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ORIGINAL ARTICLE

Intensity-modulated radiotherapy with planned Gamma Knife radiosurgery boost for head and neck cancer with extensive disease in proximity to critical structures

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Abstract

Background: To describe intensity-modulated radiotherapy (IMRT) with Gamma Knife Radiosurgery (GKRS) boost for locally advanced head and neck cancer (HNC) with disease near dose-limiting structures.

Methods: Patients with HNC treated with IMRT/GKRS as part of a combined modality approach between 2011 and 2021 were reviewed. Local control, overall survival and disease-specific survival were estimated using the Kaplan Meier method.

Results: Twenty patients were included. Nineteen patients had T3-4 tumors. Median follow-up was 26.3 months. GKRS site control was 95%. Two patients progressed at the treated primary site, one patient failed at the edge of the GKRS treatment volume, with no perineural or intracranial failure. 2-year OS was 94.7% (95% CI: 85.2%–100%). Concurrent chemotherapy was given in nine patients (45%). One patient (5%) received induction/concurrent chemotherapy. Brain radionecrosis occurred in three patients, one of which was biopsy-proven.

Conclusions: IMRT plus GKRS boost results in excellent disease control near critical structures with minimal toxicity.

KEYWORDS

Gamma Knife boost, Gamma Knife, intensity-modulated radiation therapy, head and neck cancer, normal tissue toxicity

1 | INTRODUCTION

Head and neck cancer often presents as locoregionally advanced disease (LA-HNC), and a proportion of these cases have extensive local spread either via direct extension along adjacent anatomic structures or via perineural tumor spread.[1–3] This presents a therapeutic challenge when unresectable gross disease is immediately adjacent to critical organs at risk (OARs). In these cases, safe delivery of a sufficient dose of radiotherapy to provide meaningful disease control is difficult using photon intensity-modulated radiotherapy (IMRT) without excess toxicity. While an aggressive multidisciplinary approach involving surgery, radiotherapy, and chemotherapy is standard in the treatment of LA-HNC, locoregional failure remains a problem.[4,5] Given the high risk of local failure in areas that receive insufficient dose to respect critical OAR constraints and the potential futility/extreme morbidity of salvage surgery, a safe and effective method of dose escalation is needed to increase tumor control.

Stereotactic radiosurgery (SRS) is most often used in the treatment of brain metastases, but has been reported as a technique facilitating dose escalation in definitive and salvage therapy for LA-HNC, skull base and cavernous sinus metastases, with high rate of marginal failure observed with GKRS alone.[6–14] Few studies report outcomes of definitive IMRT plus radiosurgery boost as a primary treatment. The high level of conformity made possible by Gamma Knife radiosurgery (GKRS) represents an attractive option to deliver sufficient doses while minimizing toxicity. We report our experience with IMRT plus planned GKRS boost in the definitive setting.

2 | METHODS

2.1 | Patient population and interventions

In this IRB-approved cohort study, we reviewed the records of 20 patients between 2011–2021 with LA-HNC undergoing GKRS. Patients treated for brain metastases or with GKRS alone were excluded. Patients were selected for this approach in situations where target coverage was not feasible using IMRT alone without overdosing critical adjacent OARs, and so a conformal GKRS boost was utilized. Though in some cases, due to clinical or radiographic factors concerning for inability to achieve target and OAR parameters with IMRT alone, a planned IMRT/GKRS boost paradigm was selected upfront. Patient demographic and disease characteristics were obtained from the medical record. Treatment details were recorded. IMRT plans were created to cover gross disease as well as high risk areas using 1.8–2.2 Gy/fraction. GK site was designed in collaboration with radiosurgery experts.

Generally, for patients with incidental/pathologic perineural invasion of a large-caliber (0.1 mm or greater) or named nerve but without gross clinical or radiographic PNI, IMRT was delivered to the paths of involved nerves to the skull base using an elective (microscopic disease) dose. For patients with gross clinical or radiographic perineural tumor spread, the IMRT plan delivered elective-dose RT to the entire path of the nerve to its origin at the brainstem, and a boost to the gross disease was delivered using either IMRT or GKRS or both, depending on the extent/distribution of the gross neural involvement.

