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Original Article

Treatment planning comparison for head and neck cancer between photon, proton, and combined proton–photon therapy – From a fixed beam line to an arc

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ABSTRACT

Background and purpose: This study investigates whether combined proton–photon therapy (CPPT) improves treatment plan quality compared to single-modality intensity-modulated radiation therapy (IMRT) or intensity-modulated proton therapy (IMPT) for head and neck cancer (HNC) patients. Different proton beam arrangements for CPPT and IMPT are compared, which could be of specific interest concerning potential future upright-positioned treatments. Furthermore, it is evaluated if CPPT benefits remain under inter-fractional anatomical changes for HNC treatments.

Material and methods: Five HNC patients with a planning CT and multiple (4–7) repeated CTs were studied. CPPT with simultaneously optimized photon and proton fluence, single-modality IMPT, and IMRT treatment plans were optimized on the planning CT and then recalculated and reoptimized on each repeated CT. For CPPT and IMPT, plans with different degrees of freedom for the proton beams were optimized. Fixed horizontal proton beam line (FHB), gantry-like, and arc-like plans were compared.

Results: The target coverage for CPPT without adaptation is insufficient (average V95%=88.4 %), while adapted plans can recover the initial treatment plan quality for target (average V95%=95.5 %) and organs-at-risk. CPPT with increased proton beam flexibility increases plan quality and reduces normal tissue complication probability of Xerostomia and Dysphagia. On average, Xerostomia NTCP reductions compared to IMRT are −2.7 %/-3.4 %/-5.0 % for CPPT FHB/CPPT Gantry/CPPT Arc. The differences for IMPT FHB/IMPT Gantry/IMPT Arc are + 0.8 %/-0.9 %/-4.3 %.

Conclusion: CPPT for HNC needs adaptive treatments. Increasing proton beam flexibility in CPPT, either by using a gantry or an upright-positioned patient, improves treatment plan quality. However, the photon component is substantially reduced, therefore, the balance between improved plan quality and costs must be further determined.

Introduction

Head and neck cancers (HNC) are a major indication for radiotherapy (RT), with state-of-the-art treatment usually involving photon-based irradiation techniques such as IMRT/VMAT or tomotherapy [1–4]. Such treatments are widely available in RT clinics, relatively cheap and are considered to be relatively insensitive to the anatomical changes of a patient that are common during RT in the head and neck region [5–7]. Nevertheless, many cases remain challenging for photon RT [8,9]. As such, alternative techniques such as pencil beam scanning (PBS) proton therapy (PT) [10,11] are increasingly being used for HNCs [12–16], as they provide additional flexibility for sparing normal tissues in this challenging treatment area. For instance, using the model-based approach (MBA), whereby HNC patients are selected for proton therapy using comparative treatment planning with IMRT, it has been reported that more than 35 % of H&N patients could benefit from proton therapy,

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whereby benefit in this study is defined as a 5–15 % decrease in the predicted probability of grade 2/3 acute toxicities [16,17]. Interestingly, it has also been reported that this proportion may increase if new methods for proton therapy delivery, such as Spot scanning Proton Arc Therapy (SPArc) [18–22], are introduced.

Despite the increasing number of PT centers and the consequent increase of HNC patients being treated, the delivery of PT treatment to HNC patients on a global scale remains limited in most countries due to the low number of PT centers [23,24], mainly due to the technically more demanding equipment, larger space requirements, and higher costs [25]. Consequently, not all patients with an estimated benefit can be treated with PT [26]. In addition, the finite range of protons triggers concerns about their robustness to anatomical changes [27], even if this issue may be somewhat mitigated through the use of adaptive therapy [3,28–30] or SPArc [31,32]. Consequently, different options are being discussed to make PT more accessible. One option is to tackle the optimal allocation of the limited PT treatments [16,17,33,34], whilst there is also growing interest in treating patients in the upright patient position [35–39], particularly for proton therapy, whereby large and expensive gantries are then avoided.

Another approach that is being investigated is the concept of combined proton–photon therapy (CPPT) [40]. CPPT consists of two approaches to increase accessibility to protons [41–44]. In the first approach, one treatment plan is optimized for photons and one for protons, and both deliver a homogeneous dose to the target. For a patient cohort, the optimal allocation of the given limited PT slots can then be calculated such that only some fractions of the treatment are delivered by protons [41]. The other approach of CPPT considers adding a fixed horizontal proton beam line (FHB) to a conventional photon LINAC room [42]. As such, the gantry, one of PT's most expensive and space-demanding elements, would not be needed, and the photon LINAC would compensate for the lost proton beam angle flexibility, as with an FHB, only horizontal proton beams are available. This approach showed promising results for patients with HNC, non-small cell lung cancer, and breast cancer [42–44]. Of importance for this work, however, CPPT has an additional rationale besides increasing access to PT. Previous work also suggested that multi-modality treatment might outperform single-modality treatments when considering treatment delivery uncertainties [45–47]. This work also investigates the robustness of plans to anatomical changes, in particular, to determine whether CPPT plans can reduce the sensitivity of the plans to such changes or if adaptive strategies are necessary. As such, this work goes beyond the initial motivation of cost-effectiveness.

