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# Conventionally fractionated large volume head and neck re-irradiation using multileaf collimator-based robotic technique: A feasibility study

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ABSTRACT

*Purpose:* To report on the feasibility and performance of conventionally fractionated multileaf collimator (MLC)-based robotic stereotactic body re-irradiation of the head and neck region using MLC-based Cyberknife (CK) technology.

*Methods:* Patients treated for recurrent or second primary head and neck cancer (HNC) with curative proton therapy to a target volume > 30 $cm^3$ between 2011 and 2015 were included. MLC-based CK plans were generated using the CK M6 InCise2 MLC system. Dose statistics from MLC-based CK plans were compared to proton beam therapy (PBT) plans according to the following metrics: target coverage, target homogeneity index, gradient index, Paddick conformity index (CI), prescription isodose volume (PIV), treatment time (tTime) for one fraction as well as doses to organs at risk (OAR). Wilcoxon signed-rank test was used to compare dose metrics.

*Results:* Eight patients were included; the tumor sites included: salivary glands, pharynx (oropharynx, hypopharynx and retropharynx) and sinonasal cavities. Five of 8 patients were treated with multifield optimisation intensity modulated proton therapy, 3 were treated with passive scattering proton therapy. Median dose was 67 Gy (range 60–70) in 32 fractions (range 30–35). The median high-dose planning target volume (PTV) was 45.4 $cm^3$ (range 2.4 – 130.2 $cm^3$) and the median elective PTV was 91.9 $cm^3$ (range 61.2 – 269.7 $cm^3$). Overall, the mean target coverage (mean 98.3% vs. 96.2% for CK vs. PBT, respectively), maximum dose to PTV (mean 111% vs. 111%, p = 0.2) and mean dose to PTV (mean 104% vs. 104%) were similar across modalities. Highly conformal plans were achieved with both modalities, but mean CI was better with PBT (0.5 vs. 0.6 for CK vs. PBT, p = 0.04). Homogeneity and gradient indexes were similar between the 2 modalities; mean tTime with PBT and CK was 17 vs. 18 min, respectively (p = 0.7). Case-based study revealed that CK and PBT plans allowed for excellent sparing of OAR, with some clinical scenarios associated with better performance of CK while others with better performance of PBT.

*Conclusion:* Our study has demonstrated the dosimetric performance of large volume head and neck re-irradiation using MLC-based CK in various clinical scenarios. While conformity was generally better achieved with PBT, MLC-based CK allowed for high dose gradient leading to rapid dose drop-off and sparing of OAR. Conventionally fractionated MLC-based CK could be a competitive alternative in large volume head and neck re-irradiation that deserves further investigation in the clinical setting.



## 1. Introduction

The management of locoregional recurrence (LRR) and/or second primary cancer of the head and neck region within a previously irradiated area is challenging due to concerns over normal tissue complications. Re-irradiation of the head and neck region is not an uncommon situation, with rates of locoregional recurrence after curative radiotherapy estimated between 10 and 40% [1,2] and rates of second primary in previously treated head and neck cancers patients reaching up to 20% [3,4]. When possible, surgery followed by re-irradiation is often the preferred approach [5–7]. As many patients are not amenable to surgery, upfront radiotherapy with or without concurrent systemic therapy is a possible alternative. Whether delivered post-operatively or upfront,

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re-irradiation (often in combination with chemotherapy) is an important component of the management for optimal locoregional control. With re-irradiation being associated with up to 40% severe or life-threatening toxicities, including sclerosis, trismus, osteoradionecrosis, feeding tube dependence or carotid blowout [8–11], the risks versus benefits of re-irradiation should be carefully weighted. Conversely, uncontrolled locoregional disease is associated with severe morbidity, quality of life impairment and painful death [12–14], highlighting the need for effective locoregional control strategies.

While initial studies have reported outcomes of re-irradiation in the era of 3D conformal radiotherapy using hyperfractionated regimens, several alternative treatment strategies using more conformal techniques have emerged. These include conventionally fractionated intensity modulated radiotherapy (IMRT) and proton beam therapy (PBT), or hypofractionated stereotactic body radiotherapy (SBRT) [15–18]. Conventionnally fractionated PBT is regarded as the state of the art modality for re-irradiation of large volumes in the head and neck region, as it allows for highly conformal dose deposition with no or minimal exit dose to surrounding normal tissues [19]. SBRT consists in the delivery of large radiation doses in a small number of fractions (typically 1 to 5), using robust image-guidance for maximal precision. Due to concerns of safety, efficacy and prolonged treatment delivery time, SBRT is most commonly reserved for small tumor volumes [17]. The concept of conventionally fractionated stereotactic radiotherapy combines the precision of stereotactic positioning with the radiobiologic advantage of dose fractionation. Tumor motion in the head and neck region are usually within 3 mm but the extent of motion can vary widely, reaching up to 12.0 mm in certain cases [20], thus suggesting that there could be a significant gain from increased accuracy of treatment delivery in head and neck re-irradiation. To our knowledge, the concept of conventionnally fractionated stereotactic radiotherapy was never previously been investigated in the context of large volume re-irradiation of the head and neck region.

The Cyberknife™ (CK) stereotactic radiosurgery delivery system (Accuray, Sunnyvale, CA) consists in a 6-MV linear accelerator mounted on a 6 axes robotic arm and allows for near-real time target tracking. The recent CK M6™ Series system is associated with a InCise-2 multileaf collimator (MLC) and has a maximum field size of 115 mm × 100 mm; the latter features allow for treatment of larger and irregularly shaped targets, with significantly reduced radiation delivery time [21]. The purpose of this dosimetric study is to report on the feasibility and performance of conventionally fractionated MLC-based robotic stereotactic body re-irradiation of the head and neck region using CK M6 technology.

## 2. Material and methods

### 2.1. Patients and treatment planning

Eight patients treated for a recurrent or second primary head and neck cancer with curative intent PBT between December 2011 and February 2015 and fulfilling the following criteria were included in this dosimetric study: head and neck re-irradiation with overlap of at least 25% of the current planning target volume (PTV) with the previously treated area, target volume > 30 $cm^3$, and a field size less than 10 × 12 cm. All patients had a 2.5 mm slice-thickness simulation computed tomography extending from the vertex to the carina, without intravenous contrast, in supine position. Patients were immobilized with customized thermoplastic mask of the head, neck and shoulders, polyurethane foam headrest (CIVCO Medical Solutions, Orange City, IA) and a bite block. For patients treated with definitive radiotherapy, gross target volume (GTV) was defined by disease on radiographic and clinical examinations. High-dose PTV ($PTV_{HD}$) included the GTV or surgical bed plus a margin accounting for microscopic extension (5–8 mm) and a margin for positioning and motion uncertainty (3–5 mm). An elective dose PTV ($PTV_{ED}$) involving areas at risk of microscopic disease could be used and was individualized on a case by case level by the treating physician.