2.2 | Gamma Knife stereotactic radiosurgery

GKRS was performed on a Leksell Gamma Knife Perfexion or ICON unit. In brief, a Leksell headframe was applied followed by contrast-enhanced stereotactic magnetic resonance imaging (MRI) of the brain using a 3.0 Tesla unit. GammaPlan® (Elekta AB, Stockholm, Sweden) was used to develop a treatment plan with a dose selected based on the size of the target as well as prior IMRT dose. Patients were treated with 4 point (two anterior and two posterior) stereotactic frame immobilization, and no special accommodations were made for regions in the prior low-dose IMRT volumes.

The highest priority for GK planning was to keep the optics (chiasm and optic nerves) to below the tolerance doses. Inverse-planning using the GammaPlan treatment planning system was generally used to achieve plan conformality. Dose was selected in order to keep the optics under tolerance and to achieve an equivalent dose of at least 70 Gy (2 Gy/fraction). Physician discretion was used as some histologies such as adenoid cystic carcinoma may have been treated with more aggressive dosing. As the GammaPlan system inverse planning selects shot location automatically, there was no effort on the planners to minimize angles used heavily by EBRT. The plan was reviewed by central nervous system specialists and the treating head and neck physician.

2.3 | Outcome measures and statistical analysis

Post-treatment response assessment occurred within 6 months of treatment. Failure was defined as clinical, radiographic, or pathologic evidence of disease recurrence. Local failure was defined as recurrence within the

50% isodose line (IDL) of the GKRS plan. Marginal failure was defined as recurrence adjacent to the GKRS site, outside of the 50% IDL. Primary site failure was defined as recurrence within the original site of disease. Regional failure was defined as recurrence in the draining lymphatics, and distant failure as development of metastatic disease. Outcomes were defined based on duration of time from the start of IMRT to the date of the event, with specific definitions as follows; GKRS site local control (LC): date of LF or last radiographic follow-up (right-censor); recurrence-free survival (RFS): date of first disease recurrence (local, marginal, primary site, regional or distant failure) or last follow-up; overall survival (OS): death from any cause or last follow-up. Toxicity outcomes including headache, brain/brainstem necrosis, cranial nerve dysfunction, diplopia, and paresthesia were noted from follow-up visits.

Composite IMRT/GKRS plans were calculated for all patients as a part of this analysis using MIM (MIM Software Inc., Cleveland, OH) to construct a cumulative dose map accounting for both the IMRT and the GKRS plans. The IMRT plan was registered to the GKRS treatment planning MRI using rigid registration, and the doses to critical OARs in close proximity to the GKRS target volume was calculated and reported as equivalent cumulative doses in 2-Gy fractions (EQD2) using an $\alpha/\beta = 3$, a widely accepted standard for reporting normal tissue doses.[15] The brain contour was based on the brain volume delineated at the time of external beam planning, for which a co-registered MRI was often not available. In these cases, the brain as an OAR structure was outlined manually based on CT imaging by the treating physician. For the transferring of the dose information and structures from the GK MRI to the CT used for the IMRT, rigid box based alignment registration was performed. The brain contour used for dosimetric evaluation was the structure used during IMRT planning which was primarily delineated by CT-based anatomy, either manually or automatically using the interior skull surface. The doses reported are the EQD2 composite doses intended to account for differences in biological equivalence between different dose/fractionation schemes.

Descriptive analyses were performed and time-to-event outcomes were estimated using the Kaplan–Meier method with date of IMRT start as time zero.

3 | RESULTS

3.1 | Patient and treatment characteristics

Twenty patients were analyzed and are summarized in Table 1. Histology included 11 squamous cell carcinomas (6 mucosal and 5 cutaneous), 3 adenoid cystic and one each of the following: intestinal-type adenocarcinoma, melanoma, neuroendocrine, sinonasal undifferentiated carcinoma, nasopharyngeal carcinoma, angiosarcoma, and chondrosarcoma. Tumor classification was primarily advanced: T2 ($n = 1$), T3 (n = 1), T4 (n = 18). All but one patient was treated with conventional fractionation for their IMRT course. One patient with neuroendocrine carcinoma of the clivus was treated with induction chemotherapy followed by concurrent chemotherapy with IMRT followed by GKRS boost.

