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A need for automation

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Original Article

Dosimetric advantages of adaptive IMPT vs. Enhanced workload and treatment time – A need for automation

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ABSTRACT

Introduction: In head-and-neck IMPT, trigger-based offline plan adaptation ($Offline_{trigger\text{-}based}$) is often used. Our goal was to compare this to four alternative adaptive strategies for dosimetry, workload and treatment time, considering also foreseen further technological advancements, including anticipated automation.

Materials and methods: Alternative strategies included weekly offline re-planning ($Offline_{weekly}$), daily plan selection from a library ($Library_{static}$ and $Library_{progsressive}$) and a fast, approximate daily online re-optimization approach ($Online_{re\text{-}opt}$). Impact on CTV coverage and NTCPs was assessed by simulations based on repeat-CTs from 15 patients. Full daily re-planning was used as dosimetric benchmark. Increases in workload and treatment time were estimated.

Results: Both for coverage and NTCPs, fast $Online_{re\text{-}opt}$ performed as well as full re-planning. Compared to current practice, $Online_{\mathbf{re}\text{-}opt}$ showed enhanced probabilities for high coverage, and resulted in reductions in grade $\geq$ II NTCPs of 4.6 $\pm$ 1.7 %-point for xerostomia and 4.2 $\pm$ 2.3 %-point for dysphagia. $Offline_{weekly}$ and library strategies did not show coverage enhancements and resulted in smaller NTCP improvements. Further automation can largely limit workload and treatment time increases. With anticipated further automation, adaptation-related workload of $Offline_{weekly}$, $Library_{static}$, $Library_{progressive}$, and $Online_{re\text{-}opt}$ was expected to increase by 3, 8, 21, and 66 h for 35 fraction treatment courses compared to $Offline_{trigger\text{-}based}$. The corresponding adaptation-related prolonged treatment times were estimated to be 0, 4, 6, and 29 min/fraction.

Conclusion: Online adaptive strategies could approach dosimetric quality of full re-planning at the cost of additional workload and prolonged treatment time compared to the current offline adaptive strategy. Automation needs to play a key role in making more complex adaptive approaches feasible.

Introduction

To improve daily IMPT dose delivery, various offline and online plan adaptive strategies have been explored [1–10]. Although dosimetrically attractive, such strategies can become time- and workload intensive in offline preparations. Moreover, online adaptive approaches can result in daily treatment time prolongations. The relative dosimetric advantages of different adaptive strategies in the context of workload and treatment time increases, have not yet been studied.

In current clinical practices, pragmatic approaches that use ad-hoc or trigger-based ('per protocol') offline re-planning are most prevalent [11]. Suggested alternative adaptive strategies encompass weekly adaptation [12], plan library approaches where upfront a range of plans is generated for different anatomical situations with daily selection of the plan that best fits with the daily anatomy [9,11,13], and strategies that daily re-optimize treatment plans online [3,4,8,14,15].

To select the most appropriate adaptive strategy, relative dosimetric comparisons are required. In literature, developed approaches have only been separately compared to non-adaptive radiotherapy [3,4,16] or the institutional standard clinical offline adaptive strategy [13,15,17].

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Bobić *et al.* (2021) [12] compared weekly online plan adaptation to daily online plan adaptation.

Furthermore, the dosimetric potential of online adaptive strategies is still not fully known for H&N IMPT. Borderías-Villaroel *et al.* (2022) [14] and Miyazaki *et al.* (2022) [6] compared their strategies to full re-planning but they did not use smaller PTV margins or setup robustness settings, while each strategy may need its own robustness settings for optimal performance. Understanding the quality of these adaptive strategies in relation to full re-planning is essential for identifying opportunities for further dosimetric enhancements of adaptive strategies.

Apart from dosimetry, it is also essential that associated workload- and daily treatment time increases are considered in selection of a strategy to be applied in clinical practice. This is especially important considering the limited proton therapy capacity, the increasing number of patients that need radiotherapy [18], and the shortage of staff [19,20]. Most published time analyses for adaptive approaches are limited to reporting dose computation and re-optimization times. Therefore, the expected additional workload and prolonged treatment times of the full adaptation are yet unknown.

The objective of this study was to compare different adaptive strategies in terms of the trade-off between dosimetric impact, and increased workload and prolonged daily treatment time. In addition to our current trigger-based offline adaptive approach, we investigated four alternative online and offline adaptive strategies. First, we used treatment simulations based on advanced and consistent automated treatment planning to compare the current and alternative strategies in terms of dosimetry. Furthermore, we benchmarked these strategies against full daily re-planning, the latter providing an upper limit for achievable dosimetric quality. Secondly, we estimated for the four alternative adaptive approaches, the increment in workload and treatment time as a result of the adaptation activities, compared to the current clinical practice. We also included a scenario analysis exploring the impact of expected advancements in technologies, including anticipated automation, that will speed up the adaptive approaches.

Methods and Materials

Patient data.

