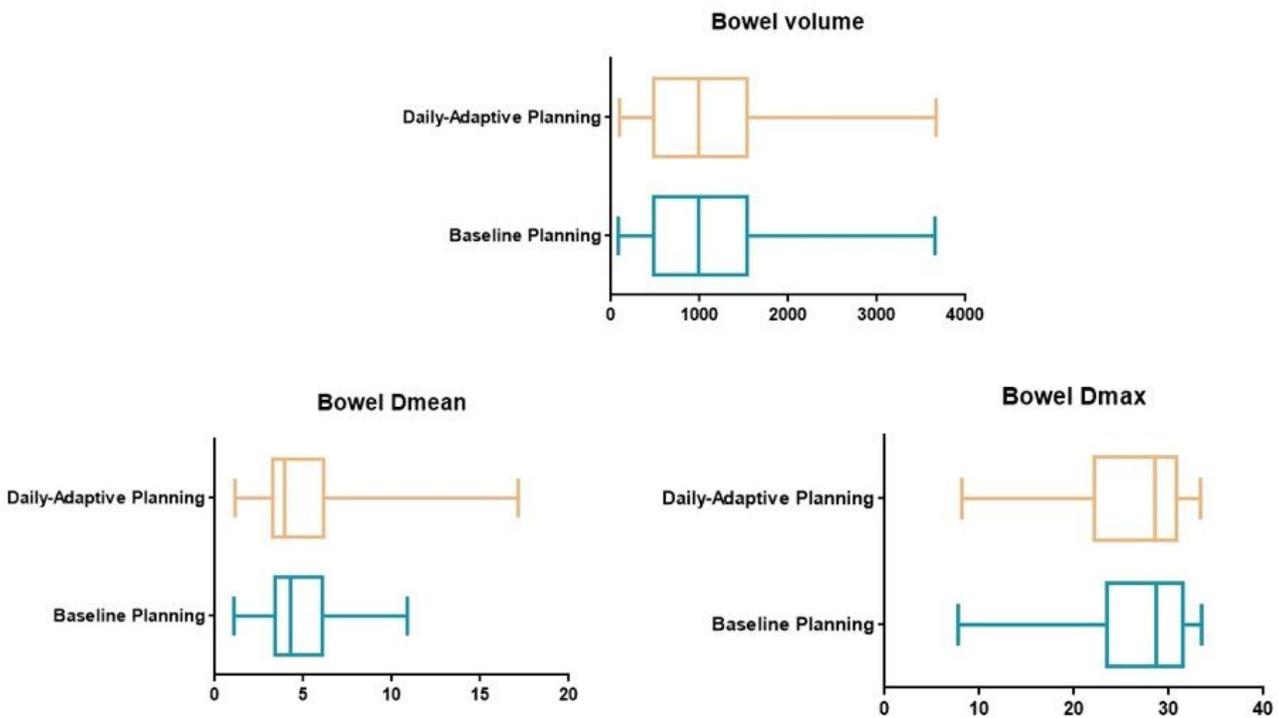


Figure 3

Bowel daily dosimetric variations

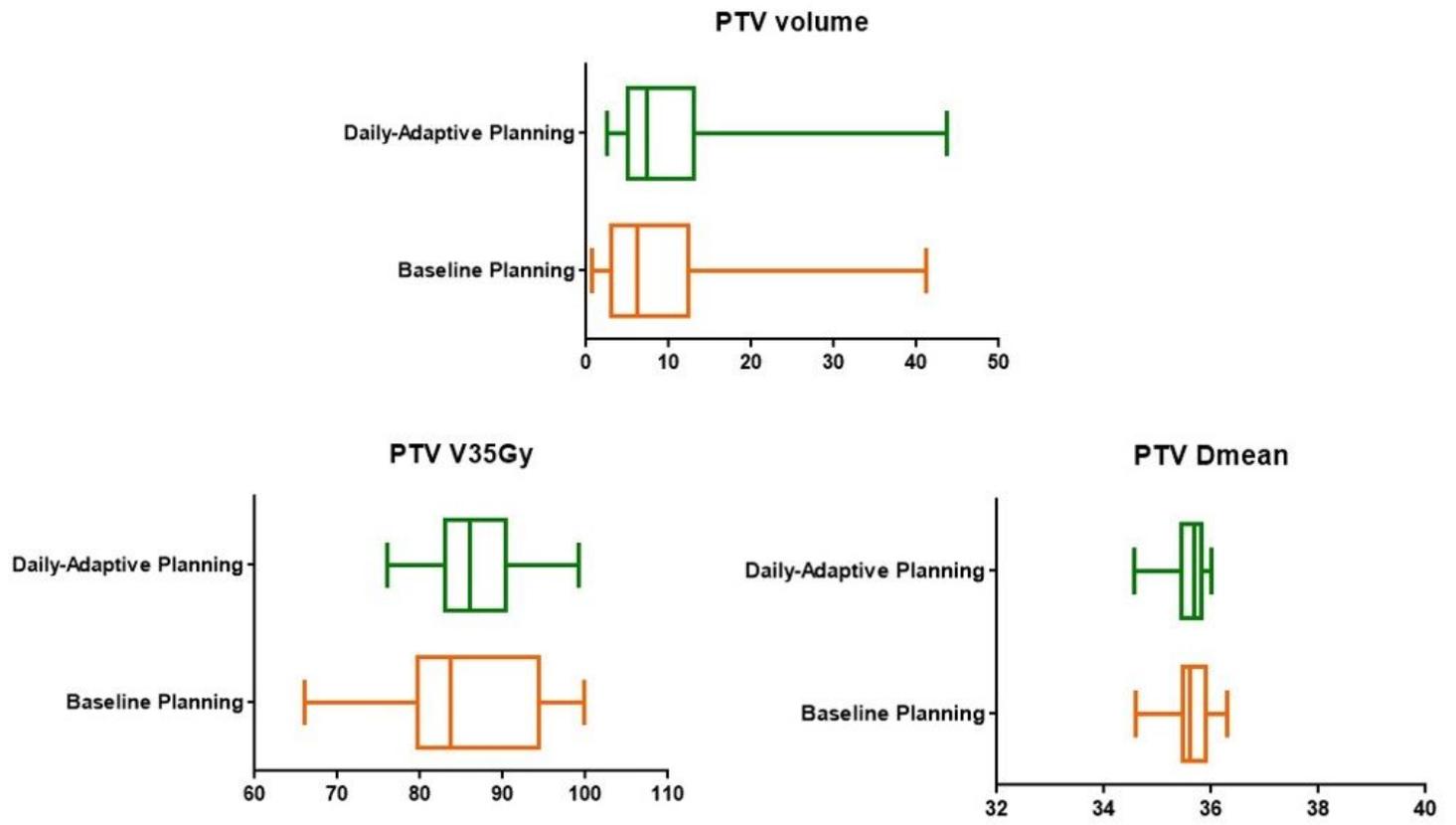


Figure 4

PTV daily dosimetric variations