Surgical resection was included in 15 patients to the primary site and 7 patients at the GKRS site. While 75%

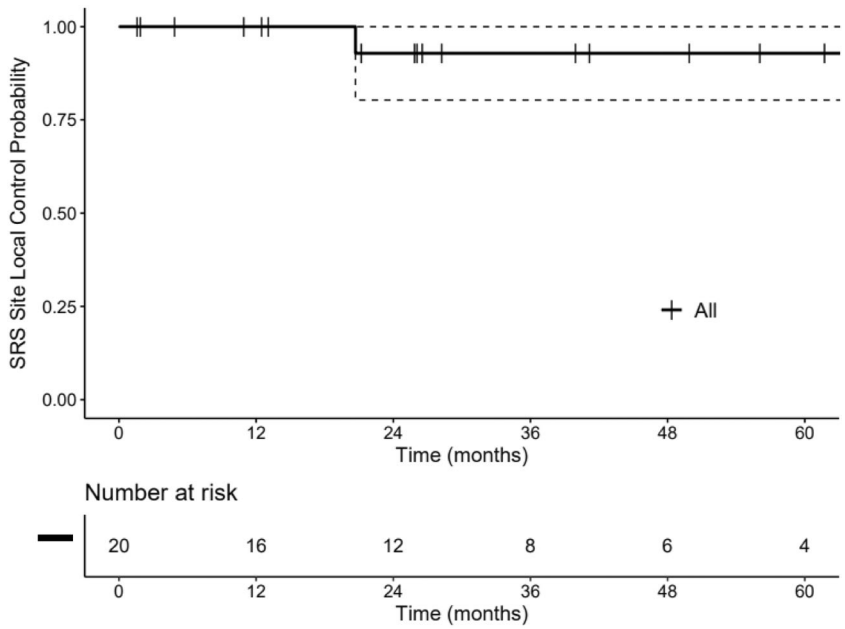

FIGURE 1 Local control at the GKRS site after IMRT plus GKRS boost

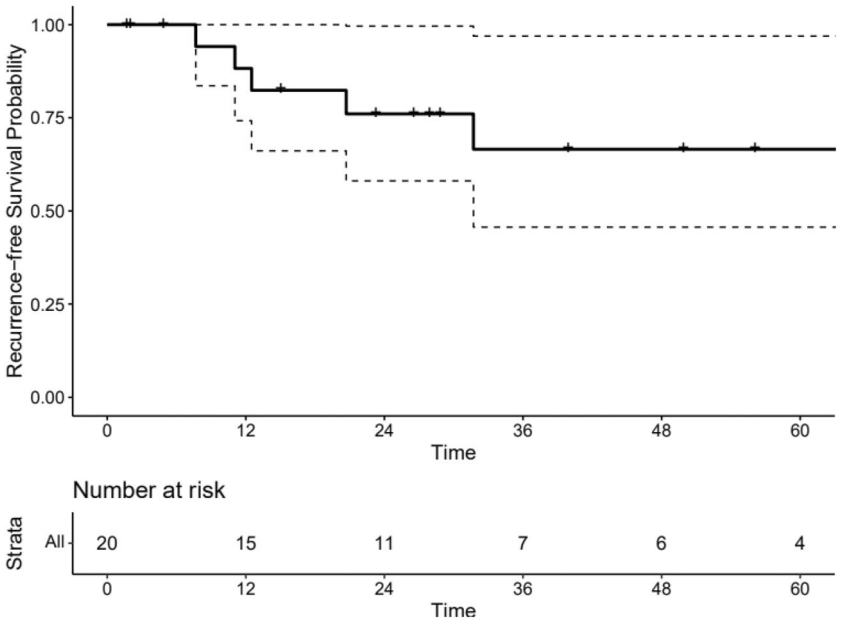

FIGURE 2 Kaplan–Meier plot of recurrence free survival after IMRT plus GKRS boost