Image data from 15 primary H&N cancer patients treated with IMPT at the Holland Proton Therapy Center (HollandPTC) (2019–2020) with 3–6 repeat-CTs was included. The data used in this study originates from the research database of Holland Proton Therapy Center. This database consists of data from all consenting patients treated at HollandPTC. The local Institutional Review Board of Leiden University Medical Center waived the need to assess the protocol of the research database. An offline trigger-based adaptive protocol was in place that could result in plan adaptions based on the repeat-CTs (see next section for details). Assuming a constant Relative Biological Effectiveness (RBE) of 1.1, patients were treated with 70 GyRBE to the gross disease sites (Clinical Target Volume 7000, CTV_{7000}) and 54.25 GyRBE to the elective areas (CTV_{5425}, with the CTV_{7000} as part of the CTV_{5425}), in 35 fractions. More detailed information on the patient data, including details on inclusion criteria, patient characteristics, CT acquisition, patient positioning and immobilization, contours on repeat-CTs, and the employed treatment machine can be found in Supplementary Data A.

Treatment planning and computer simulation of adaptive strategies.

For all investigated adaptive approaches, including resimulation of our clinical trigger-based offline re-planning strategy, treatment planning was performed with wish-list driven fully-automated multi-objective robust optimization as implemented in Erasmus-iCycle [21–23]. Robustness was ensured by mini-max scenario-based optimization [24,25]. Apart from differences between the adaptive approaches in applied robustness settings, the applied wish-list was the same for all approaches. Target coverage constraints were $V_{95\%} \geq 98$ % of the prescribed dose in the voxelwise-minimum dose distribution, for both CTVs. All generated treatment plans were ensured to comply with CTV and organ-at-risk (OAR) constraints. More details on treatment planning can be found in Supplementary Data A.

This study investigated the following six adaptive strategies, with employed robustness settings in Table 1:

1. A resimulation of our clinical trigger-based offline re-planning strategy ($Offline_{trigger\text{-}based}$), in which decisions to generate a new plan are guided by anatomical evaluation of sequential daily CBCTs and dose evaluation on repeat-CTs.
2. A weekly offline re-planning strategy based on repeat-CTs ($Offline_{weekly}$).
3. A static plan library approach ($Library_{static}$), as described in [13], where prior to the start of the fractionated treatment five treatment plans with different setup robustness are generated. Every fraction, the plan with the smallest robustness settings that meets target constraints on the daily in-room CT is selected for treatment.
4. A novel progressive plan library strategy ($Library_{progressive}$), which follows the $Library_{static}$ approach, except that at the end of each week, 5 new treatment plans with different setup robustness settings are generated offline to extend the library, based on the last in-room CT of the week.
5. A fast daily online re-optimization strategy ($Online_{re\text{-}opt}$), as proposed in [15].
6. Daily full re-planning: for every fraction full re-planning is performed.

Detailed descriptions of the strategies, including employed robustness settings, can be found in Supplementary Data B1. $Offline_{weekly}$, $Library_{static}$, $Library_{progressive}$, and $Online_{re\text{-}opt}$ (strategies 2–5) were investigated as possible (future) alternatives to the current $Offline_{trigger\text{-}based}$ (strategy 1), meaning that both dosimetric- and workload/treatment time comparisons were performed. As full re-planning (strategy 6) was only used for dosimetric benchmarking of strategies 1–5, no workload/treatment times were estimated. Note that the proposed adaptive workflows for strategies 3–6 are based on in-room-CTs, while for this study only out-of-room repeat-CTs were available. For the purpose of this study, we assumed that these repeat-CTs were acquired with the in-room CT on rails system.

Dosimetric comparisons of adaptive strategies with treatment simulations.

For dosimetric comparison, we performed treatment simulations using the same approach as Oud *et al.* (2022) [13]. A graphical representation of the approach for treatment simulations is provided in Fig. 1. For all strategies 1–6 above, for each patient, 25 treatment courses of 35 fractions were simulated in order to also take into account residual setup (e.g., intra-fraction motion) and range errors in the treatment simulations. As 3–6 repeat-CTs per patient were available, the CTs were re-used 6–10 times (equally distributed) as substitute for daily images (for more information: Supplementary Data B2). For each simulated treatment course, one systematic range error, one systematic setup error, and 35 random setup errors were randomly generated from Gaussian distributions and applied to the repeat-CTs by scaling the stopping power and shifting the isocenter, after first performing a rigid 6-D match between the repeat-CT and planning-CT. The applied range and setup errors in

Table 1
Investigated adaptive strategies with their abbreviations and employed robustness settings.

	Adaptive strategy	Abbreviation	Robustness settings (setup/range)
1	Clinical trigger-based offline re-planning strategy	$Offine_{trigger\text{-}based}$	3 mm/3%
2	Weekly offline re-planning	$Offline_{weekly}$	2 mm/3%
3	Plan library static	PL_{static}	[0,1,2,3,5] mm/3%
4	Plan library progressive	$PL_{progressive}$	[0,1,2,3,5] mm/3%
5	Online re-optimization	$Online_{re\text{-}opt}$	1 mm/3%
6	Full re-planning	–	1 mm/3%

