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Original Article

Identification of patients with locally advanced pancreatic cancer benefitting from plan adaptation in MR-guided radiation therapy

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ABSTRACT

Background and purpose: MR-guided radiation therapy (MRgRT) with daily plan adaptation is a novel but time- and resource-intensive treatment for locally advanced pancreatic cancer (LAPC). We analyzed the benefit in target coverage and organ-at-risk (OAR) sparing of daily plan adaptation in 36 consecutive LAPC patients treated with MRgRT to 40 Gy in 5 fractions.

Materials and methods: Adaptive planning was assessed for 180 fractions by comparing non-adapted plans with re-optimized plans using (a) GTV coverage and OAR high-doses, and (b) compliance with institutional objectives for GTV coverage and high-dose OAR constraints. Using these criteria, plan adaptation for each fraction was characterized as "not needed", "beneficial", or "no benefit". Decision-tree analysis was performed to identify subgroups most likely or not to benefit from routine plan adaptation.

Results: The percentage of plans fulfilling institutional constraints increased from 43.9% (non-adapted plans) to 83.3% after online plan adaptation, with significant improvements in GTV coverage and lower V_{33Gy} OAR doses. Adaptive re-optimization was found to be "not needed" in 80 fractions (44.4%), "beneficial" in 95 fractions (52.8%) and of "no benefit" in 5 fractions (2.8%). Decision-tree analysis identified a grouping based on distance from tumor to OAR of $\leq$3 mm and GTV size, respectively, to be the major determinants for the benefit of daily plan adaptation.

Conclusion: MRgRT with daily plan adaptation for LAPC was of benefit in approximately half of fractions, improving target coverage and OAR sparing. Plan adaptation appeared to be relevant mainly in cases where the GTV to adjacent OAR distance was $\leq$3 mm.

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Despite the use of chemotherapy, either alone or combined with conventionally fractionated radiotherapy, patients with locally advanced pancreatic cancer (LAPC) have a poor prognosis. In the recently published randomized LAP07 study, chemoradiation (CRT) increased local control, but the addition of fractionated radiation therapy was not associated with a survival benefit [1]. In contrast, a systematic review including more than 8500 LAPC patients, reported that CRT was associated with a modest improved median survival (13.5 vs. 10.6 months) with multi-agent chemotherapy being an independent predictor of survival [2]. This relatively small survival benefit of CRT has to be weighed against the cost of the prolonged duration and toxicity associated with treatment. Although the use of intensity-modulated radiotherapy (IMRT) appears to have decreased both early and late toxicity [3], further advancements in precise radiation delivery, tumor motion management, and shortening overall treatment duration using e.g. stereotactic body radiation therapy (SBRT) remain warranted. The combination of SBRT with modern multi-agent chemotherapy such as FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) merits investigation. However, a key concern with SBRT applied for LAPC remains the risk for gastrointestinal toxicity [4].

MR-guided radiation therapy (MRgRT) allows for a combination of precise soft tissue setup, real-time planar imaging during treatment and gated delivery with only minimal GTV to PTV margins, and radiation plan adaptation for each fraction [5–8]. MRgRT with plan adaptation can improve target coverage and normal tissue sparing, which may result in improved local control and/or decreased toxicity [9]. However, MRgRT with daily plan adaptation is both cost- and resource intensive, among others because daily plan adaptation requires the presence of the physician and/or physicist at the treatment console for re-contouring, plan review and approval [10]. It is therefore essential to quantify not just average dosimetric benefits of daily plan adaptation, but also to identify LAPC patients who are likely to benefit or not from this approach. In order to achieve the latter, we used decision-tree

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analysis to explore predictive characteristics to identify subgroups of patients with LAPC who are likely to benefit or not from routine daily adaptive planning.

Materials and methods

Data from 36 consecutive patients (180 fractions) with LAPC or locally recurrent pancreatic cancer who underwent MRgRT on the MRIdian system (ViewRay, Cleveland, USA) between May 2016 and June 2018, were prospectively collected and analyzed after treatment. The study population included 18 females (50%) and 18 males (50%) with an age ranging from 36 to 88 years. Thirty-two patients had primary LAPC, four patients were treated for locally recurrent disease after surgery. The vast majority of patients had been treated with initial chemotherapy, usually FOLFIRINOX. The MRgRT prescription dose in all patients was 40 Gy in 5 fractions. The mean (range) value of the baseline gross tumor volume (GTV) was 30.4 cc (7.0–117.2 cc).