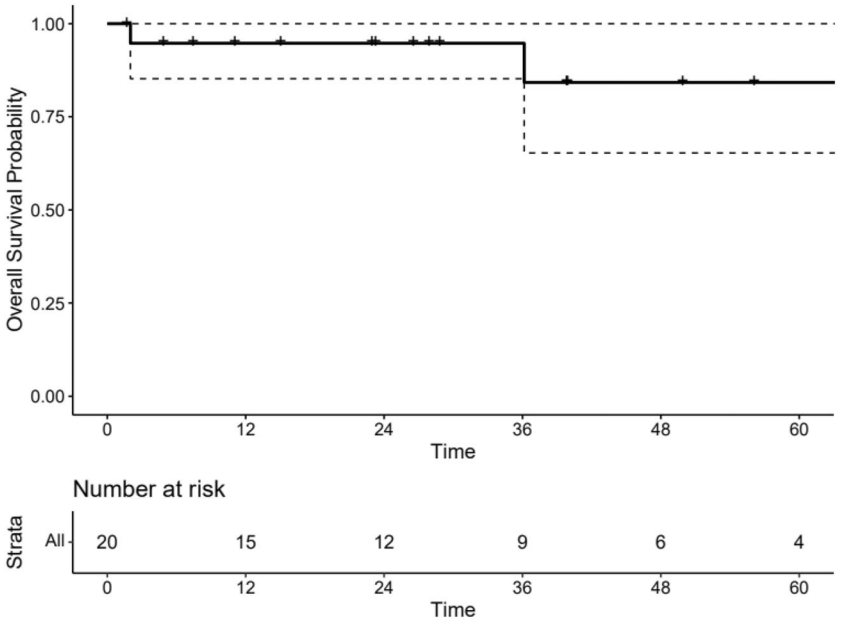

FIGURE 3 Kaplan–Meier plot of overall survival after IMRT plus GKRS boost

of the cohort did have surgery, this refers to surgical excision of the primary lesion, not necessarily the specific region of the tumor encroaching on a critical structure. Only 35% of patients had surgical resection that approached the GKRS prescription site (Table 1). Of these, three had microscopically positive margins and four had grossly positive residual disease. Additional surgical details for each patient are highlighted in Table S1. The remaining 65% had disease in locations deemed to be unresectable and was targeted by the GKRS plan.

Median IMRT dose to the primary site was 59.4 Gy (range: 30.6–70.0 Gy) in 30 fractions (17–35) and 50 Gy (range: 30.6–60.0) to the GKRS site. Median GKRS dose was 10 Gy (range: 8–17), prescribed to the 50% IDL (range: 48–61%) delivered in a single fraction in 19 patients. One patient received 20 Gy in 4 fractions using the ICON system. Median D95% to GKRS target (EQD2, $\alpha/\beta = 10$) from EBRT alone was 51.7 Gy (IQR 46.3–52.6) with composite dose including GKRS reaching 73.3 Gy (IQR 69.6–82.9). Five patients received GKRS boost to gross unresectable disease following surgery. In those patients, median IMRT dose to the primary post operative bed was 59.4 Gy (range 45–60 Gy), median IMRT dose to GKRS site was 50.4 Gy (range 45–60 Gy), and median GKRS boost dose was 12 Gy (range: 9–14 Gy), all prescribed to 50% IDL. Two patients

TABLE 1 Patient and treatment characteristics

Number of patients	20
Median age (years)	63
Smoking	10 (50)
Prior radiation therapy	3 (15)
Dose of prior radiation therapy (Gy)	63 (60–70)
Tumor classification	
T2	1 (5)
T3	1 (5)
T4	18 (90)
Recurrent	9 (45)
Histology	
Mucosal squamous cell carcinoma	6 (30)
Cutaneous squamous cell carcinoma	5 (25)
Adenoid cystic carcinoma	3 (15)
Other[a]	1 (5)
GKRS site[b]	
Cavernous sinus	13 (65)
Base of skull	6 (30)
Mucosal sinus	3 (15)
Intracranial	1 (5)
Orbit	1 (5)
Perineural invasion	9 (35)
Pathologic nerve resection	5 (25)
IMRT dose to primary site (Gy)	59.4 (49.1–60)
IMRT dose to GKRS site (Gy)	50 (45–50.4)
GKRS dose to the 50% IDL (Gy)[c]	10 (9–12.1)
IMRT D95% to GKRS Target Site (Gy)	51.7 (46.3–52.6)
Total Composite D95% to GKRS Target Site	73.3 (69.6–82.9)
Neck treatment using IMRT	7 (35)
Reimaging of GKRS site prior to boost (CT/MR)	20 (100)
Surgical intervention to primary site	15 (75)
Surgical intervention to GKRS site	7 (35)
Positive microscopic margin (R1)	2 of 7 (29)
Gross residual disease (R2)	5 of 7 (71)
Chemotherapy	
Concurrent with IMRT	9 (45)
Induction followed by concurrent with IMRT	1 (5)

Note: Data are summarized using *n* (%) and median (interquartile range) unless otherwise specified.