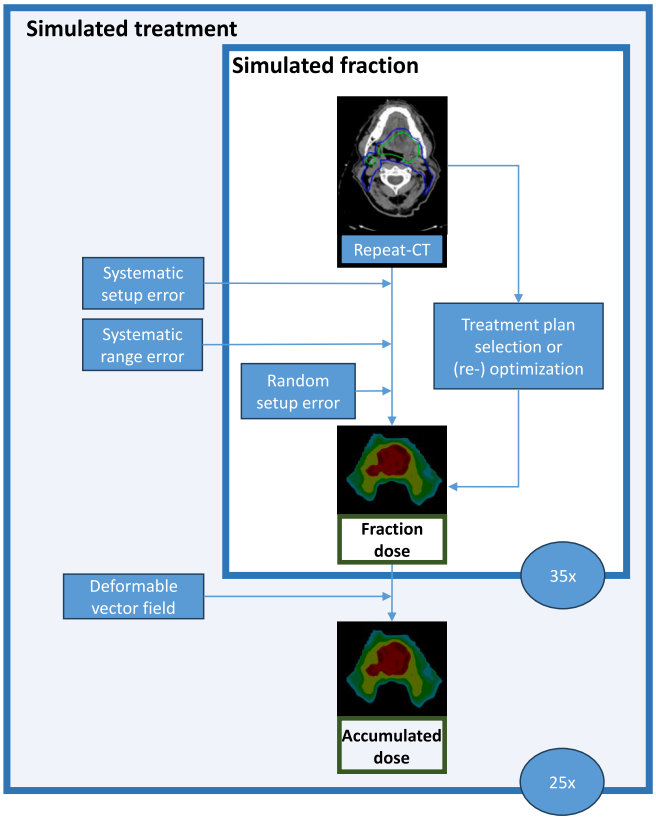

Fig. 1. Graphical representation of the approach for simulations of the adaptive strategies which was used for the dosimetric evaluation. For each patient, the fractions were equally divided over the 3–6 available repeat-CTs, assuming a stable anatomy in between repeat-CTs, but applying a different random setup error for every fraction. The treatment plan was selected for the plan library strategies, and re-optimized for $Online_{re\text{-}opt}$ and optimized for full daily re-planning. For $Offine_{trigger\text{-}based}$ and $Offine_{weekly}$ this step was skipped because there was one treatment plan available. The deformable vector field depended on the repeat-CT (see text). In the dosimetric evaluations, fraction doses and accumulated doses were compared.

the 25 simulated treatment courses were equal for all six strategies. During treatment simulations, a stable anatomy in between repeat-CTs was assumed. This may introduce more systematic changes in patient anatomy compared to the true anatomy.

The applied standard deviations (SD) of the Gaussian distributions were derived from beam QA and patient setup data at HollandPTC, which included the squared sum of the isocentric errors in the CT (systematic) and gantry (systematic and random), uncertainties in couch positioning (random), registration with the MR (systematic), online matching (random) and intra-fraction motion (systematic and random). This resulted in SDs of 0.88, 0.88 and 0.91 mm for the systematic setup errors, and 0.78, 0.75 and 0.82 mm for the random errors in lateral, longitudinal and vertical directions, respectively. The Gaussian distribution of range errors was assumed to have a SD of 1.5 % in correspondence to [26].

The dosimetric evaluations consisted of comparisons of the simulated fractions and simulated fractionated treatments between the adaptive strategies. For the simulated treatments, dose accumulation of the simulated fractions was performed on the planning-CT using the non-rigid registration framework as proposed by Vasquez Osorio et al. [27], which determines the deformable vector field between contours on the planning-CT and repeat-CT.

For CTVs, the per-fraction and accumulated $V_{95\%}$ were compared between the strategies. For OARs, normal tissue complication probabilities (NTCPs) for xerostomia and dysphagia grade $\geq$ II and grade $\geq$ III complications were calculated using the models in the Dutch National Indication Protocol [28]. For each patient, mean NTCPs in the 25 simulated treatments were used for the analyses. Statistical significance of dosimetric differences between treatment strategies was assessed using the Wilcoxon Signed-Rank test ($\alpha < 0.05$).

Assessment of impact of adaptive strategies on workload and daily treatment time.

All required activities and involved team members for the adaptive strategies were systematically identified. Required activities could be out-of-room (contributing to workload) or in-room (contributing to workload and daily treatment times). The investigated $Offline_{trigger\text{-}based}$ and $Offline_{weekly}$ adaptive strategies only have out-of-room activities needed for plan adaptations, while $Online_{re\text{-}opt}$ only has in-room activities, and $Library_{static}$ and $Library_{progressive}$ have both out-of-room and in-room activities. Activity times were estimated for an average patient using either time measurements, scheduled time, questionnaires filled out by involved team members, and extraction from literature. Reported activity times included time for hands-on work plus unavoidable waiting periods that could not be used for other tasks. E.g., during the in-room activity "Online re-optimization", there is unavoidable waiting time, which was included in the reported time. In offline adaptive strategies, during out-of-room treatment plan computation, team members can do other tasks. Therefore, this computation time was not included in the reported time for the activity 'Treatment plan generation'. Workloads were calculated by multiplying the activity times by the number of team members involved.

Current practice and a scenario considering the impact of foreseen technological advancements:

For each activity, two time estimations were obtained: one in current practice, with currently available technology, and one in a scenario exploring the potential impact of foreseen technological advancements, e.g., automation, on activity times. In the scenario anticipating technological advancements, activities that were expected to be fully or partially automated or replaced in the near future by introducing faster technology/approaches were identified through a discussion among the authors (MO, SB, MG, SH, ZP, BH, MH) to achieve full consensus. This group consisted of medical physics experts with photon and proton radiotherapy experience, physicists, and an applied mathematician. This group has collective experience in automation, IMPT and adaptive strategies with > 80 individual peer-reviewed publications on these topics in the past 5 years. The near future, in this context, was defined as 5 years from now. The technological advancement should have reached a Technology Readiness Level of 8 [29,30], meaning that the feasibility and efficacy are proven in prospective studies, but widespread clinical translation may not have happened yet. For activities for which no full consensus could be achieved on the level of automation after discussions, each author independently estimated the degree of expected time reduction, and the resulting average was used.

