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CLINICAL INVESTIGATION

Retreatment of Recurrent or Second Primary Head and Neck Cancer After Prior Radiation: Executive Summary of the American Radium Society Appropriate Use Criteria

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Retreatment of recurrent or second primary head and neck cancers occurring in a previously irradiated field is complex. Few guidelines exist to support practice. We performed an updated literature search of peer-reviewed journals in a systematic fashion. Search terms, key questions, and associated clinical case variants were formed by panel consensus. The literature search informed the committee during a blinded vote on the appropriateness of treatment options via the modified Delphi method. The final number of citations retained for review was 274. These informed 5 key questions, which focused on patient selection, adjuvant reirradiation, definitive reirradiation, stereotactic body radiation, and reirradiation to treat nonsquamous cancer. Results of the consensus voting are presented along with discussion of the most current

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evidence. This provides updated evidence-based recommendations and guidelines for the retreatment of recurrent or second primary cancer of the head and neck.

Summary of Recommendations

1. Patient selection

   1.1. The committee strongly recommends careful patient selection when considering aggressive curative intent salvage therapy. Selection should be based primarily on multidisciplinary review, patient goals of care, and published prognostic variables such as time between courses, disease extent, organ dysfunction, and alternative treatment options.

   1.2. Patients highly unlikely to achieve long-term (>2 year) progression-free or overall survival should be spared the morbidity of aggressive surgery and/or high-dose reirradiation and rather be offered a combination of systemic therapies, palliative reirradiation, and best supportive care.

   1.3. Prognostic models such as nomograms and recursive partitioning analyses are available to aid in patient selection.

2. Resectable disease

   2.1. The committee strongly recommends surgical treatment for recurrent or second primary cancers that can be completely resected with acceptable functional outcomes.

   2.2. Curative-intent reirradiation without resection should only be offered to patients with resectable disease if the patient declines the recommended operation after consultation with a qualified head and neck surgeon.

   2.3. The committee strongly recommends that systemic therapy alone is usually not appropriate treatment for locoregional recurrent or second primary cancers that are resectable.

   2.4. After resection, the committee concluded that it was usually appropriate to offer adjuvant systemic therapy with reirradiation to a dose of 60 to 66 Gy for cancers with adverse risk factors. The committee did not reach consensus on the appropriateness of postoperative reirradiation alone (60 Gy) or observation without reirradiation. The committee did not reach consensus on the appropriateness of adjuvant stereotactic body radiation (SBRT), considering the limited and evolving data.

3. Unresectable disease

   3.1. The committee strongly recommends that fractionated reirradiation to 60 to 70 Gy with consideration of concurrent systemic therapy is usually appropriate for locoregional recurrences with favorable prognostic factors.

   3.2. The committee strongly recommends that elective nodal irradiation is usually not appropriate in the reirradiation setting.

   3.3. The committee strongly recommends that hyperfractionation warrants consideration but is not mandatory.

   3.4. The committee did not reach consensus on the role of SBRT to 35 to 44 Gy in comparison to fractionated reirradiation. The committee felt strongly that SBRT to 30 Gy or less is usually not appropriate.

   3.5. For patients who were otherwise considered eligible for higher dose reirradiation, the committee did not reach consensus on the appropriateness of systemic therapy alone or with palliative reirradiation. This likely relates to the nuances of patient wishes in this complex scenario.

4. Role of SBRT

   4.1. The committee did not reach consensus on the role of SBRT in comparison to more protracted fractionation schemes, even when considering cancers with a combination of adverse prognostic factors. Most considered SBRT delivered to 35 to 44 Gy more appropriate than lower doses.

   4.2. The committee strongly recommended that for cancers with adverse prognostic factors, systemic therapy alone with palliative reirradiation may be appropriate depending on patient preference.

5. Reirradiation for nonsquamous histologies

   5.1. The committee recommended that patients with nonsquamous histologies could be appropriately offered reirradiation with similar techniques and doses to squamous histologies.

   5.2. The committee recommended that for nonsquamous histologies, observation with palliative reirradiation may be appropriate, depending on the natural history and symptoms of the particular patient in a heterogeneous population.

Introduction

Radiation therapy is an important modality in the initial treatment of many head and neck cancers. Despite best current therapy, 20% to 40% of patients will develop locoregionally recurrent disease and 5% to 20% will develop a second cancer.[1,2]

The management of recurrent or second primary (RSP) cancers originating in an irradiated region is complex. Reirradiation may be an option for selected patients with RSP cancers, but the therapeutic window of reirradiation is narrow with a high risk of both disease progression and normal tissue toxicity.

In 2011, the American College of Radiology Expert Panel on Head and Neck Cancer developed appropriateness criteria for the delivery of reirradiation.[3] Here, we present an updated review of relevant literature along with updated appropriate use criteria for representative clinical scenarios.

Methods and Materials

For this updated review, the American Radium Society convened a multidisciplinary expert panel composed of radiation, medical, and surgical oncologists. A systematic review of the medical literature was conducted through PubMed, Embase, and Scopus databases. The search strategy and subject-specific keywords were developed based on the expert panel's consensus. Articles published from January 2000 to December 2020 restricted to the English language were considered. The search took place on December 24, 2020. The following subject-specific keywords were used: (("intensity-modulated radiation therapy" OR "IMRT" OR "proton" or "brachytherapy" or "carbon ion" or "intensity-modulated radiotherapy") AND ("re-irradiation" or "reirradiation" or "RERT") AND ("head and neck" or "head neck" or "HN" or "oropharynx" or "larynx" or "oral cavity" or "nasopharynx" or "hypopharynx" or "larynx")) AND ("2000/01/01"[date - publication]: "3000"[date - publication]).

The population of interest consisted of patients with recurrent or second primary cancers of the head and neck treated with curative-intent reirradiation by any technique. "Second primary" cancers were included in this report considering that in practice, the delineation from recurrence is often arbitrary and difficult to discern. Considering most literature on reirradiation does not seek to differentiate between the 2, both categories were included in the review. Time between treatment courses, a continuous variable and frequent surrogate for the delineation, is the focus of the following discussion.

Key questions were generated by 3 authors MCW, SAK, RLB in collaboration with the committee. These questions are presented in Box 1. Articles identified were removed if they focused on salvage therapies other than reirradiation or were not otherwise deemed relevant for any form of citation in the revised narrative text. Two authors MCW and RLB reviewed full-text articles and matched citations to the questions addressed and included, for in-text citation. For each key question, prospective clinical trials, systematic reviews, and meta-analyses published from 2011 to 2020 were selected for full-text review and included in the complete data table with evidence grading according to the American College of Radiology 2019 and American Radium Society 2021 methodology.[4,5] If insufficient sources were available for a particular question, the highest level of evidence (multi- or single-institution retrospective series) was included in the data table.

Box 1 Key questions

KQ1	Is aggressive local therapy for rapid, large, and incurable locoregional-only recurrences appropriate?
KQ2	What are appropriate treatment options for resectable disease?
KQ3	What is the appropriate management of patients treated nonoperatively?
KQ4	Is there an appropriate role for stereotactic body radiation?
KQ5	What is the appropriate role of re-RT for nonsquamous histologies?

After construction of the data table and narrative, a well-established methodology (modified Delphi) was used by the expert panel to rate the appropriate use of procedures for each key question.[6]

Results

Summary of evidence

The literature review process is summarized in the flowchart presented in Figure E1. A total of 686 citations were identified through the aforementioned search terms within the 3 databases interrogated. Two hundred thirty-one citations were duplicates. The authors added 8 citations identified outside the search: one randomized trial published after the date of the systematic review, and 7 others identified in the bibliography of other manuscripts. Publications excluded due to the reasons summarized in the figure totaled 189. The final set of articles retained for review totaled 274. Table 1 lists the citations by study type, and the detailed evidence is presented in Table E1.

