Curr Oncol Rep (2017) 19: 82
DOI 10.1007/s11912-017-0639-9

Reirradiation of Skull Base Tumors With Advanced Highly Conformal Techniques

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Published online: 28 October 2017

Abstract
Purpose of Review Skull base reirradiation is challenging due to complex anatomy, enrichment of treatment-resistant clonogens, and increased risk of severe treatment complications. Without local therapy, early mortality is certain and tumor progression can result in debilitating symptoms. Modern radiotherapy advancements, such as image-guided radiation therapy (IGRT), intensity-modulated radiation therapy (IMRT), particle therapy, and stereotactic radiation therapy (SRT), are attractive for skull base reirradiation.
Recent Findings Although limited by their retrospective nature and heterogeneous patient populations, several studies have demonstrated that reirradiation with these highly conformal techniques is feasible. Compared to IMRT or particle therapy reirradiation, SRT reirradiation appears promising with lower toxicity and increased convenience.
Summary Here, we provide thorough explanations for each technology and summarize the most relevant and recent studies, with particular attention to efficacy and toxicity. Skull base reirradiation using these extremely conformal therapy techniques requires meticulous treatment planning and should be delivered by experienced teams.

Keywords Head and neck cancer · Skull base · Reirradiation · Stereotactic · Radiosurgery · Proton therapy

This article is part of the Topical Collection on *Head and Neck Cancers*

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Introduction

Locoregional recurrence after definitive therapy is the most common cause of death in patients with head and neck cancer (HNC) [1–4]. Treatment strategies for recurrences include surgery and curative-intent reirradiation. In the absence of local therapy options, the standard of care consists of platinum-double chemotherapy with or without cetuximab, which offers a median survival of 7–10 months, only slightly better than 4–5 months with supportive care [3, 5].

Skull base recurrences are associated with a high rate of mortality and debilitating morbidity due to local destruction of surrounding critical organs. Unfortunately, these recurrences are typically unresectable, and reirradiation offers the only chance for durable disease control and symptom palliation. However, skull base reirradiation is very challenging. The proximity of critical structures, such as the brainstem, spinal cord, optic apparatus, cochlea, cranial nerves, and brain parenchyma, can lead to potentially devastating radiation-induced complications. Often, there are only submillimeter distances between tumor and vital structures, and one must simultaneously spare multiple critical structures (with varying dose tolerances) while delivering a sufficient tumoricidal dose.

General Radiotherapy Principles and Fractionation

The overall goal of radiotherapy is to widen the therapeutic window by maximizing the tumor control probability while minimizing the normal tissue complication probability. Several common concepts and terms used in radiation oncology are listed in Table 2. For skull base tumors, the therapeutic window is particularly narrow because of the intimate association of tumor with vital structures.

Fractionation is the concept of breaking up the total radiation dose into smaller fractions to exploit the radiosensitivity difference between rapidly growing tumor cells and most normal tissues. The conventional fractionation of 1.8–2 Gy per fraction per day is felt to be optimal for effective normal tissue sparing.

Hyperfractionation breaks up standard fractionation into smaller doses given with higher frequency, and accelerated fractionation shortens the overall treatment time. These fractionation schedules were tested in HNC trials, demonstrating not only improved tumor response but also increased acute toxicity in early responding tissues (e.g., skin and mucosa).

Hypofractionation increases the dose per fraction and decreases the number of fractions, resulting in a significantly shorter treatment course, which increases patient convenience. The benefits of hypofractionation have been demonstrated in patients with breast, prostate, and lung cancers [6–10]. However, hypofractionation was not initially considered for reirradiation because of concern for late toxicity in patients with preexisting toxicity from their initial radiation.

The emergence of stereotactic radiation therapy (SRT) has challenged the long-standing dogma of fractionation. When a large ablative dose in SRT is used, the sparing effect of fractionation does not apply. The goal of SRT is tumor ablation with extremely high precision to preserve the adjacent normal tissue. SRT was once considered impractical due to insufficient imaging quality and dose delivery capability, but is now increasingly utilized for skull base tumors due to technological advances in image-guided radiation therapy (IGRT) and treatment delivery capabilities that enable precise dose delivery with minimal margins and steep dose fall-off outside the target.

Modern Radiotherapy Techniques and Image-Guided Radiation Therapy

Radiation oncology is an image-guided intervention. The simulation CT scan is a snapshot of the tumor and the patient's position at a single time point, which is used to develop the treatment plan. However, it would be erroneous to assume that the dose delivered through the entire course exactly matches the dose calculated on the simulation CT. To compensate for these uncertainties, planning target volume (PTV) margins up to 2 cm could be used to ensure adequate target coverage, but this wide inclusion of normal tissue is not acceptable for skull base radiotherapy. IGRT is a method of imaging during treatment, and making corrections to ensure accuracy, and decrease the necessary PTV margins. Recommended PTV margins for conventional intensity-modulated radiation therapy (IMRT)/intensity-modulated proton therapy (IMPT) with daily IGRT are 5–8 mm. PTV margins for skull base SRT are typically < 3 mm and require online IGRT (performed before/during treatment). For single-fraction stereotactic radiosurgery (SRS) utilizing head frame-based stereotactic localization, PTV margins are typically 0–1 mm.