Since part of the activities required in $Online_{re\text{-}opt}$ (online re-optimization, online QA) are not yet possible within our current clinical systems, no estimation for workload and prolonged treatment time was obtained for current practice. Note that plan library workflows are not implemented in our clinical systems yet either, however, all separate required activities are available within our clinical software.

Results

Fig. 2 shows for the six strategies for both CTVs the percentage of the simulated fractions (top) and treatments (bottom) that complied with the objective ($V_{95\%}$>x% of the volume) on the x-axis. Fast $Online_{re\text{-}opt}$ and full re-planning achieved highly similar coverage levels and consistently outperformed the other strategies for both CTVs, and both for single fractions and for full treatments. For both, 98 % of the simulated fractions had a CTV_{7000} $V_{95\%} \geq 95.3$ %. $Offline_{weekly}$ performed relatively poorly for CTV_{7000} in the per-fraction analyses (upper left panel), with 98 % of simulated fractions having $V_{95\%}$ >84.1 %, which

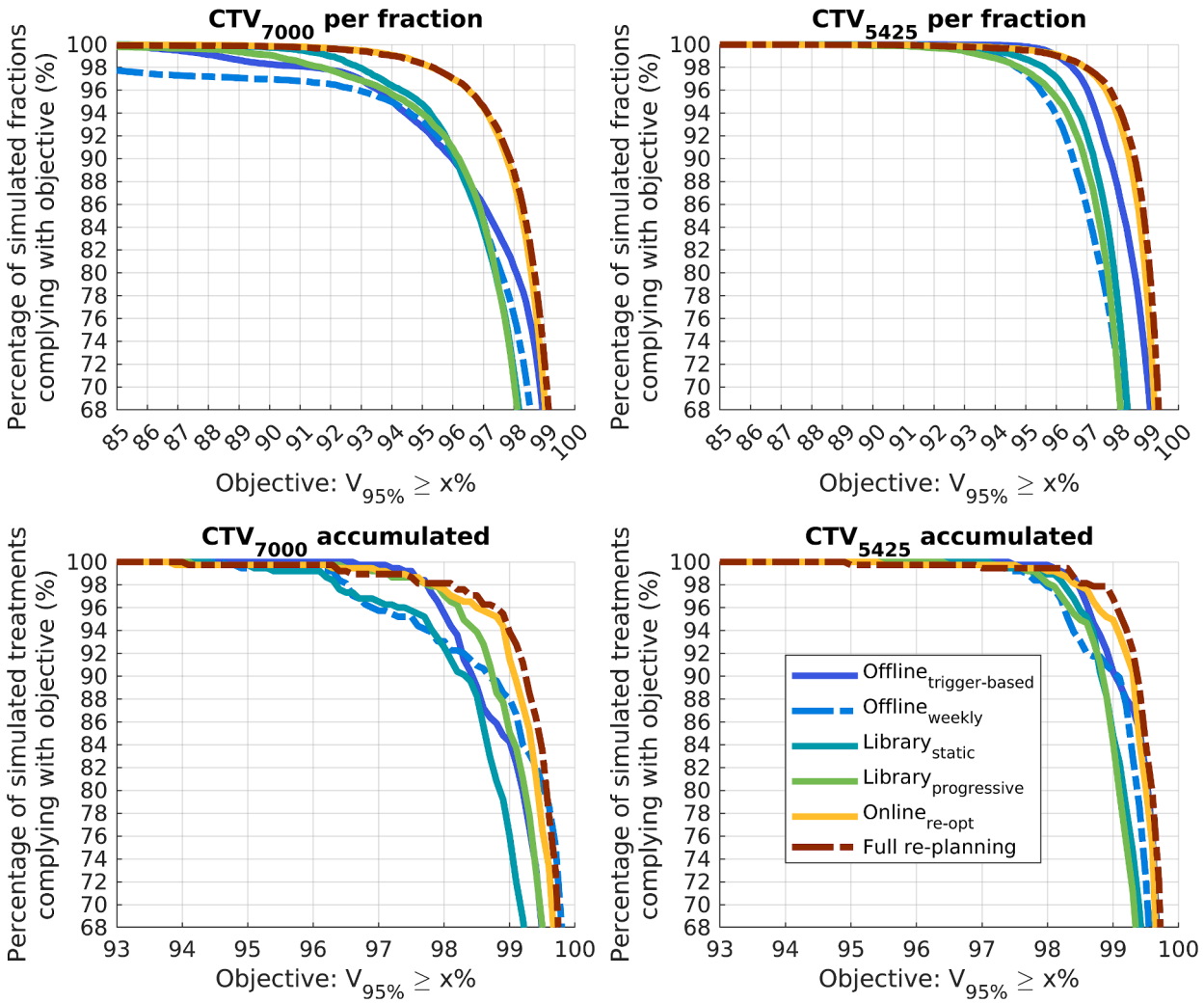

Fig. 2. For CTV_{7000} (left) and CTV_{5425} (right), percentages of the 13,125 simulated fractions complying with $V_{95\%}$>x% of the volume (top panels), and percentages of the 375 simulated fractionated treatments with $V_{95\%}$>x% of the volume for accumulated doses (bottom panels).

improved to $V_{95\%}$ >96.5 % for full treatments (lower left panel).