Either with photons or protons or through a combination of the two, there could be a number of potential options for treating HNC patients with RT/PT in the future. Therefore, this work performs a comprehensive exploratory comparison of IMRT, PT, SPArc and different combinations of these in the form of CPPT treatments. In addition, the sensitivity of all modalities to anatomical changes will be investigated, as will the effectiveness and necessity of treatment adaption. Of note, comprehensive here pertains specifically to the analysis and evaluation of the numerous treatment modality scenarios under consideration. The focus is on elucidating the strengths and limitations of each modality, to investigate the treatment landscape of CPPT.

Materials and methods

Patient cohort

The patient cohort for this treatment planning study consists of five retrospectively selected HNC patients initially treated with IMPT at PSI. One planning CT (planCT) and multiple repeated CTs (repCTs) were acquired for each patient. The number of acquired repCTs depended on the visually inspected magnitude of anatomical changes during treatment. This visual inspection concurs with the retrospectively calculated volume change in the region of interest (Table 1). Otherwise, repeated CT's were acquired weekly if no clinically relevant changes were observed (e.g. Patient 4). The patient characteristics, including cancer type, number of repCTs, target sizes, and the anatomy volume change, are summarized in Table 1. In addition, the target sizes and the evolution of the body volume change for the individual CTs are visualized in the supplementary material (figure A1).

Three patients (P1, P2, P5) had three planning target volumes (PTV), a high-risk PTV, an intermediate-risk PTV, and the elective-nodal PTV, while the other two patients (P3, P4) had no intermediate-risk PTV defined. The treatment planning aim was to deliver 70 Gy to the high-risk PTV, 60 Gy to the intermediate-risk PTV, and 54 Gy to the elective-nodal PTV. Additionally, objectives for OARs and the mean dose to the healthy tissue were defined. The objective function was kept the same for all treatment types to be as fair as possible between the different treatment plan types. The specific objective functions can be found in the supplementary material.

Treatment plan scenarios

The following treatment scenarios have been studied for each patient, as visualized in Fig. 1. Note, All *CPPT* plans in the following list have been optimized as described in the following section.

a) *IMRT:* For the photon plan, an IMRT plan was calculated with 19 equispaced fields to simulate a plan close to a volumetric arc therapy (VMAT) plan. A real VMAT plan optimization is not possible with the in-house developed optimizer used for CPPT. For consistency reasons however, the same optimizer is used for all plans [42].

b) *IMPT FHB:* A proton-only treatment assuming a FHB only.

c) *IMPT "Gantry" (3-fields):* A limited field, gantry-based proton-only plan [48–50].

d) *IMPT "Arc" (19-fields):* A simulated proton-only arc treatment.

e) *CPPT FHB:* Combined IMRT with FHB-only protons.

f) *CPPT "Gantry":* Combined IMRT with a limited field, gantry-based proton therapy.

g) *CPPT "Arc":* A scenario exploiting the full flexibility of both IMRT and proton arc therapy.

For CPPT treatments, the proton and photon beamlines/gantries, could either be in the same room as visualized in Fig. 1 or in two different rooms. The potential challenges will be further discussed below. Additionally, note plans c), d), f) and g) can either be delivered by a proton gantry and a photon LINAC or, considering the increased interest in the community in upright patient positioning, these plans could also be delivered with an FHB and seated patient [35–39]. The beam angles for each plan can be found in the supplementary material in

Table 1
Summary of the patient (P1-P5) cohort.

Patient	Age [years]	Gender	# repeated CTs	Size high-risk PTV [cc]	Size elective nodal PTV [cc]	Volume Body planCT [cc]	Volume Body last repCT [cc]	Absolute volume difference [cc]	Relative volume difference
P1	44	male	6	239	971	8715	8120	595	6.8 %
P2	70	male	6	180	704	16,570	15,394	1176	7.1 %
P3	56	male	5	108	258	10,901	10,325	576	5.3 %
P4	44	female	4	83	534	9348	9304	45	0.5 %
P5	48	female	7	141	706	8264	7600	664	8.0 %

