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Carbon-Ion Radiotherapy for Head and Neck Mucosal Melanoma: Preliminary Clinical Outcomes and the MedAustron Approach for Reporting RBE-Weighted Dose With 2 Models

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ABSTRACT

Purpose: Head and neck mucosal melanomas (HNMMs) are aggressive, radiotherapy-resistant cancers. Previous JCROS studies demonstrated improved local control with carbon-ion radiotherapy (CIRT). This study evaluates early outcomes of CIRT for HNMM using the European and Japanese relative biological effectiveness (RBE)-adapted dose prescriptions.

Materials and Methods: Between November 2019 and April 2023, 14 HNMM patients received CIRT treatment. Postoperative CIRT for R2 resection: 9 cases; biopsies only: 5 cases. Immune checkpoint inhibitors used as primary treatment: 6 cases; salvage: 8 cases. CIRT delivered in D_{RBE} dose of 68.8 (64.5-68.8) Gy (RBE)/16 fractions, optimized with the local effect model I (LEM-I, European) for RBE-weighted dose, recalculated using the modified-microdosimetric kinetic model (mMKM, Japanese).

Results: HNMM tumor and nodal stages: cT3: 2 (14%), cT4: 12 (86%), cN1: 1 (7%). The median follow-up was 22 months (range, 4-54). The 2-year local recurrence-free survival, regional recurrence-free survival, overall survival, and distant metastasis-free survival were 100%, 89% (CI, 71-100), 64% (CI, 44-95), and 43% (CI, 22-84), respectively. The median relative volumetric tumor regression at 3, 6, and 12 months post-CIRT was 40%, 63%, and 72%, respectively. CIRT-associated late toxicities were G3 mucositis: 2 (14%) and G3 anosmia: 1 (7%). The immune checkpoint inhibition-related late toxicities were G2 hypophysitis: 1 (11%) and G3 peripheral neuropathy: 1 (11%). The average attainable D_{RBE} coverage for 95% of high-dose clinical target volume was 63.2 ± 6 Gy (RBE) (LEM-I) and 57.4 ± 5 Gy (RBE) (mMKM). The LETd distribution in high-dose clinical target volume was satisfactory, $LETd_{50\%}$ (median) = 57.3 ± 6 keV/µm and $LETd_{98\%}$ (near minimum) = 46.5 ± 6.1 keV/µm.

Conclusion: Bi-RBE model (LEM-I, mMKM) optimized CIRT protocol improved dose comparability of plans between different systems. It also improved intratumoral LETd distribution and resulted in rapid tumor regression, favorable toxicity profile, and excellent early loco-regional control. It provides a promising alternative to surgery, though distant metastasis remains the key prognostic factor.

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Introduction

Mucosal melanomas are exceptionally rare tumors, occurring at a rate of only 1.5 per million annually.[1] The predominant sites affected are the head and neck (41%), followed by anus and vulva.[2] Currently, there are no established treatment guidelines for head and neck mucosal melanomas (HNMMs). However, surgery remains the primary treatment for most HNMMs. While adjuvant radiotherapy has shown efficacy in improving local control (LC) for macroscopically resected HNMMs, it has not significantly impacted overall survival (OS).[3-7] For HNMMs deemed inoperable at the locoregional level, photon radiotherapy has demonstrated only moderate and short-lived LC.[8-11] Unlike cutaneous melanoma, where innovative systemic treatments have revolutionized the management of advanced and metastatic cases, HNMMs exhibit a lower responsiveness to these therapeutic agents.[12,13]

A cutting-edge approach to tackling intrinsic resistance to radiation therapy is through heavy ion radiation therapy. This treatment modality has been available for more than 30 years but is still not widely available. In a study by Mizoe et al[14] involving HNMM patients treated with carbon-ion radiotherapy (CIRT), encouraging outcomes were observed, with a notable proportion experiencing complete response (50%-70%).[14] Furthermore, the addition of concomitant chemotherapy (Vincristin + dimethyl triazino imidazole carboxamide [DTIC] + Nimustine hydrochloride) improved OS without affecting LC and with an acceptable toxicity profile.[14-16] In Europe, chemotherapy is not routinely employed for the treatment of HNMMs, in particular in the era of targeted and immune therapy, and data on the combination of CIRT and immunotherapy with immune checkpoint inhibitors (ICIs) for the treatment of HNMMs is limited.

In this manuscript, we discuss the treatment strategy and the early clinical results in patients treated for unresectable/inoperable/R2 resected HNMMs with hypofractionated CIRT ± immunotherapy. The relative biological effectiveness (RBE)-weighted dose for CIRT plans at MedAustron was prescribed and optimized with the local effect model I (LEM-I). Additionally, all the plans were recalculated using the Japanese RBE model—modified microdosimetric kinetic model (mMKM) for evaluation.

Materials and methods

Patient characteristics

Fourteen patients with nonmetastatic HNMM, aged 55 to 89 years and with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, received hypofractionated CIRT at MedAustron Ion Therapy Center between November 2019 and April 2023. Informed consent was obtained for anonymized data analysis and publication, as part of an institutional prospective Registry Study (clinicaltrials.gov: NCT03049072, ethics committee: GS1-EK-4/350-2015). Patients with prior radiotherapy at the same site were excluded. CIRT was offered as first-line treatment in cases not suitable for R0 resection, in technically resectable cases deemed inoperable for medical reasons, to patients refusing surgery, or as salvage therapy for residual macroscopic disease after R2 resection or local recurrence after R0/R1 resection. Patients eligible for immune ICIs received this systemic therapy along with CIRT in neoadjuvant, concurrent, and adjuvant settings based on individualized prescriptions by dermatologists. Pretreatment evaluation included endoscopy, magnetic resonance imaging (MRI) of the whole brain and head/neck, FDG-PET-CT or chest/abdomen CT, ophthalmological and endocrine evaluations, audiometry, and preventive dental care.