[a]Other includes: adenocarcinoma, melanoma, neuroendocrine tumor, sinonasal undifferentiated carcinoma, nasopharyngeal carcinoma, chondrosarcoma.

[b]Number of patients treated with GK boost to individual sites, out of $n = 20$ patients.

[c]All but one delivered as a single fraction (one plan delivered as 20 Gy in 4 fractions).

underwent GKRS boost to areas of microscopically positive margins. In that subset of patients, IMRT dose to the primary post operative bed was 57.8 and 63 Gy, IMRT dose to GKRS site was 57.8 and 45 Gy, and GKRS boost dose was 10 and 9 Gy respectively, both prescribed to 50% IDL. Of the 13 patients that did not have surgical resection involving their GKRS site, median IMRT dose to the primary/postoperative bed was 59.4 Gy (IQR 46.4–60), median IMRT dose to the GKRS site was 45 Gy (IQR 45–50.3), and median GKRS dose was 10 Gy (IQR 9–12). Eighteen patients had reimaging with dedicated MRI between the end of IMRT and GKRS for planning purposes with two cases using the CT simulation for planning. Involved structures requiring GRKS are listed in Table 1. Eighteen patients (90%) received GKRS boost after completion of IMRT; median time from the end of IMRT to GKRS was 18 days (IQR 9–22). Two cases (10%) were treated with GKRS boost prior to EBRT (29 and 55 days). Nine patients had perineural involvement and five underwent resection of involved nerve. Seven patients (35%) received radiation to cervical lymphatics as part of their IMRT plan. Images demonstrating cumulative dose IMRT and GKRS boost plans with clinical vignettes explaining the doses and targets utilized for each individual patient in this series are provided (Supplemental Table 1).

Concurrent chemoradiotherapy was administered in 10 patients (50%) with 1 patient additionally receiving induction chemotherapy. Chemotherapy regimens included carboplatin/etoposide (one patient), carboplatin/paclitaxel (five patients), cisplatin/etoposide (one patient), and cisplatin (three patients).

The dose ranges for IMRT and GKRS depending on GKRS boost site (cavernous sinus, base of skull, mucosal sinus, intracranial, and orbital) and resection status (microscopically positive [R1] or gross disease/gross residual disease after surgery [R2], if applicable) are summarized as follows. Seven patient underwent surgical resection involving their GKRS site. For two patients with microscopically positive margins, sites of involvement were intracranial at the left frontal dural convexity with IMRT dose to the GKRS site being 57.8 Gy with a 10 Gy boost prescribed to the 50% IDL, and base of skull for the other patient with involvement of the cavernous sinus and pterygopalatine fossa with IMRT dose to the GKRS site 45 Gy with a 9 Gy GKRS boost prescribed to the 50% IDL. For those that underwent surgery involving their GKRS site with resultant gross residual disease (R2), sites included cavernous sinus, mucosal sinus, and base of skull with IMRT doses to the GKRS site of 45 to 60 Gy with corresponding GKRS dose ranges were 9–14 Gy.

For those patients that did not undergo surgical resection of their GKRS site (13 patients), gross disease was present in the cavernous sinus of nine of these patients

with IMRT dose to the GKRS site ranging from 30.6–60 Gy with corresponding GKRS doses of 8–17 Gy. Two patients with gross disease in the mucosal sinus received 30.6 and 50.4 Gy dose contribution from their IMRT plans with a 10 and 12 Gy GKRS boost, respectively. Four patients had skull base involvement and received IMRT doses of 45–50.4 Gy to their GKRS site with 8–17 Gy GKRS boost. One patient had unresected disease involving the orbit and received 45 Gy IMRT with a 10 Gy GRKS boost.