Of the 274 therapeutic references included in the American Radium Society Appropriateness Criteria, 203 were

Table 1 Number and types of studies identified in the literature search

	KQ1	KQ2	KQ3	KQ4	KQ5	Discussion only
SR/MA	0	2[132,133]	1[46]	1[134]	0	5[15,65,128,130,135]
RCT	0	2[24,25]	3[32,86,136]	0	0	0
Prospective, single arm	0	2[137,138]	16[7,8,113-120,139-144]	3[41,42,145]	0	8[84,85,104,146-150]
Retrospective, multi-institution	4[19,20,50,151]	6[19-21,151-153]	8[19-21,23,33,66,154,155]	1[43]	0	1[156]
Retrospective, single-institution	14[22,157-168]	27[18,27-29,38,54,63,68,94-96,99-102,105,106,169-178]	82[18,26,27,35-39,54,63,67,68,93,95,98,100,103,108-111,127,170,172-174,177-228]	31[47-49,88,229-255]	8[55-62]	41[30,31,34,51,73-83,87,89-91,97,107,126,256-274]
Other	0	0	7[275-281]	2[282,283]	3[284-286]	12[40,71,92,112,287-294]

The number of studies is in regular script; the reference numbers of specific studies are in superscript. Shaded cells included in the data table indicate that the study was published within the period from 2011 to 2020 (Table E1).

Abbreviations: KQ = key question; RCT = randomized controlled trial; SR/MA = systematic review/meta-analysis.

single-institution retrospective case series (category 3). There were 20 other retrospective multi-institutions case series (category 3). There were 29 single-arm prospective studies, of which 10 were moderately well designed, accounted for the most common biases and were directly relevant to the key questions (category 2). There were 4 high-quality prospective randomized trials and one meta-analysis that were directly related to the key questions (category 1). Table 1 lists the citations by study type. Overall, the 33 studies included in the data table provided good evidence to inform the case variants.

Definition of reirradiation

Reirradiation is defined as "an additional course of radiation which at least partially irradiates the same tissue as a prior course, with a biologically meaningful dose." Within this definition are a broad range of dose, volume, and fractionation options. Like classic studies in the field, this monograph concerns the delivery of regimens with a 2 Gy equivalent (EQD2) of 45 Gy or more to tissues that have previously received 45 to 75 Gy (EQD2).[7,8]

In select cases, lower-dose regimens may be appropriate. Such schedules do not typically carry the expectation of disease control beyond a few months, but rather are intended to reduce local symptoms temporarily without significant risk of acute sequelae. Examples of such regimens include the "quad-shot" (14-14.8 Gy in 4 fractions delivered twice daily), or 20 to 30 Gy delivered over 5 to 10 daily fractions.[9,10] These lower-dose reirradiation regimens will be termed "palliative" in the accompanying case variants and are not the primary focus of this text.[11]

Rationale for reirradiation

To date, no randomized level I evidence demonstrating a survival benefit from reirradiation exists, perhaps due to failure of such trials to accrue or competing causes of mortality.[12,13] Many practitioners are reluctant to recommend reirradiation because of the significant risks involved, although trends suggest increased utilization in recent years.[14,15] Advocates of reirradiation argue that survival after reirradiation often exceeds the 10- to 15-month median survival afforded by modern chemoimmunotherapy regimens.[16,17] Supporters cite occasional patients who experience long-term (5 years or more) survival, which is rare for systemic therapy alone. Locoregional progression can be associated with concerning symptoms such as pain, bleeding, dysphagia, dysphonia or airway compromise, dermal ulceration, and foul odors; it reduces patients' participation with their society and family. Securing locoregional control with reirradiation may confer improved quality of life compared with uncontrolled locoregional cancer progression. Whether these observations reflect selection bias and isolated circumstances is unclear, but

for selected patients, reirradiation seems a useful option for RSP cancers.

Evaluation and patient selection

Patient selection is perhaps the single most important step in obtaining a beneficial outcome after reirradiation. Along with the reirradiation evaluation, a qualified surgeon should discuss the advantages and limitations of resection, which will aid in clarifying the role of a second course of radiation therapy. When discussing reirradiation, the patient should understand that reirradiation is only rarely a curative endeavor. If the patient wishes to proceed, a thorough understanding of the patient's disease course, current functional status and medical history is required to assure candidacy, as is an informed discussion surrounding goals and expectations.

The assessment before reirradiation should include a complete physical examination, positron emission tomography (PET) imaging along with a computed tomography (CT) of the neck with intravenous contrast. Magnetic resonance imaging (MRI) may be useful if other modalities provide insufficient information. The diagnosis should be confirmed pathologically, with human papillomavirus (HPV) and/or Epstein-Barr virus status as appropriate. For squamous cell carcinomas, programmed cell death ligand 1 status may be useful if systemic therapy incorporating immune checkpoint inhibitors (henceforth "immunotherapy") is considered.

Patient factors to consider include tolerance to the first course of radiation therapy, persistent late effects, swallowing function, pain, general performance status, social support, and smoking status. Organ dysfunction is an important prognostic factor and is defined in the literature as a composite of feeding-tube dependence, tracheostomy dependence, and soft-tissue damage.[18]

Disease characteristics of both the index and RSP cancer are helpful guides. For instance, the amount of time between the previous and the new course should be considered. The initial studies by the Radiation Therapy Oncology Group (RTOG) required at least 6 months from the previous course for inclusion.[7,8] However, time is a continuous variable, and a threshold is difficult to define. Retrospective data suggest that survival decreases dramatically as the time between the 2 courses decreases, and enthusiasm for retreatment should be tempered at shorter timepoints.[19] The one notable exception to the "time rule" occurs when the initial treatment course was inadequate due to either insufficient target coverage or early cessation of therapy, in which case short-interval full-dose reirradiation may be appropriate depending on location and nearby organs at risk.

As with the index tumor, an understanding of the RSP cancer's size, depth of invasion, proximity to critical structures, and histology are all important. Patients with distant metastatic disease are typically not considered for reirradiation with curative intent but may benefit from palliative treatment (eg, patients with symptomatic local progression despite systemic therapy). However, enthusiasm for aggressive treatment of oligometastatic disease, supported indirectly by studies with few patients with head and neck cancer, may also prompt consideration of locoregional reirradiation.

Various prognostic systems are available to help the clinician in patient selection. A recent 9-institution collaborative study Multi-Institution Re-Irradiation collaborative (MIRI) performed a recursive partitioning analysis (RPA) of patients with RSP squamous carcinoma treated with modern intensity modulated radiation therapy (IMRT).[19] The RPA identified 3 cohorts. The most favorable (class I) were patients who were more than 2 years from their initial diagnosis and were able to undergo surgical resection. The least favorable (class III) were 2 years or less from initial radiation therapy and were experiencing organ dysfunction at the time of their new diagnosis, regardless of surgical resection status. Patients in class I experienced a 2-year overall survival of 62% with a 4-year survival exceeding 40%. However, despite aggressive reirradiation, none of the class III patients survived 4 years. Hence, the class III patients may be better served by less morbid interventions. The RPA system has recently been externally validated by a multi-institution series from Korea.[20] A separate multi-institution study failed to validate the RPA system, although that review included only 16 squamous patients in RPA class I, limiting the strength of its conclusion.[21] For patient-specific estimates, nomograms have been promulgated to predict overall survival, locoregional failure, and late effects.[18,22,23]

The process of patient selection is highlighted via Case Variant 1. This case highlights a rapid recurrence in an RPA class III patient with a marginal performance status. Although nonmetastatic, given these features, the most aggressive options were felt by the panel to be usually not appropriate.

Resectable disease

Multidisciplinary evaluation with surgical, radiation, and medical oncologists is necessary before treatment decisions. If the tumor is technically resectable with a reasonable functional outcome, surgery is typically preferred. Indeed, a recent randomized phase 3 study of resectable, recurrent nasopharyngeal cancer demonstrated significantly improved survival for patients randomized to surgery compared with repeat IMRT.[24]

The appropriateness for surgery consultation is highlighted in Case Variant 2a. This variant highlights a complex resection that is technically achievable and congruent with patient wishes; the panel felt that this is usually appropriate, with definitive reirradiation only when the patient declines the proposed surgery.