Fig. 3 shows NTCP differences for xerostomia and dysphagia grade ≥ II and ≥ III compared to $Offline_{trigger\text{-}based}$. Average differences between $Offline_{trigger\text{-}based}$ and daily full re-planning were 4.1 ± 1.9 %-point for grade ≥ II xerostomia and 3.9 ± 2.2 %-point for grade ≥ II dysphagia, in favor of full re-planning. Differences between $Offline_{trigger\text{-}based}$ and fast $Online_{re\text{-}opt}$ were similar and in favor of $Online_{re\text{-}opt}$ with average differences of 4.6 ± 1.7 %-point and 4.2 ± 2.3 %-point. Comparing $Library_{progressive}$ to $Offline_{trigger\text{-}based}$ differences were 2.7 ± 1.9 %-point and 2.3 ± 1.7 %-point in favor of $Library_{progressive}$. This means that with $Library_{progressive}$, 59 % (xerostomia) and 55 % (dysphagia) of the full sparing potential for grade ≥ II NTCP reduction could be achieved. For $Offline_{weekly}$, these percentages were 40 % and 45 %. Differences in grade ≥ III xerostomia and dysphagia followed the same trends, but differences were smaller.

Fig. 4 presents an overview of the required activities for the adaptive strategies, along with the estimated required activity times. A detailed breakdown of the complete workflow, including a description of the tasks, the allocation of team members, and the activities that were expected to be automated or replaced in the scenario anticipating technological advancements can be found in Supplementary Data C. Regarding this scenario, it was assumed that CT-on-rails was mostly replaced by high-quality CBCT. Furthermore, it was assumed that fully automated treatment plan generation would become available within 5 years. Other foreseen technological advancements include improvements in contouring, plan QA physics, image processing procedures, and hands-on work in treatment plan evaluations and checks. For further details on these, see Supplementary Data C.

Fig. 5 summarizes for the alternative adaptive strategies 2–5, the balance between dosimetric impact on the one hand (Figs. 1 and 2), and adaptation-related increased workload and prolonged treatment time on the other (derived from Fig. 4 and Supplementary Data C), compared to $Offline_{trigger\text{-}based}$ (strategy 1). This figure shows that the obtained dosimetric improvements have significant costs in workload and treatment time. With the currently available technology, the total workload increases compared to $Offline_{trigger\text{-}based}$ were estimated to be 39, 75, and 205 h/patient per treatment course for $Offline_{weekly}$, $Library_{static}$, and $Library_{progressive}$, respectively. $Library_{static}$ and $Library_{progressive}$ would result in prolonged treatment times of 29 and 31 min per fraction, respectively. In the scenario anticipating technological advancements, the respective workload increases with the alternative adaptive strategies were expected to be respectively 3.2, 8.4, 21, and 66 h/patient per treatment course for $Offline_{weekly}$, $Library_{static}$, $Library_{progressive}$, and $Online_{re\text{-}opt}$. The corresponding prolonged treatment times for the strategies were estimated to be 0, 3.7, 5.5, and 29 min.

Discussion

This study systematically compared adaptive strategies in terms of dosimetry, workload, and treatment time, also exploring the potential

