Reirradiation for recurrent head and neck squamous cell carcinoma: international expert consensus recommendations endorsed by the Reirradiation Collaborative Group, the European Society for Radiotherapy and Oncology Reirradiation Focus Group, and the American Society for Radiation Oncology

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Reirradiation can be considered for some patients with recurrent or second primary head and neck squamous cell carcinoma arising within previously irradiated regions, a clinical scenario associated with few therapeutic options. The increasing use of modern conformal radiotherapy techniques, including intensity-modulated radiotherapy, proton therapy, and stereotactic body radiotherapy, has expanded the feasibility of reirradiation in clinical practice. However, evidence remains heterogeneous, and clinical choices are challenged by substantial variability in patient presentation, previous treatments, and toxicity risk. This international expert consensus statement aims to provide pragmatic guidance across key domains, including patient selection, imaging, target delineation, treatment planning, dose accumulation, and toxicity management. Developed through a structured expert consensus process with formal agreement assessment, this document reflects current expert practice. By offering a shared clinical framework, this consensus seeks to promote more consistent practice, facilitate communication across centres, and support future research efforts in this complex and evolving field.

Introduction

Despite progress in head and neck squamous cell carcinoma (HNSCC), 15–50% of patients develop recurrence or a second primary tumour.[1] Therapeutic options are scarce when disease occurs within a previously irradiated region, with relatively low-level evidence supporting specific treatment algorithms. Salvage surgery is preferred when feasible, with possible postoperative reirradiation for some high-risk patients.[2] Otherwise, definitive-intent reirradiation can be considered in specific cases. If neither curative-intent surgery nor reirradiation is feasible, palliative systemic therapy can be offered.[3,4]

The adoption of conformal radiotherapy techniques, including intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy, proton therapy, and stereotactic body radiation therapy (SBRT), has improved the therapeutic ratio of reirradiation in the past 20 years.[5,6] Although encouraging results have been reported, the role of reirradiation in the modern era remains undefined.[7]

Alongside ongoing efforts of the Reirradiation Collaborative Group (ReCOG) to synthesise evidence on reirradiation, this expert-driven clinical practice statement provides pragmatic guidance on patient selection, treatment planning, and radiotherapy techniques for definitive and postoperative reirradiation in recurrent HNSCC. Nasopharyngeal cancers (covered by 2021 international recommendations[8]) and rare histologies are excluded.

ReCOG expert-derived guidelines

In the following sections, key clinical practice guidelines on reirradiation for HNSCC are presented, developed from available literature. The preliminary draft was first circulated among core ReCOG experts involved in the conceptualisation: six radiation oncologists (JB, ABe, NM, CBS, SSY, and PBl), three physicists (MS, CM, and KCP), and one senior research fellow (EVO). After iterative revisions, consensus was reached on the key clinical practice statements. The final manuscript (including the supporting literature) and the complete list of statements were then circulated to an international ReCOG panel (of 17 radiation oncologists) for a single formal voting round. Each statement was rated with three options: agree, disagree, or no opinion. Agreement was reported as the percentage of panellists selecting agree, with a fixed denominator that included all 17 panellists for every statement (ie, no opinion responses were retained in the denominator). Consensus thresholds were predefined as high (≥85%), moderate (70–84%), or low (<70%). Statements were reported with their observed agreement percentage; no additional voting rounds were done.

For each statement, we provide an evidence-level descriptor reflecting the highest available direct clinical

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See Online for appendix

For more on the **Reirradiation Collaborative Group** see https://recog.care

evidence supporting the recommendation, adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence:[9] level 1 (randomised evidence), level 2 (non-randomised, prospective, clinical evidence, including prospective, single-arm studies and non-randomised trials), level 3 (retrospective, observational evidence), and level 4 (expert consensus and indirect evidence or extrapolation). When multiple evidence types were available, the level assigned corresponds to the highest level of direct clinical evidence. A schematic overview of the consensus development process is provided in the appendix (p 3).

A total of 31 clinical practice statements were submitted to formal voting, of which 24 (77%) reached a high level of consensus (≥85% agreement). The distribution of agreement levels across statements is shown in the appendix (p 4). The seven statements with moderate agreement were not randomly distributed but clustered around well defined areas of clinical uncertainty, including patient subgroups with unfavourable prognosis, scenarios characterised by a narrow therapeutic ratio, and treatment-related variables for which heterogeneous practices persist, particularly dose prescription and fractionation.

After completion of the consensus process, the final manuscript was submitted for endorsement to relevant international scientific societies. The recommendations were formally endorsed by the Reirradiation Collaborative Group (ReCOG), the European Society for Radiotherapy and Oncology (ESTRO) Reirradiation Focus Group, and the American Society for Radiation Oncology (ASTRO).

Panel 1: **Key clinical practice statements on patient selection**

- A thorough review of the previous radiation plan is advised to distinguish between in-field recurrence and marginal failures. Consensus: high (100%); evidence level: 3.
- Reirradiation is generally not advised for recurrences occurring within 6 months of previous irradiation, except in urgent or exceptional palliative circumstances (eg, uncontrolled bleeding). Consensus: high (100%); evidence level: 2.
- For recurrences occurring between 6 months and 12 months, reirradiation should be considered only in highly selected cases, typically when the recurrent tumour is small, localised, and outside high-dose regions, and after thorough multidisciplinary evaluation. Consensus: high (88%); evidence level: 2.
- Post-operative reirradiation should be considered for patients in RPA class I (operated recurrence >2 years after first irradiation) with high-risk features: positive margins or extracapsular extension. Consensus: high (100%); evidence level: 2.
- Due to the inherent limitations of margin assessment in reirradiated tissues, reirradiation can be considered in cases in which an R0 resection is unlikely (based on preoperative imaging, poorly limited tumour, surgical assessment, etc), even if final pathology does not clearly report positive margins. Consensus: moderate (82%); evidence level: 4.
- Patients with RPA class III (recurrence <2 years plus feeding tube or tracheostomy dependence) should generally not be offered curative-intent reirradiation. Consensus: moderate (76%); evidence level: 3.