The decision whether to reirradiate after resection of an in-field RSP is complex. This choice is informed by the phase 3 GORTEC study by Janot et al.[25] This protocol

randomized patients who had recurrent squamous carcinoma occurring in an area previously treated to at least 45 Gy who underwent resection to either reirradiation with concurrent chemotherapy or observation. Inclusion required deep infiltration (>1 cm) or a nodal recurrence. Isolated nodal recurrences must have exceeded 3 cm, and larynx cancers must have included extralaryngeal spread on resection (rT4). There must have been a 6-month interval or more between previous radiation and RSP surgery, and no gross residual disease was allowed. The reirradiation regimen included 6 total cycles of 10 Gy with a 9-day rest period between cycles. Concurrent fluorouracil and hydroxyurea chemotherapy was delivered, and conventional radiation techniques were employed. The majority of the 130 enrolled had either positive margins or extracapsular extension. Nearly all had at least one risk conventional risk factor including lymphovascular space or perineural invasion. The study met its primary endpoint with reirradiation demonstrating a statistically significant improvement in disease-free survival (approximately 18%-38%) and locoregional control (approximately 20%-60% at 2 years) albeit without improvement in overall survival (a secondary endpoint). This study is informative but not representative of modern treatment regimens or radiation techniques, which may produce still more favorable outcomes. The split-course technique was widely used in the early era of reirradiation to improve safety but has fallen out of favor in the modern era in favor of continuous course regimens.[26]

In general, reirradiation is considered most appropriate for motivated patients after operations with final pathology demonstrating positive margins, extensive extracapsular extension or multiple associated risk factors; good wound healing; and a prolonged time between the previous course of radiation (or recurrence due to inadequate initial treatment). Typically, in the modern era, reirradiation is delivered to the resection bed plus margin, with either no elective nodal coverage or of no more than one adjacent nodal bed. Patterns-of-failure analyses show that out-of-field progression is a common cause of recurrence after postoperative re-RT and often occurs in unpredictable locations.[27] In view of the unpredictable patterns of progression in the RSP situation, and the morbidity of elective reirradiation, prophylactic neck irradiation in a region of overlap is not generally recommended.

If an autologous tissue flap was used for reconstruction, target volumes are delineated similarly to de novo cases, with ongoing investigation into the utility of avoiding the flap versus including the entire flap in the radiation target volume. By virtue of transposing unirradiated tissue into the operative bed, the use of flaps may reduce fibrosis and other late effects of reirradiation.[28-31] The dose delivered for postoperative reirradiation ranges from 56 to 66 Gy, and hyperfractionation is not mandatory.[32] Retrospective data do not suggest a benefit to dose escalation above 60 Gy in the adjuvant setting regardless of risk factors.[33] The appropriateness of adjuvant reirradiation is highlighted in Case Variant 2a.

Unresectable disease

For cancers determined to be technically unresectable, or resectable only with unacceptable morbidity, nonoperative "definitive" reirradiation may be appropriate with curative intent. This is supported by prospective data such as the 2 single-arm phase 2 trials from the RTOG which demonstrated the feasibility of definitive reirradiation, despite a grade 5 toxicity rate of 7% to 8%.[7,8] As single-arm studies, these do not establish superiority over less-aggressive approaches, such as palliative radiation therapy with systemic therapy, but can be considered after a thorough discussion. As noted previously, "split course" regimens are no longer in regular use for "definitive" therapy, and most now favor continuous courses of therapy.[26]

Treatment is typically delivered to gross disease detected by physical examination, endoscopy, CT, MRI, or PET imaging plus margin. The margin used for clinical target volume (CTV)/planning target volume (PTV) expansion is controversial and heterogeneous in the referenced literature, but typically for fractionated IMRT-based treatment, the committee members use an anatomically constrained 3- to 7-mm CTV expansion on gross disease, which may be further edited manually to include adjacent areas of concern. This CTV is then expanded isometrically by 3 to 5 mm to form the PTV. Given concern for normal tissue sequelae, robust immobilization, and daily image guidance are ubiquitous among the committee members, particularly when using the narrow PTV margins suggested. Typically, daily cone beam CT is the daily image guidance method of choice, with daily kV imaging an acceptable alternative.

Similar to the adjuvant setting, elective nodal treatment is typically not performed or at most, limited only to the nearest echelon.[34] Doses for definitive care are typically between 60 to 72 Gy.[35-39] There may be a benefit to doses of 66 Gy or higher, although selection bias complicates interpretation of these data.[19]

Hyperfractionation once was considered critical for reirradiation. In the modern IMRT era, multiple institutions have demonstrated similar safety and efficacy for regimens delivered on a daily schedule. Fractionation was the subject of 2 recent randomized trials highlighted in Table E1. One randomized study delivered a split-course daily approach versus hyperfractionation, the other standard versus mild hypofractionation.[32,33,136] Both demonstrated relative tolerability in the daily course, although the risk of nasopharyngeal mucosal damage and hemorrhage was higher in the more protracted course. Ultimately, it is felt that with modern techniques, hyperfractionation is not mandatory but may carry benefits such as dose escalation, acceleration with the possibility of improved local control (in the absence of chemotherapy), and a reduction in late effects (particularly optic or other serial structures). However, hyperfractionation may carry an excessive burden for some patients and may increase acute toxicity. Common fractionation regimens used by institutions submitting data to the MIRI

collaborative include 72 Gy in 60 fractions twice daily or 66 Gy in 30 to 33 fractions daily.[19] The management of unresectable disease is highlighted in Case Variant 3. This case features a primary-only recurrence in an RPA class II patient without organ dysfunction who declines resection.

Stereotactic body radiation therapy (SBRT)

Stereotactic body radiation therapy is an evolving option for selected patients with RSP carcinomas. The primary advantage of SBRT is the significant dose delivered in a short timeframe. Such a course carries logistic and cost benefits but may still provide durable local control seen with more protracted regimens.[40]

The role for SBRT in comparison to more protracted courses is controversial and not well delineated in the literature. SBRT has been investigated in a series of systematic prospective single-institution studies.[41,42] These demonstrate control and survival rates similar to those produced by more protracted regimens and support SBRT as a standard option in the retreatment setting.

When selecting between the 2 options, the only direct comparison available is a matched retrospective multi-institution cohort.[43] Two analytical techniques were used to control for biases and compare SBRT to protracted courses of reirradiation. Subgroup analysis suggested that for RPA class II "larger" cancers (>25 mL in volume or rT3-4 classification), protracted courses were favored with regard to overall survival (OS). This was not well demonstrated on multivariable regression, with minimal differences between the techniques. Physician-reported late effects were also similar between techniques in this study.

In view of the limitations of the available data, controversy remains in the current role for SBRT. Some institutions consider SBRT a standard option for nearly all RSP retreatment cases, citing logistical benefits for a patient population with guarded prognostic expectations. Other institutions express concern over late effects due to hypofractionation and possible inferior control due to total dose. Although SBRT reirradiation is under investigation in combination with pembrolizumab in the multi-institution setting via the RTOG 3507 study, these controversies are likely to persist in the near future.[44]

Despite the controversy, it appears that RPA class III patients (defined as those with a recurrence ≤2 years from prior radiation with pretreatment organ dysfunction, regardless of resection status) are suboptimal candidates for protracted courses of reirradiation, as mentioned previously. These patients, if still interested in more aggressive treatment, stand to benefit the most from the favorable logistics of SBRT. SBRT may achieve durable local control compared with a more palliative approach, but in a scenario where a course of hyperfractionated IMRT with systemic therapy would likely consume a significant portion of the patient's remaining quality and quantity of life. For RPA class II patients (particularly those with larger tumors), the decision will remain provider-dependent until additional data develops.