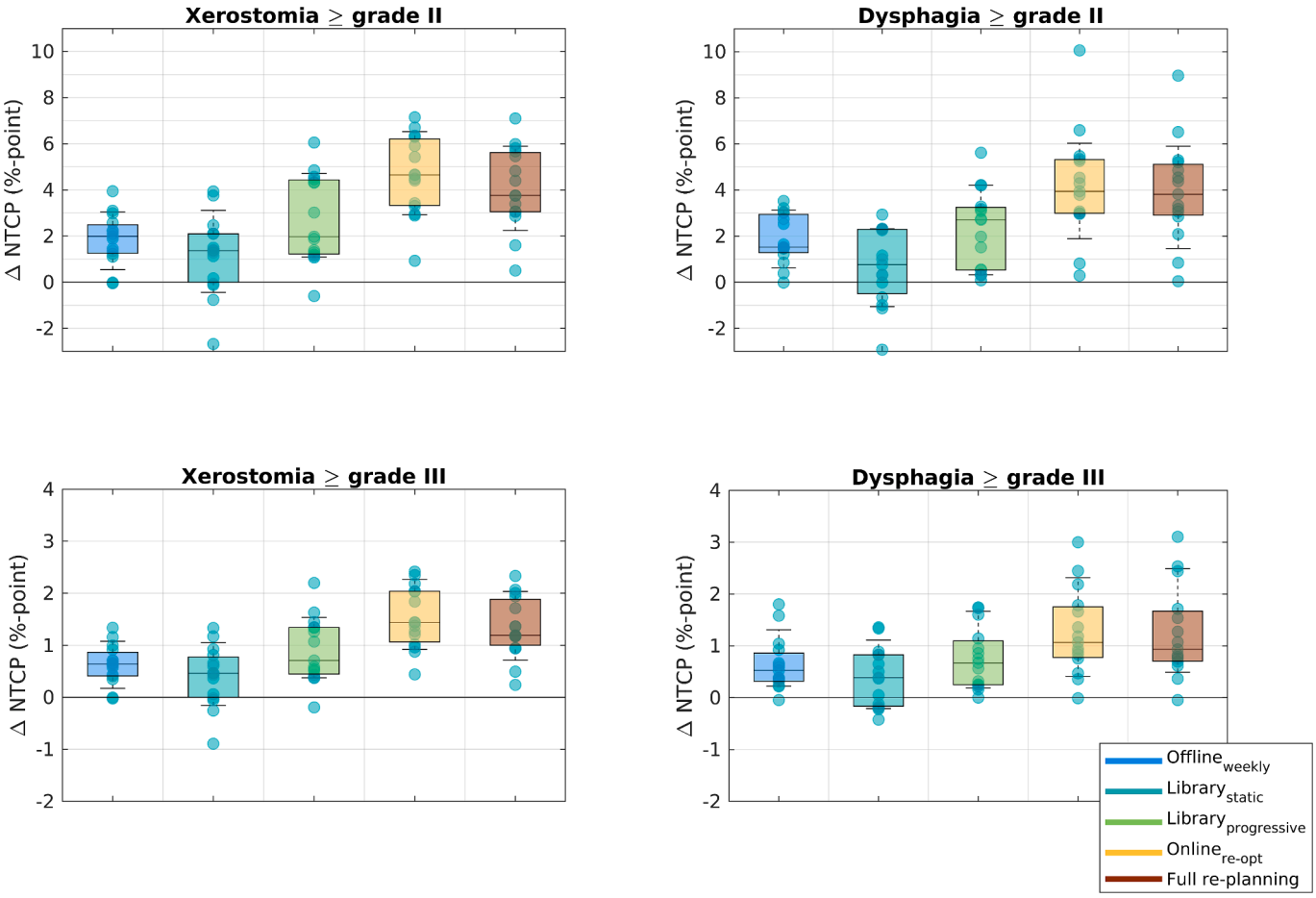

Fig. 3. NTCP differences for 15 patients (each indicated with a blue dot) of the evaluated adaptive strategies compared to current $\text{Offline}_{\text{trigger-based}}$. For each patient, the mean NTCPs in the 25 simulated treatments were used. Negative values are in favor of $\text{Offline}_{\text{trigger-based}}$. In each boxplot, whiskers extend to 90 % of the data, horizontal bars are median values. In each of the four panels, the inter-strategy differences in the presented NTCP differences with $\text{Offline}_{\text{trigger-based}}$ were all statistically significant, apart from the NTCP differences between $\text{Offline}_{\text{weekly}}$ and $\text{Library}_{\text{static}}$ for grade ≥ II and ≥ III xerostomia and grade ≥ III dysphagia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

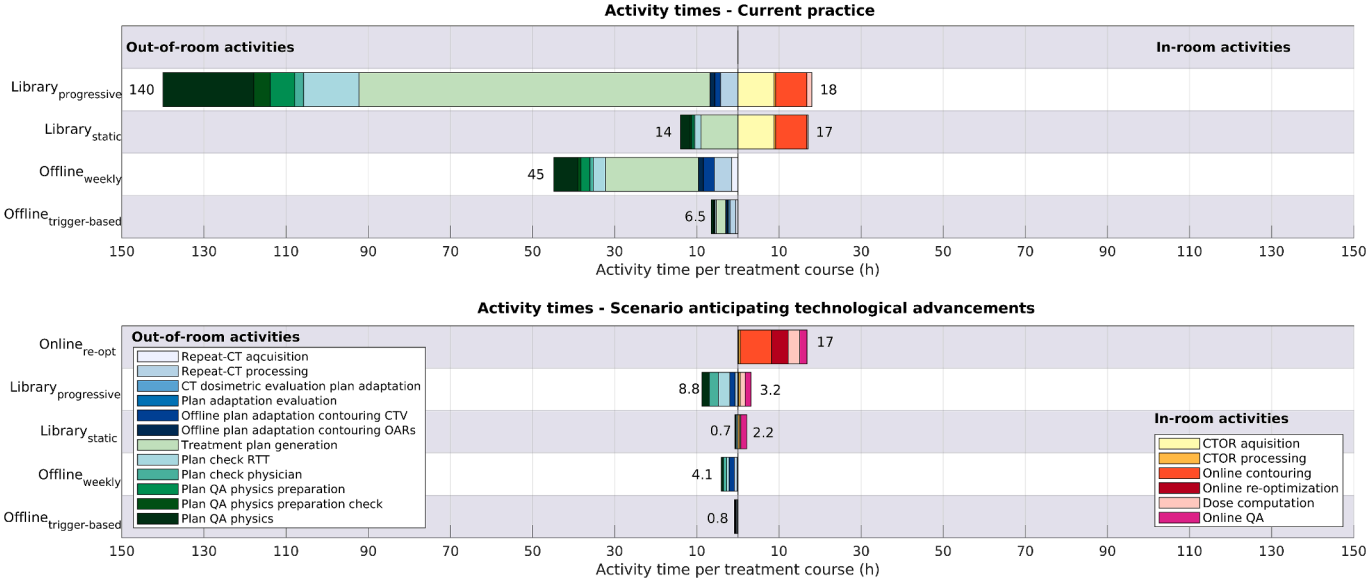

Fig. 4. Estimated activity times per treatment course consisting of 35 fractions for the investigated adaptive strategies in current practice (top) and the scenario anticipating technological advancements in ≤ 5 years (bottom) for out-of-room (left) and in-room (right) activities. Abbreviations: Quality Assurance (QA), CT-on-rails (CTOR), Organs-at-risk (OARs), Clinical Target Volume (CTV). Descriptions of the activities and further explanations can be found in Supplementary data C.