3.2 | Disease control and survival outcomes

With a median follow-up of 26.3 months (range 1.6–111.0), GKRS LC was 95% (single failure was adenoid cystic carcinoma) (Figure 1). Failures were noted as primary site (n = 2), marginal failure (n = 1), draining lymphatics (n = 2), intracranially (n = 2), and distant (n = 2) with no perineural failure. The 2- and 5-year RFS was 76% (95% CI: 58%–99.6%) and 66.5% (95% CI: 45.7%–96.9%), respectively (Figure 2). The 2- and 5-year OS were 94.7% (95% CI: 85.2%–100%) and 84.2% (95% CI: 65.3%–100%), respectively (Figure 3).

TABLE 2 Central nervous system toxicity after IMRT plus GKRS boost for head and neck cancer

Toxicity	Number of events (%)	CTCAE grade
Headache	0 (0%)	NA
Brain radionecrosis	3 (14%)	Grade 1 ($n = 2$) Grade 3 ($n = 1$)[a]
Brainstem radionecrosis	0 (0%)	NA
Radiation induced optic neuropathy	0 (0%)	NA
CN III dysfunction	1 (5%)	Grade 1 ($n = 1$)
CN V dysfunction	0 (0%)	NA
New paresthesia	2 (10%)	Grade 1 ($n = 2$)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.
[a]Biopsy with laser interstitial thermal therapy (LITT).

3.3 | Toxicity and cumulative dose measures

Central nervous system toxicity rates are displayed in Table 2. Radionecrosis of the brain occurred in three patients, with Grade 1 ($n = 2$) and Grade 3 ($n = 1$) toxicity, one of which was biopsy-proven. Composite brain maximum cumulative doses (EQD2, $\alpha/\beta = 3$) in these cases were 98.2, 93.8, and 77.1 Gy. No patients experienced change or worsening of vision, headache, diplopia, paresthesia, trigeminal nerve pain, osteomyelitis, mucosal or skull base necrosis. Median (range) cumulative $D0.03_{cc}$ (maximum dose to 0.03 cc; EQD2, $\alpha/\beta = 3$) to CNS structures are described in Table 3. The median cumulative $D0.03_{cc}$ to the right and left optic nerves and optic chiasm were 46.5, 36.8, and 41.2 Gy, respectively. Corresponding median cumulative doses to the brainstem, cervical spinal cord, and brain were 47.9, 14.6, and 93.8 Gy, respectively.

4 | DISCUSSION

Local control remains a significant issue for LA-HNC, and salvage surgery in these cases has been shown to result in considerable morbidity, particularly in patients with multiple comorbidities and T3–T4 primary tumors, still with high rates of 1-year mortality.[17] Our results demonstrate the potential for safe application of GKRS boost to IMRT as a means of conformal dose escalation with excellent LC. This may avoid or delay morbid salvage surgical management. Most prior studies have focused on use of radiosurgery for a particular histology of HNC in the upfront setting or its use as monotherapy in the recurrent/salvage setting.[12,13,18] Studies examining this approach have reported similar LC ranging from 82% to 100% with low rates of toxicity.[10,12] Our study confirms that planned IMRT plus GKRS boost facilitates the delivery of tumoricidal doses while sparing adjacent critical OARs with acceptable rates of severe toxicity. It is worth noting that we observed excellent rates of LC for patients with a wide variety of primary histologic types, several considered radioresistant.

TABLE 3 Maximum cumulative dose ($D0.03_{cc}$; EQD2, $\alpha/\beta = 3$) to select organs at risk structures (Gy)

Structure	Median	Maximum	Minimum	Interquartile range
Right optic nerve	46.46	94.18	7.91	32.0–52.4
Left optic nerve	36.825	58.31	13.86	25.6–53.7
Optic chiasm	41.17	59.51	11.49	26.9–47.7
Brain	93.78	235.97	54.06	77.1–144.0
Brainstem	47.9	92.8	11.74	34.2–56.62.4
Cervical spinal cord	14.59	46.56	0.82	5.8–23.0

