Review Article

Role of reradiation in head and neck cancer from limits to option

ABSTRACT

Locoregional recurrence (LRR) or second primary malignancy in the previously treated area continues to be a major cause of treatment failure with significant morbidity and mortality in head and neck cancer. Prognosis of recurrent disease is dismal. To manage LRR is a therapeutic challenge for multidisciplinary head and neck team and more so if it is in a previously irradiated area. Though surgery is the mainstay of treatment but curative resection is feasible in only minority of patients. Systemic therapy alone has no long-term response rate or survival advantage in the management of inoperable recurrences. Full dose reradiation (RERT) with or without concurrent systemic therapy (CRERT) remains the only viable treatment option offering long-term survival in carefully selected patients. RERT is not a new concept but traditionally been avoided because of concern regarding toxicity due to limitations of conventional radiotherapy techniques. Initial studies were restricted to brachytherapy with its limitations. During the past two decades with the revolution in radiation therapy treatment delivery, more precise treatment techniques such as intensity-modulated radiation therapy, image-guided radiation therapy (IGRT), adaptive radiation therapy, stereotactic body radiotherapy, stereotactic radiosurgery, tomotherapy, intensity modulated proton therapy, image-guided brachytherapy in combination with better imaging modalities to define the target with the concept of biological target volume, offer various options for RERT with improved survival and limited toxicity. Pattern of failure even after full dose RERT is mainly infield, inside recurrent gross tumor volume (r GTV); radioresistance and tumor hypoxia may be the probable explanation. Though RERT has been established as a mainstream treatment option, there is a lack of prospective multi-institutional studies and absence of phase III randomized trial except one in adjuvant setting. Optimum treatment is yet to be defined. We have reviewed the literature and attempt has been made to provide guidance to the priorities on which future investigation should focus. There is a need to reevaluate prognostic factors for survival, selection criteria for patients undergoing RERT, measures to reduce the infield recurrence and morbidity, reradiation tolerance of normal tissue in IGRT era, toxicity antagonist and molecular marker as a diagnostic and prognostic tool. There is a need of multi-institutional prospective randomize trial with uniform data reporting.

Key words: Head and neck cancer; recurrence or second primary; reradiation.

Introduction

Head and neck cancer (HNC) is the sixth most common malignancy worldwide.[1] Majority (70%) of patients present with locally advanced stage at diagnosis and despite advances of modern multidisciplinary care, locoregional recurrence (LRR) remains the predominant mode of failure in 20–57% of patients and accounts for approximately 40–60% of cancer-related deaths.[2] Even human papillomavirus- positive favorable patients have LRR rate of 15%.[3] There is also a 3–5% risk of second primary malignancy (SPM) per year.[4-6] LRR has a significant morbidity in terms of pain, bleeding, infection, disfigurement, and functional outcome (speech and swallowing) with grave psychosocial impact.

Autopsy studies have suggested a correlation between the presence of persistent locoregional disease and development

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of distant metastasis.[7] Recurrent disease usually has a poor prognosis with a median survival of approximately 6 months with best supportive care alone.[6] Though surgery has been the mainstay of treatment with 5-year survival rates ranging from 23% to 55%, it is feasible in only 15–20% of patients and up to 55% of patients develops second recurrence after salvage surgery.[8] Goodwin (1980–1998), demonstrated the 5-year survival rate of 39% for all 1080 patients included in a meta-analysis of 32 surgical series from 28 different institutions. Efficacy of salvage surgery correlates with recurrent stage, recurrent site, and time to pre-salvage recurrence.[9] Systemic therapy alone for inoperable recurrences results in 1-year overall survival (OS) of 10–15% with no data available for long-term control or survival.[10]

High dose RERT is the only treatment option available with any potential for cure or palliation. As most recurrences occur in the first 2-year after primary treatment and 80% arise in previously high dose radiated volumes, RERT is a challenge. As there is substantial incidence of high-grade toxicity associated with RERT, it should be judiciously used. Due to heterogeneity of this population with LRR with respect to patient related, treatment related, and disease-related parameters, nonuniform reporting of data, and lack of level I evidence in literature, it is difficult to draw firm conclusion. However, with evolving technologies there is emergence of data in favor of feasibility and efficacy of RERT, this will be reviewed in this article, which will help us in decision making and formulating future directions. Reradiation studies of nasopharyngeal carcinoma alone were excluded in this review.