Clinical treatment simulation and planning

Patients were positioned using personalized thermoplastic masks ± mouthpiece/tongue depressor devices, based on tumor extension, in supine straight or rotated positions for CT and MRI scans in the treatment position. Target volume delineation included contouring the gross tumor volume (GTV) based on postcontrast enhanced T1-weighted, T2-weighted, and DWI MRI sequences. High-dose clinical target volume (CTV) (HD-CTV) was defined as a 10 mm geometric expansion of GTV, adapted anatomically. Low-dose CTV encompassed regions at risk of local and submucosal infiltration, including the whole sinus if partially involved. ENI was considered for areas at risk, recommended only for cases with high nodal spread risk. Standard organs at risk (OARs) were delineated, along with medial canthus and oral-pharyngeal mucosa near HD-PTV (mucosa-to-spare) in selected cases. CIRT planning utilized RayStation software with MFO and LEM-I model. HNMMs were treated following institutional policies, with the median dose prescribed based on ICRU report 93.[17]

Both the LEM-I and mMKM RBE models are currently employed in clinical practice, each has its own distinct advantages. However, there are significant differences in the dose distribution of plans optimized with these 2 RBE models. The LEM-I model as compared to Japanese RBE models (MBM/mMKM) tends to overestimate the RBE in the central and proximal portions of the target and underestimates RBE in distal part of beam where the high LET region lies. Consequently, when optimizing CIRT plans with the LEM-I model, mMKM dose recalculation of the plan reveals D_{RBE} hot spots at the end of the beam range, despite a uniform dose distribution with LEM-I. In order to make sure that our CIRT plans are comparable to those optimized with MBM/mMKM models in JCROS studies, we employed 2 RBE models: LEM-I for prescription and optimization and mMKM for evaluation. The prescribed dose was $D_{RBE|LEM\text{-}I}$ = 68.8 (60.2-68.8) Gy (RBE) in 15 to 16 fractions which corresponds to mMKM doses of 60.8 (57-64) Gy (RBE) in 15 to 16 fractions. This translation between 2 RBE models was published earlier by Fossati et al[18] To minimize differences in D_{RBE} distribution between the 2 models (LEM-I and mMKM), a conversion system was developed to translate dose fractionation.[18] Conversion factors ranging from 1.04 to 1.15 were applied for various dose fractionations for various sites and tumor histologies. For instance, in translating mMKM to LEM-I dose prescriptions for HNMMs, a factor of 1.13 is used to convert the prescription D_{RBE} from 3.6 to 4 Gy (RBE) to 4.1 to 4.3 Gy (RBE) per fraction. All the CIRT plans were optimized with the LEM-I model, and then the doses for these plans were recalculated using the mMKM model for evaluation. Dose distribution analysis was performed on both LEM-I optimized and mMKM recalculated plans. The clinical goals for LEM-I and mMKM models are described in Table S1, and these were already published.[19,20] If mMKM dose distribution was inadequate, reoptimization using LEM-I was triggered when possible. During this study period, mMKM optimization was not available as a clinical TPS tool; hence, we relied on LEM-I reoptimization to fulfill mMKM dose distribution and dose constraints criteria. In the case of proximity critical OARs like optic structures, the HD-CTV coverage of $D_{RBE|mMKM|95\%}$ > 64 Gy (RBE) ± 5% of the prescription dose, and $D_{RBE|mMKM|95\%}$ > 57 Gy (RBE) were required to fulfill the acceptability of the treatment plan. In case of severe discrepancy, preference was given to LEM-I dose distribution. Reevaluation CT scans were performed during treatment to ensure adherence to target and OAR dose constraints. To the best of our knowledge, this is the first paper in which the results of patients treated, taking into consideration both CIRT RBE models simultaneously, are reported. The simultaneous optimization with 2 models will be described in detail in a separate paper.

Prospective LETd optimization was not applied in these patients; however, the adequacy of LETd distribution was evaluated retrospectively using Research TPS.

D_{RBE} and LETd evaluation

Patient CT scans, structure sets, CIRT plans and CIRT doses, and DICOM files were imported into the research version of TPS RS2023B to evaluate $D_{RBE|LEM\text{-}I}$, $D_{RBE|mMKM}$, and LETd parameters. LETd

in RS2023B was computed using trichome algorithm.[21] Different D_{RBE} and LETd parameters were assessed, including D_{RBE} and LETd values at 2%, 50%, 95%, and 98% of the target volumes. For serial OARs, D_{RBE} and LETd values at 0.1 cm^3, 1 cm^3, and 2% volumes were considered. Mean D_{RBE} and LETd values were evaluated for parallel OARs.

Clinical follow-up

Patients underwent physical examinations every 3 to 4 months during the initial 2 years post-CIRT, followed by 6-monthly examinations. MRI scans of the head and neck (including T1 postcontrast, T2-weighted, and DWI sequences) were conducted at each follow-up to assess local tumor status. Evaluation for metastatic disease via chest CT or PET-CT occurred at 6 months post-CIRT and subsequently as clinically indicated. Local failure was defined as tumor regrowth within the PTV, while regional failure encompassed regional lymph node recurrence or mucosal skip lesions outside the PTV. Post-CIRT, volumetric tumor regression was documented, with the GTV recontoured on MR images at each follow-up and recorded as a percentage of baseline volume. Treatment-related toxicities were recorded following the Common Terminology Criteria for Adverse Events v5. Late treatment-related side effects were identified as new symptoms emerging post treatment or worsening of symptoms' severity without local disease progression or other pathology.

Statistical analysis

Statistical analysis was performed using R-software and Microsoft Excel software 2021. The median follow-up was calculated using the reverse Kaplan-Meier method. Survival analysis was conducted using Kaplan-Meier analysis.

Results

The median follow-up was 22 months (range, 4-54). Tumor staging: cT3: 2 patients (13%), cT4: 12 patients (87%), cN1: 1 patient (7%). Among them, 2 patients (14%) underwent CIRT for locally recurrent HNMMs after previous surgeries, while the remaining 12 received it in the primary setting. Nine patients had prior surgical interventions, such as trans-nasal endoscopic resection or tumor debulking, before CIRT due to unresectable residual disease or as an alternative to further invasive surgery. The median time between surgery and CIRT was 4 months (range, 2-13). The average gross tumor volume (GTV) was 35 cm^3 (range, 2-129). The patient with the cN1 stage received CIRT for the primary tumor and positive nodes, while bilateral uninvolved neck lymph node stations were treated with sequential proton therapy (PBT). The median overall treatment duration was 27 days (range, 22-49)..