Safety is a critical concern when delivering SBRT-based reirradiation and can be addressed with careful patient selection and treatment planning. SBRT is typically delivered in the definitive setting to 35 to 50 Gy over 5 fractions on alternating days.[45] Such dosing is supported by the recent "Hypofractionated Treatment Effects in the Clinic" (HyTEC) systematic review.[46] This strategy is based in part on dose-response data which demonstrated significant improvement in 3-year local control when escalating from 35 to 44 Gy for larger (eg, ≥25 cc) lesions.[41,46,47] The target for SBRT is typically gross disease plus a narrow PTV margin of 5 mm without expansion for a CTV. Severe toxicity is more common among larynx and hypopharynx tumors, although it is not clear if this risk is improved by protracted fractionation or if this is inherent to this location.[48] SBRT has been used in the postoperative setting with limited data supporting its application.[49] The appropriateness of SBRT for an RPA class III patient with a symptomatic retropharyngeal-only recurrence is highlighted in Case Variant 4.

Unique scenarios

There are a few discrete scenarios which can be considered independently. RSP nasopharyngeal carcinoma is disease that is associated with superior survival compared with that of other disease sites such as oral cavity, or neck recurrences.[50] Resection may be challenging in this area, but when possible is associated with favorable outcomes, as demonstrated by recent randomized data.[24,51] Consultation with an experienced skull base surgeon is recommended. Reirradiation is associated with favorable outcomes, but also carries the possibility of unacceptable risks to the mucosa, carotid artery, brain stem, and optic structures, which risk hemorrhage and/or vision loss. This topic is the subject of a recent dedicated consensus statement.[295] Proton therapy or induction chemotherapy may be useful approaches to reduce dose to critical normal tissues in this region.

Perineural invasion, particularly common among cutaneous or oral cavity squamous carcinomas and adenoid cystic carcinomas, presents a challenge when considering reirradiation. Such skull base cases are anatomically similar to nasopharynx cancer. A high degree of suspicion is appropriate based on examination for RSP cutaneous squamous carcinoma in a radiated field, and an MRI with contrast is often beneficial before treatment. Irradiation of the involved nerves and elective targeting of adjacent pathways of spread similar to de novo cases is recommended, if feasible.[52]

HPV-mediated squamous carcinoma carries a relatively more favorable prognosis upon recurrence. For instance, a pooled analysis of data from the RTOG suggests that p16-positive cancers progressed at a similar time point, compared with p16-negative cancers, those with p16-positive disease experienced improved overall survival (2-year 54.6% vs 27.6%).[53] However, data from the MIRI study with longer

follow-up would suggest that p16 status does not overcome other prognostic factors, such as time to recurrence, surgical resection, and organ dysfunction. Long-term "cure" often remains elusive even in p16-positive cases.[19] In the current era, therefore, HPV+ status in a reirradiation patient is a prognostic but not predictive factor that plays only a minor role in management strategies. If the patient initially received de-escalated therapy for HPV+ disease, this may allow more room for safe reirradiation, but given the biology of an unlikely local recurrence in this scenario, salvage treatment with intensity similar to other cancers is recommended.

Other nonsquamous histologies

Patients with RSP cancers of the head and neck are a heterogeneous group. Most data reflect squamous carcinomas, but institutional series often include some sarcomas and salivary cancers. These histologies are often associated with a prolonged natural history, and late effects should be considered with particular care in view of the reduced competing risks. Reirradiation techniques mirror those for squamous carcinomas.[54] The appropriateness of reirradiation for nonsquamous carcinomas is highlighted in Case Variant 5 and must take into account the particular behavior of each tumor type. The literature search identified only single-institution retrospective data on the topic, highlighting the rare and heterogeneous nature of these lesions. Re-treatment often seems appropriate but is supported only by extrapolation from the squamous experience and the single-institution studies identified.[55-62]

Proton therapy

Proton therapy is an alternative radiation modality that typically carries less low to intermediate-dose deposition and integral dose to surrounding normal tissue due to lack of exit dose distal to the Bragg peak.[63] This beam characteristic may, in selected cases, improve normal tissue toxicity. Most authors suggest the use of intensity modulated proton therapy in the treatment of head and neck cancer, although passive scatter techniques have been used.[63] There are important considerations in proton planning that must consider the potential higher RBE at the distal edge of the Bragg peak, and the enhanced sensitivity to tissue density change during and between treatments. These are highlighted in a recent work suggesting increased late toxicity with proton-based therapy for advanced nasopharyngeal carcinoma.[64]

Proton-based reirradiation is the topic of a systematic review and multiple retrospective studies.[63,65-68] In general, if proton therapy is accessible to the patient, this technique warrants consideration. Although patient selection is challenging, cases which may be more likely to benefit from proton therapy may include sinonasal, periorbital, cases with perineural invasion, nasopharynx, and well-lateralized cases such as salivary or neck recurrences, each of which were heavily represented in the cited retrospective series. Targets near serial structures such as the spinal cord, brain stem and brachial plexus may also benefit significantly. Comparative planning remains necessary to evaluate the patient-specific benefits of proton therapy.[69,70]

Carbon ion therapy

Carbon ions are hypothesized to extend the proposed benefit of proton therapy further through utilization of a heavier charged particle. The carbon ion's increased mass not only carries the advantageous Bragg peak beam profile but also may augment control rates of radioresistant disease by an increase in the relative biological effectiveness (RBE) via the high linear energy transfer (LET) and subsequent decreased intrafraction DNA repair. This may have oncologic advantages, particularly when applied to radioresistant histologies. Furthermore, the lateral penumbra at depth is often superior with carbon ions compared with proton therapy. Dosimetric studies confirm that, compared with photons (and often protons), multiple organs at risk experience reduced exposure with carbon ions.[71,72]

Carbon therapy is the subject of multiple single-institution retrospective studies, which suggest favorable outcomes compared with historical controls, although these data are difficult to interpret due to potential for bias.[73-83] Nonsquamous salivary histologies and skull base recurrences are heavily represented in the single-institution series reported. One ongoing prospective phase 1/2 study from Shanghai is investigating the maximum tolerated dose for reirradiation of nasopharynx cancer without chemotherapy and completed to a dose of 63 GyE, whereas a similar study with concurrent cisplatin was terminated for toxicity concerns (NCT02795195 and NCT02801487); a phase 3 study is ongoing.[84] The role for heavy ion therapy will continue to evolve as access increases worldwide.

Brachytherapy

Brachytherapy is a common subject reported in the literature, but its use is infrequent in the United States due to the technical challenges associated with treatment delivery. Brachytherapy can be performed in the perioperative setting[85] or as definitive therapy for unresectable disease. It carries the advantage of a dose gradient allowing very rapid falloff beyond the implant. Brachytherapy is an effective modality, as evidenced by a single-institution randomized trial from Lithuania which enrolled 64 patients with recurrent head and neck carcinomas to either 50 Gy in 25 fractions of external beam reirradiation or HDR-brachytherapy.[86] This study demonstrated a survival increase from 32% at 2 years with 3-dimensional EBRT to 67% with brachytherapy ($P < .001$). Whether this outcome is a function of small numbers from a single institution or an insufficient dose of external beam in the control arm is unclear. However, multiple single-institution retrospective

studies confirm that brachytherapy is a feasible option when performed at an experienced center.[87-112] Specifics regarding techniques for brachytherapy are beyond the scope of this article, but the data suggest that proper case selection and expertise makes brachytherapy an appropriate treatment in select situations.