RPA=recursive partitioning analysis.

Patient selection

Patient selection is important for safe and effective reirradiation in HNSCC, given the substantial risks of both acute and late toxicities. Although modern techniques have improved safety compared with historical series, careful patient selection remains essential. Selection should consider tumour-related factors (eg, volume, location, site, time since first irradiation, and recurrence *vs* second primary), patient-related factors (eg, performance status, comorbidities, and previous toxicity), and technical considerations (eg, dosimetric feasibility and tolerance of critical organs at risk).[7] Review of the previous plan and dose distribution is essential to distinguish true in-field failure from marginal or geographical miss. Key consensus recommendations regarding patient selection are summarised in panel 1.

To evaluate prognosis, Ward and colleagues[10] identified three prognostic classes through recursive partitioning analysis (RPA). This classification (illustrated in figure 3 of the original publication)[10] stratifies patients into three groups based on time since previous radiotherapy, surgical resection status, and organ dysfunction (feeding tube or tracheostomy dependence). RPA class I (n=91) included patients with recurrence occurring more than 2 years after previous radiotherapy and treated with salvage surgery, with a reported 2-year overall survival of 61·9%. RPA class II (n=230) included patients with unresected recurrence occurring more than 2 years after previous radiotherapy, or recurrence within 2 years without organ dysfunction, with a 2-year overall survival of 40·0%. RPA class III (n=81) included patients with recurrence within 2 years and organ dysfunction, with a 2-year overall survival of 16·8%. In this model, the interval since previous radiotherapy emerged as a key prognostic factor guiding patient selection for reirradiation.

Other than that from Ward and colleagues, there is little evidence specifically addressing patients with RPA classes II and III. Most available data supporting reirradiation concern patients with favourable prognostic features, corresponding to RPA class I. Several studies have focused on patients at high risk of recurrence after salvage surgery, including those with microscopically positive surgical margins, perineural invasion,

lymphovascular invasion, or extracapsular extension. However, margin assessment is often challenging because recurrent tumours are frequently composed of small islets embedded in dense post-radiation fibrotic tissue, without a clear boundary.[11] Relatively favourable outcomes have been reported in these specific patients receiving adjuvant reirradiation.[12–14] A literature review of 16 studies, including 522 patients undergoing salvage surgery followed by adjuvant reirradiation, showed wide ranges of local control (21–100%), 2-year overall survival (24–81%), and rates of severe mucositis or dysphagia (11–52%).[15]

Outcomes of reirradiation of HNSCC

Normofractionated reirradiation: historical data

Several historical phase 2 and 3 trials have evaluated three dimensional (3D) normofractionated reirradiation in inoperable or postoperative HNSCC. Key clinical outcomes from landmark reirradiation studies are summarised in the appendix (p 5). Key consensus recommendations regarding treatment techniques are summarised in panel 2. In two Radiation Therapy Oncology Group (RTOG) phase 2 studies that used split-course reirradiation with concurrent chemotherapy, estimated 2-year overall survival was 15·2% (95% CI 7·3–23·1) among 79 evaluable patients in RTOG 9610 and 25·9% among 105 enrolled patients in RTOG 9911, with substantial severe toxicity (grade 3–4 in up to 34% of patients) and treatment-related mortality around 8%; longer intervals from previous radiotherapy were associated with better outcomes.[16,17] The GORTEC 2008–01 phase 2 trial (48 patients)[18] reported a median overall survival of 9 months (95% CI 7·3–12·6), with smaller recurrence size (<35 mm) as a key prognostic factor. Two (7%) of 28 evaluable patients had late grade 4 toxicities (one soft-tissue necrosis and one laryngeal), and one patient died from carotid rupture. In the only randomised, non-surgical trial (GORTEC 98–03), reirradiation with concomitant hydroxyurea and 5-fluorouracil produced higher response rates compared with methotrexate alone, including several complete responses, but did not translate into an overall survival benefit compared with methotrexate alone.[19] In the postoperative randomised GORTEC-GETTEC trial (n=130), surgery plus reirradiation improved locoregional control and relapse-free survival versus surgery alone without an overall survival benefit. Five treatment-related deaths were reported in 60 patients receiving reirradiation.[4]

Contribution of IMRT in normofractionated reirradiation

The advent of IMRT in HNSCC led to reirradiation dose-fractionation regimens closer to primary treatment, typically 60–66 Gy in 1·8–2·0 Gy fractions without planned breaks.[20,21] In the large, retrospective cohort by Ward and colleagues (n=412),[10] 330 (80%) patients received normofractionated reirradiation (median dose 60 Gy), 195 (47%) underwent surgery, and 309 (75%) received concomitant systemic therapy (mainly platinum-based). Median overall survival was 16·5 months (95% CI 13·9–19·4). Better outcomes were associated with previous surgery, absence of organ dysfunction, longer interval between radiotherapy courses, and better performance status, whereas multivariable analysis did not suggest a benefit from concomitant chemotherapy. Severe toxicities occurred in 78 (19%) of 412 patients and fatal toxicities in five (1%) of 412, lower than historical 3D series.[4,16,17,22]