Six patients (43%) received immune ICIs as part of their primary treatment, either before, during, or after CIRT. The ICIs included PD-1 inhibitors such as Nivolumab or Pembrolizumab either alone or in combination therapy with Ipilimumab (CTLA4 inhibitor), as outlined in Table 2. Chemotherapy was not administered to any patients for treating primary HNMMs.

$D_{RBE|LEM-I}$ and $D_{RBE|mMKM}$ and LETd analysis for targets and OARs

The mean HD-CTV volume was 87.9 ± 61.2 cm^3. The target coverage for HD-CTV was adequate both in terms of the $D_{RBE|LEM-I}$ and $D_{RBE|mMKM}$. According to the extensively already published analysis,[18,19,22,23,24] the $D_{RBE|LEM-I}$ prescription of 68.8 Gy (RBE) corresponds to $D_{RBE|mMKM}$ between 57.6 Gy (RBE) and 64 Gy (RBE). The average achievable dose coverage for 95% of HD-CTV with LEM-I ($D_{RBE|LEM-I|D95\%}$) was 63.2 ± 6 Gy (RBE) (the desired $D_{RBE|\ LEM-I|D95\%}$ = 65.4 Gy [RBE]) and the average $D_{RBE|mMKM|D95\%}$ was 57.4 ± 5 Gy (RBE) (the desired $D_{RBE|\ mMKM|D95\%}$ = 57 Gy [RBE]). In situations where vital OARs were located near targets, a slight decrease in dose coverage of up to −5% of the prescribed dose was deemed acceptable. The LETd distribution for HD-CTV was also satisfactory: $LETd_{50\%}$ (median) = 57.3 ± 6 keV/µm, $LETd_{98\%}$ (near minimum) = 46.5 ± 6.1 keV/µm. Dose constraints for all the OARs were respected in both models. Doses $_{to}$ mucosa-to-spare were $D_{RBE|LEM-I|0.1\ cm^3}$ = 62.2 ± 14.6 Gy (RBE), $D_{RBE|mMKMI|0.1\ cm^3}$ = 58.2 ± 15.6 Gy (RBE). The D_{RBE} and LETd statistics for and OARs are described in Figure 1 and S1 (D_{RBE} constraints for HD-CTV and OARs, in Table S1). The above-reported prescription doses are based on clinical experience from patients treated with definitive CIRT for macroscopic disease of mucosal melanoma under prospective dose escalation trials.[14-16] Considering the use of RBE-weighted doses based on stated RBE models with variable RBE instead of absorbed physical dose as described for photon radiotherapy, it is not straightforward to compare these dose prescriptions with normal fractionated photon or proton radiotherapy data.

Table 1
Patient characteristics.

Patient/Tumor characteristics		HNMM (n = 14)
Age	Median (years)	65
	Range (years)	55-89
Gender	Male	5 (36%)
	Female	9 (64%)
Follow-up	Median (months)	22
	Range (months)	(4-54)
Site	Nasal cavity/Paranasal sinus	13 (93%)
	Oral cavity/hard palate	1 (7%)
Stage	T3	2 (14%)
	T4	12 (86%)
	cN0	13 (93%)
	cN1	1 (7%)
Treatment	CIRT alone	2 (14%)
	CIRT + Surgery	2 (14%)
	CIRT + Surgery + Immunotherapy	3 (21%)
	CIRT + Immunotherapy	6 (44%)
	CIRT + PBT + Immunotherapy	1(7%)
CIRT dose	Median [Gy (RBE)]	68.8
	Range [Gy (RBE)]	60.2-68.8
GTV	Median (range) [cm^3]	35 (2-129)

Abbreviations: HNMM, head and neck mucosal melanomas; CIRT, carbon-ion radiotherapy; PBT, proton beam therapy.

Clinical outcomes of head and neck mucosal melanomas-carbon-ion radiotherapy

Only 2 patients received neoadjuvant ICIs. One patient showed stable disease after 4 cycles of combined ICIs. The other initially responded to induction ICIs but had to stop combination ICIs and switch to single-agent pembrolizumab due to severe immune-related gastroenteritis. This patient subsequently developed local progression and was referred for CIRT. All patients experienced partial relief of pre-CIRT symptoms by the end of CIRT, with nearly complete resolution within 3 months post-CIRT. To assess primary tumor volume reduction, we outlined the GTV on follow-up MRI images using various MR sequences. Median tumor volume regression at 3, 6, and 12 months post-CIRT was 40%, 63%, and 72% of the initial pre-CIRT volume (Figure 2).

Only 1 patient (7%) encountered marginal local recurrence outside the LD-PTV 38 months post-CIRT completion. This patient underwent re-CIRT salvage therapy along with a combination of ICIs (Nivolumab + Ipilimumab). Another patient (7%) experienced regional nodal recurrence beyond the radiation field 1-year post-CIRT, managed through regional neck dissection and immunotherapy. Both were loco-regionally and distantly controlled at the last follow-up.

Among the 8 patients with distant metastases, 5 received systemic therapy, including ICIs, chemotherapy, or oral tyrosine kinase inhibitors. One patient underwent wedge resection for solitary lung metastasis and received combination ICIs, maintaining disease control for

Table 2
Treatment details.