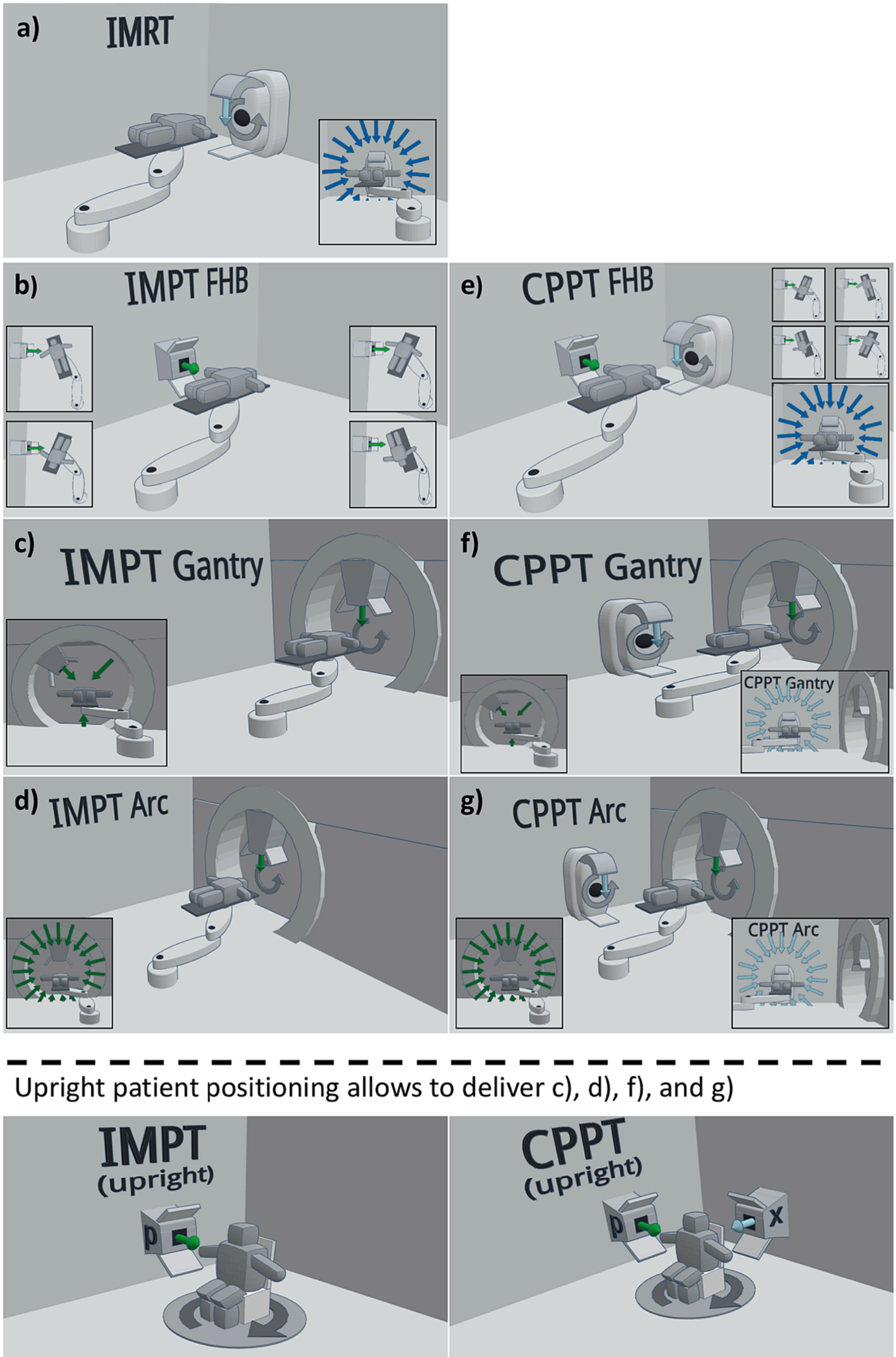

Fig. 1. Visualization of all considered treatment scenarios. Green indicates proton beams, while blue indicates photon fields. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

table A2.

CPPT optimization

For all CPPT scenarios, proton and photon components are considered to be delivered in the same fraction. As such, CPPT plans have been created by simultaneously optimizing IMPT and IMRT plans. The optimization is based on the physical doses of the proton and photon components. Mathematically the following optimization problem is solved:

$$\min_{x^{\gamma},x^{p}} f(\boldsymbol{d}^{\gamma}+\boldsymbol{d}^{p})$$

$$\text{subject to } d_i^{\gamma}=\sum_j D_{ij}^{\gamma}x_j^{\gamma}\forall i$$

$$d_i^{p}=\sum_j D_{il}^{p}x_l^{p}\forall i$$

$$x_j^{\gamma},x_l^{p}\geq 0\forall j,l$$

for which *f* is the objective function defining the clinical goals. The specific objective function for this work can be found in the supplementary material. The objective function is evaluated on the cumulative dose of protons and photons. The delivered dose by photons and protons is denoted by d^{γ} and d^{p}. Furthermore, D_{ij}^{γ} and D_{il}^{p} are the elements of the dose-influence matrices for photons, respectively protons, calculated with the open-source planning toolkit matRad [51]. The intensities of a beamlet j and pencil beam l, are given by x_j^{γ} and x_l^{p}. The proton dose d^{p} was scaled by a constant relative biological effectiveness of 1.1. Robust optimization based on range and potential positional offsets of patients has not been used, as it is currently not supported in the optimization tools used in this work.

Treatment plan evaluation

The evaluation of the treatment plan was performed in the following way.

First, a visual inspection of the resulting plans was performed to check the basic quality of the optimized and recalculated plans. Furthermore, a visual inspection gives the chance to have a first comparison between the different plans and to visualize the proton and photon components for CPPT. The proton and photon contribution for the CPPT was calculated as the percentage of dose each modality delivered to the elective-nodal PTV and specific OARs. For a more quantitative analysis, DVHs and DVH parameters were investigated. Additionally, the normal tissue complication probabilities (NTCPs) were calculated for Xerostomia and Dysphagia $\geq$ grade 3 using the models from the Dutch model-based proton–photon selection system [16,33]. For all patients, no baseline Xerostomia or Dysphagia was assumed.

Robustness to anatomical changes for all was evaluated and compared by considering both non-adaptive and adaptive approaches to investigate the impact of anatomic variation. For the non-adaptive treatment strategy, plans were optimized for each patient on the planCT and recalculated on the rigidly registered repCTs. For the adaptive treatment, the plans were optimized for each CT of the patient. The adaption was performed on the repCTs rigidly registered to the planCT. An experienced medical doctor delineated the targets and OARs on all CTs manually slice-wise in Eclipse version 16.1 (Varian Medical Systems, Palo Alto, USA) to take into account the anatomical changes between each CT.