Stereotactic reirradiation

Several non-randomised, phase 2 trials and retrospective cohorts have reported the results of SBRT for reirradiation (appendix p 4) for inoperable patients. The phase 2 trial by Lartigau and colleagues included 56 patients treated with 36 Gy in six fractions over 2 weeks (CyberKnife with 85% isodoseline).[23] The 3-month objective tumour

***Panel 2:* Key clinical practice statements on treatment techniques**

- Postoperative reirradiation should preferably be delivered with normofractionated IMRT rather than SBRT due to little available data supporting the use of SBRT in this setting. Consensus: high (94%); evidence level: 3.
- For patients in RPA class II with small, unresected tumours (≤25 cc, approximately 3 cm or cT1–T2), reirradiation with either normofractionated IMRT or SBRT appears to provide similar outcomes. Consensus: high (88%); evidence level: 3.
- For patients in RPA class II with larger unresected tumours (>25 cc), reirradiation with normofractionated IMRT appears to offer superior oncological outcomes compared with SBRT. Consensus: high (88%); evidence level: 3.
- Reirradiation with SBRT should be considered with caution for unresected laryngeal or hypopharyngeal recurrent tumours due to the increased risk of severe toxicity. Consensus: high (94%); evidence level: 3.
- The use of concomitant chemotherapy can be discussed on a case-by-case basis, especially for large tumours in fit patients. Consensus: high (88%); evidence level: 3.
- Reirradiation with proton therapy can be considered in selected cases to reduce dose to critical organs at risk, although there are little data comparing proton therapy with IMRT in the reirradiation setting. Consensus: high (88%); evidence level: 3.
- Brachytherapy (interventional radiotherapy) remains a valid definitive or adjuvant reirradiation option for small-volume (<25 cc), well delineated tumours in the oral cavity or oropharynx, preferably in expert centres. Consensus: high (88%); evidence level: 3.

IMRT=intensity-modulated radiation therapy. RPA=recursive partitioning analysis. SBRT=stereotactic body radiation therapy.

response rate was 58% (95% CI 43–72), and 1-year overall survival was 48% (31–62). Acute grade 3 or above toxicity occurred in seven (12·5%) patients (mucositis or dysphagia), with one death from haemorrhage and malnutrition. An updated retrospective analysis (n=110) reported similar outcomes: median overall survival 20·8 months (95% CI 16·5–26·3) and a 2-year incidence of grade 2 or higher late toxicity of 42% (33–51), including two grade 4 haemorrhages but no treatment-related deaths.[24] The phase 2 trial by Vargo and colleagues[25] included 48 patients treated with 40–44 Gy in five fractions over 1–2 weeks (CyberKnife, Trilogy, or TrueBeam). The 1-year overall survival was 40% (95% CI 26–54). Grade 3 toxicities included acute toxicities in three (6%) patients and late events, such as dysphagia or fistula, in three others. One patient had a grade 4 carotid rupture. In their larger retrospective series (n=291),[26] toxicity was strongly site-dependent, with the highest severe toxicity rates in laryngeal or hypopharyngeal recurrences (up to 50%) compared with 6–20% at other subsites. The authors noted that they initially favoured CyberKnife treatments but transitioned to treatments delivered almost exclusively by conventional linear accelerators with volumetric modulated arc therapy as embedded CBCT imaging and processing techniques advanced. The group also reported postoperative SBRT (n=28) for R1 margins or extracapsular extension using 40 Gy in five fractions, with no acute grade 3 or higher toxicity and late grade 3 or higher toxicity in 8% (including grade 4 infection and grade 4 arterial haemorrhage).[27]

Comparison between SBRT and normofractionated IMRT

A multi-institutional, retrospective study by Vargo and colleagues[28] published in 2018 compared normofractionated IMRT (n=217; median 60 Gy) and SBRT (n=197; median 40 Gy in five fractions) for reirradiation in inoperable recurrences and second primaries, stratified by RPA classes II–III.[10] For patients in RPA class III (n=61), overall survival and locoregional control were similar between techniques. However, for patients in RPA class II (n=353), IMRT provided significantly better 2-year overall survival (35·4% [95% CI 29·3–42·8]) compared with SBRT (18·6% [11·7–22·7]; p<0·001). When restricting the analysis to patients in RPA class II treated with SBRT of 35 Gy or more in five fractions for small target volumes (≤25 cc or T1–T2 tumours; n=142), no significant difference in overall survival was observed between SBRT and IMRT, suggesting a potential role for SBRT in carefully selected patients. For the 414-patient cohort, grade 4 or higher acute events were more frequent with IMRT (21 [5·1%] of 414) than SBRT (two [0·5%] of 414), whereas late toxicity was similar.

In parallel, a phase 1 dose-escalation trial showed the safety and feasibility of combining SBRT (≤40 Gy in five fractions) with concurrent cisplatin (15 mg/m² per fraction) in previously irradiated, unresectable recurrent HNSCC.[29] No dose-limiting toxicities were observed at 35–40 Gy, and 2-year overall survival reached 22% (95% CI 9–53).

These results are consistent with a patient-adapted and volume-adapted strategy: SBRT (≥35 Gy) could be preferentially considered for small-volume, well defined recurrences in RPA class II and III patients, whereas normofractionated IMRT remains the standard for larger or more infiltrative disease.