	Primary treatment					Salvage treatment			Status
Patient No	Surgery	Neoadjuvant	Concurrent	CIRT Gy (RBE)	Adjuvant	Local progression	Regional progression	Distant progression	
1	-	-	Nivolumab × 4 cycles	68.8	Nivolumab	-	-	Oral imatinib	LRC Distant progression (Lung, liver)
2	Rhinectomy + tumor resection	-	-	68.8	-	-	-	Chemotherapy + ICI	LRC Distant progression (abdomen lymph nodal metastasis)
3	-	Ipilimumab + Nivolumab x 4 cycles	Nivolumab	68.8	Nivolumab (upto 1 year)	-	Surgery (Neck lymphadenectomy) + Nivolumab	-	LRC, DC
4	Lateral Rhinotomy + tumor resection	-	-	68.8	-	-	-	-	Died due to unknown causes
5	Tumor debulking	-	-	68.8	-	-	-	NA	Died due to distant progression (Bone, lung)
6	Endoscopic transnasal resection	-	Pembrolizumab × 2 cycles	68.8	Ipilimumab + Nivolumab × 4 cycles		-	Wedge resection for solitary lung nodule– > Nivolumab	LRC, DC
7	-	-	-	68.8	-	CIRT 68.8 Gy RBE/ 16 fractions) + ICI (Ipilimumab + Nivolumab x 4 cycles)	-	-	LRC, DC
8	Tumor debulking	-	Ipilimumab + Nivolumab	68.8	Ipilimumab + Nivolumab – > Nivolumab	-	-	-	LRC, DC
9	-	Ipilimumab + Nivolumab × 4 cycles → Pembrolizumab × 10 cycles	-	68.8 (+ 45 Gy RBE PBT/15 fractions for cN0 neck)	-	-	-	ICI	LRC Distant progression (Lung, breast)
10	Endonasal tumor resection	-	-	65.6	-	-	-	-	LRC, DC
11	-	-	-	68.8	-	-	-	-	Died due to distant progression (Lung)
12	Endonasal resection of Melanoma	-	-	68.8	-	-	-	-	Died due to unknown causes
13	Excisional Biopsy	-	-	68.8	-	-	-	Nivolumab x 1 cycle – > Nivolumab + Ipilimumab 4 cycles	LRC Distant progression (Lung)
14	Tumor debulking	-	Nivolumab	64.5	Nivolumab	-	-	Ipilimumab + Nivolumab × 4 cycles– > Nivolumab × 2 cycles	Died due to distant progression (Lung)

Abbreviations: LRC, Locoregional control; DC, Distant control; PBT, proton beam therapy.