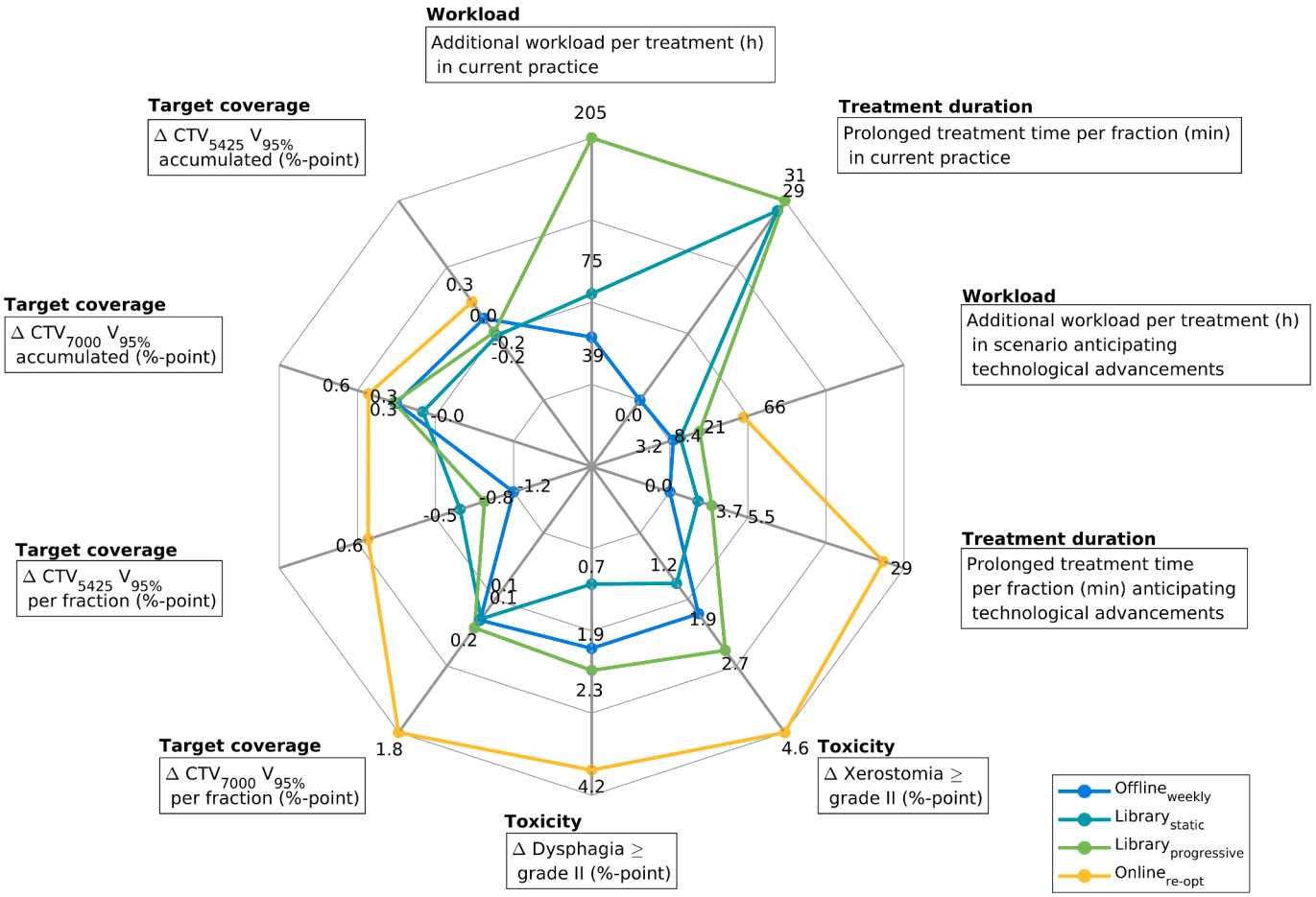

Fig. 5. For the 4 alternative adaptive approaches, the additional required workload per patient per treatment course, prolonged daily treatment duration, and the dosimetric gains compared to $Offline_{trigger\text{-}based}$. Additional workload and prolonged treatment time are provided for the current technological situation and for anticipated technological advancements in $\leq$ 5 years. For online re-optimization, time estimations are solely available for the anticipated scenario. Dosimetric differences included the difference in the 90 percentiles of the $V_{95\%}$ for the simulated fractions and treatments, for both the CTV_{7000} and CTV_{5425}. Axes extend to the smallest (or 0) and the largest obtained values for the $V_{95\%}$, NTCP, workload and treatment time.

impact of technological advancements. To the best of our knowledge, no other studies on adaptive IMPT have put dosimetric advantages of more complex adaptive approaches in the context of accompanying enhanced workload and treatment time. Additionally, we are not aware of other studies providing detailed quantitative estimates of workload and treatment time for complete adaptive pipelines.

We used full daily re-planning as a dosimetric benchmark for adaptive strategies, which in principle should provide the upper limit for achievable dosimetric quality. $Online_{re\text{-}opt}$ matched full re-planning in terms of target coverages and NTCPs. Furthermore, $Online_{re\text{-}opt}$ outperformed the $Offline_{trigger\text{-}based}$ protocol with high and consistent target coverage for every fraction, while also obtaining average reductions of 4.6 %-point and 4.2 %-point for the risk of grade $\geq$ II xerostomia and dysphagia. Interestingly, NTCPs for the approximate $Online_{re\text{-}opt}$ were slightly better than for full re-planning, possibly due to a clinically insignificant, slightly worse conformity. The three other alternative adaptive strategies also improved NTCPs compared to $Offline_{trigger\text{-}based}$, although to a lesser extent, and they did not consistently improve target coverage.