Systemic therapy

The role of systemic therapy in conjunction with reirradiation is currently undefined. Multiple prospective trials cited previously each delivered concurrent cytotoxic chemotherapy and/or targeted therapies such as cetuximab.[7,8,25,113-120] In the modern era, a platinum-based concurrent regimen is appropriate, based on efficacy demonstrated within the initial treatment setting. For platinum-refractory disease, cetuximab is a common option, and has also been delivered concurrently with SBRT.[41]

Immunotherapy via programmed cell death 1 (PD-1)/programmed cell death ligand 1 checkpoint inhibitors presents an interesting option for these patients. Currently, checkpoint inhibitors are not typically delivered in combination with reirradiation outside of clinical trials. A forthcoming clinical trial proposed by the Eastern Cooperative Oncology Group (ECOG EA3191) will evaluate the role of reirradiation with either pembrolizumab or platinum in comparison to pembrolizumab as sole treatment.[121] The aforementioned RTOG 3507 study is evaluating the role of pembrolizumab concurrently with SBRT-based reirradiation.[44]

The role of induction chemotherapy is often questioned in the RSP setting. In general, induction chemotherapy has not demonstrated a survival benefit compared with concurrent therapy in the initial setting and its routine use is discouraged.[122,123] However, as noted previously, skull base or nasopharynx cases may be an exception to this if adjacent to the brain stem or optic pathway where a robust response to induction may make reirradiation more feasible. Furthermore, induction chemotherapy has also been proposed as a strategy to achieve stable disease in attempt to delay reirradiation or as "chemoselection" for aggressive local treatment. Robust data on these strategies are lacking but deserve further investigation.

Normal tissue toxicity and dose constraints

A significant risk of normal tissue damage is inherent to reirradiation, and severe toxicities unique to this setting can occur. As stated previously, patients should be clearly informed regarding the risks and controversies. Once the decision to proceed is made, careful plan design and evaluation is required to reduce risk as much as possible.

Specific constraints for treatment planning in the reirradiation setting are difficult to define due to the heterogeneity of previous courses, time, location, and extent of re-treatment fields. A general approach to treatment planning and evaluation is described in Figure 1. Once the treatment plan is generated, a quantitative evaluation of the composite plan is required. Quantitative goals are outlined in Table 2 for conventionally fractionated techniques. These goals were identified during the aforementioned systematic literature search, as well as via a search of ClinicalTrials.gov for recent ongoing multi-institution studies enrolling at least 50 patients with an accessible protocol document.

During such quantitative analysis, organs at risk should be prioritized according to "critical" structures versus general avoidance structures. Critical structures can be defined as those in which the risk of an intolerable adverse event must be minimized.[124,125] Examples of intolerable adverse events which should be prioritized during treatment planning include bilateral blindness, myelopathy and brain stem necrosis. Other toxicities unique to reirradiation include tissue injury such as mucosal necrosis, temporal lobe necrosis, cranial neuropathies, skull base osteoradionecrosis, and the like. The variety of injuries cannot always be predicted and speaks to the challenges presented in these cases and the importance of expertise and a strong multidisciplinary team.

Other organs at risk such as salivary glands and soft tissues may be prioritized according to the patient's wishes and risk aversion, but no specific dose constraints can be reasonably inferred from the literature. One helpful study correlated late effects such as feeding tube dependence, esophageal strictures, and carotid blowout to dosimetric parameters, but most practice is built on first principles (ie, ALARA, as low as reasonably achievable).[126] The anatomic location of reirradiation correlates to the risk of severe toxicity, with larynx/hypopharynx treatment conferring a high risk often requiring a tracheostomy.[48,127]

"Carotid blowout" is a common concern. Carotid blowout syndrome itself is rare, particularly when differentiated from tumor-related invasion of vascular structures, which is likely the most common explanation for major hemorrhage after reirradiation. A systematic review quantified the risk of carotid rupture at 2.6%, which remained <5% regardless of dose, fractionation, or chemotherapy use.[128] If far from the target, the radiation to the carotid should be limited as much as possible. When the target is adjacent to carotid, cumulative doses may exceed 120 Gy, and bleeding is an inherent risk regardless of treatment approach. Dosimetric modeling of bleeding risk in the hypofractionated (SBRT) setting is available in the recent "Hypofractionated Treatment Effects in the Clinic" (HyTEC) report.[129] Free-tissue transfer during salvage neck dissections should be considered when possible, but there is no consistent evidence to demonstrate that this reduces the risk of bleeding, which may also occur from other major vessels.[28-31] Treatment options such as stenting or occlusion could be considered for threatened or active hemorrhage from the carotid.[130]

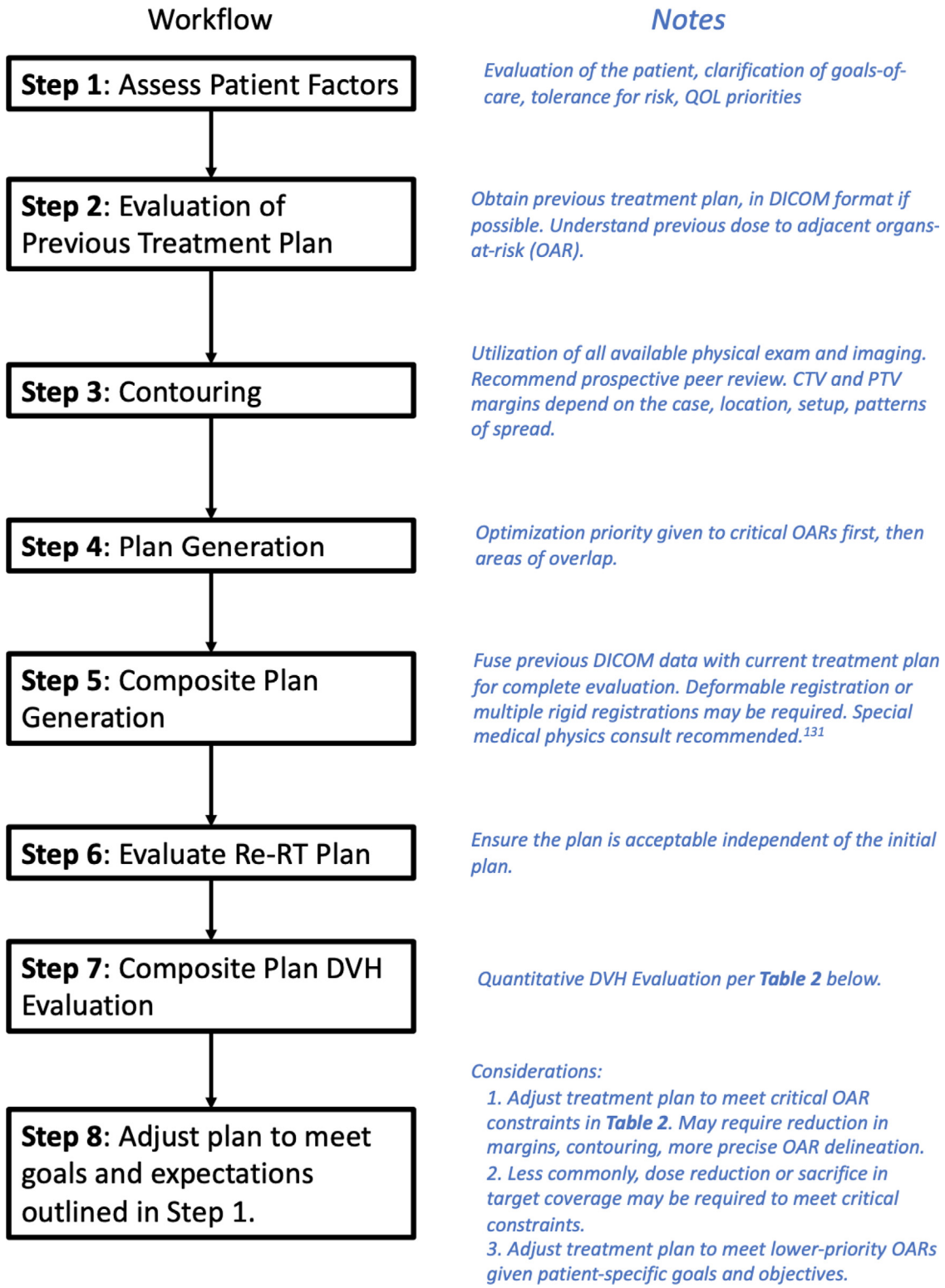

Fig. 1. Qualitative approach to reirradiation planning. *Abbreviations:* CTV = clinical target volume; DICOM = Digital Imaging and Communications in Medicine; DVH = dose-volume histogram; PTV = planning target volume; QOL = quality of life; re-RT = re-irradiation.