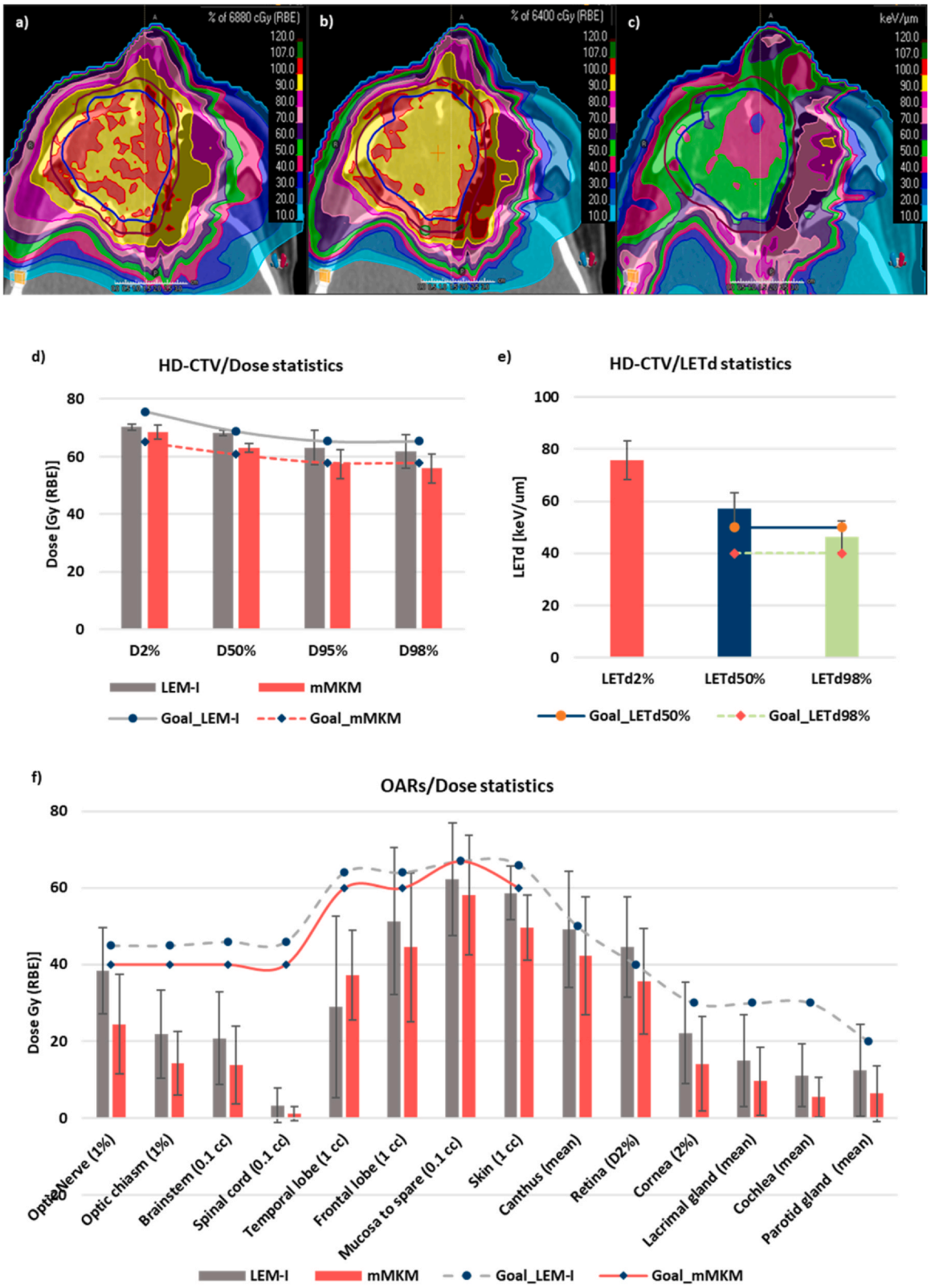

Figure 1. (a) $D_{RBE|LEM\text{-}I}$ distribution, (b) $D_{RBE|mMKM}$ distribution, and (c) LETd distribution in a representative case of HNMM. Target volumes: GTV (red), HD-CTV (blue). (d) $D_{RBE|LEM\text{-}I}$ and $D_{RBE|mMKM}$ and (e) LETd statistics for HD-CTV, (f) D_{RBE}, LEM-I, and mMKM statistics for OARs in locally advanced HNMM patients treated with CIRT (n = 14). (Note: Lines labeled Goal_LEM-I, Goal_mMKM, and Goal_LETd represent dose and proposed LETd constraints, not yet validated. Translation of LEM-I dose constraints to corresponding mMKM constraints available for optic nerves, chiasm, brainstem, spinal cord, temporal and frontal lobe, mucosa to spare, and skin. However, mMKM to LEM-I dose constraints are validated only for optic nerves, chiasm, and brainstem). Desired $D_{RBE|LEM\text{-}I|D95\%}$ = 65 Gy (RBE) and $D_{RBE|mMKM|D95\%}$ = 57 Gy (RBE); however, if critical OARs were close to targets, a compromise in target dose coverage up to −5% of desired dose constraint was accepted. Abbreviations: HD-CTV, high-dose CTV; LEM-I, local effect model I; mMKM, modified-microdosimetric kinetic model.

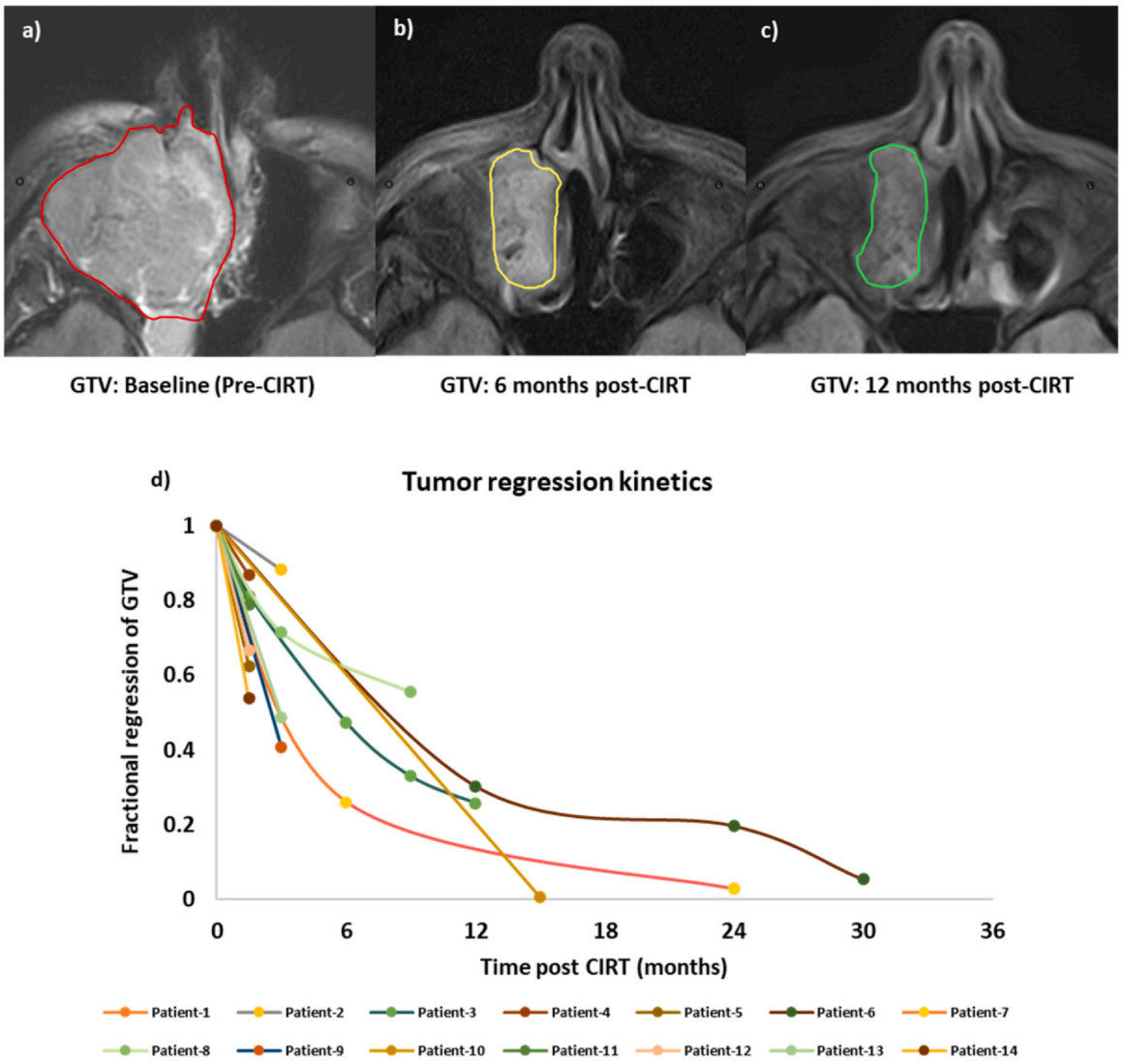

Figure 2. Rapid radiographic regression of local tumor following CIRT shown on sequential MRI images in a representative sino-nasal HNMM case. a) Baseline GTV (red), b) tumor at 6 months post-CIRT (yellow), c) residual tumor 12 months post-CIRT (green). d) Tumor regression kinetics post-CIRT in locally advanced HNMM patients treated with CIRT (n = 14). Abbreviation: CIRT, carbon-ion radiotherapy.

49 months post-CIRT. Unfortunately, 3 patients succumbed to progressive metastatic disease, while 2 passed away from unknown causes without local or locoregional progression.

The 1.5-year actuarial local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), OS, and distant metastasis-free survival (DMFS) were 100%, 89% (CI, 71-100), 64% (CI, 44-95), and 43% (CI, 22-84), respectively (Figure 3). According to a Koto et al[15] study, tumor volume $< 25\,cm^3$ significantly predicted favorable OS in HNMM patients treated with CIRT. In our study, half of the patients had a tumor volume $> 25\,cm^3$. However, within our cohort, there was no significant difference in OS, LRFS, RRFS, and DMFS between patients with GTV volume $> 25\,cm^3$ compared to those with $< 25\,cm^3$.