A simulation MR scan and CT scan were performed in supine position, with one or both arms up, during shallow inspiration breath-hold. The GTV was delineated on the simulation MR aided by diagnostic imaging, in collaboration with a gastro-intestinal intervention radiologist. The True Fast Imaging with Steady State Free Precession (True FISP) sequence is currently the only clinically available sequence on the MRIdian, on which the pancreatic tumor can usually be clearly identified as a hypodense lesion, albeit with the difficulty of evaluating the exact local extension as is the case with all diagnostic imaging for pancreatic cancer. During contouring, on an adjacent screen the diagnostic CT scan with intravenous contrast (both 40–50 s delayed (pancreas) and 60–70 s delayed CT scan (portal phase)) was displayed to assist in contouring. The planning target volume for daily re-optimization (PTV_{OPT}) was generated using an isotropic margin of 3 mm around the GTV, excluding any overlap with OARs. The latter was performed in order to avoid undue high doses to surrounding critical OARs. Baseline treatment plans ($PLAN_{BASELINE}$) were generated using IMRT step-and-shoot with 5–7 beam groups where each beam group had three equidistant beams corresponding with the three ^{60}Co sources on the gantry [5]. Dose calculation was performed with a Monte-Carlo algorithm (statistical uncertainty of 1% and a grid size of 0.3 cm × 0.3 cm × 0.3 cm) using the deformed electron density map from the simulation CT scan. Planning aimed for the maximum achievable coverage of the $PTV_{OPT,}$ with a priority assigned to adhering to the following high-dose OAR constraints: V_{33Gy} and V_{25Gy} equal or less than 1 cc and 20 cc, respectively, for duodenum, stomach and bowel loops. The objectives for target coverage were a $V_{95\%}$ of the GTV ≥90% and a $D_{1\%}$ up to 125% of the prescribed dose.

At our center, we have opted to perform daily plan re-optimization or adaptation for each fraction for each patient as a routine strategy. In order to allow for robust and fast online adaptation, we developed an in-house strategy which can be performed within several minutes and which requires checking (and where necessary) manually adjusting the GTV and relevant OAR contours within the first 3 cm of the PTV_{OPT} [5]. Briefly, our workflow for daily plan adaptation consists of the following steps: (1) A repeat MR scan in shallow breath-hold at each fraction, followed by 3D alignment of the baseline and repeat MR-scan based on the GTV; (2) Automatic deformation of OAR contours followed by manual adjustment within a distance of 3 cm from the PTV_{OPT}; (3) Recalculation of $PLAN_{BASELINE}$ on the current anatomy using the deformed simulation CT ($PLAN_{PREDICT}$); and (4) Routine adaptation of the $PLAN_{PREDICT}$ to derive a $PLAN_{REOPTIMIZED}$. This plan re-optimization uses the same beam numbers, beam directions and optimization objectives as $PLAN_{BASELINE}$. The variation in OAR structures within the first 3 cm of the PTV_{OPT} guides the daily plan re-optimization (5). Patient-specific QA is performed with an independent Monte-Carlo dose calculation algorithm and gamma analysis prior to each treatment delivery while the patient remains on the table in treatment position [11]. From the start of MRgRT with routine plan adaptation in our center, we have timed the different steps in our procedure. On average, the time needed for OAR re-contouring (within 3 cm from the PTV_{OPT}), plan re-optimization and patient-specific QA using our MRgRT workflow was 15 minutes per fraction. We have found that this average of 15 minutes is also valid for other indications for MRgRT with plan adaptation, such as adrenal metastases, renal cell cancer and prostate cancer. Real-time planar cine MR images (4 frames per second) during treatment allow for respiratory-gated MRgRT. The MRIdian system automatically shuts-off delivery when the target (GTV) is outside pre-specified safety margins (PTV_{OPT}). An in-house developed visual video feedback system uses real-time projection of the target volume and safety margins from the cine MR onto a monitor. Radiation was delivered in sequential breath-holds spells, while patients observed the monitor to determine the appropriate phase for breath-hold [12]. With treatment delivery time and patient comfort in mind, this treatment generally was delivered in shallow inspiration.

