American Radium Society® (ARS) Appropriate Use Criteria (AUC) for Retreatment of Recurrent or Second Primary Head and Neck Cancer After Prior Radiation: Systematic Review and Guidelines

Expert Panel on Radiation Oncology - Head and Neck Cancer:

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Conflict of Interest Disclosure Statement

All panelists were required to declare all potential conflicts of interest dating back for 36 months prior to initiating work on this document. These complete disclosure forms are permanently retained by the American Radium Society™.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document’s committee and approved participation of the panelists prior to starting development of this work.

Disclosures potentially relevant to the content of this guideline are provided.

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Summary of Recommendations

1. Patient selection:
   1.1. The committee strongly recommends discernment when selecting patients for aggressive curative-intent salvage therapy.
   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 re-irradiation 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 re-irradiation 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 re-irradiation to a dose of 60-66 Gy for cancers with adverse risk factors. The committee did not reach consensus on the appropriateness of postoperative re-irradiation alone (60 Gy) or observation without re-irradiation. The committee did not reach consensus on the appropriateness of adjuvant SBRT, considering the limited and evolving data.

3. Unresectable Disease
   3.1. The committee strongly recommends that fractionated re-irradiation to 60-70 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 re-irradiation 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 35-44 Gy in comparison to fractionated re-irradiation. 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 re-irradiation, the committee did not reach consensus on the appropriateness of systemic therapy alone or with palliative re-irradiation. 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 35-44 Gy more appropriate than lower doses.

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

5. Re-irradiation for Non-squamous Histologies

5.1. The committee recommended that patients with non-squamous histologies could be appropriately offered re-irradiation with similar techniques and doses to squamous histologies.

5.2. The committee recommended that for non-squamous 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, 20-40% of patients will develop locoregionally recurrent disease and 5-20% will develop a second cancer.1,2

The management of recurrent or second primary (RSP) cancers originating in an irradiated region is complex. Re-irradiation may be an option for selected patients with RSP cancers, but the therapeutic window of re-irradiation 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 re-irradiation.3 Here, we present an updated review of relevant literature along with updated appropriate use criteria for representative clinical scenarios.

Materials and Methods

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]) ("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 re-irradiation by any technique. Key questions were generated by three authors (SK, MW, RB) in collaboration with the committee. These questions are presented in Box 1. Articles identified were removed if they focused on salvage therapies other than re-irradiation or were not otherwise deemed relevant for any form of citation.
in the revised narrative text. Two authors (MW and RB) 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 2011-2020 were selected for full-text review and included in the complete data table with evidence grading according to the ACR 2019 and ARS 2021 methodology. 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.

Following 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.

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<th>BOX 1: Key Questions</th>
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<td>KQ1</td>
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<td>Is aggressive local therapy for rapid/large/incurable locoregional-only recurrences appropriate?</td>
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<td>KQ2</td>
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<td>What are appropriate treatment options for resectable disease?</td>
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<td>KQ3</td>
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<td>What is the appropriate management of patients treated nonoperatively?</td>
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<td>Is there an appropriate role for SBRT?</td>
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<td>KQ5</td>
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<td>What is the appropriate role of Re-RT for non-squamous histologies?</td>
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Summary of Evidence

The literature review process is summarized in the flowchart presented in Supplemental Figure 1. A total of 686 citations were identified through the search terms above within the three databases interrogated. Two hundred thirty-one citations were duplicates. The authors added 8 citations identified outside the search: one randomized trial published following 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 table is presented in Supplemental Table 1.

Of the 274 therapeutic references included in the ARS Appropriateness Criteria, 203 were 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 four 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 Re-Irradiation
Re-irradiation 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 45-75 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 20-30 Gy delivered over 5-10 daily fractions.9,10 These lower-dose re-irradiation regimens will be termed “palliative” in the accompanying case variants and are not the primary focus of this text.11

Rationale for Re-Irradiation

To date, no randomized level I evidence demonstrating a survival benefit from re-irradiation exists, perhaps due to failure of such trials to accrue or competing causes of mortality.12,13 Many practitioners are reluctant to recommend re-irradiation because of the significant risks involved, although trends suggest increased utilization in recent years.14,15 Advocates of re-irradiation argue that survival after re-irradiation often exceeds the 10-15 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 re-irradiation may confer improved quality-of-life compared to uncontrolled locoregional cancer progression. Whether these observations reflect selection bias and isolated circumstances is unclear, but for selected patients, re-irradiation 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 following re-irradiation. Along with the re-irradiation 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 re-irradiation, the patient should understand that re-irradiation 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 prior to re-irradiation should include a complete physical examination, PET imaging along with a CT of the neck with intravenous contrast. 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 (EBV) status as appropriate. For squamous cell carcinomas, programmed cell death ligand 1 (PD-L1) 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 radiotherapy, 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.\textsuperscript{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 RTOG required at least 6 months from the previous course for inclusion.\textsuperscript{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 two courses decreases, and enthusiasm for re-treatment should be tempered at shorter timepoints.\textsuperscript{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 re-irradiation 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 re-irradiation with curative intent but may benefit from palliative treatment (e.g. 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 re-RT.

Various prognostic systems are available to help the clinician in patient selection. A recent 9-institution collaborative study (“MIRI”) performed a recursive partitioning analysis (RPA) of patients with RSP squamous carcinoma treated with modern IMRT.\textsuperscript{19} The RPA identified three 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 radiotherapy and were experiencing organ dysfunction at the time of their new diagnosis, regardless of surgical resection status. Importantly, patients in class I experienced a 2-year overall survival of 62\% with a 4-year survival exceeding 40\%. However, despite aggressive re-irradiation, 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.\textsuperscript{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.\textsuperscript{21} For patient-specific estimates, nomograms have been promulgated to predict overall survival, locoregional failure, and late effects.\textsuperscript{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 non-metastatic, 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 prior to treatment decisions. If the tumor is technically resectable with a reasonable functional outcome, surgery is typically preferred. Indeed, a recent randomized phase III study of resectable,
recurrent nasopharyngeal cancer demonstrated significantly improved survival for patients randomized to surgery when compared to repeat IMRT. 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 re-irradiation only when the patient declines the proposed surgery.