When considering IGRT corrections for skull base radiotherapy, both the translational and rotational uncertainties should to be accounted for. Standard IGRT approaches correct errors along the translational axis, but modern IGRT systems can provide high-resolution 3D and 4D images for target localization, as well as tracking motion and volume changes. Studies have demonstrated that rotational movements of even a few degrees can significantly change the actual dose delivered to the tumor and critical structures [11]. In-room orthogonal X-ray systems such as the ExacTrac X-ray 6D system provide high-resolution images for bony alignment of the cranium and 6 degrees of freedom setup verification before and during each treatment to account for translation and rotational errors. ConeBeam CT (CBCT) uses X-ray detectors mounted on the linear accelerator (LINAC) treatment beam to create volumetric CT images to correct for discrepancies in soft tissue anatomy. This allows tracking of soft tissue targets that move independently of bony anatomy (i.e., internal organ motion), which is necessary when the target is below C1 or near the mandible where bony alignment alone may be suboptimal for accurate tumor localization.

Immobilization and Real-Time Tracking

We recommend utilizing an immobilization and/or tracking system (in addition to IGRT) to further reduce setup uncertainty and minimize the PTV [12, 13••]. Stereotactic head frames are used for SRS and provide targeting accuracy of < 1 mm. However, head frames are bulky and require insertion of pins into the cranium. Thus for multi-session SRS, frameless systems are considered, which increase patient safety and comfort.

For LINAC-based SRT, we recommend a customized three-point immobilization system consisting of a custom posterior cushion, mask, and bite block immobilization device. In an analysis of 105 treatment sessions with SRT for recurrent skull base tumors, the translation and rotational setup errors were < 1 mm and < 1°, respectively, with a calculated PTV margin of 1.6 mm when used together with IGRT for online setup correction [13••]. More recently, frameless, surface imaging-guided platforms have become available, which provide real-time monitoring through infrared camera tracking of facial topography. The geometric accuracy approaches 1 mm, and early reports demonstrate comparable outcomes to frame-based Gamma Knife (GK)-SRS for the treatment of skull base tumors [14]. However, its use should be limited to situations when the external surface is a reliable surrogate for the internal target.

Early Reirradiation Trials

Early radiotherapy techniques utilized two-dimensional fluoroscopic imaging for treatment planning, which were designed primarily to ensure generous coverage of target volumes, resulting in a significant amount of normal tissue also receiving the prescribed dose. Three-dimensional conformal radiation therapy (3D-CRT) incorporated CT imaging and computerized treatment planning and delivery systems to improve normal tissue sparing.

Many early reirradiation protocols used a split-course radiation regimen of 1.5 Gy per fraction BID for 5 days every other week (×4 cycles to 60 Gy). RTOG 9610 used 2D techniques, delivered with concomitant fluorouracil and hydroxyurea [15]. This study demonstrated that full-dose reirradiation in patients with inoperable recurrent HN cancer was feasible but associated with significant severe treatment toxicity (up to 40%) and up to 20% treatment-related deaths. Alternatively, RTOG 9911 evaluated concurrent cisplatin and paclitaxel with split-course BID radiation [16•]. CT planning was required, and 3D-CRT or IMRT was allowed, although the actual number of those receiving IMRT is unknown. The survival rates appeared superior to results observed in RTOG 9610, but toxicity was still substantial with a ~ 30% incidence of G4–5 toxicity, including ~ 10% treatment-related deaths. There were a small proportion of cases (~ 10–16%) with long-term disease-free survival, indicating that reirradiation might be suitable for some.

Intensity-Modulated Radiation Therapy

The advent of more sophisticated conformal techniques such as IMRT with multi-leaf collimation (MLC) allowed greater precision and sharper dose gradients, enabling treatment of irregularly shaped tumors. IMRT incorporated inverse planning and placement of dose constraints on critical structures, which has led to our current understanding of the dose-volume effects for late complications in normal tissues [17]. Volumetric-modulated arc therapy (VMAT) is an application of IMRT that delivers radiation in a continuous arc instead of the static 6–12 beam arrangement of IMRT. Compared to IMRT, VMAT results in faster delivery, less radiation exposure, and improved dosimetry and plan quality. More conformal plans for complex skull base targets can be achieved using non-coplanar treatment planning and smaller (3–5 mm) MLC leaflets available on newer LINACs.