Doses were prescribed in grays (Gy) relative biological effectiveness (RBE), assuming a RBE value of 1.1 for protons. Contours were reviewed for quality assurance by a team of head and neck radiation oncologists. Treatment planning and dose calculation was done on an Eclipse proton therapy treatment planning system (version 8.9, Varian Medical Systems, Palo Alto, CA). Pertinent organs at risk (OAR) with specified dose constraints were contoured for treatment planning. Patients were treated with intensity modulated proton therapy (IMPT) or passive scattering proton therapy. Custom apertures and compensators were used for the passive scatter boost fields to provide the greatest degree of lateral conformity. For IMPT, 2–3 spot scanning beams were typically used. For MLC-based CK replanning, initial planning CT along with target and OAR structures were transferred to Accuray Precision™ Treatment planning system (Version 2.0.0.0, Accuray Inc.). All treatment plans were generated by an Accuray physicist, using the CK M6 InCise2 MLC system. Non-coplanar beam targeting was used.

For both PBT and MLC-based CK, treatment plans were normalised so that the prescription dose covered at least 95% of the PTV volume. Target coverage goals and dose constraints used for MLC-based CK plans were identical to those used in the PBT plans. Spinal cord and brainstem dose constraints were set as low as possible, with an assumption of 50% dose tolerance recovery for a retreatment interval ≥ 12 months. Dose constraints for previously irradiated structures were determined on a case by case level, taking into account previous dose received by each structure, and were discussed at quality assurance meetings.

### 2.2. Assessment of plan performance and statistics

Dose statistics from the PBT and MLC-based CK plans were extracted. Treatment plans were evaluated according to the following metrics: target coverage, target homogeneity index (HI), gradient index (GI), Paddick conformity index [22] (CI), prescription isodose volume (PIV), treatment efficiency measured as treatment time (tTime) for one fractionm as well as doses to OAR. HI was defined as the ratio between the dose to 95% of the PTV (D95%) and the dose to 5% of the PTV (D5%) and was calculated using the high risk PTV. The PIV, $PIV_{50}$ and $PIV_{20\text{-}50}$ were defined as the irradiated volume by prescription isodose line, the irradiated volume enclosed by the 50% prescription isodose line, and the volume that received between 20% and 50% of the prescription isodose, respectively. $R_{50}$ and $R_{20\text{-}50}$ were defined as the ratio of $PIV_{50}$ over PTV, and the ratio of $PIV_{20\text{-}50}$ over PTV, respectively. The GI was defined as the ratio of $PIV_{50\ over}$ PIV, representing the extent of dose fall-off at 50% of prescription dose. For patients who had an elective target volume, the GI, PIV, $PIV_{50}$, $PIV_{20\text{-}50}$ were calculated based on $PTV_{ED}$. The tTime for MLC-based CK plans was estimated by the Accuray Precision treatment planning system and included real time imaging and target tracking time. The tTime for PBT plans was estimated based on the results of quantitative analysis of treatment process time for patients treated in our institution and included beam irradiation time, mean equipment setting time and beam requesting time [23–24]. Wilcoxon signed-rank test was used to compare dose metrics of the PBT and MLC-based CK plans. All reported *P* values were 2 sided, and levels < 0.05 were considered statistically significant. SPSS 24 (IBM, Armonk, NY) was used for statistical analysis.

## 3. Results

### 3.1. Patients' characteristics

Table 1 presents characteristics of the patients included. Median age at recurrence was 65 year-old (range = 28–76). Median interval time between initial radiotherapy course and re-irradiation was 2.3 years (range = 1.2–8.9). Recurrence sites included the salivary glands (parotid and submandibular glands), pharynx (oropharynx, hypopharynx and retropharynx) and sinonasal cavities (maxillary sinus, orbit). Histologies included squamous cell carcinoma (5/8 patients), adenocarcinoma, neuroendocrine tumor and ex-pleomorphic adenoma. Half of the patients had surgery at time of recurrence and half had weekly concurrent chemotherapy. Five of 8 patients were treated with IMPT while 3 were treated with passive scattering proton therapy. Median dose was 67 Gy (range 60–70) in 32 fractions (range = 30–35). In addition, 5 patients were treated to an elective volume ($PTV_{ED}$).

### 3.2. Dosimetric performance of MLC-based CK plans in comparison with PBT plans

The median $PTV_{HD}$ volume for the 8 patients was 45.4 $cm^3$ (range 2.4 – 130.2 $cm^3$); the median t $PTV_{ED}$ for the 5 patients treated to an elective volume was 91.9 $cm^3$ (range 61.2 – 269.7 $cm^3$). Table 2 presents the combined dosimetric performance of CK M6 and PBT plans for all patients. Overall, the mean target coverage (mean 98.3% vs. 96.2% for CK M6 vs. PBT, respectively; p = 0.1), maximum dose to PTV (mean 111.4 vs. 110.8, p = 0.2) and mean dose to PTV (mean 104.4 vs. 104.4, p = 0.9) were similar across both modalities. As demonstrated by the CI and low-dose spillage metrics of R50, R20-50, CK M6 plans generally had inferior dose conformity compared to PBT, but the homogeneity and gradient were comparable between the 2 modalities. The estimated mean tTime was 18.1 min (range = 15–26) for CK M6 vs. 17.0 min for PBT (range = 9–31) (p = 0.7).

**Table 2**
Overall Dosimetric Comparison of Proton vs. CK plans.

| | CK | PBT | P value |
|---|---|---|---|
| | Mean (±SD) | Mean (±SD) | |
| $PTV_{HD\_max}$ (Gy) | 111.4 ± 1.8 | 110.8 ± 1.7 | 0.2 |
| $PTV_{HD\_mean}$ (Gy) | 104.4 ± 1.9 | 104.4 ± 1.2 | 0.9 |
| % PTV coverage | 98.3 ± 2.0 | 96.2 ± 3.8 | 0.1 |
| PTV > 107% (cc) | 19.8 ± 30.6 | 9.9 ± 11.0 | 0.3 |
| PIV (cc) | 279.3 ± 296.5 | 190.4 ± 203.6 | 0.1 |
| PIV50 (cc) | 866.9 ± 940.5 | 685.8 ± 926.5 | **0.05** |
| PIV20 (cc) | 2252.3 ± 2185.9 | 1582.0 ± 2187.3 | **0.01** |
| PIV20-50 (cc) | 1385.4 ± 1266.3 | 896.2 ± 1275.5 | **0.008** |
| R50 | 8.1 ± 3.2 | 5.5 ± 2.6 | **0.03** |
| R20-50 | 14.1 ± 7.4 | 6.9 ± 6.3 | **0.01** |
| HI | 1.1 ± 0.0 | 1.1 ± 0.0 | 0.5 |
| GI | 3.0 ± 0.5 | 3.4 ± 1.4 | 0.4 |
| CI | 0.5 ± 0.9 | 0.6 ± 0.2 | **0.04** |
| tTime (min) | 18.1 ± 3.9 | 17.0 ± 6.9 | 0.7 |

CK = Cyberknife; PBT= proton beam therapy; SD = standard deviation; $PTV_{HD\_max}$ = Maximum dose to high dose PTV; $PTV_{HD\_max}$ = mean dose to high dose PTV; PTV = planning target volume; PIV = prescription isodose volume; PIV50 = volume of the 50% prescription isodose; PIV20-50 = volume between the 20 and 50% prescription isodoses; R50 = irradiated volume to PTV ratio, R20-50 = low dose volume to PTV ratio; HI = homogeneity index; GI = gradient index, tTime= treatment delivery time.