The decision whether to re-irradiate after resection of an in-field RSP is complex. This choice is informed by the phase III GORTEC study by Janot et al. 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 re-irradiation 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 re-irradiation regimen included six 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 re-irradiation demonstrating a statistically significant improvement in disease-free survival (approximately 18% to 38%) and locoregional control (approximately 20% to 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 utilized in the early era of re-irradiation to improve safety but has fallen out of favor in the modern era in favor of continuous course regimens.26 In general, re-irradiation 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, re-irradiation 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. In view of the unpredictable patterns of progression in the RSP situation, and the morbidity of elective re-irradiation, 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 re-irradiation. The dose delivered for postoperative re-irradiation ranges from 56-66 Gy, and hyperfractionation is not mandatory. Retrospective data do not suggest a benefit to dose-escalation above 60 Gy in the adjuvant setting regardless of risk factors. The appropriateness of adjuvant re-irradiation is highlighted in Case Variant 2b.
Unresectable Disease

For cancers determined to be technically unresectable, or resectable only with unacceptable morbidity, non-operative “definitive” re-irradiation may be appropriate with curative intent. This is supported by prospective data such as the two single-arm phase II trials from the RTOG which demonstrated the feasibility of definitive re-irradiation, despite a grade 5 toxicity rate of 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 above, “split course” regimens are no longer in regular use for “definitive” therapy, and most now favor continuous courses of therapy.

Treatment is typically delivered to gross disease detected by physical exam, endoscopy, CT, MRI or PET imaging plus a wide margin respecting normal tissue boundaries. As with adjuvant re-irradiation, IMRT, SBRT, or charged particle therapy is now appropriate for delivery of external radiation. Similar to the adjuvant setting, elective nodal treatment is typically not performed or at most, limited only to the nearest echelon. Doses for definitive care are typically between 60-72 Gy. There may be a benefit to doses of 66 Gy or higher, although selection bias complicates interpretation of these data. Hyperfractionation is not mandatory but may allow dose-escalation above 66 Gy. For example, common fractionation regimens utilized by institutions submitting data to the MIRI collaborative include 72 Gy in 60 fractions twice daily or 66 Gy in 30-33 fractions daily. 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

Stereotactic body radiotherapy or SBRT 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.

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. These demonstrate control and survival rates similar to those produced by more protracted regimens and support SBRT as a standard option in the re-treatment setting.

When selecting between the two options, the only direct comparison available is a matched retrospective multi-institution cohort. Two analytic techniques were used to control for biases and compare SBRT to protracted courses of re-irradiation. Subgroup analysis suggested that for RPA class II “larger” cancers (>25 cc in volume or rT3-4 classification), protracted courses were favored with regard to 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 re-treatment 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 re-irradiation 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 pre-treatment organ dysfunction, regardless of resection status) are suboptimal candidates for protracted courses of re-irradiation, as mentioned above. 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 as compared to 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.

Regarding technique, SBRT is typically delivered in the definitive setting to 35-50 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 (e.g. ≥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 utilized 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 to 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. Re-irradiation is associated with favorable outcomes, but also carries the possibility of unacceptable risks to the brainstem and optic structures. 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 re-irradiation. Such skull base cases are anatomically similar to nasopharynx cancer. A high degree of suspicion is appropriate based on exam for RSP cutaneous squamous carcinoma in a radiated field, and an MRI with contrast is often beneficial prior to 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 to 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.\textsuperscript{19}

Other Non-Squamous 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. Re-irradiation techniques mirror those for squamous carcinomas.\textsuperscript{54} The appropriateness of re-irradiation for non-squamous carcinomas is highlighted in \textbf{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.\textsuperscript{55–62}

Proton Therapy

Proton therapy is an alternative radiation modality that typically carries less low to intermediate-dose deposition to surrounding normal tissue due to lack of exit dose distal to the Bragg peak.\textsuperscript{63} This beam characteristic may, in selected cases, improve normal tissue toxicity. However, there are important considerations in proton planning that must take into account the potential higher RBE at the end of the beam, 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.\textsuperscript{64} Proton-based re-irradiation is the topic of a systematic review and multiple retrospective studies.\textsuperscript{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, nasopharynx and well-lateralized cases such as salivary or neck recurrences--each of which were heavily represented in the cited retrospective series. However, comparative planning is necessary because some patients may be as well-served by IMRT as by proton therapy.\textsuperscript{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, but acute and late toxicity remains a concern. The carbon ion’s increased mass not only carries the advantageous Bragg peak beam profile but also may benefit control rates by an increase in the relative biological effectiveness (RBE) via the high linear energy transfer (LET). Dosimetric studies confirm that, when compared to photons (and often protons), multiple organs at risk experience reduced exposure with carbon ions.\textsuperscript{71,72} Carbon therapy is the subject of multiple single-institution reviews, which suggest favorable outcomes compared to historical controls, although these data are difficult to interpret due to potential for bias.\textsuperscript{73–83} Non-squamous salivary histologies and skull base recurrences are heavily represented in the single-institution series reported. One ongoing prospective phase I/II study
from Shanghai is investigating the maximum tolerated dose for nasopharynx cancer re-irradiation with concurrent cisplatin. 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 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 re-irradiation or HDR-brachytherapy. This study demonstrated a survival increase from 32% at 2-years with 3D EBRT to 67% with brachytherapy (p<0.001). 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. Specifics regarding techniques for brachytherapy are beyond the scope of this manuscript, 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 re-irradiation is as yet undefined. Multiple prospective trials cited above each delivered concurrent cytotoxic chemotherapy and/or targeted therapies such as cetuximab. 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. Immunotherapy via PD-1/PD-L1 checkpoint inhibitors presents an interesting option for these patients. Currently, checkpoint inhibitors are not typically delivered in combination with re-irradiation outside of clinical trials. A forthcoming clinical trial proposed by the Eastern Cooperative Oncology Group (ECOG EA3191) will evaluate the role of re-irradiation with either pembrolizumab or platinum in comparison to pembrolizumab as sole treatment. The RTOG 3507 study mentioned above is evaluating the role of pembrolizumab concurrently with SBRT-based re-irradiation.

The role of induction chemotherapy is often questioned in the RSP setting. In general, induction chemotherapy has not demonstrated a survival benefit compared to concurrent therapy in the initial setting and its routine use is discouraged. However, as noted above, skull base or nasopharynx cases may be an exception to this if adjacent to the brainstem or optic pathway where a robust response to induction may make re-irradiation more feasible.
Normal Tissue Toxicity & Dose Constraints

The risk of normal tissue damage is inherent to re-irradiation. As stated above, 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 re-irradiation 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 systematic literature search above, 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 (OARs) should be prioritized according to “critical” structures vs. 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 brainstem necrosis.