Qualitative evaluation of practical and economic aspects of the treatment options

The investigated treatment options all have their treatment scenario-specific practical challenges. Additionally, the different delivery system options present different cost drivers for such treatments. To set the resulting treatment plans into context with these aspects, the practical challenges specific to the treatments were determined, and summarized but not further investigated in the scope of this paper. Additionally, cost drivers for the different treatment delivery systems compared to a conventional IMRT treatment were identified.

Results

First, the results of the planCTs are described before discussing the non-adaptive and adaptive approach's results.

Treatment planning

Fig. 2 shows all nominal treatment plans optimized on the planCT for Patient 1. Additionally, for the other patients, all plans are visualized in the supplementary material in figures A2-A5. Starting from the previously discussed approach of CPPT without a gantry, and taking a closer look at the plan parameters of IMRT, IMPT FHB, and CPPT FHB, it can be seen that the findings on the planCT for the patients included in this study are in-line with previously published results [42], including reduced doses for the parotids and pharyngeal constrictor muscles (PCMs) compared to IMRT for the CPPT FHB and IMPT FHB, and comparable reduction of integral dose for CPPT FHB as for IMPT FHB. CPPT FHB reduces the mean doses to the contralateral parotid averaged over the five patients by −5.2 % compared to IMRT and −7.9 % compared to IMPT FHB. The higher dose for IMPT FHB is due to the limited possibility

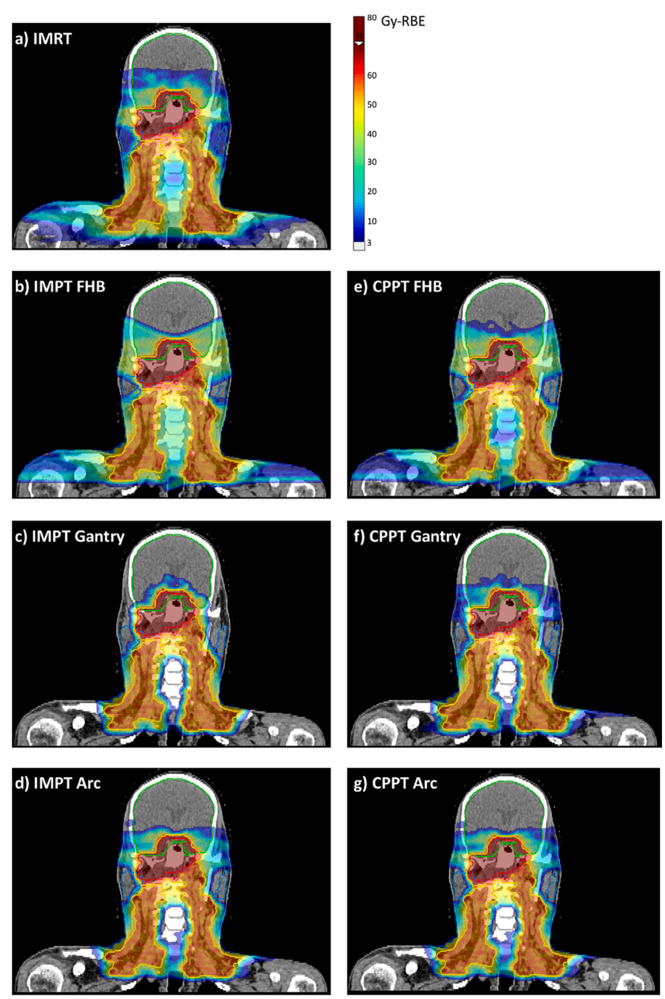

Fig. 2. Optimized treatment plans on the planCT for patient 1.

of sparing the parotids using only a FHB, especially with the target area distal to the parotids. For the mean dose to the PCMs, reductions are −4.2 % and −5.9 %. It is observed that IMPT with only a FHB misses some degrees of freedom to spare some OARs optimally, which can be compensated by CPPT due to the additional degrees of freedom provided by the photon component. This can be seen well for the parotids in Fig. 2, for which the parotids cannot be spared as well with IMPT FHB as with CPPT FHB. In figure A6-A10 in the supplementary material, showing the proton and photon contributions, it is observed that photons are predominantly used close to the parotids to compensate for the limitations of the IMPT FHB arrangement. More details about the proton and photon contributions and the results from the other plans are