As a result of the described workflow, in addition to a $PLAN_{BASELINE}$, also a $PLAN_{PREDICT}$ and $PLAN_{REOPTIMIZED}$ were available for analysis from each fraction. The dosimetric benefit of plan adaptation was assessed offline, i.e. actual treatment had been delivered on the adapted plans. All 396 plans (36 $PLAN_{BASELINE}$, 180 $PLAN_{PREDICT}$ and 180 $PLAN_{REOPTIMIZED}$) were evaluated for adherence with institutional planning objectives and constraints; i.e. a $V_{95\%}$ of the GTV ≥90%, a V_{33Gy} ≤1 cc and a V_{25Gy} ≤20 cc, respectively for duodenum, stomach as well as bowel. Statistical analysis used for plan comparisons was performed using the Wilcoxon Signed-Rank test (IBM® SPSS Statistics v20, Armonk, NY, USA). A p-value <0.05 was considered to be statistically significant.

The benefit of online plan re-optimization was qualitatively analyzed for each fraction using the following definitions:

(1) "*not needed*" if the $PLAN_{PREDICT}$ already complied with all constraints.
(2) *"beneficial"* if the $PLAN_{PREDICT}$ violated institutional constraints, while the $PLAN_{REOPTIMIZED}$ corrected this completely ***or*** achieved a GTV $V_{95\%}$ improvement of at least 10% and/or an OAR $V_{33\ Gy}$ dose reduction in at least 0.5 cc.
(3) *"no benefit"* in case of a $PLAN_{REOPTIMIZED}$, which failed to achieve the earlier mentioned dosimetric benefit for GTV coverage and/or OARs' high-doses.

A decision tree analysis (Exhaustive CHAID, IBM® SPSS® Modeler 18) was used to explore predictive characteristics, in order to identify patients where routine daily adaptive planning may or may not be beneficial [13]. A database was assembled from baseline patient-specific characteristics, geometric-, volumetric- and dosimetric information extracted from the $PLAN_{PREDICT}$ and $PLAN_{REOPTMIZED}$ (Table 1). The qualitative adaptive benefit variable ("*not needed*", *"beneficial"*, "*no benefit*") was selected as the target variable for decision tree analysis, all other variables mentioned in Table 1 were selected as input variables. The significance level for node splitting was set at $p < 0.05$. Stopping parameters to prevent overfitting were applied by setting the minimum number of records in a leaf to be at least 10% of the full training data set.

Finally, this decision tree was evaluated in five patients with LAPC (25 fractions) treated more recently (Supplementary Table 1). Based on patient-specific baseline characteristics, the decision tree predicts if a patient (and thus for all 5 fractions) would benefit

Table 1
Overview and description of predictive "input" variables used in decision tree analysis.

Predictive variables	Description	mean	(range)
BMI	Patients Body Mass Index	22.1	(17.9–29.9)
GTV (cc)	Volume of GTV	30.4	(7.0–117.2)
PTV_{OPT} (cc)	Volume of (PTV minus overlap with OAR)	48.2	(14.1–152.8)
		(49.44–53.16)	(46.69–53.58)
		49.95	49.90
		(48.61–51.26)	(45.96–53.38)
GTV to OAR (cm)	Shortest distance between GTV and OAR	0.1	(0.0–0.6)
Duodenum (cc)	Volume duodenum within 3 cm of PTV_{OPT}	43.7	(3.5–93.2)
		1.17	1.17
		(0.91–1.32)	(0.75–1.40)
Stomach (cc)	Volume stomach within 3 cm of PTV_{OPT}	54.2	(1.9–452.1)
		(7.85–11.28)	(7.11–12.9)
		9.2	8.89
		(8.48–10.50)	(7.07–11.08)
Bowel loops (cc)	Volume bowel within 3 cm of PTV_{OPT}	32.1	(0–75.6)
		(36.00–79.00)	(33.0–76.00)
		50	45.36
		(31.00–80)	(30.00–73.00)
Volume OARs (cc)	Volume all OARs within 3 cm of PTV_{OPT}	91.8	(12.42–218.4)
Beam depth (cm)	Mean beam depth (skin to isocenter)	13.9	(11.6–16.7)

from plan adaptation. Several performance metrics (Table 3) were calculated to assess the accuracy of the configured decision tree.