Other OARs 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 (i.e. ALARA, as low as reasonably achievable).126 The anatomic location of re-irradiation 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 re-irradiation. 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

Conclusion

Re-irradiation 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 re-irradiation is illustrated in the case scenarios presented.
Figure 1: Qualitative Approach To Re-Irradiation Planning

**Workflow**

**Step 1:** Assess Patient Factors

**Step 2:** Evaluation of Previous Treatment Plan

**Step 3:** Contouring

**Step 4:** Plan Generation

**Step 5:** Composite Plan Generation

**Step 6:** Evaluate Re-RT Plan

**Step 7:** Composite Plan DVH Evaluation

**Step 8:** Adjust plan to meet goals and expectations outlined in Step 1.

**Notes**

- Evaluation of the patient, clarification of goals-of-care, tolerance for risk, QOL priorities

- Obtain previous treatment plan, in DICOM format if possible. Understand previous dose to adjacent organs-at-risk (OAR).

- Utilization of all available physical exam and imaging. Recommend prospective peer review. CTV and PTV margins depend on the case, location, setup, patterns of spread.

- Optimization priority given to critical OARs first, then areas of overlap.

- Fuse previous DICOM data with current treatment plan for complete evaluation. Deformable registration or multiple rigid registrations may be required. Special medical physics consult recommended.

- Ensure the plan is acceptable independent of the initial plan.

- Quantitative DVH Evaluation per Table 2 below.

**Considerations:**

1. Adjust treatment plan to meet critical OAR constraints in Table 2. May require reduction in margins, contouring, more precise OAR delineation.
2. Less commonly, dose reduction or sacrifice in target coverage may be required to meet critical constraints.
3. Adjust treatment plan to meet lower-priority OARs given patient-specific goals and objectives.
Table 1: Number and Types of Studies Identified in the Literature Search

<table>
<thead>
<tr>
<th></th>
<th>KQ1</th>
<th>KQ2</th>
<th>KQ3</th>
<th>KQ4</th>
<th>KQ5</th>
<th>Discussion Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR/MA</td>
<td>0</td>
<td>2&lt;sup&gt;132,133&lt;/sup&gt;</td>
<td>1&lt;sup&gt;46&lt;/sup&gt;</td>
<td>1&lt;sup&gt;134&lt;/sup&gt;</td>
<td>0</td>
<td>5&lt;sup&gt;15,65,128,130,135&lt;/sup&gt;</td>
</tr>
<tr>
<td>RCT</td>
<td>0</td>
<td>2&lt;sup&gt;24,25&lt;/sup&gt;</td>
<td>3&lt;sup&gt;32,86,136&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prospective,</td>
<td>0</td>
<td>2&lt;sup&gt;137,138&lt;/sup&gt;</td>
<td>16&lt;sup&gt;7,8,113–120,139–144&lt;/sup&gt;</td>
<td>3&lt;sup&gt;41,42,145&lt;/sup&gt;</td>
<td>0</td>
<td>8&lt;sup&gt;84,85,104,146–150&lt;/sup&gt;</td>
</tr>
<tr>
<td>Single Arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective,</td>
<td>4&lt;sup&gt;19,20,50,151&lt;/sup&gt;</td>
<td>6&lt;sup&gt;19–21,151–153&lt;/sup&gt;</td>
<td>8&lt;sup&gt;19–21,23,33,66,154,155&lt;/sup&gt;</td>
<td>143</td>
<td>0</td>
<td>1&lt;sup&gt;156&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multi-Institution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-Institution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>7&lt;sup&gt;275–281&lt;/sup&gt;</td>
<td>2&lt;sup&gt;282,283&lt;/sup&gt;</td>
<td>3&lt;sup&gt;284–286&lt;/sup&gt;</td>
<td>12&lt;sup&gt;40,71,92,112,287–294&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Number of studies in regular script; reference numbers of specific studies in superscript. SR/MA: Systematic Review/Meta-analysis, RCT: Randomized Controlled Trial, KQ: Key question. Shaded cells were included in the data table if published 2011-2020 (Supplemental Table 1).
Table 2: Planning Objectives for Fractionated IMRT-based Re-irradiation