Evaluation and Work Up for Recurrent Disease

Once the recurrence is histopathologically confirmed, careful restaging evaluation is mandatory for further management. Multidisciplinary head and neck team consisting of Surgical Oncologist, Medical Oncologist, Radiation Oncologist, Radiologist, Histopathologist, Dentist, Occupation therapist, Psychosocial worker, and Physiotherapist should undertake treatment decision at tertiary cancer center equipped with resources and expertise to manage the complexities and toxicities of retreatment. Treatment should be tailored to the individual patient. Distant metastasis should be ruled out. Proper imaging should be done to assess the locoregional extent of disease. Positron emission tomography-computed tomography (PET-CT) has a sensitivity of 86–91% and specificity of 84–93% for detecting distant metastasis.

The American College of Radiology (ACR) expert panel HNC reviewed the relevant literature and established the appropriate criteria for RERT. Patient selection is a key step in determining which patient should be offered RERT. Evaluation should include careful restaging imaging, a detailed history, assessment of life expectancy, assess to the prior radiotherapy details including dose received by critical structures such as the spinal cord, brain stem, optic apparatus, mandible, brain, and carotid arteries. Comorbidities, performance status, speech, swallowing, and hearing assessment, squeal of previous treatment, that is, fibrosis, carotid stenosis, osteoradionecrosis (ORN), cartilage necrosis, and arytenoid edema or other severe toxicity. Mucosal tumor extent should be properly assessed by physical examination including palpation and fiber optic endoscopy. For patients with tumor involving or in close proximity to carotid artery, Doppler ultrasound should be performed, and appropriate vascular intervention including stent placement should be considered.

The ACR recommends that patients with a reasonable performance status who do not have severe soft tissue or bone toxicities from prior therapy and do not have distant metastatic disease are likely to be benefited by RERT.[11]

Adjuvant Rert for Operable Recurrences

Multiple single institution studies and one and only multicenter randomized trial supports adjuvant RERT after salvage surgery in patients with high-risk histopathological features like extracapsular extension (ECE) or positive surgical margin.

Institute Gustave Roussy evaluated 25 patients with ECE or positive surgical margin treated with CRERT to a dose of 60 Gy (2 Gy daily) in alternate week with 5FU + hydroxyurea and observed 4 years OS of 43%. ORN was observed in 16% of patients.[12] Similarly, University of Pennsylvania evaluated 16 such patients treated with split course hyperfractionated CRERT regimen to a dose of 54–60 Gy (1.5 Gy bid) with 5FU and CISPLATIN and found 3 years OS of 63%.[13]

GETTEC and GORTEC accrued 130 patients in a multicentric phase III trial comparing CRERT (60 GY with 5FU and hydroxyurea) with observation following RO/R1 resection of previously irradiated recurrent HNC patients. Interim analysis revealed improved locoregional control (LRC) and progression-free survival (PFS) in adjuvant therapy arm with hazard ratio of 1.6 (95% confidence interval, 1.1–2.4, $P = 0.01$).[14]

ACR appropriateness criteria also favored CRERT over RERT in the setting of positive surgical margin or ECE after salvage surgery in previously radiated recurrent disease.

Suh *et al*. retrospectively evaluated the outcome and complications of re-irradiation of recurrent HNC after salvage surgery and microvascular reconstruction and concluded that microvascular free flap reduces the incidence of severe late complications of reradiation.[15]

Rert for Inoperable Recurrences-Survival and Toxicity Analysis

Two trials with level I evidence were prematurely closed. RTOG 0421, a multicentric phase III trial comparing salvage CRERT with doublet chemotherapy alone was closed due to poor accrual. GORTEC 9803 phase III randomized trial compared palliative intent CRERT with indefinite single-agent methotrexate (40 mg/m^2) has poor accrual and will not be discussed further as it has included advanced disease not suitable for curative treatment.