The marginal failure rate in the present series was low ($n = 1$), which compares favorably well to radiosurgical series previously published in which SRS alone was used as salvage in head and neck cancers extending to the skull base. In a study published by Ayer et al, SRS alone was used to treat cavernous sinus tumors from predominantly HNCs and 6 of 19 tumors experienced marginal failure.[14] The low marginal failure rate in the present study speaks to the synergism of the combination of IMRT and GKRS boost. The IMRT provides a margin of therapeutic dose to account for microscopic spread, while the GKRS boost increases biologic dose to the gross disease. Our efforts to re-create the accumulated doses delivered with IMRT plus GKRS boost are, to our knowledge, the only reported dosimetric outcomes of this paradigm. While methodologies using rigid registration are likely reasonably accurate, given most of the targets' proximity to cranial structures, there are inherent limitations to this process. Therefore, the calculated EQD2 presented herein must be interpreted with caution. Additionally, the study is limited by its relatively short median follow-up, as many late effects may not occur for several years following completion of therapy with as long as 7.7 years reported as the median time to radiation induced cranial neuropathies.[16] Therefore, these effects may not be entirely captured in our analysis.

In terms of timing of therapy, GKRS boost either prior to or following EBRT treatment delivery seems reasonable. The benefit of upfront GKRS boost includes lack of bothersome IMRT side effects, potentially resulting in better tolerability of the GKRS boost. Additionally, it may be easier to delineate gross disease due to lack of IMRT associated inflammation or lack of treatment response which could obscure target. Potential problems encountered when GKRS is delivered upfront include difficulty with rapid GKRS scheduling at some institutions due to high volume of patients treated with this modality for other indications. At our institution, we favor the upfront EBRT followed by GKRS boost sequence. This is primarily to take advantage of smaller treatment volumes if a response has been achieved from IMRT. Treating with GKRS boost in the outback setting theoretically could also potentially allow for GKRS dose reduction.

Other potential strategies reported in the literature that could be considered to address these very locally advanced cases include linac-based SRS/SBRT, although toxicity may be higher with this approach.[19] A lower degree of dose conformality would also be expected with linac-based approaches compared with GKRS.[20] Hyperfractionation in head and neck cancers has also been studied with a goal of improving the therapeutic ratio by reaching tumoricidal doses with potentially lower rates of late normal tissue toxicity.[21] Extensive surgical resection with its expected anatomical, functional and cosmetic defects is a less desirable approach in these circumstances. Lastly, symptom palliation with less invasive external radiation or palliative chemotherapy could be considered in these very advanced situations.

Considering the unavoidable heterogeneity in histology, primary site, critical structure(s) at risk, and treatment of our study population, it is difficult to formulate concise yet generalizable recommendations for dose and target planning. It is impossible to understate the importance of clinical judgment and interdisciplinary management to determine the optimal therapy with regard to surgical resection, RT dose and targeting for patients treated with this highly personalized paradigm. Given our experience with this complex treatment, we have formulated very generalized dosing schemes for patients treated with IMRT plus GKRS. For patients with gross disease (or after R2 resection at the GKRS site near critical structures): IMRT doses of 45–56 Gy at 1.6–2.0 Gy per fraction and GKRS boost doses of 8–14 Gy are frequently considered to bring the total EQD2 ($\alpha/\beta = 10$) cumulative dose to at least 66–70 Gy or higher, depending on the particular critical structure at risk and its tolerance. For patients who have undergone surgical resection with microscopically (R1) positive margins adjacent to critical structures, IMRT doses of 50–54 Gy at 1.6–2.0 Gy per fraction and GKRS boost doses of 8–10 Gy to bring the total EQD2 cumulative dose to at least 60–66 Gy, limited by critical structure tolerance. It should be noted that this particular dosing regimen has not been prospectively validated and is not meant to dictate current practice. A future prospective clinical trial is planned to confirm the safety and efficacy of this treatment modality. Additionally, the authors recommend this highly specialized treatment technique, if performed, should be performed by providers with extensive experience in both head and neck and CNS radiotherapy/GKRS.

This study has limitations inherent to its nature as a single-institution retrospective cohort study. As a result, the techniques utilized herein may not be directly generalizable to other institutions. The large study period and the relatively short follow-up for more recent patients also limit the generalizability of the findings. Despite these limitations, this study provides data supporting future study of this relatively uncommon treatment paradigm. Larger, ideally prospective studies are required to confirm these results with regard to disease control and toxicity.

5 | CONCLUSIONS

Planned IMRT plus GKRS results in excellent control near critical IMRT dose-limiting structures with

acceptable rates of toxicity. This paradigm represents a promising means of dose escalation for LA-HNC with disease adjacent to critical organs at risk.

FUNDING INFORMATION

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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