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Limit</th>
<th>Limit Type</th>
<th>Notes/Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brainstem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International NPC (Ng 2021)(^a)^295</td>
<td>Review/Expert Consensus</td>
<td>Desirable: $\leq 70.2$ D0.03 cc Acceptable: $&lt; 81$ Gy D0.03 cc</td>
<td>Cumulative/Lifetime</td>
<td>130% and 150%, assuming recovery. EQD2, same spatial region.</td>
</tr>
<tr>
<td>Heidelberg (Held 2019)(^b)^6,80</td>
<td>Retrospective, Single-Institution</td>
<td>60 Gy $&lt;$2 years 72 Gy $&gt;$2 years Dmax</td>
<td>Cumulative/Lifetime</td>
<td>Carbon ions with RBE/EQD2 adjustments. Per institution’s experience.</td>
</tr>
<tr>
<td>Awan 2018(^113)</td>
<td>Protocol, Completed</td>
<td>60 Gy</td>
<td>Cumulative/Lifetime</td>
<td>Dmax</td>
</tr>
<tr>
<td>Chen 2011(^141)</td>
<td>Protocol, Completed</td>
<td>55-60 Gy</td>
<td>Cumulative/Lifetime</td>
<td>Dmax</td>
</tr>
<tr>
<td>ECOG EA3191(^121)</td>
<td>Protocol, Ongoing</td>
<td>$\leq 12$ Gy per protocol, $\leq 14$ Gy D0.03 cc variation acceptable</td>
<td>ReRT Course Only</td>
<td>Dmax</td>
</tr>
<tr>
<td>MSK Proton Phase II(^296)</td>
<td>Protocol, Ongoing</td>
<td>64 Gy surface Dmax 53 Gy core Dmax</td>
<td>ReRT Course Only</td>
<td>Core defined as 3 mm diameter central structure within. Do not exceed whichever ReRT only or cumulative constraint is met first.</td>
</tr>
<tr>
<td>CARE Carbon RCT(^297)</td>
<td>Protocol, Ongoing</td>
<td>60 Gy ($&lt;$2 years) 78 Gy ($\geq$2 years)</td>
<td>Cumulative/Lifetime</td>
<td>EQD2, $\alpha/\beta$=2. Recovery beyond 2 years assumed, numbers based on institutional experience. Dmax, surface.</td>
</tr>
<tr>
<td><strong>Spinal Cord</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International NPC (Ng 2021)(^a)^295</td>
<td>Review/Expert Consensus</td>
<td>Desirable: $\leq 58.5$ Gy D0.03 cc Acceptable $&lt; 67.5$ Gy D0.03 cc</td>
<td>Cumulative/Lifetime</td>
<td>130% and 150%, assuming recovery. EQD2, same spatial region.</td>
</tr>
<tr>
<td>Heidelberg (Held 2019)(^b)^6,80</td>
<td>Retrospective, Single-Institution</td>
<td>50 Gy $&lt;$2 years, 60 Gy $&gt;$2 years Dmax</td>
<td>Cumulative/Lifetime</td>
<td>Carbon ions with RBE/EQD2 adjustments. Per institution’s experience.</td>
</tr>
<tr>
<td>Awan 2018(^113)</td>
<td>Protocol, Completed</td>
<td>54 Gy</td>
<td>Cumulative/Lifetime</td>
<td>Dmax</td>
</tr>
<tr>
<td>Study/Protocol</td>
<td>Status</td>
<td>Cumulative/Lifetime</td>
<td>Dmax</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>---------------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>Chen 2011¹⁴¹</td>
<td>Protocol, Completed</td>
<td>55-60 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neider 2018¹²⁵</td>
<td>Expert survey</td>
<td>75 Gy</td>
<td>Case report of a bone metastasis treated with a 3rd course, no consensus reached.</td>
<td></td>
</tr>
<tr>
<td>RTOG 9911²⁸</td>
<td>Protocol, Completed</td>
<td>50 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG EA3191¹²¹</td>
<td>Protocol, Ongoing</td>
<td>≤10 Gy D0.03 cc per protocol, ≤12 Gy D0.03 cc acceptable</td>
<td>ReRT Course Only</td>
<td></td>
</tr>
<tr>
<td>MSK Proton Phase II²⁹⁶</td>
<td>Protocol, Ongoing</td>
<td>64 Gy surface Dmax 53 Gy core Dmax</td>
<td>ReRT Course Only</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 Gy D0.1cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARE Carbon RCT²⁹⁷</td>
<td>Protocol, Ongoing</td>
<td>45 Gy (&lt;2 years) 54 Gy (≥2 years)</td>
<td>Cumulative/Lifetime</td>
<td></td>
</tr>
<tr>
<td>Optic Chiasm</td>
<td>International NPC (Ng 2021)²⁹⁵</td>
<td>Review/Expert Consensus</td>
<td>Desirable ≤70.2 D0.03 cc, Acceptable &lt;81 Gy D0.03 cc</td>
<td>Cumulative/Lifetime</td>
</tr>
<tr>
<td></td>
<td>Heidelberg (Held 2019)²⁸⁶</td>
<td>Retrospective, Single-Institution</td>
<td>54 Gy &lt;2 years, 64.8 Gy ≥2 years Dmax</td>
<td>Cumulative/Lifetime</td>
</tr>
<tr>
<td></td>
<td>ECOG EA3191¹²¹</td>
<td>Protocol, Ongoing</td>
<td>≤12 Gy D0.03 cc per protocol, ≤14 Gy acceptable</td>
<td>ReRT Course Only</td>
</tr>
<tr>
<td></td>
<td>MSK Proton Phase II²⁹⁶</td>
<td>Protocol, Ongoing</td>
<td>58 Gy mean 60 Gy D0.05cc</td>
<td>ReRT Course Only</td>
</tr>
</tbody>
</table>

**Notes:**
- ReRT Course Only
- Do not exceed whichever ReRT only or cumulative constraint is met first.
- EQD2, α/β=2. Recovery beyond 2 years assumed, numbers based on institutional experience.
- Risk/acceptability of unilateral vs. bilateral blindness should be considered & discussed with patient. 130% and 150% initial, assuming recovery. 150% reached only moderate consensus with concerns. EQD2, same spatial region.
- Carbon ions with RBE/EQD2 adjustments. Per institution’s experience.
<table>
<thead>
<tr>
<th>Location</th>
<th>Study/Protocol</th>
<th>Protocol/Ongoing</th>
<th>Dose Details</th>
<th>Cumulative/Lifetime</th>
<th>Constraint Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optic Nerve</strong></td>
<td>International NPC (Ng 2021)</td>
<td>Review/Expert Consensus</td>
<td>Desirable cumulative ≤70.2 Gy D0.03 cc, Acceptable bilateral &lt;81 Gy D0.03 cc</td>
<td>Cumulative/Lifetime</td>
<td>130% and 150%, assuming recovery. EQD2, same spatial region. No constraint for unilateral if patient accepts risk of blindness.</td>
</tr>
<tr>
<td></td>
<td>Heidelberg (Held 2019)</td>
<td>Retrospective, Single-Institution</td>
<td>54 Gy &lt;2 years, 64.8 Gy &gt;2 years Dmax</td>
<td>Cumulative/Lifetime</td>
<td>Carbon ions with RBE/EQD2 adjustments. Per institution’s experience.</td>
</tr>
<tr>
<td></td>
<td>ECOG EA3191121</td>
<td>Protocol, Ongoing</td>
<td>≤12 Gy D0.03 cc per protocol, ≤14 Gy acceptable</td>
<td>ReRT Course Only</td>
<td>Dmax</td>
</tr>
<tr>
<td></td>
<td>MSK Proton Phase</td>
<td>Protocol, Ongoing</td>
<td>60 Gy D0.05cc</td>
<td>ReRT Course Only</td>
<td>One side may be exceeded if the contralateral is functional. Do not exceed whichever ReRT only or cumulative constraint is met first.</td>
</tr>
<tr>
<td></td>
<td>CARE Carbon RCT</td>
<td>Protocol, Ongoing</td>
<td>54 Gy EQD2 (&lt;2 years) 64.8 Gy EQD2 (≥2 years)</td>
<td>Cumulative/Lifetime</td>
<td>α/β=3. Recovery beyond 2 years assumed, numbers based on institutional experience. Written consent for blindness allowed.</td>
</tr>
<tr>
<td><strong>Temporal Lobe</strong></td>
<td>International NPC (Ng 2021)</td>
<td>Review/Expert Consensus</td>
<td>Desirable cumulative ≤91 Gy D0.03 cc Acceptable: ≤105 Gy D0.03 cc</td>
<td>Cumulative/Lifetime</td>
<td>130% and 150%, assuming recovery. EQD2, same spatial region.</td>
</tr>
<tr>
<td><strong>Brachial Plexus</strong></td>
<td>Chen 2017298</td>
<td>Retrospective, Single-institution</td>
<td>Low risk &gt;2 years out and &lt;95 Gy cumulative (9% toxicity)</td>
<td>Cumulative/Lifetime</td>
<td>Dmax</td>
</tr>
<tr>
<td>Carotid Artery</td>
<td>Protocol, Ongoing</td>
<td>Avoid hotspots/ALARA</td>
<td>ReRT Course Only</td>
<td>Dmax</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>ECOG EA3191\textsuperscript{121}</td>
<td>Protocol, Ongoing</td>
<td>Avoid hotspots/ALARA</td>
<td>ReRT Course Only</td>
<td>Dmax</td>
<td></td>
</tr>
<tr>
<td>MSK Proton Phase</td>
<td>Protocol, Ongoing</td>
<td>65 Gy D95  70 Gy Dmax</td>
<td>Cumulative/Lifetime</td>
<td>ALARA</td>
<td></td>
</tr>
</tbody>
</table>