Other reirradiation techniques

Brachytherapy

Although less commonly used nowadays, interstitial brachytherapy (interventional raditherapy) remains a reirradiation option for selected, small-volume, accessible HNSCC, delivered either as adjuvant treatment or in some inoperable cases, particularly in expert centres.[30–33] Most reported cases use low-dose-rate or pulsed-dose-rate regimens. A few series have explored high-dose-rate brachytherapy, including a single-institution study from the Memorial Sloan Kettering Cancer Center that used intraoperative high-dose-rate brachytherapy. A single intraoperative reirradiation fraction (10–20 Gy) was delivered with iridium-192, yielding 2-year local progression-free survival of 56% and overall survival rates of 55%, with acceptable toxicity.[34] Of note, tumours amenable to salvage brachytherapy are often also amenable to curative salvage surgery.

Proton therapy

Proton therapy could improve sparing of surrounding healthy tissues in previously irradiated volumes.[5,35–38] A multicentre, retrospective study (52 [57%] of 92) with HNSCC (median reirradiation dose 61 Gy relative biological effectiveness) reported a 1-year overall survival of 65%.[39] Acute grade 3 or higher toxicity occurred in less than 10% of patients, with late grade 3 toxicity in 8·5%. Two patients died from treatment-related haemorrhage. Another retrospective study (n=60; 75% underwent pencil-beam scanning and 73% underwent concurrent chemotherapy) reported 1-year locoregional control of 68% and overall survival of 84%, with grade 3 acute toxicity of 13% and late toxicity of 20%, and rare osteoradionecrosis (including one fatal hyoid event).[40] In a large, single-institution cohort (n=242), 154 patients underwent curative-intent normofractionated proton reirradiation (median 70 Gy cobalt gray equivalents) with 1-year local control of 72% (95% CI 63–79) and overall survival of 67% (46–74), whereas 88 patients underwent a hypofractionated quad shot palliative approach (median 44·4 Gy cobalt gray equivalents) with 1-year local control of 62% (46–74) and overall survival of 29% (19–38); grade 5 late events occurred in five (2%) of 242 patients.[41] Overall, these data suggest proton therapy can provide favourable control with acceptable toxicity in selected patients, although optimising patient selection is crucial.

Delineation and treatment doses

Despite increasing experience, creating clear guidelines on dose, fractionation, delineation, or margins in reirradiation remains difficult because published data are highly heterogeneous. Key consensus recommendations regarding delineation and treatment doses are summarised in panel 3.

Delineation

Definitive reirradiation

Most studies recommend at least one contrast-enhanced CT for gross tumour volume (GTV) delineation, often complemented by MRI or PET-CT.[42–44] Popovtzer and colleagues[45] showed, in 66 patients treated with 3D reirradiation, that 45 (96%) of 47 relapses occurred within the 95% high-dose isodose line when a 5 mm planning target volume (PTV) margin around the GTV was used. In an SBRT cohort, planning was done without additional margins, with the PTV, clinical target volume (CTV), and GTV defined as equivalent volumes.[46] They showed that adding a 5 mm margin around the GTV retrospectively increased coverage of subsequent recurrence sites (CT planning: 12% increased to 48%; PET-CT planning: 45% increased to 94%).[46] A report highlighted heterogeneity in SBRT practices among 15 international institutions.[47] Variations in GTV to CTV margins ranged from 1 mm to 10 mm, and CTV to PTV margins ranged from 1 mm to 5 mm.

Postoperative reirradiation

Postoperative target volumes are based on imaging, surgical reports, and pathology. In a study of salvage surgery followed by adjuvant reirradiation (IMRT ≥60 Gy), recurrences occurred in 23 (42%) of 55 patients and included ten (44%) in-field, four (17%) marginal, and nine (39%) out-of-field failures based on deformable image registration analysis; mucosal recurrences had poorer salvage than nodal failures, and failures were frequently close to free flaps when used.[48] The first CTV typically included the entire tumour bed with a margin (0·8–1·0 cm) and an additional CTV to cover the operative bed. Another series defined the postoperative CTV as the postoperative bed or the area of highest concern (after surgeon or pathology review), with a 1·0–1·5 cm margin and a 5 mm PTV expansion.[21] In the 11 isolated locoregional recurrences in postoperative patients, three (27%) were isolated in-field failures, one (9%) was an isolated marginal failure, and seven (64%) included an out-of-field component.

Elective neck

Different studies have raised the question of elective nodal irradiation (ENI) for IMRT-based reirradiation in HNSCC. A large retrospective cohort study from Caudell and colleagues[49] included 505 patients from eight institutions. ENI was delivered in 186 (36·8%) of patients. ENI did not result in a decrease in the risk of locoregional failure or improvement of overall survival. However, ENI was associated with an increased risk of acute toxicity. Thus, ENI is typically avoided in the reirradiation setting.

***Panel 3:* Key clinical practice statements on delineation and treatment doses**

- For definitive reirradiation, a margin of 5 mm around the GTV to obtain the CTV is appropriate. Consensus: high (94%); evidence level: 4.
- For postoperative reirradiation, the rules for high-risk CTV delineation are the same as for primary irradiation. Consensus: moderate (82%); evidence level: 4.
- Elective nodal irradiation is not recommended, as it does not improve overall survival and increases toxicity. Consensus: high (100%); evidence level: 3.
- For definitive reirradiation with IMRT, a total dose of 66 Gy is commonly used. Consensus: moderate (82%); evidence level: 4.
- Hyperfractionated reirradiation with IMRT is an option, although it has not clearly shown improved outcomes in head and neck squamous cell carcinoma. Consensus: moderate (76%); evidence level: 3.
- In the postoperative setting, a total dose of 60 Gy is commonly used. Consensus: high (94%); evidence level: 3.
- For stereotactic body radiation therapy, an equivalent dose of approximately 40 Gy in five fractions is generally recommended. Consensus: moderate (76%); evidence level: 3.