Clinical data for IMRT HNC reirradiation is emerging (Table 1). Overall, disease control and late toxicity rates appear lower compared to historic 2D and 3D data. In the early IMRT experience, Lee et al. [18] from Memorial Sloan Kettering compared 105 patients who received IMRT (70%) or 3D-CRT. IMRT was associated with improved LRC (52% IMRT vs. 20% 3D-CRT). The incidence of G3 toxicity was 15%. In a subsequent report from the same institution of 257 patients (78% received IMRT), the 2-year G3+ toxicity rate was 31%, with three grade 5 events. In a more contemporary series of the largest IMRT reirradiation study to date evaluating 206 patients treated at MD Anderson, Takiar et al. [27••] reported the grade 3 toxicity rates of 32% at 2 years and 48% at 5 years. The 5-year LRC was 49%. Among those with nasopharynx and skull base disease (n = 34), the 5-year LRC was 65%, and for those receiving curative reirradiation alone (n = 19), the 5-year LRC was 83%. Several smaller IMRT series have been reported [19, 20, 28–31]. In a study from Curtis et al. [19] on 81 patients (95% received IMRT) from the Mayo Clinic, the authors did not grade toxicity, but reported "uncommon" late serious toxicities, including two cases of osteoradionecrosis and one non-fatal case of carotid artery rupture (CAR). Sher et al. reported on 35 patients treated at Dana-Farber with IMRT reirradiation with concurrent chemotherapy. Toxicity rates were more substantial in this cohort, with 46% developing late grade 3 or higher toxicity and 11% developing grade 5 toxicity.

When evaluating these IMRT reirradiation series in aggregate, representing approximately 700 patients, the 2-year LRC and OS rates were 47–67 and 37–57%, respectively. Among studies that reported on prognostic factors affecting outcome, nasopharynx site, non-oral cavity site, higher reirradiation dose, and non-SCC histology were associated with an improved prognosis. The 2-year G3+ toxicity rate across all studies was 27–32%. Only Takiar et al. reported on risk factors for toxicity, showing that a higher late G3+ toxicity rate was associated with retreatment volume > 50 cm^3 and use of concurrent chemotherapy (CRT). In fact, no G3+ toxicity was observed for tumor volumes < 25 cm^3.

Particle Therapy

Because of their favorable physical characteristics, particle radiation such as proton therapy (PRT) and carbon ion therapy are well suited for skull base tumors. The Bragg peak results in a sharp drop off in dose distal to the target (Table 2). The absence of an exit dose beyond the target is appealing for skull base tumors in proximity to the brainstem. A rapid dose fall-off towards the brainstem can be achieved without compromising tumor coverage [32••]. Passive scatter proton therapy (PSPT) uses brass apertures and range compensators and is applicable to well-lateralized targets with uniform depth. For irregularly shaped targets in the central skull base, an active scanning beam technique using pencil-thin beam and inverse planning, known as IMPT, is ideal because it results in increased conformality compared to PSPT.

There are three studies available on PRT reirradiation. In a study of 60 patients treated at MD Anderson (25% PSPT and

Table 1 Modern highly conformal reirradiation studies

Study	ReRT type	Dose median (range) (Gy)	Pt. number (%)	Location	Median f/u (m)	2-year LRC	2-year OS	Late G3 or higher toxicity	Predictors of improved LRC/OS	Predictors of increased toxicity
Takiar et al. [27••] MDA	IMRT	66 (50–70)	206 (84% SCC) (51% surgery) (67% CRT)	9% skull base/sinonasal/orbit	25.1	65% (59% SCC)	57% 51% (SCC)	2 years 32%	(LRC) CRT, site, RT dose (70 Gy)	CTV1 ≥ 50 cm^3 CRT
Riaz et al. [50] MSK	IMRT (78%)	59.4 (1.8–72)	257 (86% SCC) (67% CRT)		32.6	2 years 47%	2 years 43%	31% G3+ 2% G5	(LRC) > 50 Gy, surgery, non-oral cavity, < stage 4, no organ dysfunction	–
Lee et al. [18] MSK	IMRT (70%) and 3D-CRT	59.4 (30–70)	105 (86% SCC) (34% surgery) (71% CRT)	17% paranasal 20% NPC	35	42% (52% IMRT)	37%	15% G3–4	(LRC) IMRT, NP site (OS) Non-SCC, RT dose, NP site	–
Curtis et al. [19] Mayo Clinic	IMRT	Definitive 69.6 (48–76.8) PORT 60 (12–70)	81 (100% SCC) (52% surgery) (74% CRT)	6% sinus/nasal cavity	78.1	60%	50%	2% ORN 1% CAR	(LRC) No CRT (p = 0.06)	–
Sher et al. [20] Dana-Farber	IMRT	60 Gy (IQR, 60–64)	35 (> 90% SCC) (49% surgery) (100% CRT)		27	67%	48%	46% G3+ 11% G5	None found	None found
Phan et al. [48] MDA	Proton (75% scanning)	Post-op 61.5 (50–70) Definitive 66 (50–70)	60 (67% SCC) (58% surgery) (73% CRT)	52% skull base	13.6	73% (62% SCC)	70% (60% SCC)	20% G3 3% G5 2 years G3+ 26%	None found	CTV1 ≥ 50 cm^3
Romesser et al. [21] MSK	Proton (passive)	60.6 (50–66.1)	92 (57% SCC) (39% surgery) (39% CRT)	23% skull base	10.4	1 year 75%	1 year 65%	2% G5 CAR/bleeding 3%	–	–
McDonald et al. [49]	Proton (passive)	70 (36–75.6)	61 (53% SCC) (48% surgery) (28% CRT)	90% skull base	15.2	80%	33%	25% G3+ 4% G5	(LRC) lower GTV, higher dose, cutaneous primary(OS) Higher KPS, no feeding tube before reRT	–
Uhl et al. [22••] Germany	Carbon ion	51 Gy (45–60) (63 BED)	25 (Chordoma/chondrosarcoma)	100% skull base	14	2 years 79%	–	4% G3	(LRC) PTV < 100 cm^3, dose > 51 Gy	–