| International NPC (Ng 2021)\textsuperscript{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)\textsuperscript{271} | Retrospective, Single-Institution | 2 carotid blowout events both >100 Gy EQD2 | Cumulative/Lifetime | Italy/Norway series, original photon, re-treat proton/carbon ions |

| Heidelberg (Held 2019)\textsuperscript{76,80} | Retrospective, Single-Institution | No constraint/ALARA | Cumulative/Lifetime | Carbon ions with RBE/EQD2 adjustments. Per institution’s experience. |

| Bots 2017\textsuperscript{173} | Retrospective, Single-Institution | Cumulative 128-130 Gy in those that bled | Cumulative/Lifetime | Dmax |

| ECOG EA3191\textsuperscript{121} | Protocol, Ongoing | Avoid Hotspots/ALARA | Cumulative/Lifetime | 6% vs. 25% bleed rate with cut-point of 120 Gy cumulative |

| Wake Forest\textsuperscript{126} | Retrospective, Single-Institution | <120 Gy | Cumulative/Lifetime | 6% vs. 25% bleed rate with cut-point of 120 Gy cumulative |

| Mandible | Protocol, Ongoing | ≤63 Gy D0.03 cc recommended | ReRT Course Only | Guidance only, not scored for plan quality |
| Heidelberg (Held 2019)\textsuperscript{76,80} | Retrospective, Single-Institution | No constraint/ALARA | Cumulative/Lifetime | Carbon ions with RBE/EQD2 adjustments. Per institution’s experience. |

| Bots 2017\textsuperscript{173} | Retrospective, Single-Institution | 104-128 Gy cumulative in 5 patients who experienced ORN (27%), none (0%) when <100 Gy | Cumulative/Lifetime | Dmax |

<p>| ECOG EA3191\textsuperscript{121} | Protocol, Ongoing | ≤63 Gy D0.03 cc recommended | ReRT Course Only | Guidance only, not scored for plan quality |</p>
<table>
<thead>
<tr>
<th>OAR</th>
<th>Protocol, Ongoing</th>
<th>Dose and Constraints</th>
<th>Cumulative/Lifetime</th>
<th>ALARA Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochlea ECOG EA319121</td>
<td>Protocol, Ongoing</td>
<td>≤35 Gy D0.03cc (2nd plan contribution)</td>
<td>ReRT Course Only</td>
<td>Guidance only, not scored for plan quality</td>
</tr>
<tr>
<td>MSK Proton Phase II296</td>
<td>Protocol, Ongoing</td>
<td>55 Gy Dmax</td>
<td>Cumulative/Lifetime</td>
<td>ALARA acceptable. One side may be exceeded if the contralateral is functional.</td>
</tr>
</tbody>
</table>

OAR = organ at risk. EQD2 = equivalent dose at 2 Gy per fraction. D0.03 cc/D0.1cc/D0.05cc implies a single-voxel maximum dose. ALARA = as low as reasonably achievable. ReRT course only refers to the dose contribution solely from the second course of radiation, whereas “cumulative/lifetime” is the composite dose including previous course. OAR = organ at risk. EQD2 = equivalent dose at 2 Gy per fraction. D0.03 cc/D0.1cc/D0.05cc implies a single-voxel maximum dose. ALARA = as low as reasonably achievable. ReRT course only refers to the dose contribution solely from the second course of radiation, whereas “cumulative/lifetime” is the composite dose including previous courses.
Case Variants

Case 1:
**KEY QUESTION:** Is aggressive local therapy for rapid/large/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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvage surgery as above, with re-irradiation for the expected positive margins/extracapsular extension</td>
<td>U</td>
<td>7 3 2 1</td>
<td>2</td>
<td></td>
<td>19,20,22,50,151,157–168</td>
<td>3</td>
<td>M</td>
<td>↑</td>
</tr>
<tr>
<td>Definitive fractionated re-irradiation (with or without systemic therapy)</td>
<td>U</td>
<td>2 7 4</td>
<td>2</td>
<td></td>
<td></td>
<td>3</td>
<td>M</td>
<td>↑</td>
</tr>
<tr>
<td>Immunotherapy, targeted and/or cytotoxic therapy without re-irradiation with or without palliative RT (20-30 Gy in 5-10 fractions or similar)</td>
<td>A</td>
<td>1 8 3 1</td>
<td>7</td>
<td></td>
<td></td>
<td>3</td>
<td>M</td>
<td>↑</td>
</tr>
<tr>
<td>Supportive care only</td>
<td>M*</td>
<td>1 4 2 6</td>
<td>5* X</td>
<td></td>
<td></td>
<td>3</td>
<td>M</td>
<td>↓</td>
</tr>
</tbody>
</table>
1. **Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

2. **Per the UCLA/RAND Appropriateness Method** - *Disagreement, i.e., 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.

3. **Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

4. **Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

---

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

**Rating Categories:** U Usually not appropriate; M May be appropriate; A Usually 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 references associated with the recommendation.

**SQ:** Study Quality (1, 2, 3, or 4) of the references listed

**SOE:** S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**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 was diagnosed with 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 PET. 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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive re-irradiation +/- systemic therapy</td>
<td>M*</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5*</td>
<td>X</td>
<td>1-3</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>Immunotherapy, targeted and/or cytotoxic therapy without re-irradiation</td>
<td>U</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2-3</td>
<td>M</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

1. **Rating**: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
2. **Per the UCLA/RAND Appropriateness Method**: * Disagreement, i.e., 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.
3. **Strength of Evidence**: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion
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*Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.*

**Rating Categories**: U Usually not appropriate; M May be appropriate; A Usually appropriate

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**References**: Lists the references associated with the recommendation.
Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
**Case 2b:**
The same patient as above (case 2a) undergoes a neck dissection with sacrifice of the 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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Fractionated Re-Irradiation (e.g. approximately 60-66 Gy) with concurrent systemic therapy</td>
<td>A</td>
<td></td>
<td>1 1 2 4 6 1</td>
<td>7</td>
<td></td>
<td>1-3 M</td>
</tr>
<tr>
<td>Adjuvant Fractionated Re-Irradiation (e.g. 60 Gy) without concurrent systemic therapy</td>
<td>M*</td>
<td></td>
<td>3 1 6 2 1</td>
<td>5*</td>
<td>X</td>
<td>1-3 L</td>
</tr>
<tr>
<td>Adjuvant SBRT (e.g. 35-40 Gy in 5 fx)</td>
<td>M*</td>
<td></td>
<td>2 3 5 2 1</td>
<td>5*</td>
<td>X</td>
<td>3 L</td>
</tr>
<tr>
<td>Immunotherapy, targeted and/or cytotoxic therapy without re-irradiation</td>
<td>U</td>
<td></td>
<td>3 6 3 1</td>
<td>2</td>
<td></td>
<td>3 L</td>
</tr>
</tbody>
</table>
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2. **Per the UCLA/RAND Appropriateness Method** - Disagreement, i.e., 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.