CTV=clinical target volume. GTV=gross tumour volume. IMRT=intensity-modulated radiation therapy.

Doses

Normofractionated IMRT

For definitive reirradiation, the same 505-patient cohort study also raised questions regarding dose and fractionation.[49] Doses of 66 Gy or more were associated with improvements in both locoregional control and overall survival (2-year overall survival 49·3% with ≥66·0 Gy *vs* 34·2% with 60·0–65·9 Gy *vs* 30·4% with <60·0 Gy). Hyperfractionation was not associated with improved outcomes. Similar findings were reported in a German multicentre study, in which higher dose and good Eastern Cooperative Oncology Group performance status independently predicted overall survival.[50]

For postoperative reirradiation, also in the study from Caudell and colleagues, 49% of patients underwent postoperative reirradiation.[49] They reported that dose (60·1–70 Gy *vs* 60 Gy *vs* 39·6–59·4 Gy) did not obviously affect locoregional control or overall survival. A significant increase was noted in late grade 3 or higher effects (2-year rate of 41·3% *vs* 22·9%, p=0·031) for those treated postoperatively with hyperfractionation compared with daily fractionation.

SBRT

Across 15 institutions, SBRT doses varied widely (15–22 Gy in a fraction to 30–50 Gy in five to six fractions), with additional variation in prescription isodose.[47] The AAPM HyTEC review (≥300 patients) suggested improved control and overall survival with 35–45 Gy in five fractions compared with <30 Gy, supporting a pragmatic target of around 40–50 Gy in five fractions for SBRT reirradiation.[42] The 36 Gy in six fraction regimen (85% isodose line) used by Lartigau and colleagues also appears appropriate.[23]

Practical workflow and dose accumulation considerations

Reirradiation workflows from multiple institutions have been published.[51–54] Key consensus recommendations regarding dose accumulation are summarised in panel 4. Planning for HNSCC reirradiation should integrate previous radiotherapy data when available (planning CT, contours, and dose), retrieved and registered with dedicated tools.[53] Anatomical alterations between courses are frequent, including postoperative changes, tumour progression, fibrosis, and soft-tissue deformation. In many cases, rigid image registration is done as a first step.[55] However, this approach might be insufficient. Deformable image registration might be preferred when available, as, when properly commissioned, it could enable accurate local alignment despite post-treatment changes.[56] In an international survey, deformable image registration was used in 96 (42%) of 226 HNSCC reirradiation cases.[57] A 2026 systematic review has highlighted the absence of dedicated evaluation of deformable image registration performance for dose mapping in the reirradiation context,[58] emphasising the need for rigorous quality assurance. After registration, the previous dose is mapped onto the new planning CT. When feasible, summation should be done voxel by voxel in 3D and expressed as equivalent dose in 2 Gy per fraction (EQD2) to account for differing fractionation schedules; late-responding tissues typically use α/β=2–3 Gy. Although voxel-wise physical dose summation is supported by most contemporary treatment planning systems, voxel-wise radiobiological dose summation (EQD2 or biologically equivalent dose) is not routinely automated and often relies on dedicated or manual workflows.

Dose accumulation remains complex and not fully standardised. Recent guidance (national Danish consensus, ESTRO, and ReCOG) provides recommendations for 3D dose summation, acceptable alternatives when full 3D summation is not feasible, and structured uncertainty evaluation related to registration and radiobiological conversion.[54–60] Moreover, most commercial treatment planning systems cannot automatically convert physical dose to EQD2, meaning departments must rely on manual workflows. A multicentre study reported substantial interobserver variability in cumulative organ-at-risk dose estimation, highlighting the need for harmonised workflows.[61] The planning process typically involves multiple iterative steps: adjustment of dose objectives, resummation of cumulative doses, and evaluation of clinical trade-offs. Although some automated tools are being developed,[62] rigorous manual oversight remains the standard.

In the absence of validated cumulative dose constraints and recovery models, clinical judgement, particularly regarding near-maximum doses to critical serial organs, remains essential in reirradiation.

***Panel 4:* Key clinical practice statements on dose accumulation**

- Previous radiotherapy data (planning CT, contours, and dose) should be retrieved and integrated into reirradiation planning when available. Consensus: high (100%); evidence level: 4.
- Deformable image registration should be used when available to account for anatomical changes between the two courses with rigorous quality assurance. Consensus: high (88%); evidence level: 4.
- Cumulative doses to organs at risk should be expressed in EQD2 with appropriate α/β values (typically 2–3 Gy for late-responding tissues). Consensus: high (100%); evidence level: 4.
- When possible, voxel-wise three-dimensional EQD2 summation should be done to guide treatment planning. Consensus: high (88%); evidence level: 4.
- In the absence of deformable dose summation or poor deformable image registration performance, conservative manual addition of point doses to critical organs at risk (spinal cord, brainstem, and carotid arteries) remains acceptable. Consensus: high (100%); evidence level: 4.

EQD2=equivalent dose in 2 Gy per fraction.