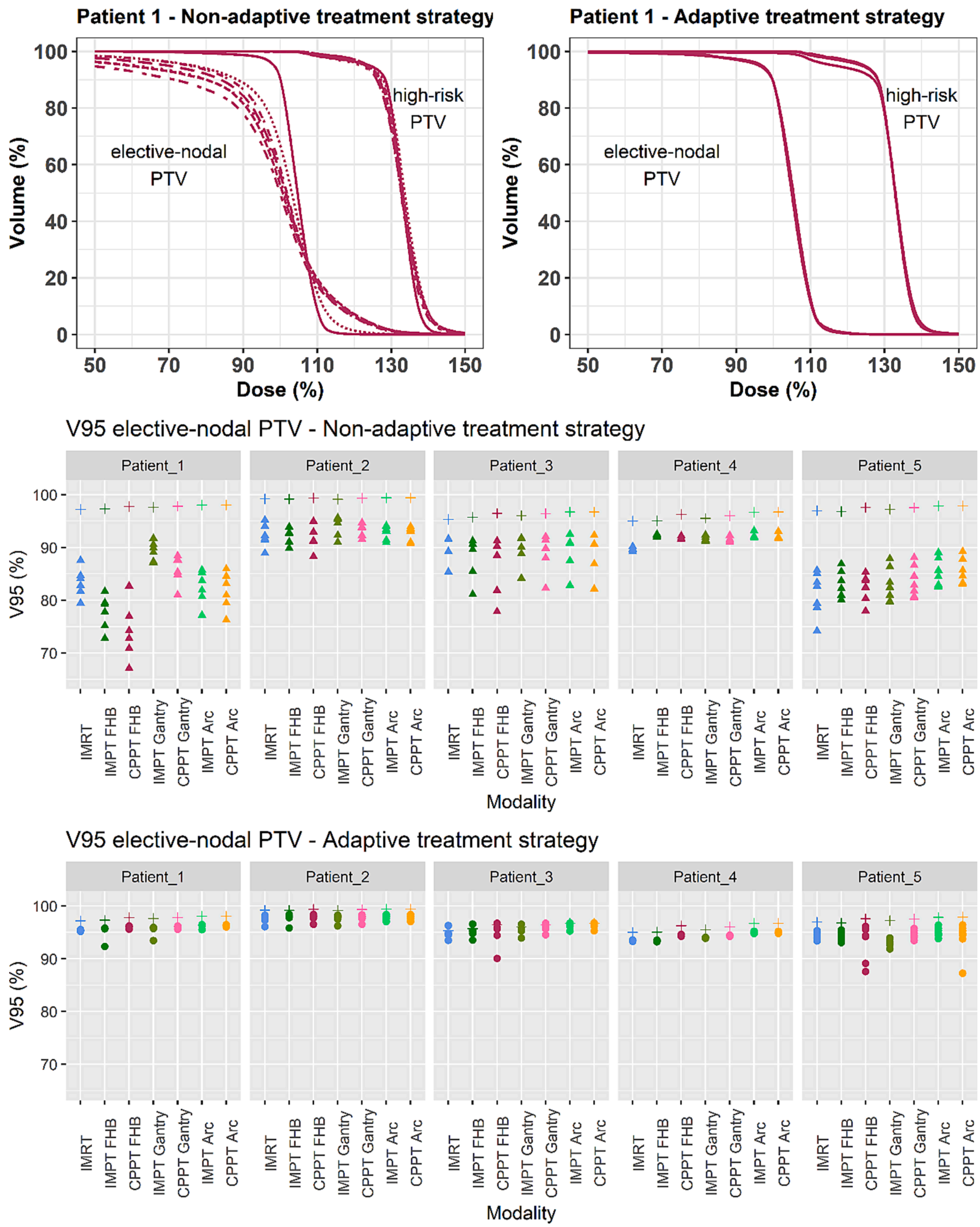

Fig. 3. DVHs for the elective-nodal PTV and the high-risk PTV for the CPPT FHB plan. The solid line represents the optimized plan, and the dashed lines recalculated plans. For the adaptive treatment strategy, most curves overlap. The V95 for the elective-nodal PTV for all patients and modalities is plotted in the two bottom panels. The cross stands for CT0, the triangles are the recalculated values on the repCTs in the non-adaptive treatment strategy, and the circles are the reoptimized values in the adaptive treatment strategy.

discussed below.

The effect of adaption

As a next step, it was investigated to what extent adaption is necessary for each of the CPPT strategies. The DVHs for the non-adaptive treatment strategy of the CPPT FHB plan for the elective-nodal PTV in Fig. 3 shows clearly that the target coverage degenerates if the plans are recalculated on the changed anatomies. This loss of coverage can also be seen in Fig. 3, with plotted V95 values for the elective-nodal PTV for the optimized and recalculated plans for all different treatment types. There is a substantial decrease in the V95 for the elective-nodal PTV for all patients and treatment types. These results indicate that a CPPT treatment without adaption is not optimal for these HNC patients. Of note, this is also true for IMPT and IMRT in our results. Due to the lack of target coverage, OAR DVH curves and DVH parameters are not discussed for the non-adaptive treatment strategy.

By adapting plans to the repeat CTs, target coverage remains good in all cases. This can be seen in the DVH curves of the CPPT FHB for Patient 1 in Fig. 3. All other patients show the same trend. Additionally, in the V95 plot for the adaptive treatment strategy in Fig. 3, it can be seen that the values for most of the CTs of all five patients are above 95 % or in close proximity to it.

NTCP evaluation

The results in the following part now summarize all optimized plans in the adaptive treatment strategy. For each patient, the NTCP values of all repeated CTs were averaged weighted by the number of fractions for which the respective CT would be the most recent image. Next to the here presented summary of the results in NTCP values, the supplementary material shows examples of DVH curves (elective-nodal PTV, high-risk PTV, healthy tissue, bilateral parotids) for the planning CT.

Over all five patients (including in total 34 CTs, 5 planCTs, and 29 repCTs), the mean NTCP for Xerostomia is reduced for five out of six IMPT and CPPT plans compared to IMRT alone (Table 2) Only for the IMPT FHB is the NTCP for Xerostomia higher, due to the problem of sparing the parotids with an FHB. Additionally, increasing the proton degrees of freedom, from an FHB through fixed field Gantry to a proton arc, improves the NTCPs for IMPT and CPPT, with the Arc treatments having the lowest NTCPs. For each, however, CPPT always improves NTCP compared to IMPT alone, meaning that even for a proton arc treatment, the photon component can help to improve treatment plan quality. However, it is also observed that the benefit of CPPT compared to IMPT reduces with increased proton beam angles. For Dysphagia, the observations are very similar. However, the reduction in NTCP is smaller between the different plans. On the other hand, there was the assumption of no baseline Dysphagia or Xerostomia. In the case of a baseline pathology, the effects of the NTCPs would be magnified.