### 3.3. Case based study

#### 3.3.1. Salivary glands (patients 1 and 2)

Patient 1 had recurrence of a left parotid adenocarcinoma treated with passive scatter proton therapy. Table 3 and Fig. 1 show the dosimetric characteristics of MLC-based CK plan compared to the PBT plan. The 2 plans had similar CI, GI and HI. CK had higher low dose distribution ($R_{20\text{-}50}$ = 12 with CK vs. 2 with PBT). The PBT plan was associated with higher maximum point dose to the brain (35 Gy with CK vs. 58 Gy with PBT) but lower mean dose to the ipsilateral cochlea (mean 9 Gy with CK vs. 4 Gy with PBT). For patient 2, high dose conformity and low dose spread were similar between the 2 modalities. Both the PBT and CK plans achieved low mean dose to oral cavity and larynx, but the maximum doses to the oral cavity, mandible and larynx were lower with the CK plan.

#### 3.3.2. Pharynx (Patients 3 to 6)

Detailed target coverage and doses to OAR of patients 3 through 6 are presented in Table 4 and Fig. 2. While MLC-based CK generally achieved good conformity, CI was better with PBT in all cases. MLC-based CK had improved coverage in patients 4 and 6.

#### 3.3.3. Sinonasal cavities (Patients 7 and 8)

Table 5 and Fig. 3 show the dosimetric characteristics of the MLC-based CK plan compared to the PBT plan for patients 7 and 8. MLC-based CK plans achieved similar target coverage as with PBT. The PBT plan showed improved CI as well as reduced low dose spread in both cases. Doses to OAR were similar across plans, with the exception of maximum dose to the brainstem and optic chiasm, which were lower with MLC-based CK plan in case 8.

## 4. Discussion

This study reports on the feasibility and dosimetric performance of InCise MLC-based CK treatment planning for large target volume head and neck re-irradiation. We demonstrated that MLC-based CK can achieve highly conformal radiation plans in the re-irradiation setting. Although the conformity was generally better

**Table 1**
Patients' characteristics.

| N | Age (y) | Gender | IIRT (y) | Site | Hist | Sx | CCT | PBT Tech | Dose | Fx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 37 | M | 8.9 | Parotid | ADK | No | No | Passive | 70 | 33 |
| 2 | 63 | M | 1.6 | SMG | NE | Yes | Cis | IMPT | 60 | 30 |
| 3 | 76 | M | 1.2 | OPX | SCC | No | No | IMPT | 70 | 35 |
| 4 | 67 | M | 4 | HPX | SCC | Yes | No | IMPT | 60 | 30 |
| 5 | 75 | F | 8 | OPX | SCC | No | Carb | Passive | 70 | 35 |
| 6 | 63 | M | 2.7 | RPX | SCC | No | Cis | IMPT | 70 | 33 |
| 7 | 72 | M | 1.8 | Orbit | SCC | Yes | No | IMPT | 60 | 30 |
| 8 | 28 | M | 1.9 | MS | Ex-PA | Yes | Cis | Passive | 63 | 30 |

N = patient number; Y = year; M = male; F = female; IIRT = Interval-time since initial radiotherapy; SMG = submandibular gland; OPX = oropharynx; HPX = hypopharynx; RPX = retropharynx; MS = maxillary sinus; Hist = histology; ADK = adenocarcinoma; SCC = squamous cell carcinoma; NE = neuro-endocrine; Ex-PA = ex- pleomorphic adenoma; Sx = surgery; CCT = concurrent chemotherapy; Cis = cisplatin; Carb = carboplatin; PBT Tech = proton beam therapy technique; IMPT = intensity modulated proton therapy; Fx = fractions.

**Table 3**
Dosimetric Comparison of MLC-based CK vs. Protons: Salivary glands.

| **Patient Number** | **1** | | **2** | |
|---|---|---|---|---|
| **Site** | **Parotid** | | **Submandibular bed** | |
| *Dose (Gy)/fx* | $PTV_{HD}$ = 70/33 | | $PTV_{HD}$ = 60/30<br>$PTV_{ED}$ = 57/30 | |
| **Technique** | **CK** | PBT | **CK** | PBT |
| *$PTV_{HD}$ (cc)* | 32 | 31 | 41 | 40 |
| *$PTV_{ED}$ (cc)* | | | 62 | 61 |
| *$PTV_{max}$ (Gy)* | 112 | 111 | 108 | 108 |
| *$PTV_{mean}$ (Gy)* | 100 | 104 | 104 | 103 |
| *PTV coverage (%)* | 99 | 100 | 99 | 94 |
| *PIV (cc)* | 81 | 61 | 118 | 76 |
| *R50* | 6 | 5 | 5 | 4 |
| *R20-50* | 12 | 2 | 5 | 3 |
| *HI* | 1 | 1 | 1 | 1 |
| *GI* | 2 | 2 | 2 | 3 |
| *CI* | 0.4 | 0.5 | 0.5 | 0.7 |
| | **Dose to relevant OAR (Gy)** | | | |
| *$Brain_{max}$* | 35 | 58 | | |
| *Ipsi $Cochlea_{mean}$* | 9 | 4 | | |
| *Oral $cavity_{mean}$* | | | 1 | 3 |
| *Oral $cavity_{max}$* | | | 52 | 41 |
| *$Mandible_{max}$* | | | 54 | 51 |
| *$Larynx_{mean}$* | | | 2 | 3 |
| *$Larynx_{max}$* | | | 42 | 28 |

Ipsi = ipsilateral; OAR = organ at risk.