Table 2 Planning objectives for fractionated IMRT-based reirradiation

	Study	Type	Limit	Limit type	Notes/assumptions
Brain stem	International NPC (Ng 2021)[295]	Review/expert consensus	Desirable: ≤70.2 D0.03 cc Acceptable: <81 Gy D0.03 cc	Cumulative/lifetime	130% and 150%, assuming recovery. EQD2, same spatial region.
	Heidelberg (Held 2019)[76,80]	Retrospective, single-institution	60 Gy <2 y 72 Gy >2 y maximum dose	Cumulative/lifetime	Carbon ions with RBE/EQD2 adjustments. Per institution's experience.
	Awan 2018[113]	Protocol, completed	60 Gy	Cumulative/lifetime	Maximum dose
	Chen 2011[141]	Protocol, completed	55-60 Gy	Cumulative/lifetime	Maximum dose
	ECOG EA3191[121]	Protocol, ongoing	≤12 Gy per protocol, ≤14 Gy D0.03 cc variation acceptable	Re-RT course only	Maximum dose
	MSK Proton Phase II[296]	Protocol, ongoing	64 Gy surface maximum dose 53 Gy core maximum dose	Re-RT course only	Core defined as 3-mm diameter central structure within. Do not exceed whichever re-RT only or cumulative constraint is met first.
			70 Gy D0.05 cc	Cumulative/lifetime	
	CARE Carbon RCT[297]	Protocol, ongoing	60 Gy (<2 y) 78 Gy (≥2 y)	Cumulative/lifetime	EQD2, $\alpha/\beta = 2$. Recovery beyond 2 y assumed, numbers based on institutional experience. Maximum dose, surface.
Spinal cord	International NPC (Ng 2021)[295]	Review/expert consensus	Desirable: ≤58.5 Gy D0.03 cc Acceptable: <67.5 Gy D0.03 cc	Cumulative/lifetime	130% and 150%, assuming recovery. EQD2, same spatial region.
	Heidelberg (Held 2019)[76,80]	Retrospective, single-Institution	50 Gy <2 y 60 Gy >2 y maximum dose	Cumulative/lifetime	Carbon ions with RBE/EQD2 adjustments. Per institution's experience.
	Awan 2018[113]	Protocol, completed	54 Gy	Cumulative/lifetime	Maximum dose
	Chen 2011[141]	Protocol, completed	55-60 Gy	Cumulative/lifetime	Maximum dose
	Neider 2018[125]	Expert survey	75 Gy	Cumulative/lifetime	Case report of a bone metastasis treated with a third course, no consensus reached.
	RTOG 9911[8]	Protocol, completed	50 Gy	Cumulative/lifetime	Maximum dose
	ECOG EA3191[121]	Protocol, ongoing	≤10 Gy D0.03 cc per protocol, ≤12 Gy D0.03 cc acceptable	Re-RT course only	

(*Continued*)

Table 2 (*Continued*)

	Study	Type	Limit	Limit type	Notes/assumptions
	MSK Proton Phase II[296]	Protocol, ongoing	64 Gy surface maximum dose 53 Gy core maximum dose	Re-RT course only	Do not exceed whichever re-RT only or cumulative constraint is met first.
			70 Gy D0.1 cc	Cumulative/lifetime	
	CARE Carbon RCT[297]	Protocol, ongoing	45 Gy (<2 y) 54 Gy (≥2 y)	Cumulative/lifetime	EQD2, $\alpha/\beta = 2$. Recovery beyond 2 y assumed, numbers based on institutional experience.
Optic chiasm	International NPC (Ng 2021)[295]	Review/expert consensus	Desirable: ≤70.2 D0.03 cc Acceptable: <81 Gy D0.03 cc	Cumulative/lifetime	Risk/acceptability of unilateral versus bilateral blindness should be considered and discussed with patient. 130% and 150% initial, assuming recovery. 150% reached only moderate consensus with concerns. EQD2, same spatial region.
	Heidelberg (Held 2019)[76,80]	Retrospective, single-institution	54 Gy <2 y 64.8 Gy >2 y maximum dose	Cumulative/lifetime	Carbon ions with RBE/EQD2 adjustments. Per institution's experience.
	ECOG EA3191[121]	Protocol, ongoing	≤12 Gy D0.03 cc per protocol, ≤14 Gy acceptable	Re-RT course only	Maximum dose
	MSK Proton Phase II[296]	Protocol, ongoing	58 Gy mean 60 Gy D0.05cc	Re-RT course only	Do not exceed whichever re-RT only or cumulative constraint is met first.
			70 Gy D0.05 cc	Cumulative/lifetime	
	CARE Carbon RCT[297]	Protocol, ongoing	54 Gy EQD2 (<2 y) 64.8 Gy EQD2 (≥2 y)	Cumulative/lifetime	$\alpha/\beta = 3$. Recovery beyond 2 y assumed, numbers based on institutional experience.
Optic nerve	International NPC (Ng 2021)[295]	Review/expert consensus	Desirable cumulative: ≤70.2 Gy D0.03 cc Acceptable bilateral: <81 Gy D0.03 cc	Cumulative/lifetime	130% and 150%, assuming recovery. EQD2, same spatial region. No constraint for unilateral if patient accepts risk of blindness.
	Heidelberg (Held 2019)[76,80]	Retrospective, single-institution	54 Gy <2 y 64.8 Gy >2 y maximum dose	Cumulative/lifetime	Carbon ions with RBE/EQD2 adjustments. Per institution's experience.

(*Continued*)

Table 2 (*Continued*)

	Study	Type	Limit	Limit type	Notes/assumptions
	ECOG EA3191[121]	Protocol, ongoing	≤12 Gy D0.03 cc per protocol, ≤14 Gy acceptable	Re-RT course only	Maximum dose
	MSK Proton Phase II[296]	Protocol, ongoing	60 Gy D0.05 cc	Re-RT course only	One side may be exceeded if the contralateral is functional. Do not exceed whichever re-RT only or cumulative constraint is met first.
			70 Gy D0.05 cc	Cumulative/lifetime	
	CARE Carbon RCT[297]	Protocol, ongoing	54 Gy EQD2 (<2 y) 64.8 Gy EQD2 (≥2 y)	Cumulative/lifetime	$\alpha/\beta = 3$. Recovery beyond 2 y assumed, numbers based on institutional experience. Written consent for blindness allowed.
Temporal lobe	International NPC (Ng 2021)[295]	Review/expert consensus	Desirable cumulative: ≤91 Gy D0.03 cc Acceptable: ≤105 Gy D0.03 cc	Cumulative/lifetime	130% and 150%, assuming recovery. EQD2, same spatial region.
	Heidelberg (Held 2019)[76,80]	Retrospective, single-institution	No constraint/ALARA		Carbon ions with RBE/EQD2 adjustments. Per institution's experience.
Brachial plexus	Chen 2017[298]	Retrospective, single-institution	Low risk: >2 y out and <95 Gy cumulative (9% toxicity) Int risk: none of the above/below (19% toxicity) High-risk: <2 y and >95 Gy cumulative (47% toxicity)	Cumulative/lifetime	Maximum dose
	ECOG EA3191[121]	Protocol, ongoing	Avoid hotspots/ALARA	Re-RT course only	Maximum dose
	MSK Proton Phase II[296]	Protocol, ongoing	65 Gy D95 70 Gy maximum dose	Cumulative/lifetime	ALARA
Carotid artery	International NPC (Ng 2021)[295]	Review/expert consensus	Desirable: cumulative ≤125 D0.03 cc Acceptable: No limit	Cumulative/lifetime	130% and 150%, assuming recovery. EQD2, same spatial region.
	Particle re-RT (Dale 2017)[271]	Retrospective, single-institution	2 carotid blowout events both >100 Gy EQD2	Cumulative/lifetime	Italy/Norway series, original photon, re-treat proton/carbon ions

(*Continued*)

Table 2 (*Continued*)