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### 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. PET/CT shows no other disease. The patient declines a total glossectomy and is able to tolerate a regular diet. Which of the following may be considered appropriate therapies? Concurrent systemic therapy could be considered for each option.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractionated IMRT 50-54 Gy to tumor with comprehensive elective nodal coverage</td>
<td>U</td>
<td>6 7 1 1</td>
<td>2</td>
<td>3</td>
<td>M</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionated IMRT 60-70 Gy to tumor only</td>
<td>A</td>
<td>1 6 8</td>
<td>8</td>
<td>2-3</td>
<td>M</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionated IMRT 60-70 Gy to tumor with comprehensive elective nodal coverage</td>
<td>U</td>
<td>4 3 5 2 1</td>
<td>3</td>
<td>3</td>
<td>M</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBRT 30 Gy in 5 fractions to tumor only</td>
<td>U</td>
<td>6 5 1 1</td>
<td>3</td>
<td>2-3</td>
<td>S</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SBRT 35-44 Gy in 5 fractions to tumor only

<table>
<thead>
<tr>
<th>Rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>X</th>
<th>2</th>
<th>M</th>
<th>↓</th>
</tr>
</thead>
</table>

**Immunotherapy, targeted and/or cytotoxic therapy without re-irradiation**

<table>
<thead>
<tr>
<th>Rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5*</th>
<th>X</th>
<th>2-3</th>
<th>S</th>
<th>↓</th>
</tr>
</thead>
</table>

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**SOR:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Case 4: **KEY QUESTION: Is there an appropriate role of SBRT?**

A 78 year-old woman with an ECOG performance status of 2, with a cT3N2b p16-negative SCC 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. PET/CT is negative for other disease. The patient is PEG dependent. Which of the following may be considered appropriate therapies? Concurrent systemic therapy with radiation could be considered for each treatment option.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractionated IMRT 50-54 Gy</td>
<td>U</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2-3 L↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionated IMRT 60-70 Gy</td>
<td>M*</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>5*</td>
<td>X</td>
<td></td>
<td></td>
<td>1</td>
<td>1-3 M↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBRT 35-44 Gy in 5 fx</td>
<td>M*</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>5*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>41,42,43,47–49,88,134,145,229–255,282,283</td>
<td>2-3 M↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBRT 30 Gy in 5 fx</td>
<td>M*</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>5*</td>
<td>X</td>
<td></td>
<td></td>
<td>1</td>
<td>1-3 M↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy, targeted and/or cytotoxic therapy without re-irradiation with or without palliative RT (20-30 Gy in 5-10 fractions or similar)</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1-3 M↑</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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**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 IMRT tracking V2 up to foramen rotundum. Although an MRI was negative one year prior, he now presents with recurrent disease limited to the Gasserian ganglion in Meckel’s cave measuring a total of 12 cc’s. On review of the initial plan, the adjacent brainstem, 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, PET/CT is negative for distant spread. Which of the following may be considered appropriate therapies?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Rating 1</th>
<th>Rating 2</th>
<th>Rating 3</th>
<th>Rating 4</th>
<th>Rating 5</th>
<th>Rating 6</th>
<th>Rating 7</th>
<th>Rating 8</th>
<th>Rating 9</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitive fractionated IMRT 60-66 Gy with or without systemic therapy</strong></td>
<td>M*</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td>5*</td>
<td>X</td>
<td>55–62,284–286</td>
<td>3</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td><strong>SBRT 35-44 Gy in 5 fractions with or without systemic therapy</strong></td>
<td>M</td>
<td></td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td><strong>Immunotherapy, targeted and/or cytotoxic therapy without re-irradiation</strong></td>
<td>M*</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5*</td>
<td>X</td>
<td></td>
<td></td>
<td>L</td>
<td></td>
</tr>
<tr>
<td><strong>Observation with future supportive care and palliative RT 20-30 Gy in 5-10 fractions as indicated</strong></td>
<td>M</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td></td>
</tr>
</tbody>
</table>