Acute and late toxicities

Regarding acute and late toxicities of normal tissues, 1 patient had acute G3 dermatitis, which resolved during irradiation. No other acute toxicities of grade 3 or higher were reported. Two patients (14%) experienced late G3 mucositis, with one requiring a PEG tube for nutritional support (Table 3). One patient developed G3 tooth infection after inadvertent tooth extraction within the irradiation field, leading to secondary osteonecrosis of the upper jaw. Additionally, 1 patient experienced late G3 anosmia. Overall, the acceptability of immunotherapy was satisfactory, with no exacerbation of CIRT-related acute toxicity when administered simultaneously with ICIs. However, 1 patient receiving combination ICIs in the neoadjuvant setting had acute grade 4 immune-related gastroenteritis, necessitating a switch to pembrolizumab therapy. Late ICI-related toxicities included grade 3 peripheral neuropathy and late grade 2 ICI-related hypophysitis in separate patients, both managed appropriately with hormonal therapy. No late grade 4 or 5 toxicities related to treatment were observed.

Discussion

Data from the RARECAREnet project in 2017 revealed poor survival rates in MM.[1] Endoscopic transnasal surgery for sino-nasal malignant mucosal melanomas demonstrated noninferiority compared to aggressive surgery.[25,26] This sparked curiosity in exploring less invasive alternatives. Adjuvant photon radiotherapy improves LC in macroscopically resected (R0/R1) HNMMs but not OS.[3-7] The results of using definitive photon-based radiotherapy for large macroscopic disease were unsatisfactory[8-11] (Table 4). Despite numerous technological developments in surgery and radiation therapy, as well as advances in systemic modalities, no increased survival advantage has been seen in MM.[27] PBT showed some promising

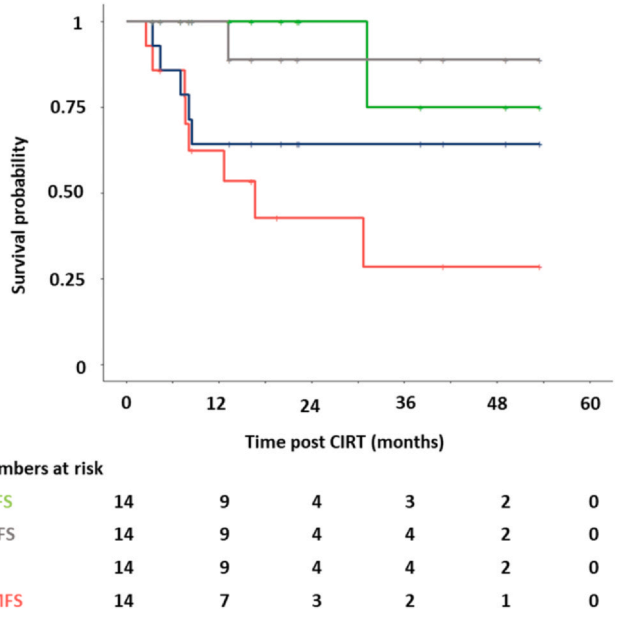

Figure 3. Kaplan-Meier survival analysis demonstrating local recurrence-free survival (green), regional recurrence-free survival (gray), distant metastasis-free survival (orange), and overall survival (blue) in locally advanced HNMM patients treated with CIRT ($n = 14$). Abbreviations: CIRT, carbon-ion radiotherapy; HNMM, head and neck mucosal melanomas.

Table 3
Late toxicity associated with CIRT and ICI.

	Gr 1	Gr 2	Gr 3
Dermatitis	6 (43%)	7 (50%)	-
Conjunctivitis	7 (50%)	3 (21%)	-
Mucositis	3 (21%)	7 (50%)	2 (14%)
Vertigo	2 (14%)	-	-
Headache	1 (7%)	-	-
Epistaxis/nasal congestion	4 (29%)	-	-
Dysphagia	1 (7%)	-	-
Xerostomia	1 (7%)	1 (7%)	-
Dysgeusia	-	1 (7%)	-
Weight loss	1 (7%)	-	-
Local pain	1 (7%)	-	-
Tooth infection/Osteonecrosis	-	-	1 (7%)
Alopecia	1 (7%)	-	-
Nausea	1 (7%)	-	-
Vomiting	1 (7%)	-	-
Anorexia	-	1 (7%)	-
Dysphagia	-	1 (7%)	-
Hearing impairment	2 (14%)	-	-
Blurred vision	1 (7%)	-	-
Anosmia	-	1 (7%)	
ICI-related peripheral neuropathy	-	-	1 (11%)
ICI-related endocrinopathy	-	2 (22%)	-

Abbreviations: CIRT, carbon-ion radiotherapy; ICI, checkpoint inhibitor.

results, with 3-year LC rates of 62% and 3-year OS rates of 46% to 68%.[28–30] However, most tumors treated with PBT were postoperative or had small residual tumors. Mohr et al[31] investigated combining CIRT boost with IMRT for sino-nasal MMs. He reported a moderate LC benefit but showed poor OS, underscoring the necessity for high LET particle therapy for treating large macroscopic MMs. The J-CROS HN1402 Study reported 260 cases of advanced HNMMs treated with CIRT (57.6-64 Gy RBE/16 fractions, Japanese RBE model) with concurrent and adjuvant DAV chemotherapy.[14-16] The 5-year LC rate was 75%, and the 5-year OS was 27% to 45%, respectively, with acceptable late toxicities. Naganawa et al[32] reported outcomes of hypofractionated CIRT for oral MMs, with 5-year LC, OS, and progression free survival (PFS) of 90%, 58%, and 52%, respectively. Takayasu et al[33] also confirmed LC benefit with hypofractionated CIRT with concurrent and adjuvant DAV in a prospective setting. Ronchi et al[34] described hypofractionated CIRT (LEM-I) for advanced HNMM with 2-year LRFS and OS rates of 84.5% and 58.6%, respectively, with manageable toxicity.