Subsequently, RTOG designed and successfully conducted two multi-institutional prospective phase II trials RTOG 9610 and RTOG 9911. Since 1980 various CRERT regimens were evaluated in several single-institution trials for salvage of inoperable recurrences with modest improvement in LRC and OS compared to chemotherapy alone with significant treatment-related toxicity.

Review of these studies (16–29) showed a 2 years OS in the range of 20–70%. Grade 3–4 toxicity occurred in up to 40% of patients and treatment-related death occurred in up to 10% of patients. Few patients had long-term disease-free survival (DFS) of 5 years or more. Various prognostic factors for LRC and OS were identified from these studies. Studies in pre-Intensity Modulated Radiation Therapy (IMRT) era are summarized in Table 1.

Radiotherapy Regimen and Normal Tissue Tolerance to Reradiation

No direct comparison of various reradiation regimens has been done so far.

Initial clinical studies used hyperfractionation with a planned break to optimize the therapeutic ratio because of concern related to late toxicity and used concurrent chemotherapy as a radiosensitizer to compensate for inadequate radiation dose.

De Crevoisier *et al*. compared three RERT schedules in 169 patients, continuous conventional 65 Gy at 2 Gy per fraction without chemotherapy, split course conventional fractionation 60 Gy at 2 Gy per fraction alternating week with chemotherapy, and hyper fractionated RERT 60 Gy 1.5 Gy per fraction twice a day with chemotherapy with no difference among three schedules.[22]

The appropriate dose constraints for RERT are controversial. Literature supports the use of guideline recommended by the quantitative analysis of normal tissue effects in the clinic. Central nervous system and soft tissue are the dose-limiting organs at risk for RERT.[30] Literature approves the cumulative spinal cord dose of 50 Gy. Soft tissue can tolerate up to 90% of the original dose. Tolerance dose of the carotid artery is uncertain, but it should be contoured as avoidance structure. Dose to mandible should be kept assuming 50% recovery. With modern technology dose, escalation is possible with less toxicity.

The ACR expert panel on HNC offered appropriateness criteria for patients with inoperable recurrence that is fit for RERT; the panel recommends CRERT. A limited RT target volume encompassing known disease with a safety margin was favored over elective nodal RERT. RERT with <50 Gy was considered inappropriate, and 60 Gy or higher was recommended. Continuous course once (2 Gy per fraction) or twice daily RT (1.2 Gy per fraction) was considered appropriate. Twice daily RT using 1.5 Gy fractions with planned split course was considered appropriate but split course once daily RT was not recommended.[11]

However, these studies were done in the pre-IMRT era. Recent trials with modern radiotherapy technique used once daily fractionation with the improved therapeutic ratio. In pre-IMRT era dose >60 Gy was not feasible due to technological constraint, but now with IG-IMRT, dose escalation up to 70–74 Gy is feasible.

Reradiation Via Intensity Modulated Radiation Therapy/Image-Guided Radiation Therapy

IMRT create highly conformal dose distribution around the target with a steep dose gradient outside the target allowing to spare organ at risk, thus, improving the therapeutic ratio. It is very critical in the setting of RERT, as mostly the critical structures are at the verge of their tolerance limit.

IMRT Studies (31–36) are summarized in Table 2.

In a study by Lee *et al*. 70% of the patients received IMRT. On multivariate analysis, IMRT was associated with improved LRC and RT dose >50 Gy with improved OS. Nasopharynx subsite was associated with significantly improved LRC and OS. No treatment related death was observed. Grade 3–4 late toxicity was seen in 11% of patients. None of the patients had a carotid blowout. This study showed significant improvement in survival for those patients who achieved LRC.[30]