Results

The baseline plan quality for all 36 patients, represented by the $V_{95\%}$ of the GTV (vertical axis) and the V_{33Gy} of the duodenum and stomach (horizontal axes) is shown in the left panel of Fig. 1. The high-dose OAR constraints were met for all patients in the baseline plan, which was the primary objective of planning, although in 8 patients this necessitated a suboptimal GTV coverage of less than 90% (GTV $V_{95\%}$ range 71.9–88.4%). Fig. 1b shows the same plan parameters for the (non-adapted) $PLAN_{PREDICT}$ in 180 fractions; i.e. the baseline plan recalculated on the anatomy of the day. The $PLAN_{PREDICT}$ complied with institutional constraints in only 79 fractions (43.9%). Constraints were violated for GTV coverage ($V_{95\%}$ <90%) in 57 fractions (31.7%), for duodenum doses ($V_{33Gy} \leq 1$ cc; $V_{25Gy} \leq 20$ cc) in 53 fractions (29.4%) and 7 fractions (3.9%), respectively. Violations in the V_{33Gy} constraints for the stomach and bowel were observed in 24 fractions (13.3%) and 3 fractions (1.7%) of the $PLAN_{PREDICT}$, respectively, whereas the V_{25Gy} was not exceeded for the latter OARs.

Daily re-optimization resulted in significant gains, particularly for the GTV- and PTV_{OPT} $V_{95\%}$ coverage and the duodenal V_{33Gy} parameters (Table 2). Plan adaptation increased the percentage of plans that complied with institutional high-dose constraints from 43.9% to 83.3% (150 plans) (Fig. 1c). Suboptimal re-optimized plans were due to modest exceeding of duodenal V_{33Gy} in two fractions (1.1 and 1.5 cc), and insufficient GTV coverage in 28 fractions (GTV $V_{95\%}$ 77.5–88.5%). Both patients with excessive duodenal V_{33Gy} also had insufficient GTV coverage. Based on the criteria defined in the Materials and Methods, adaptive re-optimization was found to be *"not needed"* in 80 fractions (44.4%), of *"benefit"* in 95 fractions (52.8%) and *"no benefit"* in 5 fractions (2.8%), respectively (Fig. 2).

The CHAID decision tree analysis resulted in the generation of three terminal nodes, representing subgroups with respect to benefit of adaptive re-planning (Fig. 3, left panel). The distance between the GTV and (any) OAR was the most significant predictor variable ($p < 0.001$). If the shortest distance between the GTV and the OAR was more than 3 mm, plan adaptation was hardly ever needed (5%; terminal node 1). In patients in which the shortest distance between the GTV and the OAR was <3 mm, a second split occurred on the basis of GTV size at the level of 41 cc ($p = 0.018$). Plan adaptation with such distance of <3 mm was beneficial in more than half of patients with smaller GTV's (terminal node 3), however, adaptation was of benefit in 97% of patients with larger GTV's (terminal node 4). A graphical illustration of the branches of the decision tree is shown in the right panel of Fig. 3.

The correct classification rate of the decision tree in the training set was 82.2% with a sensitivity of 98.2% and specificity of 55.9%, respectively (Table 3). In the smaller evaluation set, the corresponding rates were 92.0%, 100% and 83.3% for the correct classification rate, sensitivity and specificity, respectively.

In this patient cohort, only acute and subacute toxicity data are available. Grade 3 or worse gastrointestinal toxicity within three months was only observed in a single patient (2.8%) in the form of hemorrhage at three weeks following treatment. It is uncertain whether this was due to local tumor progression or radiation induced toxicity.

Discussion

The superior soft tissue imaging capabilities of MRgRT allow for daily plan adaptation in order to optimize treatment plans in response to interfractional changes in both target volumes and adjacent OARs. Due to the short overall treatment time with the five fraction MRgRT scheme used, changes in the GTV were only minimal (median variation in GTV's 0.0 cc ± 1.6 cc), however, interfractional changes relative to the simulation scan can be substantial for OARs, underscoring the importance of daily imaging and plan re-optimization. At our center, a dedicated radiation oncologist (ABR) has contoured the simulation MR-scans generated on the MRIdian of all LAPC and recurrent pancreatic cancer patients in close co-operation with a dedicated gastro-intestinal radiologist (MME). Prior to each fraction, a repeated breath-hold high-resolution MR scan was generated using the same acquisition protocol as the simulation MR, and deformable OAR contours are available for adjustment. The majority of all treatment fractions (>90%) have been either performed or supervised by the aforementioned radiation oncologist, thereby minimizing contouring errors.