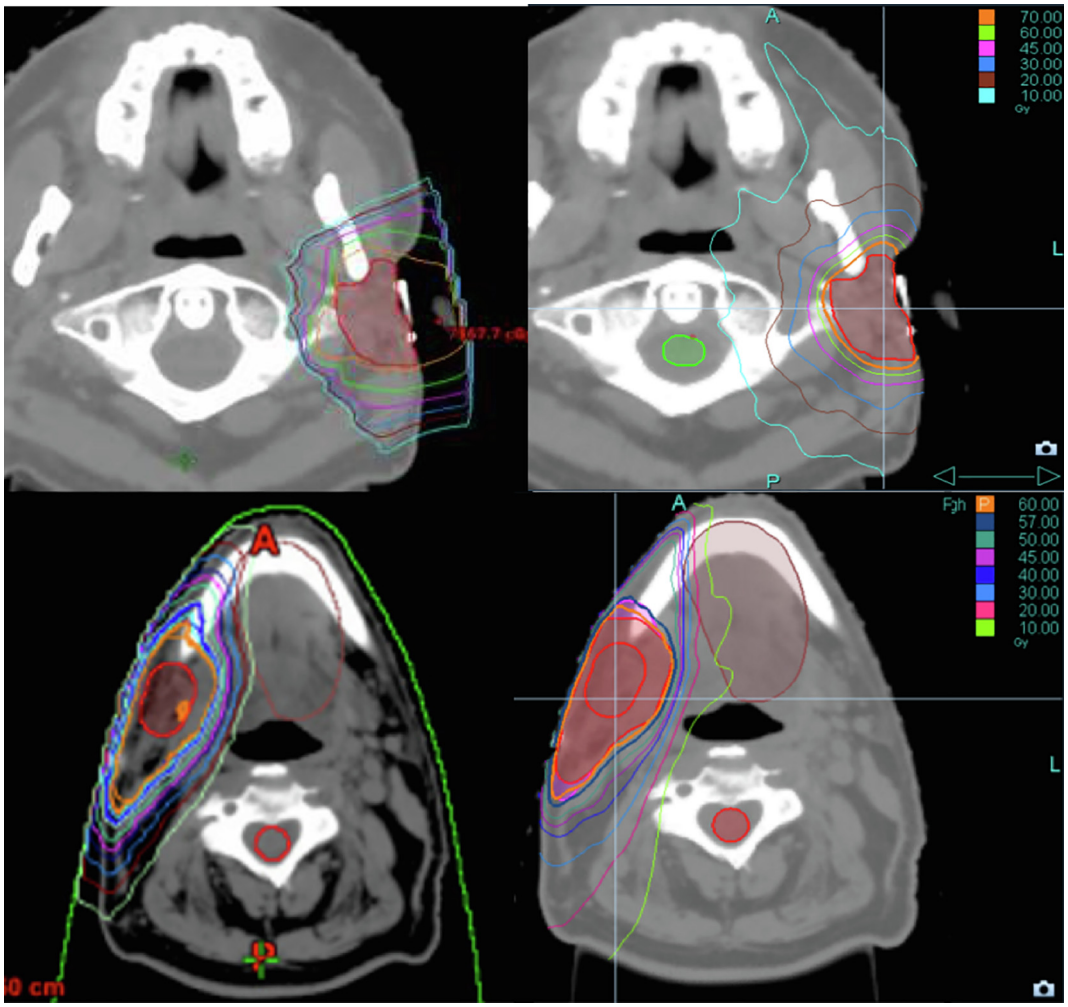


**Fig. 1.** Treatment plan of a left parotid recurrence treated to a dose of 70 Gy in 33 fractions (orange contour) using passive scatter proton therapy (upper left) vs. CK (upper right); treatment plan of a right submandibular gland bed using IMPT (lower left) vs. CK (lower right) with 2 dose volumes: 60 Gy (orange contour) and 57 Gy (dark blue contour). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
Dosimetric Comparison of MLC-based CK vs. Proton Plans: Pharynx.

| **Patient Number** | **3** | | **4** | | **5** | | **6** | |
|---|---|---|---|---|---|---|---|---|
| **Site** | **Oropharynx** | | **Hypopharynx/Larynx** | | **Oropharynx** | | **Retropharynx** | |
| Dose (Gy)/fx | $PTV_{HD}$ = 70/35<br>$PTV_{ED}$ = 59.5/35 | | $PTV_{HD}$ = 60/30<br>$PTV_{ED}$ = 54/30 | | $PTV_{HD}$ = 70/35 | | $PTV_{HD}$ = 70/35 | |
| **Technique** | PBT | **CK** | PBT | **CK** | PBT | **CK** | PBT | **CK** |
| *PTV1 (cc)* | 53 | 54 | 130 | 133 | 50 | 51 | 32 | 33 |
| *PTV2 (cc)* | 248 | 251 | 270 | 274 | – | – | – | – |
| *$PTV_{max}$ (Gy)* | 111 | 112 | 112 | 112 | 112 | 112 | 112 | 114 |
| *$PTV_{mean}$ (Gy)* | 105 | 106 | 104 | 105 | 104 | 104 | 105 | 106 |
| *PTV coverage (%)* | 97 | 99 | 91 | 100 | 98 | 97 | 91 | 94 |
| *PIV (cc)* | 600 | 971 | 410 | 348 | 73 | 121 | 36 | 98 |
| *R50* | 11 | 12 | 5 | 4 | 5 | 7 | 7 | 11 |
| *R20-50* | 14 | 16 | 8 | 9 | 8 | 10 | 18 | 30 |
| *HI* | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| *GI* | 5 | 3 | 3 | 3 | 4 | 3 | 6 | 4 |
| *CI* | 0.4 | 0.2 | 0.6 | 0.8 | 0.7 | 0.4 | 0.7 | 0.3 |
| | **Dose to relevant OAR (Gy)** | | | | | | | |
| *$Brainstem_{max}$* | 30 | 32 | *5* | *16* | 0 | 2 | 38 | 35 |
| *$Spinal\ cord_{max}$* | 43 | 39 | 27 | 25 | 1 | 2 | 16 | 16 |
| *$Ipsi\ cochlea_{mean}$* | *33* | *25* | | | 0 | 0 | 52 | 9 |
| *$Contro\ cochlea_{mean}$* | *28* | *7* | | | 0 | 1 | 0 | 1 |
| *$Oral\ cavity_{mean}$* | *15* | *32* | *5* | *15* | | | 2 | 5 |
| *$Mandible_{max}$* | 73 | 66 | *12* | *22* | 71 | 68 | 65 | 62 |
| *$Ipsi\ parotid_{mean}$* | 39 | 36 | 38 | 44 | 1 | 5 | 39 | 33 |
| *$Contra\ parotid_{mean}$* | 20 | 27 | 0 | 1 | 3 | 6 | | |
| *$Larynx_{mean}$* | *34* | *47* | | | 43 | 13 | | |
| *$Larynx_{max}$* | 65 | 70 | | | 69 | 40 | | |
| *$Oesophagus_{mean}$* | | | 27 | 27 | | | | |
| *$Oesophagus_{max}$* | | | 63 | 66 | | | | |
| *$Contra\ Carotid_{mean}$* | | | | | 28 | 19 | | |
| *$Contra\ Carotid_{max}$* | | | | | 54 | 48 | | |
| *$Ipsi\ Carotid_{mean}$* | | | | | 48 | 25 | | |
| *$Ipsi\ Carotid_{max}$* | | | | | 71 | 66 | | |

with PBT planning, homogeneity and gradient indexes between MLC-based CK and PBT plans were comparable. Both CK and PBT plans allowed for excellent sparing of OAR, with some clinical scenarios favouring MLC-based CK while others favouring PBT. There was no statistically significant difference in treatment time between MLC-based CK and proton therapy. Mean and maximum treatment times on MLC-based CK were 18 and 26 min, respectively, supporting the clinical feasibility of large volume irradiation with this technique. With the current limited access and high cost of PBT, this study suggests that conventionally fractionated stereotactic radiotherapy using MLC-based CK could offer an interesting alternative for large volume head and neck re-irradiation.