Table 1: Reradiation studies in Pre- IMRT era

Author, year, Ref no Institute	study duration years No. of pt	Study type	RT interval in months Median (range)	Radiotherapy protocol	Chemotherapy	OS (%)	Complications
Skołyszewski *et al.*, 1980[16]	(1968-1974) 20	Retrospective	26 (5-94)	TD 34-75 Gy, 2 Gy/fx Reirradiation volume: GTV +"very narrow margin"	No	3 year-70	Gr 3-4 (20%) Gr 5 (0%)
Langlois *et al.* 1985[17]	(1973-1981) 35	Retrospective	40 (4-19)	TD median 60-69 Gy, 2 Gy/fx Reirradiation volume: NS	NO	2 year-19	Gr 3-4 (29%) Gr 5 (9%)
Emami *et al.* 1987[18]	(1967-1985) 40	Retrospective	N.S.	N.S.	NO	2 year-33	N.S.
Levendag *et al.* 1992[19]	(1970-1980) 55	Retrospective	N.S.	TD mean 46 Gy, 2 Gy/fx Reirradiation volume: N.S.	49%	2 year-26	N.S.
Stevens *et al.* 1994[20]	(1964-1991) 100	Retrospective	N.S.	TD planned 50 Gy @ 1.8-2 Gy/fx Reirradiation volume: N.S.	NO	2 year-27	Gr 3-4 (9%) Gr 5 (4%)
Haraf *et al.* 1996[21] University Of Chicago	(1980-1993) 45	Retrospective	24 (1.2-137)	Alternate week radiotherapy 40 pt conventional 5 patient hyper fractionation, TD mean 50 Gy	HU +5FU by all	5 year-14.6	Gr 5 (11%)
Decrevoiser *et al.* 1998[22]	(1980-1996)						
	27	Group 1 (Retrospective)	33	TD median 65 Gy, 2 Gy/fx	NO	2 year-25	Gr 5 (3.5%)
Institute Goustav Roussy	106	Group 2 (Phase II)	40	TD median 60 Gy, 2 Gy/fx (d 1-5!9-d break)	HU +5FU	2 year-24	
	36	Group 3 (Phase II)	23	TD median 60 Gy. 1.5 Gy/fx b.i.d., (wk 1-2 ! 2wk)	MMC +5FU+CDDP	2 year-10	
Ohizumi *et al.* 2002[23]	(1984-1997) 44	Retrospective	13.5 (1-134)	TD median 53 Gy, 1.9-2 Gy/fx q.d.or 1.2-1.4 Gy/fx Reirradiation volume: GTV +10-20 mm	23%, CDDP, Bleo, 5FU, tegafur	2 year-10	Gr 3-4 (12%)
Nagar *et al.* 2004[24]	(1991-1999) 29	Retrospective	13 (3-90)	TD median 34 Gy, 1.8-2 Gy/fx Reirradiation volume: GTV +15-20 mm	CDDP+-5FU	2 year-12	N.S.
Lagendijk *et al.* 2006[25]	(1997-2003) 34	Prospective	90 (12-233)	TD 60-66 Gy, 2 Gy/fx CTV = GTV +5mm+ ELN-RT Reirradiation volume: PTV = CTV +5 mm	NO	2 year-38	
Salama *et al.* 2006[26] University of Chicago	(1986-2001) 115	Prospective	N.S.		HU +5FU, CDDP, gemcitabine, paclitaxl, irinotecan	3 years-22	Gr 5-19 OR N-18 Carotid blow out-5
Spencer *et al.* 2006[27] RTOG 9610	(1996-1999) 81	Prospective	30 (7-238)	TD 60 Gy, 1.5 Gy/fx b.i.d. (d 1-5 ! 9-d break) Reirradiation volume: GTV +20 mm	HU +5FU	2 year-15.2	Gr 5 (7.6%) Gr 4 (3%)
Langer *et al.* 2007[28] RTOG-9911	(2000-2003) 99	Prospective	40 (6-318)	TD 60 Gy, 1.5 Gy/fx b.i.d. (d 1-5 ! 9-d break) Reirradiation volume: GTV +20 mm	CDDP + paclitaxel	2 year-25.9	Gr 5 (8%)
Mcdonald *et al.* 2012[29]	1554pt	Review		1.5 Gy bid or delayed accelerating HfxRT bleeding 4.5%			