The dosimetric benefits of the alternative adaptive strategies generally came with considerable increases in workload and treatment time, particularly in the offline treatment planning, CT-on-rails acquisition, and online contouring activities. The latter two activities also contributed substantially to prolonged treatment time, potentially limiting proton therapy capacity. Our analysis clearly shows the need for technological advancements to enable the feasibility of alternative advanced adaptive strategies, including fast, fully automated treatment plan generation, CBCT-based IMPT treatment planning, fast auto-contouring and manual editing tools, and fast and automated QA. Furthermore, it is essential that these components are integrated in commercially available software solutions. Recent literature showed promising results in offline treatment planning [31–35], CBCT-based planning [36,37], and auto-contouring [38–40].

Given the scarcity of resources in healthcare, a careful assessment is necessary to determine whether the benefits of more advanced adaptive strategies for H&N IMPT justify the costs. Important factors to also consider in this discussion include improvements in quality of life, control and survival rates, and financial costs. The invested resources need to be in balance with the improvements in patient outcome. Additionally, considering the limited availability of proton therapy, an important factor to also consider is the number of patients that can be treated with proton therapy, which is influenced by the prolonged treatment time. When introducing novel adaptive strategies, the primary objective should be to optimize outcomes for the patient population as a whole.

The scenario wherein all anticipated technological advancements are fully implemented represents an optimistic outlook for treatment efficiency improvement. Conversely, the current practice represents the worst-case scenario, where no further technical improvements are realized. Possibly, not all foreseen technological progress will be realized in $\leq$ 5 years. However, our estimate for prolonged treatment time per fraction for online re-optimization (29 min on average) aligns with

values obtained from literature in online adaptive photon therapy [41–43], which could be a realistic scenario is 5 years for IMPT.

The studied adaptive strategies represent only a subset of all theoretically possible options, leaving room for potential improvements. Although the setup robustness settings, adaptation schedules (daily, weekly, trigger-based), and plan library selection criteria in this study were selected with care, possibly, the balance between dosimetry, workload, and prolonged treatment time might be further optimized by employing different configurations and combinations. Furthermore, not all variations of adaptive planning strategies were taken into account in this evaluation, such as those that involve anatomical robust optimization [44,45] and online dose restoration [1,3,6]. We also did not consider non-adaptive IMPT in this study, as ad-hoc or trigger-based (per protocol) planning is standard clinical practice (employed by 79 % of the proton centers in a recent survey [11]).

Several limitations in our dosimetric comparisons should be discussed. First, as only 15 patients were included, statistical power is limited. Because the adapted plan was simulated to be used from the next repeat-CT onwards, this also resulted in several offline adaptations that could not be taken into account when evaluating $Offine_{trigger\text{-}based}$ and $Offine_{weekly}$. Next, in this work we only used $V_{95\%}$ for target dose evaluations. However, target dose quality may also be expressed in other metrics such as different dosimetric parameters, tumor control probability, or the underdosage locations. Optimal metrics to assess the quality of delivered CTV doses are currently still unclear. Furthermore, uncertainties in employed NTCP models need to be considered when interpreting the results of this study. Lastly, the dosimetric impact of several technological advancements that were assumed to be employed in the future scenario (e.g., CBCT-based plan adaptations, automatic contour propagation) was outside the scope of this study. The dosimetric evaluation in this study was evaluated using RATING criteria for treatment planning studies [46]. The RATING score was 92 % according to the authors (Supplementary Data D).

Furthermore, it is important to acknowledge certain limitations in our analyses on adaptation-related additional workload and treatment time. First, estimations were only collected at our institute (except values obtained from literature), potentially limiting the generalizability of our findings. Second, several assumptions in the scenario assuming technological advancements highly impacted conclusions. For example, the expectation that plan library strategies can be executed with automatically propagated contours (requiring additional QA), unlike online re-optimization, highly affects the estimated increases in treatment time. Third, some potential advancements were not included in the scenario analysis that could also impact the conclusion, i.e., computer hardware advances that could improve computation times. Lastly, possible changes in minor activities such as data transfer between systems, and learning curves associated with each strategy or activity were not incorporated in our analyses. Despite the limitations, we believe that this study gives useful insight into the pros and cons of advanced adaptive IMPT approaches. It is also an important first step towards future cost-effectiveness analyses.

In conclusion, this study shows the trade-off between dosimetric benefits of adaptive strategies and increases in workload and treatment time prolongation. Especially the investigated fast online re-optimization strategy results in improved dosimetry, offering comparable quality to full re-planning. However, its routine clinical implementation requires technological advancements to render workload and treatment time feasible.

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CRediT authorship contribution statement

Michelle Oud: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Sebastiaan Breedveld:** Writing – review & editing, Visualization, Supervision, Software, Methodology, Investigation, Funding acquisition, Conceptualization. **Marta Giżyńska:** Writing – review & editing, Methodology, Conceptualization. **Yi Hsuan Chen:** Writing – review & editing, Visualization, Methodology. **Steven Habraken:** Writing – review & editing, Methodology, Funding acquisition. **Zoltán Perkó:** Writing – review & editing, Methodology, Funding acquisition. **Ben Heijmen:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Mischa Hoogeman:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110548.

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