Proton vs. photon contributions

The respective proton and photon contributions are visualized for each patient in the supplementary material (figures A6-A10). Two main trends are observed. First, a decrease of the photon contribution to the CPPT plans is observed when increasing proton beam angle flexibility from an FHB towards the Arc. For the FHB treatments, the photon contribution is used to irradiate different parts of the tumor. One observed trend across the patients is that distal to the parotids a higher photon component is seen, as the proton beams from the FHB are suboptimal to treat these regions. For the combined gantry treatments, the photon component decreases compared to the FHB. For the combined Arc treatments, only a small amount of the total dose is delivered by photons, with the photon component being mainly used at the boundaries between targets and OARs or healthy tissue in general. An example of the photon component for the CPPT Arc treatment plan of patient 5 can be found in the supplementary material in figure A11. Quantifying the contributions of protons and photons to the elective-nodal PTV (Fig. 4) shows that there is a strong decrease in the photon component with increased proton beams and angular flexibility. As a result, only about 1–2 % of the elective-nodal PTV dose for the Arc treatment plans is delivered by photons. Nevertheless, this small component improves plan quality. Furthermore, by investigating the dose contributions to specific OARs, it was observed that the photon component is typically larger, such as the oral cavity and parotids, which indicates that in these regions, more photons are used than in the homogenous target region (Figures A16-A20 in supplementary material).

Summary of practical and economic aspects of CPPT

Practical considerations related to CPPT were identified across various domains:

- Room design: In scenarios involving single-room solutions, accommodating accelerators and beam lines necessitates a larger spatial requirement. Moreover, managing radiation protection becomes more intricate. A fundamental query revolves around effectively housing the machinery within a single room. Additionally, defining prerequisites for a treatment couch capable of transitioning patients between both machines becomes imperative.
- Treatment workflow: In the context of a two-room CPPT approach, optimizing patient scheduling gains prominence, potentially involving additional patient transfers. Furthermore, the challenge arises in positioning patients accurately within two distinct rooms, potentially introducing further sources of uncertainty. Furthermore, the dose accumulation of the proton and photon components is of interest.
- Biology: Understanding the biological effectiveness of CPPT emerges as a critical factor. This aspect becomes particularly relevant if the two treatment components are administered within separate rooms,

Table 2
NTCPs in % for Xerostomia and Dysphagia for all treatment modalities and patients (P1-P5).

NTCP Xerostomia [%]	**IMRT**	**IMPT FHB**	**CPPT FHB**	**IMPT Gantry**	**CPPT Gantry**	**IMPT Arc**	**CPPT Arc**
P1	23.9	21.5	20.8	21	20.5	19.8	19.6
P2	31.1	35.1	27.3	27.4	25.3	23.6	22.9
P3	26.1	27.3	24.4	24.1	23.2	23.1	22.7
P4	29.7	31.3	27.6	30.3	27.1	26.5	25.5
P5	33.1	32.9	29.9	35.2	30.5	29.7	28.3
Average	28.8	29.6	26.0	27.6	25.3	24.5	23.8
NTCP Dysphagia [%]	**IMRT**	**IMPT FHB**	**CPPT FHB**	**IMPT Gantry**	**CPPT Gantry**	**IMPT Arc**	**CPPT Arc**
P1	13.1	11.5	10.7	11.5	10.8	10.3	9.9
P2	13.5	10.4	10.7	11.3	10.5	9.5	9.2
P3	12.2	10.2	10.3	10.3	10.2	9.7	9.6
P4	10.4	8.5	8.4	8.1	8	7.4	7.2
P5	15	13	12.2	15.6	13.4	12	11.7
Average	12.8	10.7	10.5	11.4	10.6	9.8	9.5