Comparatively to the fixed or iris collimators CK systems, the larger field size (maximum field size of 11.5 cm × 10 cm) of the InCise2 MLC system callows for a reduced number of beams and monitor units, resulting in the possibility to treat larger target volumes with shorter treatment time. Previous planning studies have compared MLC-based CK plans against fixed or Iris collimators CK plans for prostate cancer, brain metastasis, accelerated partial breast irradiation and spine SBRT [25–28] and have reported treatment time reduction by approximately 30–50% with MLC-based CK. However, Jang et al. [27] compared MLC-based plans with cone or Iris-based plans of 24 patients with brain metastasis and reported slightly inferior dose conformity of MLC-based plans for cases where OAR were located close or were abutting target volumes. The inferior dose conformity was explained by the minimum MLC opening of 7.6 mm, suggesting that targets inferior to 56.3 $cm^3$ may not be optimal for MLC-based CK plans. Interestingly, in our study, we observed that the 2 cases with the largest differences in conformity index (>0.2) between MLC-based CK and PBT had target volumes below 56.3 $cm^3$. In addition, other factors such as the static delivery (vs. sliding window or arc-based approaches) of CK MLC-based treatment can further limit the potential treatment conformity. McGuinness et al. [26] has directly compared plans from prostate and intracranial cancers planned using MLC-based CK vs. conventionally fractionated IMRT from conventional Linacs. Generation of conventionnally fractionated plans using MLC-based CK was feasible with high prescription isodose values (between 86%-92% , on average), with a mean treatment time of 25 min for whole pelvis plans and 19 min for intracranial plans. Plan conformity and doses to OAR were equivalent between the two modalities, but the large number of non-coplanar beams with MLC-based CK resulted in improved R50. Interestingly, McGuiness et al. reported a reduction in target dose homogeneity and treatment efficiency (more beams to cover the entire PTV, resulting in higher monitor units) when the field size was above 10 cm × 12 cm, as is the case in whole pelvis plans, suggesting that MLC-based CK may not be an optimal option for these specific cases.

An important aspect not taken into account in our dosimetric study is that the CK system allows for near-real time image-guidance and therefore comparatively smaller uncertainty margins could be used, which would also result in shorter treatment time than is presented here. In our study, we chose to use the same PTVs for the MLC-based CK plans as those used in the PBT plans to focus on the performance of the treatment machine and planning system rather than on the benefits derived from reduced margins. In a previous study assessing the impact of margin reduction on outcomes and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy, reducing the PTV margin from 5 to 3 mm resulted in reduced severity and rate of grade 3 toxicity and rates of feeding tube placements, suggesting that a reduction of PTV margin of only a few millimeters can translate into a clinically significant reduction in toxicity. Recent work from our group aiming to determine the optimal PTV margins to be used in stereotactic head and neck radiotherapy showed that PTV mar-