Table 1 (continued)

Study	ReRT type	Dose median (range) (Gy)	Pt. number (%)	Location	Median f/u (m)	2-year LRC	2-year OS	Late G3 or higher toxicity	Predictors of improved LRC/OS	Predictors of increased toxicity
Jensen et al. [34] Germany	Carbon ion	51 Gy (36–74) (63 BED)	52 (100% ACC)	17% skull base 37% paranasal	14	2 years 47%	2 years 63%	15% G3+ 4% G4 hemorrhage	–	–
Owen et al. [51] Mayo Clinic	GK-SRS boost (49%) palliative (29%) curative (20%)	All 1 fx boost 11.4 (8–18) palliative 14.3 (10–18) curative 15 (10–20)	184 (69% recurrent) (72% surgery) (81% SCC) (46% CRT)	22% skull base 24% cavernous sinus	17.3	1 year 73%	1 year 41%	6% G3 2% G4	(PFS) EBRT + boost, no prior surgery (OS) SRS, curative intent	CRT, prior surgery
Phan et al. [54] MDA	GK-SRS (trigeminal pain)	16 Gy (11–20), 1 f. (85%) 24 Gy, 3 f. (12%)	26 (77% SCC)	54% cavernous sinus	12.2	27% LF In non-LF pts., decrease in pain and opioid use		24% G3–4, 19% G4	–	–
Cmelak et al. [23] Vanderbilt	LINAC-SRS	Recurrent 20 (7–35), 1 fx	47 (79% recurrent) (17% reRT) (81% SCC)	Skull base (100%)	9	2 years 53%		8.4% G3+	None found	None found
Miller et al. [24] Mayo Clinic	GK-SRS	15 (12–20), 1 fx	32 (47% reRT) (25% SCC)	Skull base (100%)	27.6	2 years 95%	2 years 76%	13% G3+	–	–
Xu et al. [12] Pittsburgh	SBRT	44 (15–50) in 1–5 fx	31 (100% reRT) (26% CRT) (55% SCC)	100% skull base	11.4	88% LF	2 years 12%	15% G3	–	–
Ling et al. [25••] Pittsburgh	SBRT	44 (16–52.8) 5 f. QOD (95%)	291 (100% reRT) (50% CRT) (77% SCC)	14% skull base/nasal cavity/paranasal sinus	17.3		1 year 41% 3 years 17%	19% G3+ 2% G4 3% G5	–	Larynx/hypopharynx, ≥ 44 Gy
Phan et al. [53] MDA	SBRT	45 in 5 fx	26 (86% CRT) (81% SCC)	27% skull base	6.2	6 months 91%	6 months 79%	0 G3+	–	–
Ng et al. [unpublished data] MDA	SBRT	SBRT 45 (35–47.5), 5 fx IMRT/PRT 66 (50–70)	63 (52% SCC) (40% SBRT, 60% IMRT/PRT)	100% skull base	17.3	5 years LRFFS 67%	5 years 51%	SBRT, 4% G3 IMRT/PRT, 15% G3	–	CTV > 60 cm^3

Table 1 (continued)

Study	ReRT type	Dose median (range) (Gy)	Pt. number (%)	Location	Median f/u (m)	2-year LRC	2-year OS	Late G3 or higher toxicity	Predictors of improved LRC/OS	Predictors of increased toxicity
Coppa et al. [52] Georgetown	SBRT	25 (12.6–35) 5 f. (2–7)	31 (16% reRT) (42% recurrent) (19% SCC)	100% skull base	8.5	26% LF	1 year 36%	0% G3+	–	–
Yamazaki et al. [26•] Japan	SBRT	30 Gy (25–37) in 5 f. QD	107 (43% surgery) (23% ulceration)		15	64%	35%	22% G3+ 8% G5 CAR 10%	(LRC) NP site, no ulceration (OS) NP site, PTV ≤ 40 cm^3	Ulceration

IMRT intensity-modulated radiation therapy, *3D-CRT* 3D conformal radiation therapy, *GK-SRS* Gamma Knife stereotactic radiosurgery, *LINAC SRS* linear accelerator stereotactic radiosurgery, *SBRT* stereotactic body radiation, *RT* radiation, *fx* fraction, *SCC* squamous cell carcinoma, *ACC* adenoid cystic carcinoma, *reRT* reirradiation, *CRT* concurrent chemoradiation, *LRC* loco-regional control, *OS* overall survival, *LF* local failure, *LRFFS* local regional failure free survival, *CR* complete response, *G3* grade 3, *NP* nasopharynx, *conc.* concurrent, *GTV* gross tumor volume, *PTV* planning target volume, *CAR* carotid artery rupture, *FT* long-term feeding tube use, *LN* lymph node, *KPS* Karnofsky Performance Status, *DSS* disease-specific survival, *MDA* MD Anderson, *MSK* Memorial Sloan Kettering