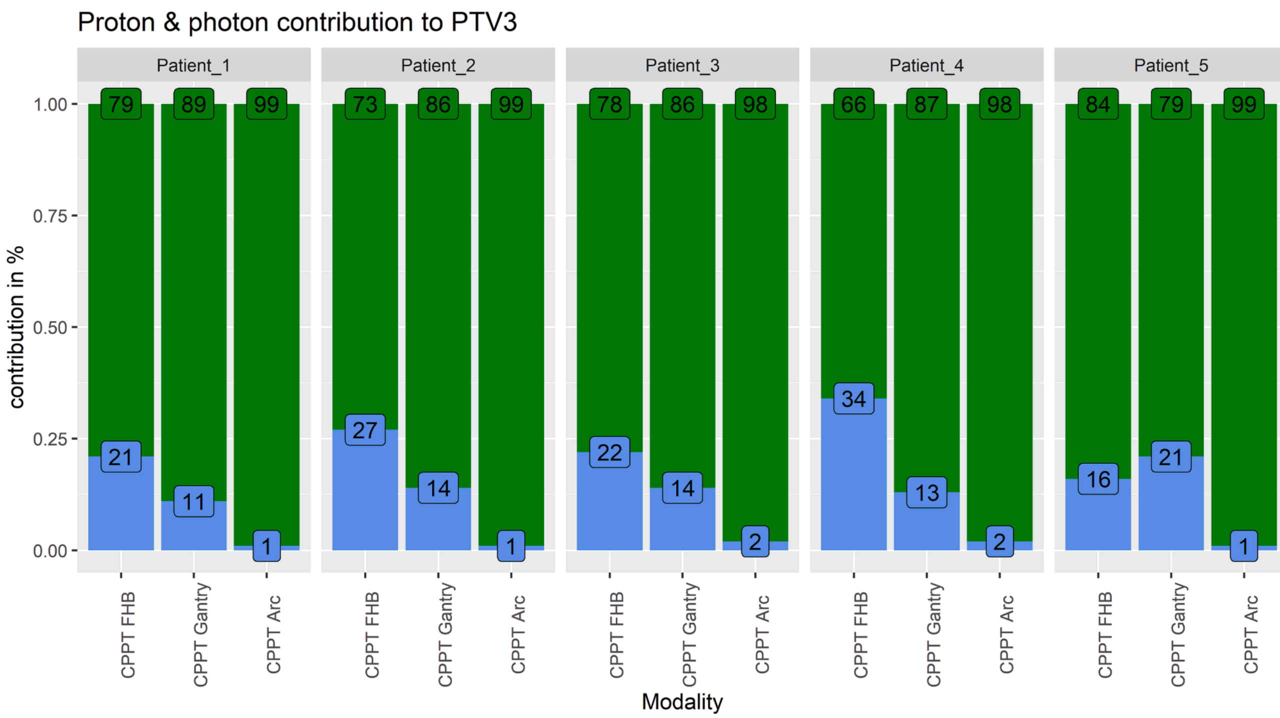

Fig. 4. Proton (green) and photon contribution (blue) in percentage to the mean dose of the elective-nodal PTV for the different proton beam flexibility scenarios for each patient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

thereby necessitating consideration of the time gap between these deliveries.

- Upright patient positioning: When implementing an upright patient positioning system, room design should be approached in a manner that minimizes excessive air gaps while accommodating this arrangement.

The identified cost drivers for different treatment modalities are summarized in the supplementary material (Table A3). As soon as a treatment involves any proton component, i.e. all discussed IMPT and CPPT treatments, a proton accelerator, and a proton beam line are needed, which are more space demanding and expansive than a photon LINAC [25]. In the case of IMPT/CPPT gantry or arc treatments with a conventionally positioned patient, the proton gantry increases the cost even more [25]. If CPPT treatments are delivered within the same room an advanced couch system is needed. If upright patient positioning will be available in the future, an upright CT and the special positioning system are required, which at least in an early phase is likely to be more expensive than a conventional CT and the conventional treatment couch. Of note, compared to proton gantry systems the costs are still likely to be lower as the space requirements would be much lower. Maintenance costs are with a large probability higher for IMPT treatments, as the accelerator and beam line is more complex compared to a photon LINAC [25]. For CPPT treatments the maintenance cost is also higher as two accelerators are involved. The treatment slots are longer for proton therapy than for IMRT treatments [52,53], therefore, also with two different machines involved for CPPT, it has to be expected that the average treatment time is longer, and the costs are higher. More personnel is needed for the maintenance of a proton therapy machine [25,53]. This has to be expected for a CPPT treatment, which includes two accelerators. In the case of the photon and proton component delivered in the same room, the room must be designed bigger than an IMRT room. Additionally, satisfying radiation protection requirements is expected to be more complex, which will also increase the costs. If CPPT is delivered in two different rooms, the required space and subsequently the costs will be higher. Furthermore, patient scheduling, patient transport, and quality assurance (QA) will need more resources.

Discussion

CPPT is a promising concept. It was primarily of interest to increase access to PT, either by optimizing the allocation of the limited number of proton fractions [41,54] or by reducing the cost of the proton component by using a fixed horizontal proton beam line, as opposed to a costly gantry, and combining this with a conventional photon LINAC [42–44]. In addition, however, previous investigations suggest that CPPT may outperform single-modality treatments in the presence of uncertainties or in terms of biological effects [45,46].

This study investigated CPPT delivering protons and photons in the same fraction. Within this approach, this study explores what is possible for CPPT in the case of different proton beam configurations, more specifically on how CPPT compares to IMPT-only treatments in the context of HNC patients. As a reference, the comparison to IMRT-only treatments was also included. Additionally, the study investigated the necessity of adaption for CPPT treatments for HNC patients.

We have demonstrated that CPPT treatments without adaption for HNC patients undergoing anatomical changes during treatment would lead to sub-optimal target coverage. Instead, in an adaptive treatment, plan quality for CPPT FHB remains on a high level, and the previously described advantages of CPPT with an FHB compared to IMRT or IMPT FHB remain. However, this indicates that further studies towards clinically realistic situations of CPPT should also consider the impact of inter-fractional anatomical changes on the CPPT plans. In this work, 4–7 repCTs were considered to evaluate the impact in a non-adaptive treatment strategy and to evaluate the quality of reoptimized plans in the adaptive treatment strategy. This corresponds to an adaption on at least a weekly basis, which earlier showed to be a possible alternative to daily adaption for HNC patients [55]. An in-depth analysis of the frequency of re-planning, or the extent of anatomical changes triggering plan adaption, might be an interesting investigation for the future. Furthermore, the use of plan library approaches instead of full plan reoptimization was shown recently to be a promising option for proton therapy [56]. This option could also be considered for future CPPT research.