The specific goal of our routine plan adaptation with MRgRT was to avoid exceeding OARs' high dose constraints, even when this would result in less optimal target coverage. The dose–toxicity relationship is clear from earlier reports, and this approach with the aim to restrict severe treatment-related gastro-intestinal toxi-

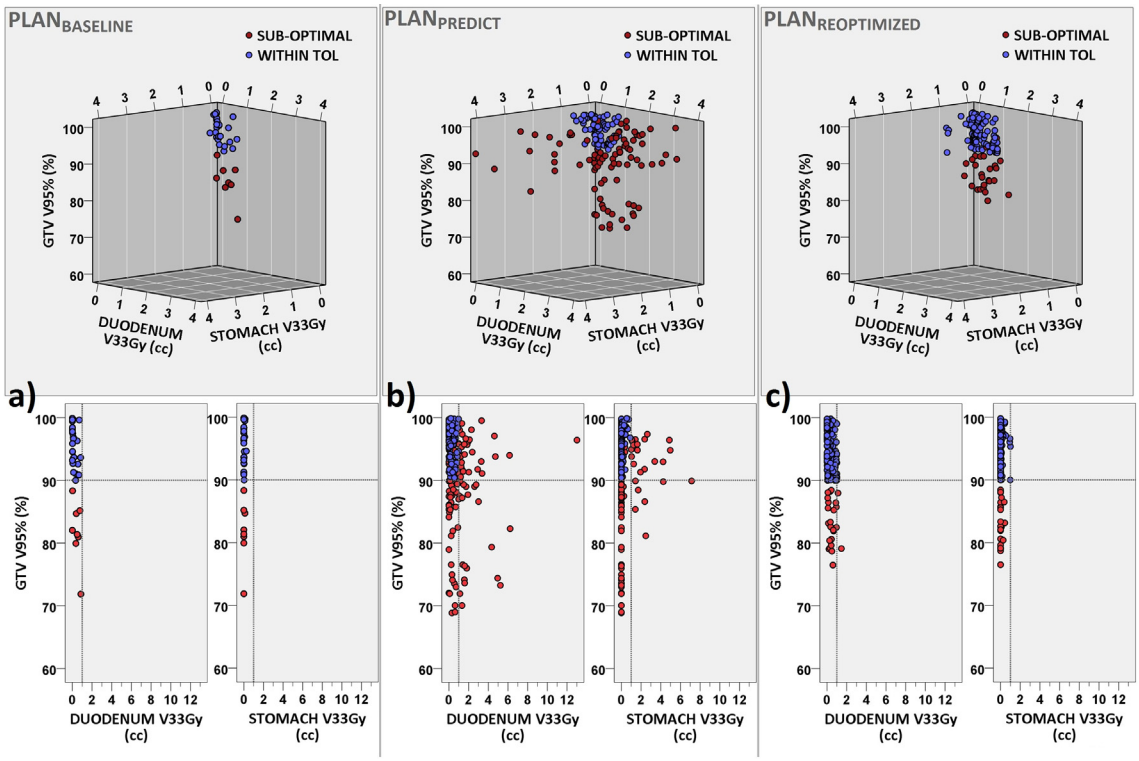

Fig. 1. 3D graph illustrating (a; left panel) the baseline GTV $V_{95\%}$ and the V_{33Gy} of the stomach and duodenum in 36 patients; (b; middle panel) the same parameters for the 180 (non-adapted) $PLAN_{PREDICT;}$ and (c; right panel) for the 180 $PLAN_{REOPTIMIZED}$. Lower panels showing 2D graph projections from the upper 3D graph. Blue and red dots represent fractions fulfilling and not fulfilling institutional constraints, respectively. Note: red dots projected into the box did not fulfill OAR constraints. Dashed gray lines illustrate the institutional constraints. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Comparison of the median and interquartile range (IQR) for the GTV $V_{95\%}$ and PTV_{OPT} $V_{95\%,}$ as well as OARs' high-dose constraints in $PLAN_{BASELINE}$ (N = 36), $PLAN_{PREDICT}$ (N = 180) and $PLAN_{REOPTIMIZED}$ (N = 180); p-values for comparison of the predicted and adapted plans.