75% IMPT) by Phan et al. [33], the 2-year OS and LRC rates were 70 and 73%. The 2-year actuarial rate of late G3 toxicity was 26%, and two patients had potentially treatment-related G5 toxicity. Similar to MD Anderson's IMRT reirradiation study [27••], retreatment volume > 50 cm^3 was associated with increased risk of G3 toxicity. There were 31 patients (52%) reirradiated for skull base recurrences. The 2-year OS and LRC for these patients were 79 and 76%, respectively. Romesser et al. [21] reported on 92 patients treated with PRT reirradiation (100% PSPT) to a median dose of 60.6 Gy. The 1-year OS and LRC rates were 65 and 75%, with 77% of locoregional recurrences occurring in the reirradiation field. G3 or higher late toxicities included skin (9%), dysphagia (7%), and two patients (3%) with G5 toxicity from treatment-related bleeding. In a large analysis of 61 patients reirradiated to the skull base, McDonald et al. reported 2-year OS and LRC rates of 33 and 80%, respectively. Increasing tumor volume and lower reirradiation dose were associated with local failure. G3 or higher acute and late toxicity rates were 15 and 25%, including three treatment-related deaths. PRT was delivered with PSPT technique to a median dose of 66 Gy for microscopic disease and 70.2 Gy for gross disease.

Carbon ions are heavier than protons and provide additional advantages of high biological effect and improved dose distribution. When carbon ions reach their Bragg peak, they can deposit even more energy than protons to induce a high amount of lethal DNA damage, yet very little energy is deposited to normal tissue distal to the tumor. Carbon ion therapy requires expensive particle accelerators (cyclotrons or synchrotrons) and larger, complex delivery systems. Currently, there are six heavy ion facilities located in Japan, Europe, and China. In one study [22••], 25 patients with locally recurrent skull base chordoma or chondrosarcoma were treated with carbon ion reirradiation to a median dose of 51 Gy in 3 Gy fractions (63.8 Gy equivalent dose in 2 Gy fractions). The 2-year local progression-free survival was 79%. They reported only one patient with G3 toxicity. The same group reported on 52 patients treated with carbon ion reirradiation for recurrent adenoid cystic carcinoma (17% base of skull, 37% paranasal) [34]. Patients received a median dose of 51 Gy (63 Gy BED). The 2-year OS and LRC rates were 63 and 47%, respectively. In total, eight patients developed serious late effects, including two patients with grade 4 internal CAR and two with grade 3 CNS necrosis.

Stereotactic Radiation Therapy

A major goal of SRT systems is to minimize unwanted dose beyond the target volume, which is achieved through rapid dose fall-off and minimizing the PTV margins [35, 36]. An example of a SRT reirradiation plan is shown in Fig. 1. Current SRT systems can achieve margins of 0–2 mm using