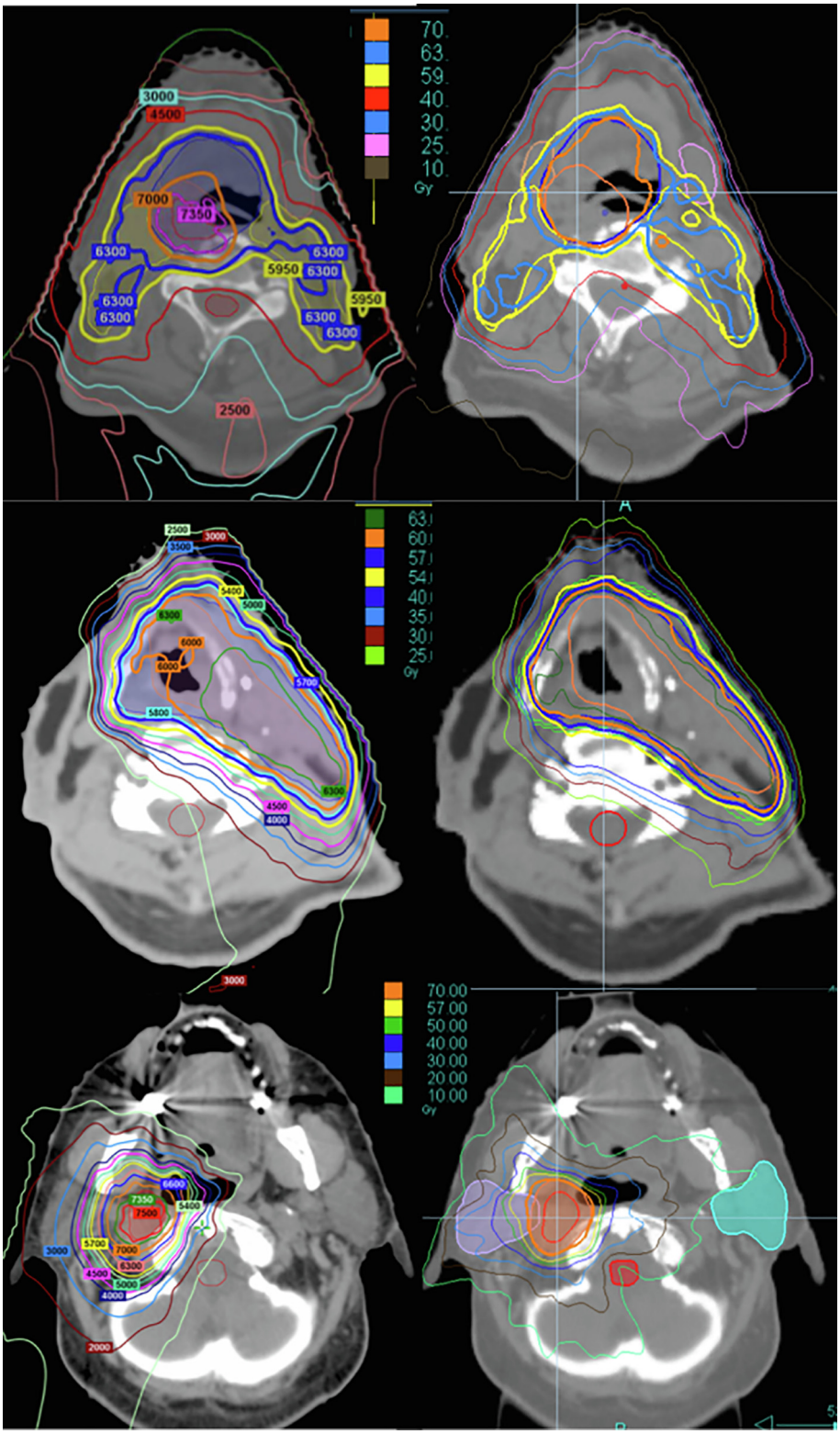


**Fig. 2.** Treatment plan of a right oropharynx recurrence treated loco-regionally to a dose of 70 Gy (orange contour) and 59.5 (yellow contour) using IMPT (upper left) vs. CK (upper right); treatment plan of a hypopharynx/larynx recurrence using IMPT (middle left) vs. CK (middle right) to a dose of 60 Gy (orange contour); treatment plan of a retropharyngeal recurrence treated with IMPT (lower left) vs. CK (lower right) to a dose of 70 Gy (orange contour). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

gins of 1.5–2 mm are sufficient for skull base tumors, whereas 2–2.5 mm is optimal for neck and mucosal targets [29], suggesting that PTV margins of 1.5–2.5 mm could be used in the CK plans comparatively to the 3–5 mm used in the PBT plans. Consequently, in clinical practise, the superior conformity of PBT plans may be offset by the proton beam range uncertainties and the additional motion and setup up margins required for safe target coverage.

**Table 5**
Dosimetric Comparison of CK vs. Protons: Sinonasal cases.

| **Patient Number** | **7** | | **8** | |
|---|---|---|---|---|
| **Site** | **Maxillary sinus** | | **Orbital Cavity** | |
| Dose (Gy)/fx | $PTV_{HD}$ = 63/30<br>$PTV_{ED}$ = 54/30 | | $PTV_{HD}$ = 60/30<br>$PTV_{ED}$ = 57/30 | |
| **Technique** | PBT | **CK** | PBT | **CK** |
| *$PTV_{HD}$ (cc)* | 2 | 2.9 | 25 | 26 |
| *$PTV_{ED}$ (cc)* | 83 | 85 | 73 | 74 |
| *$PTV_{max}$* | 109 | 110 | 113 | 111 |
| *$PTV_{mean}$* | 104 | 106 | 107 | 105 |
| *% PTV coverage* | 99 | 99 | 100 | 99 |
| *PIV* | 141 | 189 | 126 | 308 |
| *R50* | 3 | 8 | 4 | 12 |
| *R20-50* | 1 | 12 | 2 | 18 |
| *HI* | 1 | 1 | 1 | 1 |
| *GI* | 2 | 4 | 2 | 3 |
| *CI* | 0.6 | 0.4 | 0.3 | 0.2 |
| **Dose to relevant OAR (Gy)** | | | | |
| *Optic chiasm$_{max}$* | 11 | 11 | 33 | 20 |
| *Ipsi Optic Nerve$_{max}$* | 4 | 5 | | |
| *Contro Optic Nerve$_{max}$* | 18 | 16 | 17 | 17 |
| *Brain$_{max}$* | 59 | 59 | 63 | 62 |
| *Brainstem$_{max}$* | 8 | 7 | 6 | 2 |
| *Ipsi temporal lobe$_{max}$* | | | 62 | 62 |
| *Spinal cord$_{max}$* | 3 | 3 | | |
| *Ipsi Cochlea$_{mean}$* | 0 | 1 | 1 | 2 |
| *Contro Cochlea$_{mean}$* | 0 | 2 | | |