	$PLAN_{BASELINE}$ median (IQR)	$PLAN_{PREDICT}$ median (IQR)	$PLAN_{REOPTIMIZED}$ median (IQR)	p-Value
GTV $V_{95\%\ (\%)}$	94.1 (90.1–98.1)	93.8 (88.3–96.8)	94.9 (90.7–98.1)	<0.001
PTV_{OPT} $V_{95\%\ (\%)}$	91.3 (83.0–95.9)	84.3 (78.4–89.6)	88.4 (83.4–92.8)	<0.001
Duodenum $V_{33Gy\ (cc)}$	0.1 (0.0–0.5)	0.4 (0.0–1.2)	0.1 (0.0–0.5)	<0.001
Duodenum $V_{25Gy\ (cc)}$	4.7 (2.6–8.4)	6.1 (3.3–9.5)	5.8 (3.2–9.4)	0.003
Stomach $V_{33Gy\ (cc)}$	0.0 (0.0–0.1)	0.0 (0–0.2)	0.0 (0.0–0.0)	n.p*
Stomach $V_{25Gy\ (cc)}$	0.6 (0.1–3.4)	1.8 (0.1–5.2)	2.3 (0.4–4.5)	0.496
Bowel $V_{33Gy\ (cc)}$	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	n.p*
Bowel $V_{25Gy\ (cc)}$	0.1 (0.0–0.6)	0.2 (0.0–1.5)	0.2 (0.0–1.3)	0.007

* n.p: not performed.

city, which is correlated to high OAR doses, has also been used by other authors [9,14–16]. The used high-dose institutional OAR constraints in this study, i.e. a $V_{33\ Gy}$ of $\leq$1 cc for the duodenum, stomach and bowel in five fractions, are commonly used in the recent literature addressing SBRT for LAPC [14,15,17]. There is less consensus in the literature for the intermediate dose constraints (e.g. $V_{25\ Gy}$). Although late toxicity results remain to be awaited in our patient group with LAPC, we have observed only a single case of grade 3 or worse gastrointestinal toxicity within three months. Whether our adaptive MRgRT approach contributes to this relatively low complication rate remains to be confirmed with longer follow-up and in a larger group of patients.

Using the above approach, our study confirms the dosimetric benefit of daily plan adaptation for LAPC, as has recently been reported for other abdominal targets [9]. Although the median benefit in target coverage and OAR sparing proved to be relatively limited over the total population, the main achievement of daily plan adaptation was prevention of undue high fraction doses to OAR. This was clearly visualized in the $PLAN_{PREDICT}$ in Fig. 1, where e.g. duodenum and stomach V_{33Gy} constraints exceeded in 29.4% and 13.3%, respectively, and were corrected after plan adaptation.

Because plan adaptation constitutes a trade-off between target coverage and OAR sparing, we chose plan compliance to institutional constraints and objectives as the endpoint for the evaluation of the benefit of daily adaptation. We have found that plan adaptation increased the percentage of plans complying with these high-dose OARs' constraints and GTV coverage from 43.9% to 83.3%, which may be of clinical relevance. We have characterized a "benefit" of plan adaptation as follows: fractions in which the institutional constraints were violated in the $PLAN_{PREDICT}$ and corrected after plan adaptation and also fractions in which a GTV $V_{95\%}$ improvement of at least 10% and/or an OAR $V_{33\ Gy}$ dose reduction of at least 0.5 cc was achieved. We have additionally looked at stricter cut-off values for OAR dose sparing benefit, such as a reduction in V_{33Gy} ranging from 0.75 to 2 cc. The percentage of patients defined as having "benefit" of plan adaptation decreased

Table 3
Decision tree performance measures calculated from the number of True Positives *(TP)*, True Negatives *(TN)*, False Positives *(FP)* and False Negatives *(FN)* observations in relation to the total number *(n)* of observations. Performance measures were calculated for both the training (36 patients) and evaluation (5 patients) data set.

Performance measures	Description	Training (n = 180)	Evaluation (n = 25)
Correct classification rate, *C (%)*	*C = (TP + TN)/n*	82.2	92.0
Sensitivity, *Sn (%)*	*Sn = TP/(TP + FN)*	98.2	100
Specificity, *Sp (%)*	*Sp = TN/(TN + FP)*	55.9	83.3
		(49.44–53.16)	(46.69–53.58)
		49.95	49.90
		(48.61–51.26)	(45.96–53.38)
Positive Predictive Value, *PPV (%)*	*PPV = TP/(TP + FP)*	78.6	86.7
Negative Predictive Value, *NPV (%)*	*NPV = TN/(TN + FN)*	95.0	100
		1.17	1.17
		(0.91–1.32)	(0.75–1.40)
Area under the ROC curve, *AUC*	ROC curve depicts *TP* rate versus *FP* rate at various discrimination thresholds	0.81	0.91
		(36.00–79.00)	(33.0–76.00)
		50	45.36
		(31.00–80)	(30.00–73.00)

marginally from 52.8% (0.5 cc) to 46.7% (2 cc). The decision trees of stricter criteria for OAR are shown in Supplementary Fig. 1.