Table 2 Common radiotherapy terms and concepts

Radiation target volumes	There are three main target volumes used in radiation treatment planning. The gross tumor volume (GTV) is the visualized gross disease as defined by physical examination and imaging studies. The clinical target volume (CTV) is the GTV plus an additional margin to account for microscopic extensions and subclinical disease spread beyond the visualized tumor. The planning target volume (PTV) is a geometric expansion of the CTV to account for uncertainties in treatment planning and delivery, patient setup and positioning, and tumor motion. The PTV is designed to ensure that the intended radiation field covers the entire CTV with each fraction. The organ at risk (OAR) is the volume of a vital organ close to the tumor that should be spared to reduce treatment toxicity.
The alpha/beta(α/β) ratio	This is a measure of the radiosensitivity of a tumor or tissue type using the ratio of two parameters that describe how a cell responds to radiation as a function of the dose. The α component is a measure of the intrinsic radiosensitivity of the cell. The β component represents the repairable portion of radiation damage. Tissues with small α/β ratios are generally less sensitive to changes in fractionation and are observed in late-responding tissues such as brain and nervous tissue and some benign skull base tumors. Tissues with high α/β ratios are more radiosensitive and typically observed in early responding tissue such as skin and mucosal epithelia, and most malignant tumors.
Ionizing radiation	Ionizing radiation produces cell death primarily by causing DNA damage. Photons and gamma rays are the most common type of ionizing radiation used for radiotherapy. Photons are considered indirectly ionizing radiation and are generated by linear accelerators (LINACS). Gamma rays are similar to photons in property but differ in their origin and tissue penetration. Gamma rays emitted by a cobalt-60 source are used in the Gamma Knife systems.
Particle radiation	Unlike photons or gamma rays, charged particles such as protons and carbon ions are directly ionizing radiation and interact directly with their biologic target. This gives charged particles a favorable depth-dose distribution in biologic tissue that is clinically useful in the treatment of tumors. A common term used in particle therapy is the *Bragg peak*, which is the depth in tissue where charged particles release most of their energy to cause a biological effect. The *spread out Bragg peak* (*SOBP*) is a broader peak composed of multiple Bragg peaks to ensure coverage of the entire tumor. Compared to photons, proton and carbon ion radiation also causes more biological damage at a given dose.
Conformal radiotherapy	The goal of conformal radiotherapy is to achieve the best adaptation of the shape of the high dose field to the exact shape of the target. This was made possible with advances in computerized radiotherapy planning and delivery systems that allowed shaping of the radiation dose to irregular tumor volumes. Two important benefits emerged from conformal radiotherapy: the ability to reduce dose to normal structures near tumor and the ability to escalate dose to tumor. This allows the reduction of dose to normal structures near the tumor without compromising dose delivery to the intended target.
Stereotactic radiation therapy (SRT)	SRT is highly conformal radiotherapy used to deliver high doses in a single or few sessions. Stereotactic radiosurgery (SRS) was originally developed for the treatment of cranial lesions using a stereotactic head frame to deliver a focal beam of external radiation. Today, SRS often refers to the use of SRT in a single session. Fractionated SRT (FSRT) is used to distinguish multi-session SRT from single-treatment SRS. Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation therapy (SABR) are common terms for FSRT of extracranial sites. SBRT is usually delivered in three to six sessions of doses > 6 Gy per session.
Image-guided radiation therapy (IGRT)	IGRT is the use of imaging in the treatment room to correct patient setup errors and guide radiation delivery. It is considered one of the more significant innovations in radiotherapy. IGRT is used in conjunction with conformal radiotherapy and is instrumental to SRT applications, to reduce the PTV margin by minimizing positional uncertainty of CTV and OAR targets. Current IGRT systems can provide high-resolution 2D, 3D, and 4D images to localize target position and capture motion and volume changes during each treatment.

a combination of immobilization devices, IGRT, and improved treatment planning and delivery software. Platforms for SRT delivery include the Gamma Knife® unit, CyberKnife® unit, and LINAC systems such as the Varian TrueBeam® STx or Elekta Trilogy®.

The Lekskell Gamma Knife system (GK-SRS) consists of ~ 192 non-coplanar collimated beams that are arrayed hemispherically to intersect at a single isocenter. The target is localized using a stereotactic head frame fixed to the patient's skull. In situations where fractionated GK-SRS is required, a GK-Extend Frame attached to the hard palate using a vacuum-assisted bite block with custom prosthesis can be used. An advantage of the GK system is the shorter distance between the radiation source and target, resulting in smaller beam diameters and less integral dose to normal structures. In studies comparing GK to LINAC-based SRT for skull base tumors, GK plans were shown to have sharper dose gradients and better conformality, whereas dose homogeneity and treatment time favored the LINAC plans [37–39].

The CyberKnife (CK) robotic radiosurgery system consists of a compact LINAC mounted on a robotic arm, which can direct radiation beams to the target from non-coplanar positions. Although the robotic arm has nearly 360° freedom of motion, treatment is delivered at discrete positions called nodes, with a typical treatment using ~ 100 nodes. Images can be acquired at periodic intervals during treatment to guide the treatment head using 6D tracking of the skull. In a study of 80 patients with skull base lesions treated with CK that compared plan quality between simple and complex tumors based on their proximity to adjacent critical structures, the CK

planning system was able to generate highly conformal and homogeneous plans for complex skull base tumors without a drop in plan quality [40].

Many modern LINACs are capable of performing IMRT-based SRT. More advanced LINACs such as the Varian TrueBeam STx and Elekta Trilogy have VMAT capabilities, 6D treatment couches, and high-definition MLCs with 2-mm leaf size, that make them even more well suited for SRT.

Single-Fraction Stereotactic Studies

The literature of single-fraction SRT (SRS) reirradiation for malignant skull base tumors is limited. SRS doses for malignant tumors ranged from 12 to 20 Gy in a single fraction. Cmelak et al. reported the initial Stanford experience utilizing LINAC-based SRS to treat 47 patients with malignant skull base lesions [23]. Of these, 37 patients had reirradiation. The median dose was 20 Gy in one fraction. The crude local control was 69%, and survival was not reported. Major complications occurred in five patients (all reirradiation). Miller et al. evaluated 32 patients treated with GK-SRS to a median dose of 15 Gy in a single fraction at the Mayo Clinic [24]. The 3-year LC and OS rates were 78 and 72%, respectively. One patient developed G4 unilateral vision loss.

Owen et al. reported the Mayo Clinic's experience with GK-SRS in a heterogeneous population of 184 patients, of whom 80% were treated for recurrent disease, and in 49%, SRS was used as a boost in addition to EBRT. Although it is unclear what portion had SRS reirradiation, salvage SRS alone, delivered with curative intent, was given to 43 patients. The median dose was 14 Gy. In those treated with salvage SRS with curative intent, the 1-year LRC was 73% and the median OS was 15.2 months. Serious late toxicity was low, with 6 and 2% of all patients experiencing late grade 3 or 4 toxicity, respectively.