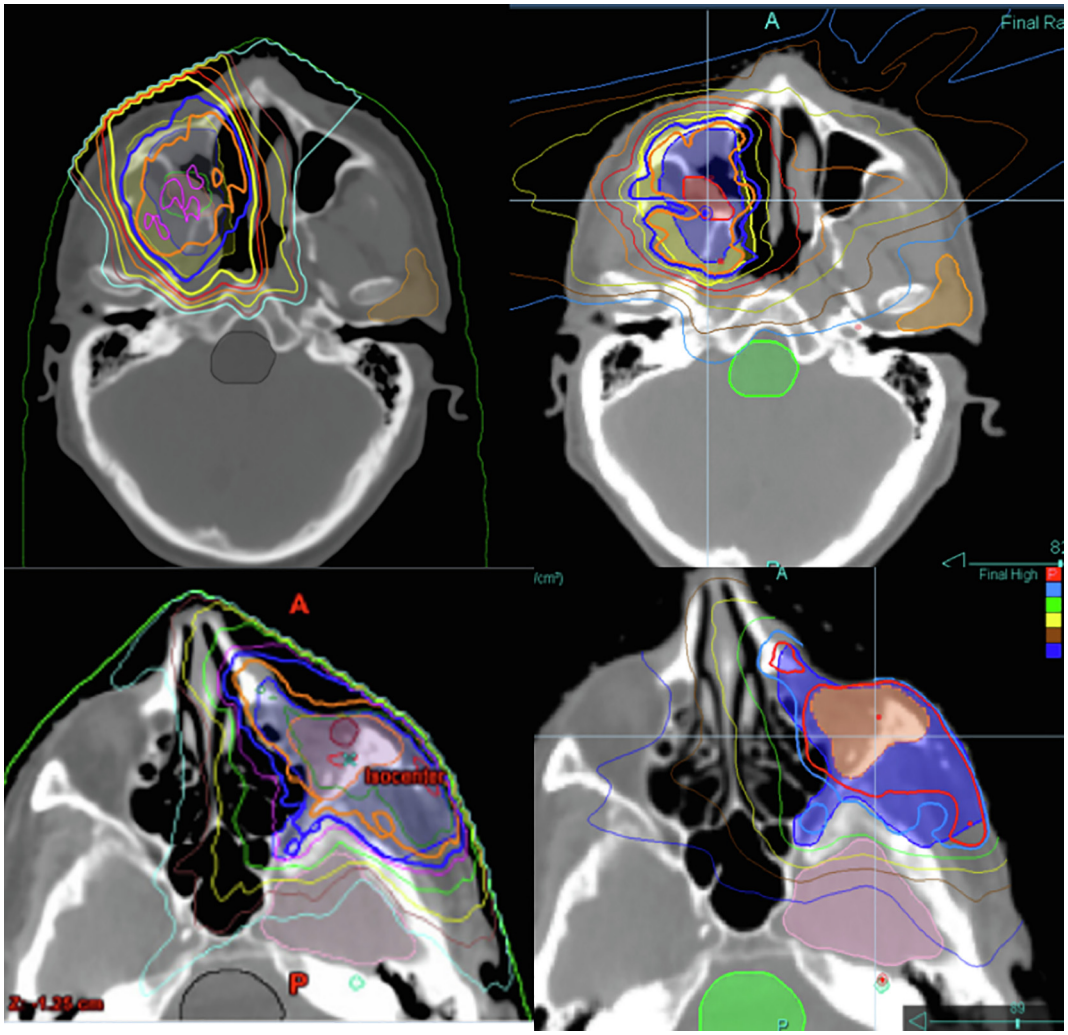


**Fig. 3.** Treatment plan of a right maxillary sinus recurrence treated to a dose of 63 Gy in 33 fractions (orange contour) using passive scatter proton therapy (upper left) vs. CK (upper right); treatment plan of a right submandibular gland operative bed using IMPT (lower left) vs. CK (lower right) with 2 dose volumes: 60 Gy (orange contour) and 57 Gy (dark blue contour). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the context of re-irradiation, optimal dose fractionation to maximize tumor control probability while minimizing normal tissue complication remains under investigation. While hyperfractionated regimens have traditionally been favoured under the assumption that small fraction size allows for sparing of late-responding normal tissues, contemporaneous studies have reported acceptable outcomes with conventional fractionation using conformal radiation modalities such as IMRT or PBT without evident increase in late toxicity outcomes [19,30,31]. On the other hand, several studies have reported promising outcomes of SBRT for small target lesions [32,33]. The excellent outcomes of SBRT suggest that the increased precision of treatment delivery achieved with image-guidance may offset the potential increase in late normal tissue complication probability associated with hypofractionation [17,34–37]. The combination of the precision of SBRT with conventional fractionation as proposed in our study may further widen the therapeutic ratio of head and neck re-irradiation by limiting late responding tissue damage. In head and neck re-irradiation, there is controversy around the necessity to treat an elective lower dose volume. In a multi-instutitionl retrospective study from Caudell et al. involving 505 patients who underwent head and neck re-irradiation, elective nodal irradiation did not decrease the risk of locoregional failure or improve overall survival but was associated with increased acute toxicity in the postoperative setting. While it has been our institutional approach to include only the high-risk volume in cases of re-irradiation, the decision to include a limited elective volume judged at risk of microscopic recurrence is taken in certain cases, based on the specific clinical scenario, after carefully weighing the risks vs. benefits. In our presented cases, the proportion of patients receiving elective irradiation is likely over-represented given the pre-specified criteria of large field irradiation. It should also be stated that the multi-institutional analysis by Caudell et al. included only patients treated with IMRT; the lack of cancer outcome advantage and the adverse toxicity rates observed with elective re-irradiation using IMRT may not apply to PBT re-irradiation. Interestingly, several cases presented in this dosimetric study included non-squamous cell histologies. The theoretical advantage of PBT for radioresistant histologies such as salivary gland tumors has previously been postulated, but remains to be clinically demonstrated [38–40]. It is not clear if this potential advantage would be attributed to an increased potency of PBT as compared to X-rays or simply due to the ability to dose escalate due to the physical properties of PBT. While pre-clinical reports have postulated that the radiobiological effectiveness (RBE) of protons was 1.1 compared to X-rays [41], protons RBE may vary significatively with factors such as linear energy transfer, dose per fraction and tissue type [38]. In addition to the impact on tumor control, this may lead to substantial dose uncertainty to OAR in the vicinity of the target volume.

Although this study is limited by its small and heterogeneous sample size, it demonstrated that head and neck re-irradiation with MLC-based CK was feasible in various clinical scenarios. Importantly, the differences in performance between modalities can also include variation in the dosimetrist's experience. Proton technology and physicists experience may have evolved in the interval, which also holds true for CK M6 planning where the physicist experience is expected to improve over time. Further studies comparing the dosimetric performance of PBT, MLC-based CK and arc-therapy in different clinical scenarios with varying target volumes, shapes and proximity to critical OAR are needed.

## 5. Conclusion

Our study has demonstrated the feasibility and competitive dosimetric performance of large volume head and neck re-irradiation using MLC-based CK, in a variety of clinical scenarios. While dose conformity was generally better achieved with PBT, MLC-based CK plans allowed for rapid dose fall-off and sparing of critical OAR. This study suggests that conventionally fractionated MLC-based CK radiotherapy could be an acceptable alternative to PBT in large volume head and neck re-irradiation and should be investigated in the clinical setting.

## 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.

## References

[1] Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. New England J Medicine 2003;349(22):2091–8.
[2] Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet (London, England). 2003;362(9388):933–40.
[3] Cooper JS, Pajak TF, Rubin P, Tupchong L, Brady LW, Leibel SA, et al. Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. Int J Radiat Oncol Biol Phys 1989;17(3):449–56.
[4] Lin K, Patel SG, Chu PY, Matsuo JM, Singh B, Wong RJ, et al. Second primary malignancy of the aerodigestive tract in patients treated for cancer of the oral cavity and larynx. Head Neck 2005;27(12):1042–8.
[5] Bachar GY, Goh C, Goldstein DP, O'Sullivan B, Irish JC. Long-term outcome analysis after surgical salvage for recurrent tonsil carcinoma following radical radiotherapy. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology -Head and Neck Surgery. 2010;267(2):295–301.
[6] Johansen LV, Grau C, Overgaard J. Supraglottic carcinoma: patterns of failure and salvage treatment after curatively intended radiotherapy in 410 consecutive patients. Int J Radiat Oncol Biol Phys 2002;53(4):948–58.
[7] Taussky D, Dulguerov P, Allal AS. Salvage surgery after radical accelerated radiotherapy with concomitant boost technique for head and neck carcinomas. Head Neck 2005;27(3):182–6.
[8] Janot F, de Raucourt D, Benhamou E, Ferron C, Dolivet G, Bensadoun RJ, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clinical Oncol: Official J Am Society Clinical Oncol 2008;26(34):5518–23.
[9] Stevens Jr KR, Britsch A, Moss WT. High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys 1994;29(4):687–98.
[10] McDonald MW, Moore MG, Johnstone PA. Risk of carotid blowout after reirradiation of the head and neck: a systematic review. Int J Radiat Oncol Biol Phys 2012;82(3):1083–9.
[11] Lee JY, Suresh K, Nguyen R, Sapir E, Dow JS, Arnould GS, et al. Predictors of severe long-term toxicity after re-irradiation for head and neck cancer. Oral Oncol 2016;60:32–40.
[12] Farrag A, Voordeckers M, Tournel K, De Coninck P, Storme G. Pattern of failure after helical tomotherapy in head and neck cancer. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2010;186(9):511–6.
[13] Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clinical Oncol: Official J Am Society Clinical Oncol 1992;10(2):257–63.
[14] Bourhis J, Le Maitre A, Baujat B, Audry H, Pignon JP. Individual patients' data meta-analyses in head and neck cancer. Curr Opin Oncol 2007;19(3):188–94.
[15] Salama JK, Vokes EE. Concurrent chemotherapy and re-irradiation for locoregionally recurrent head and neck cancer. Semin Oncol 2008;35(3):251–61.
[16] Lee N, Chan K, Bekelman JE, Zhung J, Mechalakos J, Narayana A, et al. Salvage re-irradiation for recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 2007;68(3):731–40.
[17] Rwigema JC, Heron DE, Ferris RL, Andrade RS, Gibson MK, Yang Y, et al. The impact of tumor volume and radiotherapy dose on outcome in previously irradiated recurrent squamous cell carcinoma of the head and neck treated with stereotactic body radiation therapy. Am J Clin Oncol 2011;34(4):372–9.
[18] Ho JC, Phan J. Reirradiation of head and neck cancer using modern highly conformal techniques. Head Neck 2018.
[19] Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, et al. Proton Beam Reirradiation for Recurrent Head and Neck Cancer: Multi-institutional Report