We have used decision tree analysis of pretreatment characteristics in order to determine for which patients online plan adaptation would not have been necessary. A recent paper by Tyran et al. [18] describes a different clinical workflow for plan adaptation in 7 patients (35 fractions) with pancreatic cancer. Initially a daily-image visual review of superimposed original OAR contours on the MRI of the day was used to determine whether a predicted plan (re-contouring of OARs and recalculation) should be generated, after which the results of this predicted plan are used to determine the necessity of plan adaptation. The authors conclude that generation of a predicted plan, and thus including re-contouring of OAR, is mandatory for this indication in order to decide the need for plan adaptation. Our paper goes a step beyond this conclusion and proposes a model to predict upfront which patients "benefit" from online plan adaptation in a larger cohort of patients/fractions. At our center, a predicted plan is always generated, followed by routine plan adaptation. Because the re-contouring is the most time consuming step, this final plan adaptation costs only a few minutes of extra time. Our specific aim was to identify patients in whom plan adaptation was deemed to be beneficial (or alternatively not necessary) based on derived predicted and adapted plans. From this analysis, it appeared that the distance between the GTV and adjacent OARs and to a lesser extent the size of the GTV were the most relevant factors. Our specific results for distance and GTV size, however, are directly related to our adaptive planning approach and IMRT delivery with a tri-cobalt machine, and may be slightly different for sharper beam penumbra such as with MR-linacs.

Prior to this study, our hypothesis was that online plan adaptation for each fraction in LAPC would be beneficial for the majority of the patients. Given our criteria for "benefit" of plan adaptation, we found that slightly less than half of patients would not have required daily plan adaptation, particularly those with a distance from tumor to relevant OAR of >3 mm. In addition to the described decision tree evaluation, we are currently validating these results prospectively, and until then our workflow still includes routine plan adaptation for each fraction in LAPC.

Some limitations of our study have to be acknowledged. Our analysis was performed in 180 fractions, however it was restricted to patients with LAPC including two patients with recurrent disease following surgery. The accuracy of the CHAID decision-tree analysis with this number of fractions was 82%. It is our intention to repeat the analysis at the time a larger number of patients treated will be available for analysis. Our plan adaptation focuses on restricting the dose to OAR in the 25–33 Gy, which is considered to be most relevant for clinical toxicity, however the results may be slightly different when also lower doses are taken into account. Finally, other methods of plan adaptation are possible, such as manual re-normalization in order to further increase target coverage until one of the high-dose OAR constraints is reached. This

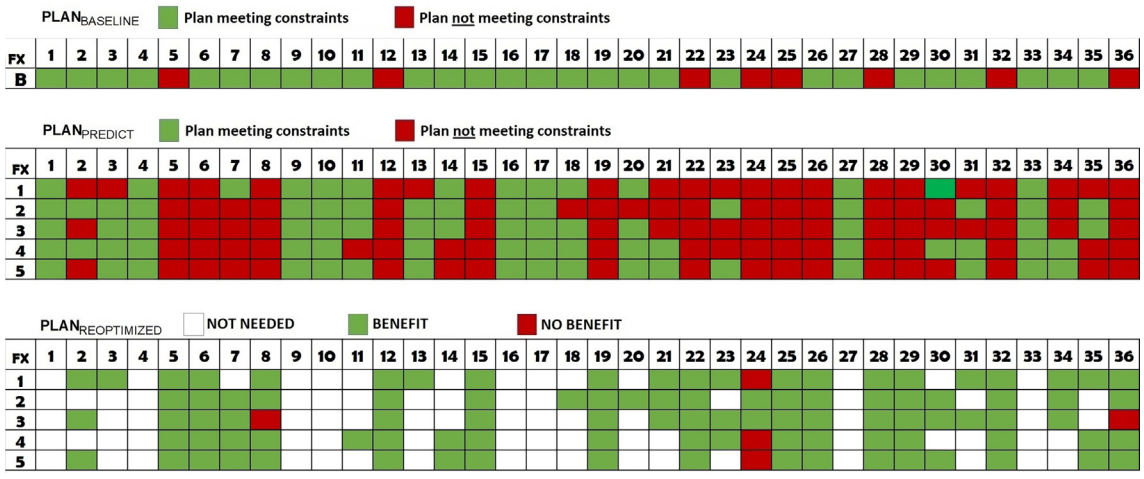

Fig. 2. Overview of qualitative analysis showing the impact of the interfractional anatomical variations and the benefit online re-optimization of the baseline plan in all fractions per patient.