Toxicity and organ-at-risk dose constraints

Severe late toxicities remain a major concern in HNSCC reirradiation despite advances in treatment planning and delivery. Key consensus recommendations regarding toxicity and organ-at-risk dose constraints are summarised in panel 5. In RTOG 9610, grade 3 or higher late toxicity occurred in 26% of patients, with treatment-related deaths in seven (8%) of 79 patients.[17] A systematic review of 39 studies (3766 patients) reported pooled rates of grade 3 or higher acute toxicities of 32% and late toxicities of 29%.[63] Severe complications included radionecrosis, trismus, feeding-tube-dependent dysphagia, brachial plexopathy, and carotid blowout (up to 4% of patients). Toxicity patterns can also vary according to the anatomical site of recurrence. For example, recurrences involving the larynx or hypopharynx have been associated with higher rates of severe late toxicity, including airway-related complications and tracheostomy dependence, than other subsites in reirradiation series.[26] In contrast,

oral cavity tumours carry a high risk of mandibular osteoradionecrosis due to cumulative mandibular irradiation.[63] These data highlight the need to balance oncological benefit against irreversible, and occasionally fatal, complications, particularly in borderline indications. Practically, critical organs at risk can be prioritised according to the severity and reversibility of associated complications, and the trade-off between local control and toxicity should be discussed with patients. In specific cases, organ-at-risk dose constraints (eg, carotids, mandible, spinal cord and brainstem, or swallowing structures) can be exceeded when local control is prioritised, provided risks are explicitly communicated and documented.

Recovery modelling

The possible partial recovery of normal tissues between courses might justify applying a tissue recovery factor based on the time elapsed since the first radiotherapy course. However, there is no consensus model to quantify this effect. In the absence of prospective validation, international recommendations advocate a cautious approach.[17] A 10–25% recovery factor has been proposed by expert opinion (and up to 50% by some), which could be applicable to latency intervals exceeding 12 months, especially for highly sensitive structures, such as the spinal cord or brainstem; however, the evidence is very low. Unless robust evidence supports such recovery, a conservative approach should be used and cumulative doses should be considered additive for high-risk organs at risk.

Panel 5: Key clinical practice statements on toxicity and organ-at-risk dose constraints

- For carotid arteries, a cumulative EQD2 of more than 120–125 Gy (α/β=2) significantly increases the risk of carotid blowout and should be avoided when feasible. Consensus: high (94%); evidence level: 3.
- Carotid encasement of more than 180° and previous ulceration elevate the risk of carotid blowout. Consensus: high (100%); evidence level: 3.
- For the mandible, the risk of osteoradionecrosis increases significantly with cumulative EQD2 of more than 114–119 Gy. Risk also depends on high-dose subvolumes, dose per fraction, dental status, and trauma. Consensus: high (100%); evidence level: 3.
- In the absence of prospective validation, any tissue recovery factors (10–25%) applied for spinal cord or brainstem cumulative EQD2 must be used with caution and explicitly documented. Consensus: high (88%); evidence level: 4.
- When achievable, a cumulative EQD2 D0·1 cc of 50 Gy or less for the spinal cord and 55 Gy or less for the brainstem should remain a target. Consensus: moderate (70%); evidence level: 4.
- When necessary, on a case-by-case basis, cautiously higher cumulative thresholds (~60 Gy) could be accepted at the surface of the spinal cord or brainstem, depending on retreatment interval, previous dose distribution, and the reliability of deformable dose accumulation. Consensus: high (94%); evidence level: 4.

EQD2=equivalent dose in 2 Gy per fraction.

Life-threatening or irreversible complications

Carotid arteries

Carotid blowout syndrome is a catastrophic complication associated with high mortality. In a retrospective cohort of 1554 patients reirradiated for HNSCC with carotid involvement, 41 (2·6%) reported carotid blowout syndrome, with a mortality rate of 29 (76%) of 38 patients with data.[64] Retrospective receiver operating characteristic analysis identified a cumulative EQD2 maximum dose of 119 Gy or more as a potential threshold for risk stratification.[65] In the setting of SBRT, the risk of carotid blowout syndrome increases with adverse factors, including cumulative carotid doses greater than 120–125 Gy EQD2 (α/β=2 Gy), tumour encasement of more than 180°, previous surgery or ulceration adjacent to the carotid, and the use of daily fractionation rather than alternate-day schedules.[66] These parameters should be considered jointly during treatment planning, acknowledging that the risk of carotid blowout is also present if the tumour progresses next to the carotid, even without reirradiation.

Mandible

Mandibular osteoradionecrosis causes clinically significant morbidity, manifesting as pain, impaired mastication, and pathological fracture. In the same systematic review mentioned previously, 18 of 39 studies reported mandibular complications, with osteoradionecrosis rates ranging from 2% to 18%.[63] A dose–effect relationship has been found between the near-maximum bone dose and osteoradionecrosis risk (area under the curve 0·74; optimal cutoff 119 Gy EQD2; sensitivity 100%, specificity 52%).[65] In a separate retrospective series, 5·8% of patients developed mandibular osteoradionecrosis after reirradiation with cumulative doses of 94–130 Gy (median 114 Gy).[67]

Spinal cord and brainstem

Dose summation is crucial for these serial organs; plans should be optimised to achieve the lowest possible near-maximum dose (D0·1 cc). Because the previous course is often delivered with IMRT or volumetric modulated arc therapy, strict cumulative limits are seldom reached, leaving some residual tolerance. When feasible, planning goals should maintain a cumulative D0·1 cc of 50 Gy or less EQD2 for the spinal cord and 55 Gy or less EQD2 for the brainstem. In some clinical scenarios, marginally higher spinal cord doses (up to ~57 Gy EQD2) might be acceptable.[68] Rarely, higher cumulative thresholds

(~60 Gy)[69] at the surface of the spinal cord might be tolerated, contingent on the retreatment interval, previous dose distribution, and the reliability of deformable dose accumulation. For the brainstem, maximum doses of 60 Gy have been considered acceptable in the primary treatment of nasopharyngeal cancers and could hence also be used as cumulative maximum doses for reirradiation. Importantly, these dose recommendations are conservative and do not take any tissue recovery into account.