	Study	Type	Limit	Limit type	Notes/assumptions
	Heidelberg (Held 2019)[76,80]	Retrospective, single-institution	No constraint/ALARA		Carbon ions with RBE/EQD2 adjustments. Per institution's experience.
	Bots 2017[173]	Retrospective, single-institution	Cumulative 128-130 Gy in those that bled	Cumulative/lifetime	Maximum dose
	ECOG EA3191[121]	Protocol, ongoing	Avoid hotspots/ ALARA		Maximum dose
	Wake Forest[126]	Retrospective, single-Institution	<120 Gy	Cumulative/lifetime	6% versus 25% bleed rate with cut-point of 120 Gy cumulative
Mandible	Heidelberg (Held 2019)[76,80]	Retrospective, single-institution	No constraint/ALARA		Carbon ions with RBE/EQD2 adjustments. Per institution's experience.
	Bots 2017[173]	Retrospective, single-institution	104-128 Gy cumulative in 5 patients who experienced ORN (27%), none (0%) when <100 Gy	Cumulative/lifetime	Maximum dose
	ECOG EA3191[121]	Protocol, ongoing	≤63 Gy D0.03 cc recommended	Re-RT course only	Guidance only, not scored for plan quality
	MSK Proton Phase II[296]	Protocol, ongoing	70 Gy D0.05 cc to mandible not in the PTV, otherwise no hotspots	Cumulative/lifetime	ALARA acceptable
Cochlea	ECOG EA3191[121]	Protocol, ongoing	≤35 Gy D0.03 cc (second plan contribution)	Re-RT course only	Guidance only, not scored for plan quality
	MSK Proton Phase II[296]	Protocol, ongoing	55 Gy maximum dose	Cumulative/lifetime	ALARA. One side may be exceeded if the contralateral is functional.

D0.03 cc/D0.1cc/D0.05cc implies a single-voxel maximum dose. The re-RT course refers only to the dose contribution solely from the second course of radiation, whereas "cumulative/lifetime" is the composite dose including previous course.

Abbreviations: ALARA = as low as reasonably achievable; EQD2 = equivalent dose at 2 Gy per fraction; CARE = Carbon ion re-irradiation trial; ECOG = Eastern Cooperative Oncology Group; MSK = Memorial Sloan Kettering Cancer Center; NPC = Nasopharynx Cancer; RBE = relative biologic effectiveness; Re-RT = re-irradiation.

Conclusions

Reirradiation of head and neck cancer may be appropriate in many settings but carries significant risk. Advances in technology and improved systemic therapies have enhanced outcomes for patients with recurrent or second primary cancers in a previously irradiated site, but more progress is required. Communication with the patient about the risks associated with treatment and meticulous patient selection are critical features of care. The appropriateness of reirradiation is illustrated in the case scenarios presented.

Case Variants

Case 1

Key question: Is aggressive local therapy for rapid, large, and incurable locoregional-only recurrences appropriate?

A 72-year-old man undergoes hemiglossectomy with bilateral neck dissection for a pT3N3b squamous carcinoma of the oral tongue. Chemoradiation to 64 Gy with cisplatin was delivered to the primary and bilateral necks. Seven months later a large locoregional recurrence is noted with dysphagia and stridor consistent with

organ dysfunction. A tracheostomy and feeding tube were placed and his current ECOG performance status is 2. Salvage surgery would require a total glossectomy, total laryngectomy and repeat neck dissection. Which of the following may be considered appropriate therapies?

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	References	SQ	SOE	SOR
Salvage surgery as above, with reirradiation for the expected positive margins/extracapsular extension	U		7	3	2			1			2		19, 20, 22, 50, 151, 157-168	3	M	↑
Definitive fractionated reirradiation (with or without systemic therapy)	U	2	7	4							2			3	M	↑
Immunotherapy, targeted and/or cytotoxic therapy without reirradiation with or without palliative RT (20-30 Gy in 5-10 fractions or similar)	A			1				8	3	1	7			3	M	↑
Supportive care only	M*			1		4	2	6			5*	X		3	M	↓

Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
Strength of evidence: EC = expert consensus; EO = expert opinion; L = limited; M = moderate; S = strong.
Strength of recommendation: ↑ = strong recommendation; ↓ = weak recommendation; − = additional considerations do not strengthen or weaken the panel's recommendation.
Abbreviations: SOE = strength of evidence; SOR = strength of recommendation; SQ = study quality.
Per the UCLA/RAND Appropriateness Method: *Disagreement, that is, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.
UCLA = University of California, Los Angeles;`

Please refer to the following supporting documentation for a more complete discussion of the concepts and their definitions.[299]

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, etc).

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the numbers of the references associated with the recommendation.

SQ: Study quality (1, 2, 3, or 4) of the references listed.

SOE: EC = expert consensus/expert opinion; L = limited; M = moderate; S = strong.

SOR: ↑ = strong recommendation; ↓ = weak recommendation; − = not strong, not weak.

Case 2a

Key question (both parts): What are appropriate treatment options for resectable disease?

A 62-year-old former smoker received a diagnosis of a cT2N2b p16-negative right tonsil squamous carcinoma and treated with definitive chemoradiation to 70 Gy with cisplatin with a complete response on 3-month positron emission tomography. Eighteen months later, a 2-cm isolated ipsilateral level IIa neck in-field recurrence is biopsy-proven with radiographic extranodal extension involving the jugular vein and sternocleidomastoid but not the skin. Disease does not invade the carotid artery, shoulder function is intact, the disease is considered resectable and the patient is willing to pursue the recommended course. Which of the following may be considered appropriate therapies?

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	References	SQ	SOE	SOR
Salvage neck dissection (with consideration of adjuvant re-RT)	A							4	6	5	8		18, 19-21, 24, 25, 27-29, 38, 54, 63, 68, 94-96, 99-102, 105, 106, 151-153, 169-178	1-3	S	↑
Definitive reirradiation ± systemic therapy	M*	1		8	3	1					5*	X		1-3	S	↑
Immunotherapy, targeted and/or cytotoxic therapy without reirradiation	U	3	6	4	1	1					2			2-3	M	↑

Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
Strength of evidence: EC = expert consensus; EO = expert opinion; L = limited; M = moderate; S = strong.
Strength of recommendation: ↑ = strong recommendation; ↓ = weak recommendation; − = additional considerations do not strengthen or weaken the panel's recommendation.
Abbreviations: SOE = strength of evidence; SOR = strength of recommendation; SQ = study quality.
Per the UCLA/RAND Appropriateness Method: *Disagreement, that is, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Please refer to the following supporting documentation for a more complete discussion of the concepts and their definitions.

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, etc).

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the numbers of the references associated with the recommendation.

SQ: Study quality (1, 2, 3, or 4) of the references listed.

SOE: EC = expert consensus/expert opinion; L = limited; M = moderate; S = strong.

SOR: ↑ = strong recommendation; ↓ = weak recommendation; − = not strong, not weak.

Case 2b

The same patient (as in case 2a) undergoes a neck dissection with sacrifice of the sternocleidomastoid (SCM). Pathology reveals a nodal conglomerate of 4.5 cm with extranodal extension 3 mm outside of the node capsule with negative margins. Postoperative swallowing function is intact and healing is complete. Which of the following may be considered appropriate therapies?

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	References	SQ	SOE	SOR
Observation	M*		1	5	4	2		1			5*	X	18, 19-21, 24, 25, 27-29, 38, 54, 63, 68, 94-96, 99-102, 105, 106, 151-153, 169-178	1-3	M	↓
Adjuvant fractionated re-irradiation (eg, approximately 60-66 Gy) with concurrent systemic therapy	A			1		1	2	4	6	1	7			1-3	M	↑
Adjuvant fractionated reirradiation (eg, 60 Gy) without concurrent systemic therapy	M*			3		1	6	2	1		5*	X		1-3	L	↓
Adjuvant stereotactic body radiation (eg, 35-40 Gy in 5 fractions)	M*		2	3	5	2			1		5*	X		3	L	↑
Immunotherapy, targeted and/or cytotoxic therapy without reirradiation	U	3	6	3			1				2			3	L	↑

Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
Strength of evidence: EC = expert consensus; EO = expert opinion; L = limited; M = moderate; S = strong.
Strength of recommendation: ↑ = strong recommendation; ↓ = weak recommendation; − = additional considerations do not strengthen or weaken the panel's recommendation.
Abbreviations: SOE = strength of evidence; SOR = strength of recommendation; SQ = study quality.
Per the UCLA/RAND Appropriateness Method: *Disagreement, that is, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Please refer to the following supporting documentation for a more complete discussion of the concepts and their definitions.