on Feasibility and Early Outcomes. Int J Radiat Oncol Biol Phys 2016;95(1):386–95.
[20] Bruijnen T, Stemkens B, Terhaard CHJ, Lagendijk JJW, Raaijmakers CPJ, Tijssen RHN. Intrafraction motion quantification and planning target volume margin determination of head-and-neck tumors using cine magnetic resonance imaging. Radiotherapy Oncology : J Eur Society Therapeutic Radiology Oncol 2019;130:82–8.
[21] D'Souza WD, Naqvi SA, Yu CX. Real-time intra-fraction-motion tracking using the treatment couch: a feasibility study. Phys Med Biol 2005;50(17):4021–33.
[22] Paddick I. A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. J Neurosurgery 2000;93(Suppl 3):219–22.
[23] Suzuki K, Palmer MB, Sahoo N, Zhang X, Poenisch F, Mackin DS, et al. Quantitative analysis of treatment process time and throughput capacity for spot scanning proton therapy. Med Phys 2016;43(7):3975.
[24] Suzuki K, Gillin MT, Sahoo N, Zhu XR, Lee AK, Lippy D. Quantitative analysis of beam delivery parameters and treatment process time for proton beam therapy. Med Phys 2011;38(7):4329–37.
[25] Goggin LM, Descovich M, McGuinness C, Shiao S, Pouliot J, Park C. Dosimetric Comparison Between 3-Dimensional Conformal and Robotic SBRT Treatment Plans for Accelerated Partial Breast Radiotherapy. Technol Cancer Res Treat 2016;15(3):437–45.
[26] McGuinness CM, Gottschalk AR, Lessard E, Nakamura JL, Pinnaduwage D, Pouliot J, et al. Investigating the clinical advantages of a robotic linac equipped with a multileaf collimator in the treatment of brain and prostate cancer patients. J Appl Clinical Medical Phys 2015;16(5):284–95.
[27] Jang SY, Lalonde R, Ozhasoglu C, Burton S, Heron D, Huq MS. Dosimetric comparison between cone/Iris-based and InCise MLC-based CyberKnife plans for single and multiple brain metastases. J Appl Clinical Medical Phys. 2016;17(5):184–99.
[28] Kim N, Lee H, Kim JS, Baek JG, Lee CG, Chang SK, et al. Clinical outcomes of multileaf collimator-based CyberKnife for spine stereotactic body radiation therapy. British J Radiol 2017;90(1079):20170523.
[29] Mesko S, Wang H, Tung S, Wang C, Pasalic D, Chapman BV, et al. Estimating PTV Margins in Head and Neck Stereotactic Ablative Radiation Therapy (SABR) Through Target Site Analysis of Positioning and Intrafractional Accuracy. Int J Radiat Oncol Biol Phys 2020;106(1):185–93.
[30] Kharofa J, Choong N, Wang D, Firat S, Schultz C, Sadasiwan C, et al. Continuous-course reirradiation with concurrent carboplatin and paclitaxel for locally recurrent, nonmetastatic squamous cell carcinoma of the head-and-neck. Int J Radiat Oncol Biol Phys 2012;83(2):690–5.
[31] Lin R, Slater JD, Yonemoto LT, Grove RI, Teichman SL, Watt DK, et al. Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy–dose-volume histogram analysis. Radiology 1999;213(2):489–94.
[32] Rwigema JC, Heron DE, Ferris RL, Gibson M, Quinn A, Yang Y, et al. Fractionated stereotactic body radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma: updated report of the University of Pittsburgh experience. Am J Clin Oncol 2010;33(3):286–93.
[33] Kim YS. Reirradiation of head and neck cancer in the era of intensity-modulated radiotherapy: patient selection, practical aspects, and current evidence. Radiation Oncol J 2017;35(1):1–15.
[34] Heron DE, Ferris RL, Karamouzis M, Andrade RS, Deeb EL, Burton S, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. Int J Radiat Oncol Biol Phys 2009;75(5):1493–500.
[35] Lartigau EF, Tresch E, Thariat J, Graff P, Coche-Dequeant B, Benezery K, et al. Multi institutional phase II study of concomitant stereotactic reirradiation and cetuximab for recurrent head and neck cancer. Radiotherapy Oncology : J Eur Society Therapeutic Radiology Oncol 2013;109(2):281–5.
[36] Cengiz M, Ozyigit G, Yazici G, Dogan A, Yildiz F, Zorlu F, et al. Salvage reirradiaton with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. Int J Radiat Oncol Biol Phys 2011;81(1):104–9.
[37] Vargo JA, Wegner RE, Heron DE, Ferris RL, Rwigema JC, Quinn A, et al. Stereotactic body radiation therapy for locally recurrent, previously irradiated nonsquamous cell cancers of the head and neck. Head Neck 2012;34(8):1153–61.
[38] Takagi M, Demizu Y, Hashimoto N, Mima M, Terashima K, Fujii O, et al. Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck. Radiotherapy Oncology : J Eur Society Therapeutic Radiology Oncol. 2014;113(3):364–70.
[39] McDonald MW. FiDisregarding RBE variation in treatment plan comparison may lead to bias in favor of proton planstzek MM. Proton therapy. Curr Probl Cancer 2010;34(4):257–96.
[40] Linton OR, Moore MG, Brigance JS, Summerlin DJ, McDonald MW. Proton therapy for head and neck adenoid cystic carcinoma: initial clinical outcomes. Head Neck 2015;37(1):117–24.
[41] ICRU. Prescribing, recording, and reporting proton-beam therapy (ICRU report 78). J ICRU 7. 2007:21–7.