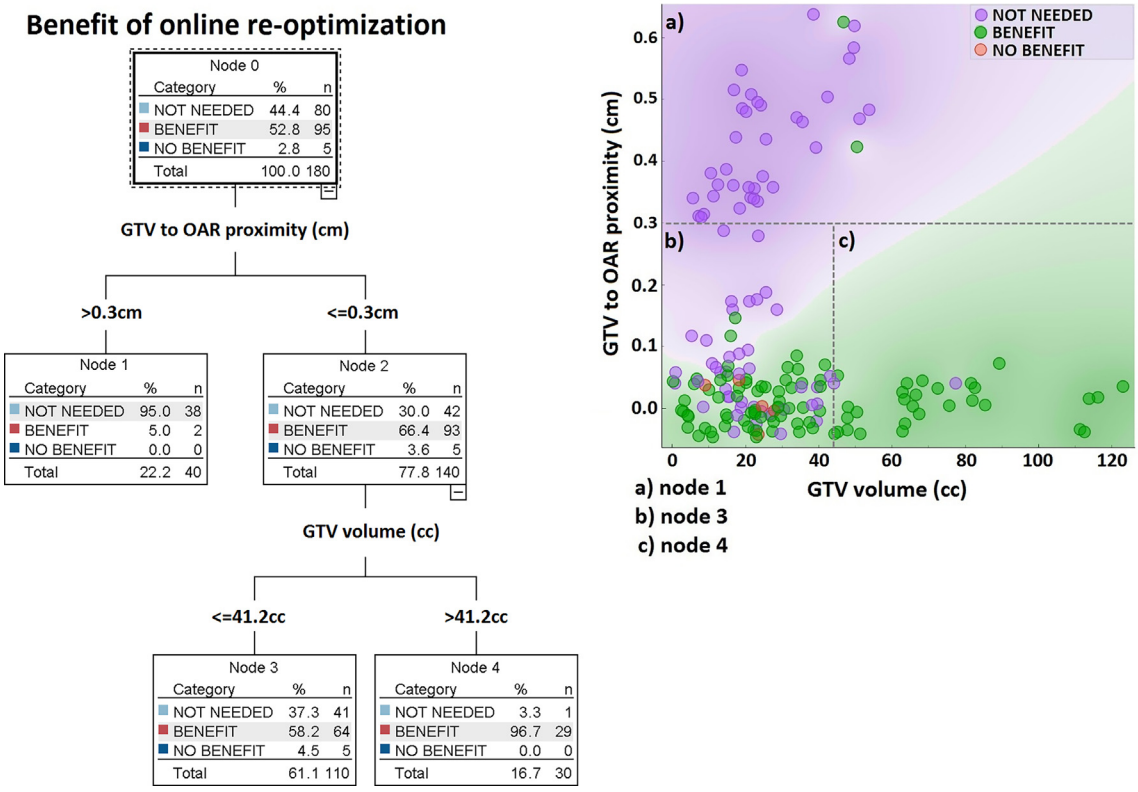

Fig. 3. CHAID decision tree analysis with a total of 4 nodes, including 3 terminal nodes which represent a class with respect to benefit of adaptive re-planning. In addition to the actual tree in the left panel, the distribution of all fractions as a function of GTV size and distance between tumor and (any) OAR is shown in the right panel (jittering is used to prevents dots overlapping and class density is used to color the graph background by class).

approach is not performed in clinical practice with MRgRT at our center, mainly because of uncertainty of intrafractional changes in OARs, in combination with the steep dose gradients obtained in SBRT.

In conclusion, daily plan adaptation was overall beneficial in approximately half of patients with LAPC, and appeared less important in cases where there was $\geq$3 mm distance between the tumor and relevant OARs. This finding allows for pre-treatment selection of LAPC patients for adaptive treatment, and this information can be used in the logistical challenges associated with MRgRT, including daily re-contouring, plan review and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.019.

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