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, etc).

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the numbers of the references associated with the recommendation.

SQ: Study quality (1, 2, 3, or 4) of the references listed.

SOE: EC = expert consensus/expert opinion; L = limited; M = moderate; S = strong.

SOR: ↑ = strong recommendation; ↓ = weak recommendation; − = not strong, not weak.

Case 3

Key question: What is the appropriate management of patients treated nonoperatively?

A 67-year-old woman with a p16-positive squamous carcinoma of the tonsil is treated with TORS and postoperative radiation to the tumor bed and bilateral necks to 60 Gy. She then presents 2.5 years later with a 4.5-cm marginal recurrence at the tongue base adjacent to the resection bed with partial overlap of the 60 Gy region. Positron emission tomography/computed tomography shows no other disease. The patient declines a total glossectomy and can tolerate a regular diet. Which of the following may be considered appropriate therapies? Concurrent systemic therapy could be considered for each option.

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	References	SQ	SOE	SOR
Fractionated IMRT 50-54 Gy to tumor only	U	2	6	3	1		1	1	1		2		7, 8, 18, 19-21, 23, 26, 27, 33, 35-39, 54, 63, 66, 67, 68, 86, 93, 95, 98, 100, 103, 108-111, 113-120, 127, 136, 139-144, 154, 155, 170, 172-174, 177-228, 275-281	2-3	M	↑
Fractionated IMRT 50-54 Gy to tumor with comprehensive elective nodal coverage	U	6	7	1		1					2			3	M	↑
Fractionated IMRT 60-70 Gy to tumor only	A						1	6	8		8			2-3	M	↑
Fractionated IMRT 60-70 Gy to tumor with comprehensive elective nodal coverage	U	4	3	5	2	1					3			3	M	↑
SBRT 30 Gy in 5 fractions to tumor only	U		6	5	1	1					3			2-3	S	↑
SBRT 35-44 Gy in 5 fractions to tumor only	M*		1	1	1	3	4	1	2		5*	X		2	M	↓
Immunotherapy, targeted and/or cytotoxic therapy without reirradiation	M*	1	2	5	2	2		1			5*	X		2-3	S	↓

Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Strength of evidence: EC = expert consensus; EO = expert opinion; L = limited; M = moderate; S = strong.

Strength of recommendation: ↑ = strong recommendation; ↓ = weak recommendation; − = additional considerations do not strengthen or weaken the panel's recommendation.

Abbreviations: IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation; SOE = strength of evidence; SOR = strength of recommendation; SQ = study quality.

Per the UCLA/RAND Appropriateness Method: *Disagreement, that is, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Please refer to the following supporting documentation for a more complete discussion of the concepts and their definitions.

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, etc).

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the numbers of the references associated with the recommendation.

SQ: Study quality (1, 2, 3, or 4) of the references listed.

SOE: EC = expert consensus/expert opinion; L = limited; M = moderate; S = strong.

SOR: ↑ = strong recommendation; ↓ = weak recommendation; − = not strong, not weak.

Case 4

Key question: Is there an appropriate role of stereotactic body radiation?

A 78-year-old woman with an Eastern Cooperative Oncology Group performance status of 2 and a cT3N2b p16-negative squamous cell carcinoma of the tonsil was treated with chemoradiation to 70 Gy with cisplatin with a complete response. Thirteen months later, an unresectable, painful, in-field 3.9-cm (30 cc) retropharyngeal nodal recurrence is biopsy-proven. Positron emission tomography/computed tomography is negative for other disease. The patient is gastrostomy-tube (PEG) dependent. Which of the following may be considered appropriate therapies? Concurrent systemic therapy with radiation could be considered for each treatment option.

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	References	SQ	SOE	SOR
Fractionated IMRT 50-54 Gy	U	2	6	4	1	1			1		2			2-3	L	↑
Fractionated IMRT 60-70 Gy	M*		1	2	2	1	3	4			5*	X		1-3	M	↓
SBRT 35-44 Gy in 5 fractions	M*			1		1	3	7	1		5*	X	41, 42, 43, 47-49, 88, 134, 145, 229-255, 282, 283	2-3	M	↓
SBRT 30 Gy in 5 fractions	M*		1	3	1	5	2	1			5*	X		2-3	L	↑
Immunotherapy, targeted and/or cytotoxic therapy without reirradiation with or without palliative radiation therapy (20-30 Gy in 5-10 fractions or similar)	M			1		8	2	1	1		5		41, 42, 43, 47-49, 88, 134, 145, 229-255, 282, 283	1-3	M	↑

Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
Strength of evidence: EC = expert consensus; EO = expert opinion; L = limited; M = moderate; S = strong.
Strength of recommendation: ↑ = strong recommendation; ↓ = weak recommendation; − = additional considerations do not strengthen or weaken the panel's recommendation.
Abbreviations: IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation; SOE = strength of evidence; SOR = strength of recommendation; SQ = study quality.
Per the UCLA/RAND Appropriateness Method: *Disagreement, that is, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Please refer to the following supporting documentation for a more complete discussion of the concepts and their definitions.

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, etc).

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the numbers of the references associated with the recommendation.

SQ: Study quality (1, 2, 3, or 4) of the references listed.

SOE: EC = expert consensus/expert opinion; L = limited; M = moderate; S = strong.

SOR: ↑ = strong recommendation; ↓ = weak recommendation; − = not strong, not weak.

Case 5

Key question: What is the appropriate role of re-RT for non-squamous histologies?

A 70-year-old man with a history of adenoid cystic carcinoma of the right hard palate was treated 3 years ago with resection and 60 Gy intensity modulated radiation therapy tracking V2 up to foramen rotundum. Although a magnetic resonance imaging was negative 1 year prior, he now presents with recurrent disease limited to the Gasserian ganglion in Meckel's cave measuring a total of 12 cc. On review of the initial plan, the adjacent brain stem, optic pathway and temporal lobe previously received a maximum point dose of 45 Gy. He is minimally symptomatic with well-controlled facial pain. Cranial nerves are otherwise intact, positron emission tomography/computed tomography is negative for distant spread. Which of the following may be considered appropriate therapies?

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	References	SQ	SOE	SOR
Definitive fractionated IMRT 60-66 Gy with or without systemic therapy	M*	1	1	3	1	1	2	2	2		5*	X	55-62, 284-286	3	L	↓
SBRT 35-44 Gy in 5 fractions with or without systemic therapy	M				4	5	1	2	1		5			3	L	↓
Immunotherapy, targeted and/or cytotoxic therapy without reirradiation	M*		3	5	2	2		1			5*	X		3	L	↓
Observation with future supportive care and palliative radiation therapy 20-30 Gy in 5-10 fractions as indicated	M		2		4	2	4	1			5			3	L	↓

Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
Strength of evidence: EC = expert consensus; EO = expert opinion; L = limited; M = moderate; S = strong.
Strength of recommendation: ↑ = strong recommendation; ↓ = weak recommendation; − = additional considerations do not strengthen or weaken the panel's recommendation.
Abbreviations: IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation; SOE = strength of evidence; SOR = strength of recommendation; SQ = study quality.
Per the UCLA/RAND Appropriateness Method: *Disagreement, that is, the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Please refer to the following supporting documentation for a more complete discussion of the concepts and their definitions.

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, etc).

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the numbers of the references associated with the recommendation.

SQ: Study quality (1, 2, 3, or 4) of the references listed.

SOE: EC = expert consensus/expert opinion; L = limited; M = moderate; S = strong.

SOR: ↑ = strong recommendation; ↓ = weak recommendation; − = not strong, not weak.

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