Patients treated in our series had either a nonresectable tumor or a macroscopic residual disease after surgery or refused surgery due to expected morbidity. CIRT was not offered as an alternative to an R0 resection except in the case of the patient's refusal. To replicate the excellent clinical results seen at CIRT centers in Japan[14-16,32,33-37] with the European RBE model, we adjusted CIRT dose prescriptions and constraints, with respect to the RBE model employed by CIRT facilities in Japan (MBM or mMKM). With the availability of the mMKM dose recomputation tool at MedAustron in 2021, we reevaluated all CIRT plans, comparing them with the original plans optimized with LEM-I and assessing both with LEM-I and mMKM models. Our bi-model evaluation of CIRT plans achieved satisfactory dose distribution in both models, making them comparable to Japanese data.[14,15]

The efficacy of CIRT against radio-resistant HNMMs is attributed to its high LET characterized by dense ionization, which enhances its biological effectiveness compared to photons and protons. Studies on various cancers treated with CIRT indicate that despite meeting defined dose distributions, lower LETd within the target area may increase relapses.[38-40] This has spurred interest in optimizing LETd distribution to enhance outcomes in photon-resistant tumors.[41-43] Kohno et al[42] explored LET painting in head and neck cancer patients undergoing CIRT, achieving LETd $>$ 44 keV/μm for tumors up to 170 cm^3. Subsequent publications by the same group reported superior early clinical response rates in cases of nonsquamous HN cancers treated with LET-optimized CIRT plans without added toxicity compared to historical controls.[44] In our cohort, average LETdmin (LETd98%) for HD-CTV was 46.5 ± 6.1 keV/μm, and LETdmedian (LETd50%) was 57.3 ± 6.1 keV/μm, which is in alignment with Kohno et al[42] findings. Optimal intratumoral D_{RBE} and high LETd distribution in our CIRT plans could partly explain the rapid tumor regression and symptomatic relief observed in our patients. Recognizing the potential of high LET to improve outcomes, we assessed different LET optimization strategies for potential implementation in future endeavors.[45,46]

Despite rapid tumor regression observed in our study, the high incidence of distant metastases continues to be a significant contributor to cancer-specific mortality in HNMMs, emphasizing the need for systemic therapy in their management. In the J-CROS HN 1402 Study, 155 patients (60%) received concurrent and adjuvant DAV chemotherapy.[14,15] They found concurrent chemotherapy as significant predictors of OS. However, in a prospective study conducted by Takayasu et al[33] concurrent and adjuvant DAV chemotherapy did not result in any survival advantages in the primary setting but enhanced clinical responses and prolonged survival in the salvage setting.[40] Unlike cutaneous melanoma, HNMMs are not caused by UV rays and have fewer BRAF mutations,[4,47,48] PD-L1 expressions, and microsatellite instabilities,[13,49] making BRAF inhibitors and high-dose interferon (IFN) less effective for them.[50,51] The revolutionary trials KEYNOTE-006 and CheckMate-067,[52,53] developed an interest in the use of ICIs for advanced melanoma. Pooled analysis of HNMM patients (n = 121) receiving immunotherapy[54] suggests that anti-PD1 + anti-CTLA4 may offer better outcomes than anti-PD1 alone, highlighting the need for refined treatment approaches for HNMM. While anti-PD-1 therapy and combination ICIs (anti-PD1 + anti-CTLA4) show promise in retrospective studies[55]; however, there is a lack of dedicated MM trials.

Radiation holds promise as a complementary therapy with immunotherapy, triggering PD-L1 expression and an antitumor immune response.[56-58] Preclinical studies suggest that CIRT has systemic immunomodulatory properties, potentially enhancing immunotherapy more effectively than photon-based radiation. These properties of CIRT should be leveraged to improve systemic control and survival in highly immunogenic HNMMs. Combining anti-CTLA4 with radiation has been shown to promote tumor response and immunity in vivo, suggesting

Table 4
Studies treating HNMMs with definitive radiotherapy.

Publication	Site	N	Modality	Dose	Tumor outcome
Gilligan et al[8]	Sino-nasal	28	Photon	50-55 Gy/15-16 fractions	3y LRFS: 49%, 5y OS: 18%
Shibuya et al[9]	Upper jaw	28	Photon	EBRT: 50-76 Gy or interstitial brachytherapy: 90 Gy by 198Au, mold brachytherapy (72-120 Gy, ^{60}Co or cone electron beam therapy (50 to 108 Gy given in 5-10 fractions	5y OS: 47% (intraoral electron or brachytherapy)
Wada et al[10]	hard palate, nasopharynx, mesopharynx, middle ear, upper gingiva, and orbit	31 (21 with exclusive RT. 10 with surgery + RT)	Photon	32-64 Gy, @ 1.5-13.8 Gy/fraction,	3y LC: 30%, 3y CSS: 33%
Coombs et al[11]	Sino-nasal	8	Photon: IMRT	GTV: 60-68 Gy, SIB: 59 Gy	3y OS: 75%, 3y local PFS: 57%, 3y distant PFS: 29%
Mohr et al[31]	Sinonasal: 83% Orbit: 11% Pterigoid space: 6%	18	CIRT boost + Photon IMRT	CIRT 60 Gy(RBE)/20 fractions: 11% CIRT 18-24 Gy (RBE) + IMRT 48-59 Gy: 89%	3y-LC: 58%, 3y-OS 16.2%, 3y-PFS 0%
Fuji et al[29]	Sino-nasal	20	PT	70 Gy(RBE)/20 fractions	3y-LC: 62%, 5y-LC: 62%, 3y-OS 68%, 5y-OS 54%
Zenda et al[28]	Sino-nasal	32	PT	60 Gy(RBE)/15 fractions	1y-LC 75.8%, 3y-OS 46.1%
Demizu et al[30]	Sino-nasal	62	PT 53% CIRT 47%	65-70.2 Gy (RBE)/26 fractions	PT: 2y-LC: 83%, 2y-OS 58% CIRT: 2y-LC: 59%, 2y-OS 62%
Yanagi et al[16]	Sino-nasal: 83% Oral: 10% Pharynx: 7%	72	CIRT	52.8-64 Gy (RBE)/16 fractions	3y-LC: 84%, 5y-LC: 84%, 3y-OS 46%, 5y-OS 27%
Mizoe et al[14]	Sino-nasal: 76.5% Oral: 11% Pharynx: 3.5% Orbit: 7% Salivary gland: 2%	260	CIRT	57.6-64 Gy (RBE)/16 fractions	2y-LC: 90%, 3y-LC: 90%, 5y-LC: 75% 2y-OS 60%, 3y-OS 46%, 5y-OS 27%
Naganawa et al[32]	Oral	19	CIRT	57.6 Gy(RBE)/16 fractions	3y-LC: 90%, 5y-LC: 90%, 3y-OS: 68%, 5y-OS: 57% 3y-PFS: 52%, 5y-PFS: 52%
Koto et al[15]	Sino-nasal: 76.5% Oral: 11% Pharynx: 3.5% Orbit: 7% Salivary gland: 2%	260	CIRT	57.6-64 Gy (RBE)/16 fractions	2y-LC: 84%, 5y-LC: 72%, 2y-OS 69%, 5y-OS 45% 2y-PFS 40%, 5y-PFS 27%
Takayasu et al[33]	Sino-nasal: 95% Oral: 5%	21	CIRT	57.6 Gy(RBE)/16 fractions	2y-LC: 92%, 3y-LC: 92%, 2y-OS: 56%, 3y-OS: 49% 2y-PFS: 37%, 3y-PFS: 37%
Ikawa et al[35]	Oral	29/74	CIRT	57.6 Gy(RBE)/16 fractions	3y-LC: 87%, 5y-LC: 87%, 3y-OS 63%, 5y-OS 49%
Ronchi et al[34]	Sino-nasal: 90% Other: 10%	40	CIRT	65.6-68.8 Gy (RBE)/16 fractions	2y-LC: 85%, 3y-LC: 85%, 2y-OS 59%, 3y-OS 53% 2y-PFS 33%, 3y-PFS 28%