The collective experiences of several smaller series indicate that SRS reirradiation is feasible with promising local control. Chua et al. reported on 18 patients with locally persistent/recurrent NPC after primary radiotherapy, who received single-fraction SRT to a median dose of 12.5 Gy. The 2-year LRC rate was 72%. There was one case of temporal lobe necrosis. Tang et al. reported on 10 patients who received SRT for recurrent HNC with gross perineural invasion (7 received prior EBRT). SRS was given with EBRT (median 50 Gy) in seven patients and surgery in seven patients, with a median dose of 17 Gy over one to three fractions. The 2-year PFS and OS rates were 20 and 50%, respectively. There were seven local failures all occurring outside the SRS field. There was one grade 4 toxicity and one patient who developed a nasal cutaneous fistula.

In addition to local disease control, the role for SRS for symptom palliation is promising. In a study by MD Anderson [41••], 27 patients received GK-SRS reirradiation for palliation of trigeminal neuralgia secondary to recurrent malignant skull base tumors (most received single-fraction GK-SRS to a median dose of 16 Gy). Patients without recurrence and at least a 3-month follow-up ($n = 19$) were assessed, and they found a significant decrease in patient-reported pain and opioid requirement. Of the 13 patients with complete pain relief, 9 were completely off analgesic use.

Multi-Fraction Stereotactic Studies

Two studies reported on multi-fraction SRT (SBRT) exclusively of the skull base. Coppa et al. reported on 31 patients treated with SBRT to a median dose of 25 Gy in five fractions. The majority were SCC ($n = 6$) and adenoid cystic carcinoma ($n = 5$) histology. The crude tumor control rate was 74%. In the absence of tumor progression, there were no complications related to SRS. Xu et al. [12] reported the University of Pittsburgh's experience treating 31 patients with 40 skull base tumors with SBRT (44 Gy in five fractions, every other day; QOD). The outcomes seemed less favorable in this cohort. The response rate based on RECIST criteria was 7.5% complete response, 30% partial response, 30% stable disease, and 22.5% progressive disease. The 2-year OS rate was 12%, and the median time to progression was 3.3 months. Although no actuarial LRC rates were provided, 29 of 33 evaluable treatments had a local failure. All patients in this cohort had reirradiation, inoperable disease larger tumor volume (median 27 cm^2), and were predominantly SCC (55%) histology. Grade 3 toxicity occurred in 15% of patients. There were no G4–5 toxicities.

Late toxicity results from SBRT reirradiation are encouraging. In general, the rates of late G3 or higher complications across contemporary studies ranged from 4 to 22%, with late G4 rates from 0 to 9% [42–46]. These complication rates in contemporary SBRT series were lower than G3 or higher rates in reported from IMRT and PRT studies, which typically ranged from 27 to 32% at 2 years in two studies with actuarial data and a crude incidence of 15 to 48%. In a 10-year update of their institutional experience, the University of Pittsburgh evaluated predictors of toxicity in 291 patients treated with SBRT reirradiation between 2002 and 2013 for recurrent HNC [25••]. The incidence of late G3 or higher event was 18.9%, predominantly dysphagia (48%), whereas the incidence of late G4 toxicity was 5.1%. On correlative analysis, patients with larynx or hypopharynx recurrences experienced significantly more late toxicity compared with those with recurrences in other sites, including skull base.

A devastating complication of HN reirradiation is CAR. Yamazaki et al. reported on 107 patients reirradiated to a median dose of 30 Gy in five fractions daily. In the 22 patients (21%) who developed G3 or higher toxicities, 11 patients developed CAR (9 of which were fatal) at a median time of 5 months. They found that only patients with tumor invasion of the carotid > 180° developed CAR and that CAR was