Functional toxicities

Dysphagia and feeding tube dependence

Dysphagia is one of the most disabling late toxicities. Reported rates of grade 2 or higher dysphagia in the reirradiation setting vary from 3% to 33%.[63] In a retrospective cohort, 65% of patients had grade ≥2 late toxicity, in which the mean dose to the pharyngeal constrictor muscles during retreatment was significantly associated with dysphagia (area under the curve 0·78; optimal threshold 36·7 Gy; sensitivity 62%; specificity 100%).[70]

Trismus and dental complications

Trismus and dental toxicity might also occur after HNSCC reirradiation and can substantially impair mastication, oral hygiene, and quality of life. In modern reirradiation series that use IMRT or proton therapy, dysphagia, and trismus remain among the most frequently reported late toxicities.[71]

The main practical recommendations derived from these consensus statements are summarised in the figure.

Discussion

Within patient selection, moderate consensus primarily reflected uncertainty regarding the net benefit of

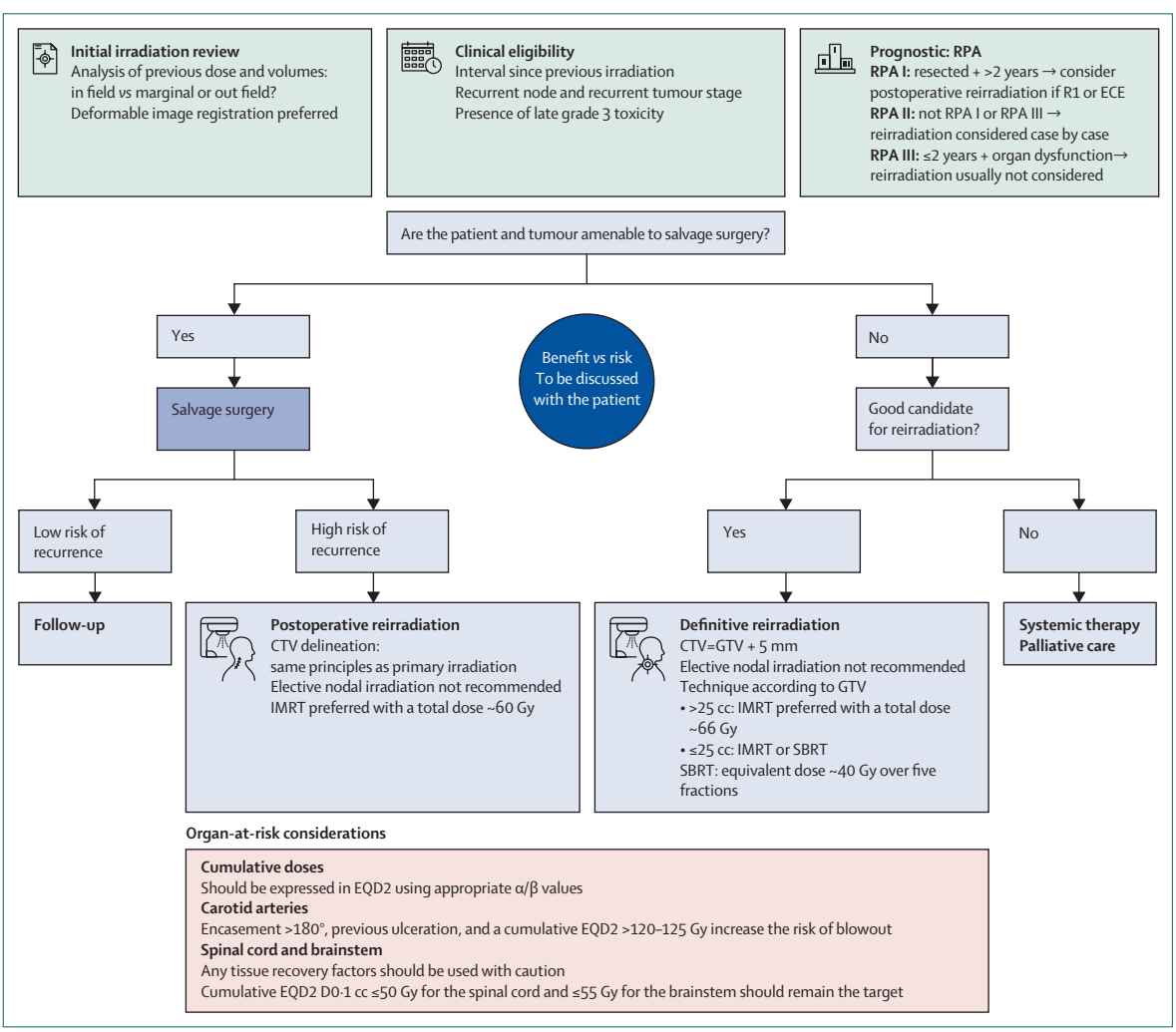

Figure: **Major practical guidelines for reirradiation in recurrent or second primary head and neck squamous cell carcinoma**
Percentages of agreement for each clinical practice statement are detailed in the panels. CTV=clinical target volume. ECE=extracapsular extension. EQD2=equivalent dose in 2 Gy per fraction. GTV=gross tumour volume. IMRT=intensity-modulated radiation therapy. RPA=recursive partitioning analysis. SBRT=stereotactic body radiation therapy.

reirradiation in clinically challenging situations. This uncertainty included postoperative cases with negative margins but suspected incomplete resection, for which experts emphasised the need for multidisciplinary decision making integrating clinical, radiological, and pathological information and consideration of close imaging surveillance with deferred, highly focal reirradiation as an alternative to immediate treatment. Similarly, for patients with RPA class III disease, divergent interpretations of baseline organ dysfunction and its relevance to reirradiation tolerance underpinned moderate agreement, with several experts cautioning against systematic exclusion and favouring individualised approaches.