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**SOR:**
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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Topic/Objective</th>
<th>Disease</th>
<th>Arm(s)/Cohort(s)</th>
<th>N</th>
<th>Median FU (Mo.)</th>
<th>Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janot, 200825</td>
<td>RCT</td>
<td>Efficacy of adjuvant ReRT</td>
<td>Resected RSP squamous H&amp;N, Any subsite</td>
<td>&quot;Wait and See&quot; vs. Split-course 60 Gy Reirradiation over 11 weeks with 5FU/Hydroxyurea</td>
<td>130</td>
<td>NR</td>
<td>DFS improved with chemo-reirradiation, no significant difference in OS.</td>
<td>1</td>
</tr>
<tr>
<td>Tian, 2014136</td>
<td>RCT</td>
<td>Dose/Fractionation</td>
<td>Recurrent Nasopharynx, Definitive</td>
<td>60 Gy in 27 fx vs. 68 Gy in 34 fx, Both IMRT alone</td>
<td>117</td>
<td>25</td>
<td>OS 44.2% short course vs. 30.3% long course (p=0.06), mucosal necrosis/hemorrhage higher with long course.</td>
<td>1</td>
</tr>
<tr>
<td>Rudžianskas, 201486</td>
<td>RCT</td>
<td>EBRT vs. Brachytherapy</td>
<td>Any recurrent H&amp;N squamous (53% oral cavity/oropharynx, about 50% postop)</td>
<td>3D-CRT Reirradiation to 50 Gy/25 fx vs. HDR-Brachytherapy (30 Gy/12 fx)</td>
<td>64</td>
<td>NR</td>
<td>2-yr OS was 67% HDR vs. 32% 3D (p=0.002). 2-yr LC 63% HDR vs. 25% 3D. Late effects favored HDR.</td>
<td>2</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Type</td>
<td>Section</td>
<td>Description</td>
<td>Patients</td>
<td>Follow-up</td>
<td>Summary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tao, 2018</td>
<td>RCT</td>
<td>Fractionation</td>
<td>Any Resected RSP Squamous H&amp;N, 60 Gy reirradiation over 11 weeks with 5FU/Hydroxyurea vs. 60 Gy BID over 5 weeks with cetuximab</td>
<td>53</td>
<td>36</td>
<td>No difference in OS, DFS or toxicity. Concluded 60 Gy in 5 weeks with cetuximab tolerable.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu, 2021</td>
<td>RCT</td>
<td>Role of Surgery</td>
<td>Resectable Recurrent Nasopharynx, Endoscopic Nasopharyngectomy vs. IMRT</td>
<td>200</td>
<td>56</td>
<td>OS benefit to surgery (3-yr OS 85.8% vs. 68.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang, 2020</td>
<td>MA</td>
<td>Role of Surgery</td>
<td>Recurrent Nasopharynx, Endoscopic Nasopharyngectomy vs. IMRT</td>
<td>761</td>
<td></td>
<td>5-yr OS 73%, presumed better than IMRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2020</td>
<td>MA</td>
<td>SBRT Outcomes</td>
<td>Recurrent H&amp;N, SBRT to 24-44 Gy in 3-6 fractions, 12% salvage surgery, 88% nonsurgical</td>
<td>10</td>
<td></td>
<td>2-yr OS of 30%, 2-yr LC 47%. Concluded that 30 Gy/5 fx appropriate but dose-escalation may be necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee, 2020</td>
<td>MA</td>
<td>IMRT Outcomes</td>
<td>Non-nasopharynx RSP H&amp;N Cancer, IMRT</td>
<td>17</td>
<td></td>
<td>2-yr LC &amp; OS 52% and 46%. Salvage surgery prognostic. Late Grade &gt;=3 toxicity 26%.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dionisi, 2019</td>
<td>SR</td>
<td>3D/IMRT Outcomes</td>
<td>RSP H&amp;N, All sites, 3D or IMRT</td>
<td>39</td>
<td>18.5</td>
<td>Pooled Grade 3+ acute 32% and late 29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Study Type</td>
<td>Patient Selection</td>
<td>Treatment</td>
<td>Number of Patients</td>
<td>Toxicity</td>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Verma, 2017</td>
<td>2017</td>
<td>SR</td>
<td>Proton Outcomes</td>
<td>RSP H&amp;N, All sites</td>
<td>Proton</td>
<td>4 H&amp;N studies, 247</td>
<td>Approximately 15</td>
<td>2-yr OS 33-69%, proton ReRT appears favorable</td>
</tr>
<tr>
<td>McDonald, 2012</td>
<td>2012</td>
<td>SR</td>
<td>Carotid Blowout</td>
<td>Re-RT H&amp;N (all sites)</td>
<td>3D or IMRT</td>
<td>27, 1554</td>
<td>Approximately 30</td>
<td>Risk of carotid blowout 2.6%, not dramatically different by fraction, dose, chemotherapy</td>
</tr>
<tr>
<td>Alterio, 2020</td>
<td>2020</td>
<td>SR</td>
<td>Carotid Blowout Treatment</td>
<td>Re-RT H&amp;N (all sites)</td>
<td>SBRT or 2D/3D/IMRT</td>
<td>35 studies</td>
<td>NR</td>
<td>Risk &lt;10%, Prevention of carotid blowout not often discussed but stenting, occlusion, ligation possible. Bleed treatment discussed.</td>
</tr>
<tr>
<td>Neider, 2013</td>
<td>2013</td>
<td>SR</td>
<td>Frequency of re-irradiation</td>
<td>Re-RT (All sites, non-H&amp;N included)</td>
<td>Any Re-irradiation</td>
<td>NR</td>
<td>NR</td>
<td>The frequency of re-irradiation is increasing across all sites.</td>
</tr>
<tr>
<td>Vargo, 2018</td>
<td>2018</td>
<td>SR</td>
<td>Dose for SBRT Re-RT</td>
<td>SBRT Re-RT (All sites)</td>
<td>SBRT</td>
<td>308</td>
<td>10-26</td>
<td>SBRT dose should be between 40-50 Gy over 5 fractions for optimal local control</td>
</tr>
<tr>
<td>Machtay, 2004</td>
<td>2004</td>
<td>SAT</td>
<td>Postoperative Re-RT with Chemotherapy, Feasibility</td>
<td>RSP H&amp;N (All sites)</td>
<td>Salvage Surgery then chemo/Re-RT. 54-66 Gy at 1.5 Gy/fx BID for 2 weeks then 1</td>
<td>16</td>
<td>35</td>
<td>3-yr OS 63%, LRC 81%. 38% late grade 3+ requires improvement.</td>
</tr>
<tr>
<td>Author</td>
<td>SAT</td>
<td>Tumor Type</td>
<td>Treatment Details</td>
<td>Week Break Duration</td>
<td>Outcome Measures</td>
<td>Notes</td>
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<tr>
<td>Kasperts, 2006</td>
<td>SAT</td>
<td>Postoperative Re-RT</td>
<td>Salvage Surgery then chemo/Re-RT</td>
<td>60 Gy at 2 Gy/fx</td>
<td>3-yr OS 44%, LRC 74%. Late effects</td>
<td>Significant.</td>
<td></td>
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<tr>
<td>Schatteman, 2018</td>
<td>SAT</td>
<td>Definitive Re-RT</td>
<td>RSP H&amp;N (All Sites)</td>
<td>60-85 Gy</td>
<td>2-yr OS 20%, LRC 38%. 20% Grade 5 late.</td>
<td>Stopped early for slow accrual and futility.</td>
<td></td>
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</tr>
<tr>
<td>Seiwert, 2013</td>
<td>SAT</td>
<td>Assess Dose/Safety</td>
<td>Unresectable Recurrent/2nd Primary H&amp;N with or without metastatic disease</td>