CIRT, carbon-ion radiotherapy; EBRT, external beam radiotherapy; HNMM, head and neck mucosal melanomas; LC, local control; LRFS, local recurrence-free survival; OS, overall survival; PFS, progression free survival.

that concurrent immunotherapy with CIRT may extend survival in HNMM patients. Combining CIRT with ICI therapy appears safe, with no increased adverse effects observed.[59-61] Hanaoka et al[60] reported improved LC and PFS survival in 10 HNMM patients receiving both treatments. Cavalieri et al[61] found no excessive toxicities in 33 advanced melanoma cases treated with CIRT and ICIs. Additionally, ICIs can be safely administered in the relapse setting after CIRT; Musha et al[62] reported a 3-year OS rate of 53.8%, without exacerbating CIRT-associated side effects. Mizoguchi et al[63] recently reported superior PFS with the use of adjuvant ICI therapy immediately post-CIRT compared to no ICI use. The incremental cost-effectiveness ratio (ICER) for adjuvant ICI therapy was within acceptable range. Similarly, in our study, we did not observe exacerbation of CIRT toxicity with concurrent or adjuvant use of ICIs.

Our study found effective loco-regional control and rapid post-CIRT response for bulky, unresectable HNMMs, partly due to optimal D_{RBE} distribution in both RBE models (LEM-I and mMKM) and intratumoral high LET distribution. Unlike Koto et al[15] we did not observe a correlation between tumor volume and outcomes. Patients with GTV $\geq 25\ cm^3$ showed no differences in OS, LRFS, RRFS, or DMFS compared to those with $< 25\ cm^3$. However, distant metastasis remained a significant cause of disease progression in the current study. This highlights the challenges in establishing an optimal combined treatment approach. Given the limited availability of global CIRT, collaborative efforts among specialized centers are crucial to disseminate knowledge about CIRT's potential in managing unresectable, radioresistant HNMMs and improving multidisciplinary management.

Despite a small sample size, our study observed rapid radiological regression and symptom relief with CIRT in nearly all patients, including those previously unresponsive to immunotherapy. This suggests significant potential for CIRT to enhance LC rates in aggressive, unresectable/inoperable HNMMs, with minimal toxicity. Achieving reasonably acceptable D_{RBE} distribution in both RBE models (LEM-I and mMKM) likely contributed to the excellent local tumor regression observed. Although our initial findings are based on small sample size, our findings align with Japanese studies on hypofractionated CIRT for HNMMs. Reporting these promising early results is crucial, given HNMMs' rarity and limited CIRT resources, highlighting CIRT as a curative alternative to extensive surgery for advanced cases.

Conclusions

In our series, CIRT has been confirmed as a very effective and safe local treatment option for HNMMs. We could achieve rapid tumor regression, favorable toxicity profile, and excellent early loco-regional control. CIRT, therefore, offers a promising alternative to mutilating surgery. Our approach of the bi-RBE model (LEM-I, mMKM) optimized CIRT could be successfully used in clinical practice. In our plans we could achieve satisfactory LETd distribution with an increase of LETd in the target and a decrease in the OARS. The favorable clinical outcomes could, at least in part, be due to our specific optimization strategy. Distant metastasis remains the main pattern of disease progression and determines the prognosis. There is preliminary but growing evidence on the use of ICI in adjuvant settings with CIRT. To improve systemic control and survival in patients with HNMMs, immunotherapy should be standardized and better integrated with CIRT in a comprehensive treatment concept.

Author Contributions

Piero Fossati and Ankita Nachankar: Conceptualization. Ankita Nachankar: Methodology, Formal analysis, Investigation, Software, Data curation, Writing- Original draft preparation, Visualization. Piero Fossati, Maciej Pelak, Mansure Schafasand, Giovanna Martino, Slavisa Tubin, Eugen Hug, Markus Stock, Antonio Carlino, Carola Lütgendorf-Caucig: Writing- Review and editing. Piero Fossati: Supervision. Piero Fossati; Markus Stock: Project administration. All authors have read and agreed to the published version of the manuscript.

Declaration of Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The corresponding author (Piero Fossati) serves in an editorial capacity for IJPT. If there are other authors, they 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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Informed Consent Statement

Informed consent was obtained from all patients involved in the study for anonymized data collection, analysis, and publication.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee for the following studies—Registry Study (clinicaltrials.gov: NCT03049072 ethics committee: GS1-EK-4/350-2015).

Data Availability Statement

The data presented in the current study are available from the corresponding author (A.N.) upon reasonable request.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijpt.2025.100738.

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