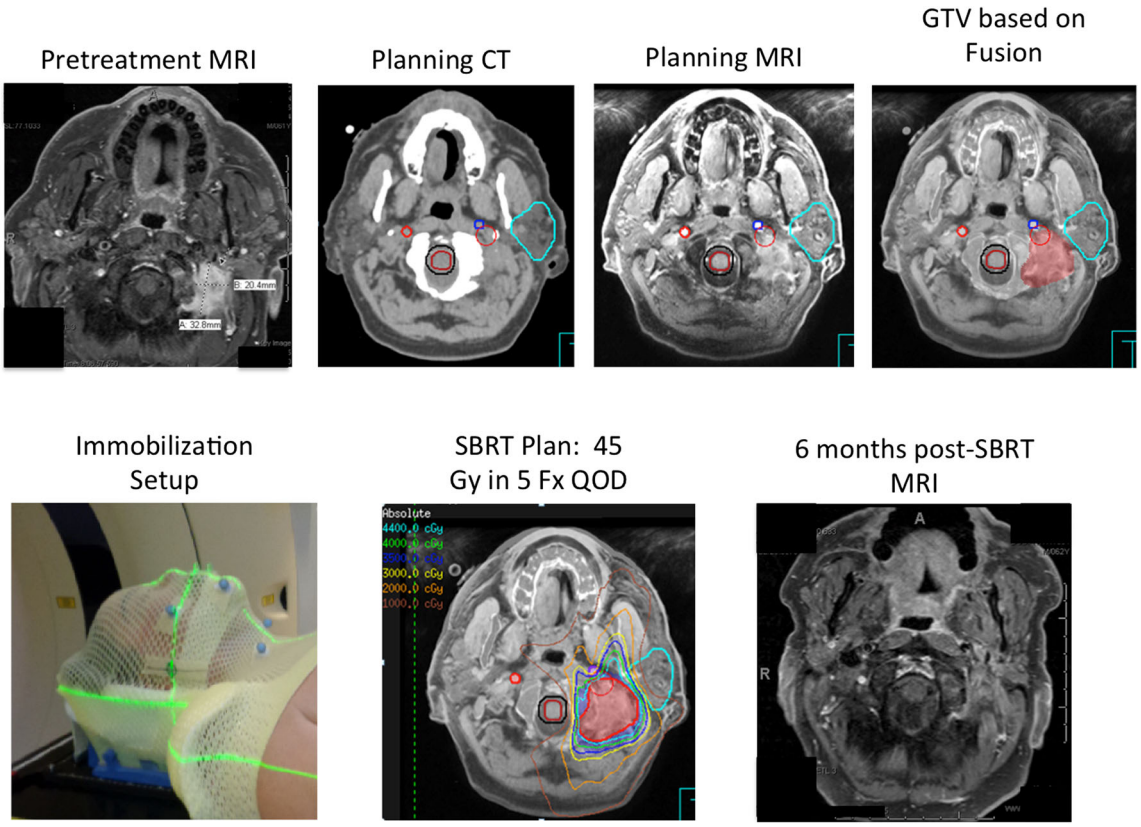

Fig. 1 Example of patient with a skull base recurrence treated with SBRT to a dose of 45 Gy in five fractions delivered every other day. The patient's diagnostic pretreatment MRI, the planning simulation CT, the high-resolution planning MRI obtained in treatment position, and the fusion of the planning MRI and planning CT scan (with the GTV shown in *red*) (*across the top row* (*left to right*)). Immobilization with a customized posterior cushion, mask, and bite block; the patient's reirradiation SBRT plan with a prescription dose of 45 Gy in five fractions every other day; and the patient's follow-up MRI at 6 months after reirradiation, showing a complete response (*across the bottom row* (*left to right*))

associated with the presence ulceration [26•]. In two smaller studies ($n = 70$ total) utilizing 30 Gy in five fractions daily, the incidence of CAR was 6 to 17%, and ~ 28% developed severe toxicity. In one study, CAR occurred in patients whose tumor surrounded half or more of the carotid artery wall and when the carotids received 100% of the prescribed dose [45].

Daily (QD) versus alternating day (QOD) treatment with SBRT appears to be an important factor in determining toxicity and CAR. The majority of studies reporting higher severe (G4 or 5) toxicity rates utilized a daily (9.7 to 17.6%) regimen versus a QOD regimen (0 to 4.5%). It is thought that an extended time is needed with hypofractionation to allow sufficient time for cellular repair. These results are mirrored in a phase II study by Lartigau et al. in which patients were treated to 36 Gy in six fractions QOD [47••]. The reported CAR rate in this study was 2% (1 in 60). More favorable outcomes were reported from MD Anderson's early SBRT reirradiation experience by Phan et al. [48]. Patients with a median tumor size of 36.4 cm^3 were treated with SBRT to a median dose of 45 Gy in five fractions QOD. Most patients (86%) received concurrent cetuximab. The 6-month OS and LRC rates were 79 and 91%, respectively. There were no acute grade 3 or higher toxicities. In a combined analysis from the same institution of 63 patients with smaller skull base tumors (< 60 cm^2) reirradiated with IMRT (30%), PRT (30%), and SBRT (40%), Ng et al. (unpublished data) reported the 5-year OS and LRF free survival rates that were 51 and 67%, respectively. One patient (4%) in the SBRT group and five patients (15%) in the IMRT/PRT group developed grade 3 late toxicity, and there were no grade 4–5 toxicities.

Conclusion

Modern advances in radiation therapy such as IGRT, SRS, and PRT offer an opportunity to widen the therapeutic window for reirradiation of recurrent skull base tumors. Prior to the advent of highly conformal radiotherapy and IGRT, it was extremely difficult to deliver tumoricidal dose to skull base tumors without exceeding the tolerance of a critical structures. IMRT, particle therapy, and SRT all appear to be feasible options, although SRT appears to have the least risk of late serious toxicity, when given over alternating days. The accurate and safe implementation of these techniques requires a treatment

team that is experienced in the use of this technology. Further prospective study is warranted to clarify the optimal modality, dose, and fractionation.

Author Contributions Both co-authors (JCH and JP) contributed to the research, writing, editing, and review of this manuscript and approved the final manuscript for submission.

Compliance with Ethical Standards

Conflict of Interest Jennifer C. Ho and Jack Phan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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