CPPT with different levels of proton beam flexibility improved dose distributions and reduced probabilities for side effects compared to IMRT for all levels. Additionally, CPPT was able to improve plan quality compared to its proton-only counterparts. The largest increase in plan quality was observed for the FHB proton configuration, as the photon component adds the most flexibility for this case. However, an essential new conclusion from this work is that even if no delivery uncertainties are evaluated, a CPPT treatment with full flexibility (CPPT Arc) can outperform a single modality proton treatment with the same proton beam flexibility (IMPT Arc). The investigation of the proton and photon components in the Arc treatments suggests that the photon part is mainly used to sharpen the dose gradients close to critical structures. This is most likely due to the sharper lateral penumbra of photons in comparison to protons.

Furthermore, we want to emphasize a number of limitations of this study, which were necessary in this early phase of CPPT investigations to make this exploratory study achievable while simultaneously advancing the understanding of CPPT:

- Regarding plan optimization, we are aware that there might be an option for even better plans depending on the objective settings during optimization, in the relative cost functions for the different modalities. However, in this work, we explicitly decided to keep the same objectives for all modalities to be as fair as possible between the different treatment types and minimize any bias. Of note, if the IMRT or the IMPT treatment plan could be improved with further optimization, then it is possible that the combination of IMRT and IMPT might also have further improved plan quality.
- We are aware that a typical arc treatment includes even more beam angles. Furthermore, we know this study's arc treatment plans are slightly different from the commercially presented solution for which the energy layers are filtered for delivery efficiency [31,57].
- Although the effects of anatomical changes have been considered, we have not taken into account residual range or spatial uncertainties into account. By rigidly registering all CTs to the planCT however, setup uncertainties were reduced to a minimum. Furthermore, reoptimization compensated for a proportion of the range uncertainties. Nevertheless, not all possible sources of range uncertainties have been considered. To account for setup and range uncertainties more rigorously further investigations are certainly required. For example, the trade-off between robustness and plan quality needs thorough investigation when proton and photon components are in interplay. Additionally, computational strategies for robust optimization of a CPPT arc are yet to be developed.
- Due to the resource-intensive nature of CPPT treatment planning the patient cohort in this study is small and the results of this study should be taken with care. Nevertheless, this study includes significantly more patients and CT scans per patient than previous CPPT studies.
- Since it was not possible to perform an analysis of the anatomical changes on a daily basis, with the present dataset, we had to weight the NTCPs accordingly. To increase the confidence on the values, additional investigation on the optimization strategies will be needed. With these limitations in mind, there may be some uncertainty associated with the reported NTCP values. However, the trends between the modalities seemed relatively stable for our patient cohort, especially when the DVH is considered in addition to the NTCPs. Furthermore, the conclusion that plan adaptation, due to anatomical changes, is necessary for the CPPT treatments should not be greatly affected by these limitations.

An additional aspect for thorough future consideration is the practical implementation and costs of different CPPT approaches. We identified several of those practical challenges but only summarized these challenges on a qualitative level, an in-depth analysis goes beyond the scope of this paper. Very complex is the evaluation of the costs and the cost-effectiveness of all these different CPPT approaches. Our summary of cost drivers is limited by the missing evaluation of the absolute costs, limiting the treatment modality intercomparison capability. However, a comprehensive analysis of all the different factors and costs goes clearly beyond the scope of the presented work and should be done in a dedicated study. Only after evaluating the costs, can one continue with cost-effectiveness studies. However, even for proton treatments of HNC, there is only a small number of such studies [58–62].

The results of our study emphasize the need for future investigations on the balance between costs and plan quality. This evaluation will also depend on the type of treatment delivery. In the case of a conventionally positioned patient, the question reduces to: "Is the gain from a CPPT with an FHB enough to treat patients without a gantry to reduce the treatment costs?" On the other hand, if we assume an upright patient positioning system with many possible beam angles, a second question arises: "is there a need to combine a proton FHB and a photon FHB when the increase in treatment plan quality is relatively small compared to the IMPT Arc?" For instance, with the increased interest in FLASH proton therapy, shoot-through proton beams are currently being investigated [63]. As such, instead of sharpening the edges of the target using photons, one might also think about using transmission proton beams instead.

Conclusion

CPPT combining a fixed proton beam line with a conventional LINAC can increase plan quality for HNC patients compared to IMRT and IMPT using an FHB. However, plan adaptation would still be necessary to mitigate inter-fractional anatomical changes, particularly for target coverage. This will be important to consider for future CPPT studies. Our exploratory study indicates that increasing proton field flexibility is helpful to increase plan quality further while reducing side effects. Even though the photon contribution was relatively minimal in the CPPT Arc deliveries, the combination exhibited a slightly superior performance compared to IMPT Arc. With an indication that the photon component was used to sharpen the dose gradient.

CRediT authorship contribution statement

Florian Amstutz: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Reinhardt Krcek:** Investigation, Writing – review & editing. **Barbara Bachtiary:** Investigation, Writing – review & editing. **Damien C. Weber:** Resources, Funding acquisition, Writing – review & editing. **Antony J. Lomax:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Jan Unkelbach:** Conceptualization, Software, Writing – review & editing, Supervision, Funding acquisition. **Ye Zhang:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109973.

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