In the domains of target delineation and dose prescription, reduced consensus reflected variability in technical practice and little high-level evidence. Experts agreed that postoperative reirradiation requires adaptation of primary radiotherapy principles rather than their strict replication, taking into account postoperative anatomy, imaging findings, and margin assessment. For definitive reirradiation with IMRT, moderate consensus regarding a reference dose of 66 Gy highlighted preference for a dose corridor adapted to tumour site, previous treatments, and feasibility. Divergent views were also observed for hyperfractionated reirradiation, with some experts citing randomised evidence and institutional experience supporting benefit in nasopharynx, whereas others cautioned against extrapolation across all HNSCC subsites.

Substantial variability in practice was also evident for SBRT in the reirradiation setting. Moderate consensus reflected differences in dose–fractionation schemes, treatment intent, and anatomical considerations, as well as frequent need for dose adaptation due to organ-at-risk constraints, supporting flexible dose corridors rather than a single standard regimen. Finally, the lowest agreement concerned cumulative dose constraints for the spinal cord and brainstem, reflecting divergent views on the conservativeness of proposed thresholds, the role of retreatment interval and tissue recovery modelling, and variability in dose metrics and cumulative dose estimation methods.

Overall, areas of reduced consensus reflect intrinsic clinical uncertainty rather than methodological inconsistency, underscoring the need for individualised decision making, transparent risk–benefit assessment, and shared discussion with patients in the complex setting of head and neck cancer reirradiation. Consistent with this perspective, proposed dose thresholds and organ-at-risk constraints should be interpreted as pragmatic planning objectives informed by available evidence and expert consensus, rather than strict evidence-based limits.

With the increasing use of immune checkpoint inhibitors (with or without chemotherapy) in recurrent or metastatic HNSCC, clinicians must frequently decide whether to initiate systemic therapy first and defer reirradiation or prioritise reirradiation. At present, no randomised data are defining the optimum sequencing of reirradiation relative to first-line systemic regimens in previously irradiated patients. Therefore, sequencing should be individualised in multidisciplinary discussion, balancing urgency of local control and symptom burden against the expected benefit–risk profile of reirradiation (including proximity to critical organs at risk, baseline organ dysfunction, and previous toxicity), while explicitly incorporating patient goals and preferences through shared decision making. Furthermore, available non-randomised data combining reirradiation with immune checkpoint inhibitors have not identified an unexpected safety signal to date, although prospective randomised sequencing data are unavailable.[72]

Conclusion

Reirradiation for recurrent or second primary HNSCC remains one of the most challenging scenarios in contemporary radiation oncology. Through an extensive review and an international expert-driven process, the ReCOG initiative provides key clinical practice statements covering patient selection, treatment technique, target delineation, dose accumulation considerations, and cumulative dose constraints. These expert-endorsed recommendations aim to support pragmatic, individualised decision making while acknowledging the substantial heterogeneity of clinical presentations and

Search strategy and selection criteria

We searched PubMed for papers published from Jan 1, 2000, to Dec 31, 2025, with the combination of MeSH terms and free-text keywords "reirradiation" and "re-irradiation", combined with disease-specific terms "head and neck cancer", "head and neck squamous cell carcinoma", "HNSCC", and anatomical subsites "oropharynx", "oral cavity", "larynx", and "hypopharynx". Additional references were identified from the authors' personal bibliographic files and manual review of reference lists.

Eligible publications included prospective and retrospective clinical studies, pooled analyses, systematic reviews, meta-analyses, and consensus or guideline papers addressing reirradiation in head and neck squamous cell carcinoma. Studies on benign disease, conference abstracts, non-peer-reviewed material, purely technical or modelling studies without clinical correlation, and very small case series (<8 cases) were excluded. The final reference list was generated on the basis of originality, relevance, and applicability to the scope of this international expert consensus statement. To improve transparency regarding the strength of supporting evidence, each recommendation was additionally assigned an evidence level based on a simplified four-tier hierarchy adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence.

institutional capabilities. While acknowledging current limitations and knowledge gaps, ReCOG is actively pursuing initiatives to consolidate evidence for future refinement.

Contributors

JB: conceptualisation, methodology, data curation, formal analysis, validation, supervision, and writing (original draft and review and editing). ABe: conceptualisation, methodology, project administration, data curation, formal analysis, validation, visualisation, and writing (original draft and review and editing). MS: methodology, investigation, and writing (review and editing). NM: methodology, investigation, and writing (review and editing). SGL: investigation and writing (review and editing). JC: investigation and writing (review and editing). AE: investigation and writing (review and editing). SN: investigation and writing (review and editing). CM: investigation and writing (review and editing). KCP: investigation and writing (review and editing). MCW: investigation and writing (review and editing). PBo: investigation and writing (review and editing). GNG: investigation and writing (review and editing). ABa: investigation and writing (review and editing). PBa: investigation and writing (review and editing). MLKC: investigation and writing (review and editing). AP: investigation and writing (review and editing). CBS: methodology, investigation, and writing (review and editing). EVO: methodology, investigation, and writing (review and editing). SSY: methodology, investigation, and writing (review and editing). PBl: conceptualisation, methodology, data curation, formal analysis, validation, supervision, and writing (original draft and review and editing).

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