<td>63-70 Gy</td>
<td>2-yr OS 7.1%, 83% LR response rate. Novel</td>
<td>Agent dose confirmed.</td>
<td></td>
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</tr>
<tr>
<td>Awan, 2018</td>
<td>SAT</td>
<td>Assess OS after Re-RT</td>
<td>Non-metastatic RSP H&amp;N Squamous Carcinoma</td>
<td>60-66 Gy/30 fx</td>
<td>2-yr OS 45%, RFS 27%.</td>
<td>Favorable compared to historical controls.</td>
<td></td>
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</tr>
<tr>
<td>Kao, 2011</td>
<td>SAT</td>
<td>Safety/Dose of Re-RT</td>
<td>Non-metastatic RSP H&amp;N Squamous Carcinoma</td>
<td>63-70.4 Gy</td>
<td>1-yr OS 55%, LRC 60%.</td>
<td>Regimen feasible &amp; active.</td>
<td></td>
<td></td>
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<tr>
<td>Study</td>
<td>Modality</td>
<td>Re-RT Details</td>
<td>Dose Details</td>
<td>Regimen Details</td>
<td>Prognostic Value</td>
<td>Notes</td>
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<tr>
<td>Brockstein, 2000(^{115})</td>
<td>SAT</td>
<td>Safety/Dose of Re-RT with concurrent Paclitaxel/5-FU/Hydroxyurea</td>
<td>Poor prognosis H&amp;N Cancer (de novo or previous RT) 71-75 Gy BID at 1.5 Gy/fx with concurrent 5-FU, Hydroxyurea, Paclitaxel</td>
<td>25 Re-RT Patients</td>
<td>23</td>
<td>Regimen feasible.</td>
<td></td>
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<tr>
<td>Rusthoven, 2010(^{117})</td>
<td>SAT</td>
<td>Safety/Dose of Re-RT with concurrent erlotinib</td>
<td>RSP H&amp;N cancer &gt;6 months from prior RT 61.6-66 Gy in 28-30 fx continuous with concurrent erlotinib</td>
<td>14 Re-RT Patients</td>
<td>8.4</td>
<td>Regimen feasible. 1 fatal bleed, 1 severe ORN.</td>
<td></td>
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<tr>
<td>Chen, 2011(^{141})</td>
<td>SAT</td>
<td>Re-RT with Daily IGRT</td>
<td>RSP H&amp;N Cancer 60-70 Gy Continuous RT Alone</td>
<td>2 Regimen feasible.</td>
<td>20</td>
<td>2-yr OS 40%, in-field control 65%. IGRT-based Re-RT Safe and Effective.</td>
<td></td>
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<tr>
<td>Lartigau, 2013(^{42})</td>
<td>SAT</td>
<td>SBRT with Concurrent Cetuximab</td>
<td>RSP H&amp;N Cancer 36 Gy in 6 fx with concurrent cetuximab</td>
<td>56 Regimen feasible.</td>
<td>11.4</td>
<td>1 yr OS 47.5%. 1 toxic death (bleed). 41 of 56 experienced at least some skin toxicity.</td>
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<tr>
<td>Vargo, 2015(^{41})</td>
<td>SAT</td>
<td>SBRT with Concurrent Cetuximab</td>
<td>RSP H&amp;N Squamous Carcinoma 40-44 Gy in 5 fx with concurrent cetuximab</td>
<td>48 Regimen feasible.</td>
<td>18</td>
<td>1-yr OS 40%, LR-PFS 37%</td>
<td></td>
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<tr>
<td>Martínez-Fernández, 2017(^{104})</td>
<td>SAT</td>
<td>Perioperative HDR Brachytherapy</td>
<td>RSP H&amp;N, All Sites 32-40 Gy in 8-10 fx BID</td>
<td>63 Regimen feasible.</td>
<td>81.6</td>
<td>2-yr OS 50%, Local failure 14%, Regional failure 31.7%, 27% wound complication or bleeding. 3 fatal bleeds and 2 fatal soft tissue necrosis.</td>
<td></td>
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</tr>
<tr>
<td>Li, 2018(^{50})</td>
<td>RMI</td>
<td>Patient Selection</td>
<td>Locally Recurrent Nasopharynx 60-70 Gy in 27-35 fx, Variable chemotherapy</td>
<td>558 Regimen feasible.</td>
<td>36</td>
<td>Prognostic model predicted OS; suggested for use in patient selection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Year</td>
<td>Study Design</td>
<td>Study Type</td>
<td>Disease Site</td>
<td>Treatment Details</td>
<td>Study Size</td>
<td>Median OS</td>
<td>Study Quality Category</td>
<td>Study Quality Definitions</td>
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<tr>
<td>2020</td>
<td>RMI</td>
<td>Patient Selection</td>
<td>RSP H&amp;N, All Sites</td>
<td>Median 59.4 Gy with or without chemotherapy</td>
<td>118</td>
<td>18.5</td>
<td>3</td>
<td>2-yr OS 43%. RPA validated.</td>
</tr>
<tr>
<td>2019</td>
<td>RMI</td>
<td>Patient Selection</td>
<td>RSP H&amp;N, All Sites</td>
<td>5-yr OS 30%. Age, rT classification and surgery prognostic.</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>RMI</td>
<td>Patient Selection</td>
<td>RSP H&amp;N, All Sites</td>
<td>Median 60 Gy with or without surgery, chemotherapy variable</td>
<td>412</td>
<td>10.4</td>
<td>3</td>
<td>2-yr OS 40%. RPA described.</td>
</tr>
<tr>
<td>2019</td>
<td>RSI</td>
<td>Non-squamous H&amp;N Sarcoma Outcomes</td>
<td>H&amp;N Sarcomas</td>
<td>54-70 GyE</td>
<td>22 RSP Re-RT</td>
<td>15.7</td>
<td>3</td>
<td>2-yr OS 100%. Proton/Carbon ion safe and effective.</td>
</tr>
<tr>
<td>2010</td>
<td>RSI</td>
<td>Salivary RSP</td>
<td>H&amp;N Salivary</td>
<td>Median 66 Gy, 48 month interval</td>
<td>14</td>
<td>18</td>
<td>3</td>
<td>5-yr OS 27%, 3-yr LRC 52%. 6 of 14 feeding tube dependent.</td>
</tr>
<tr>
<td>2018</td>
<td>RSI</td>
<td>Rare sinonasal Re-RT</td>
<td>Sinonasal</td>
<td>Median 66 Gy</td>
<td>11</td>
<td>13</td>
<td>3</td>
<td>2-yr OS 40%, LRC 47%. Re-RT for rare sites and histologies acceptable.</td>
</tr>
</tbody>
</table>


ARS Appropriateness Criteria Evidence Table Key:

**Study Quality Category Definitions**

- **Category 1** The study is well-designed and accounts for common biases.
- **Category 2** The study is moderately well-designed and accounts for most common biases.
- **Category 3** There are important study design limitations.
Category 4 The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Category M The study is a meta-analysis and has not been rated for quality because the method is designed to evaluate individual studies only.
References


41. Vargo JA, Ferris RL, Ohr J, et al. A prospective phase 2 trial of reirradiation with


121. A Phase II Randomized Trial of Adjuvant Therapy With Pembrolizumab After Resection


134. Lee J, Kim WC, Yoon WS, Koom WS, Rim CH. Reirradiation using stereotactic body


The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient’s condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.