TD - Tumor dose; fx - Fraction; GTV - Gross tumor volume; N.S. - Not specified; LC - Local Control; OS - Overall survival; q.d. - Once per daily; b.i.d. - Twice per day; RT - Radiotherapy; 5FU - 5-fluorouracil; HU - Hydroxyurea; MMC - Mitomycin C; CDDP - Cisplatin; ELN-RT - Elective lymph node radiotherapy; FUP - Follow-up; PTV - Planning target volume; PM - Pepleomycin; CTV - Clinical target volume; RTOG - Radiation therapy oncology group; CMb - Cetuximab

Table 2: IMRT reradiation studies (retrospective)

Author, year, Ref No. Institute	Study duration pt no.	Reradiation interval in months	IMRT dose PTV	Cumulative RT dose (Gy)	Other therapy	LRC (%)	OS (%)	Follow up In months	Late toxicity
Lee *et al.* 2007[31] MSKCC	(1996-2005) 74	38 (5-380)	TD median 59.4 Gy, 1.8-2 Gy/fx Reirradiation volume: PTV = GTV +10-20 mm	121.4	N.S.	42	37.0	35	Gr 3-4 (11%)
Biagioli *et al.* 2007[32]	(2001-2006) 41	25 (6-240)	TD median 60Gy 1.82 Gy/fx/week ! 9-d break, to Reirradiation volume: PTV = GTV +5-20 mm	121.2	Sx-41.5% NACT-31.7% CCT-100%	-	48.7	14	Gr 3-4 (31.7%)
Sulman *et al.* 2009[33] M.D. Anderson cancer center	(1999-2004) 78	46 (23-445)	TD median 60Gy, 1.8-2.2 Gy/fx CTV = GTV +1-2 cm, +_ELN-RT Reirradiation volume: PTV = CTV +3-5 mm	116.1	Sx-27% CT–49%	64	58	25	Gr 3-4 (20%)
Duprez *et al.* 2009[34] Ghen University Hospital	(1997-2008) 84	49.5 (5-298)	TD median 69 Gy, 2-2.5 Gy/fx Reirradiation volume: CTV = GTV +5-15 mm ELN-RT, 43%, PTV = CTV +3 mm	130	Sx-23% CT-20%	48	35	19.8	Gr 3-4 (11%)
Popovtzer *et al.* 2009[35] University of Michigan	(1994-2007) 68	37 (6-184)	TD median 68 Gy, 2 Gy/fx or 1.25 Gy/fx b.i.d. Reirradiation volume: PTV = GTV +5 m	130	Sx-33% CT-71%	27	40	42	Gr 3-4 (19%)
Nadeem *et al.* 2014[36]	(1996-2011) 257	32.4 (N.S.)	TD median 59.4 Gy, 1.8-2 Gy/fx	125		47	43	32.6	N.S.

TD - Tumor dose; fx - Fraction; GTV - Gross tumor volume; N.S. - Not specified; OS - Overall survival; q.d. - Once per daily; b.i.d. - Twice per day; RT - Radiotherapy; 5FU - 5-fluorouracil; LRC - Locoregional control; ELN-RT - Elective lymph node radiotherapy; PTV - Planning target volume; CTV - Clinical target volume; Gr - Grade; S - Surgery; CT - Chemotherapy; NACT - Neoadjuvant chemotherapy

Biagioli *et al*. and Sulman *et al*. observed similar results, confirming the superiority of IMRT over conventional technique in RERT.[31,32]

Duprez *et al*. on multivariate analysis found stage T4, short time interval between two radiation, absence of surgery, and hypopharyngeal cancer as independent prognostic factors for worse OS.[33]

Popovtzer *et al*. observed 71% of LRF and 96% of recurrences occurred in 95% isodose line. This study concluded that a prophylactic field is not needed in RERT at present.[34]

The University of California demonstrated the usefulness of daily image-guided radiation therapy (IGRT) in reducing the set-up uncertainties and planning target volume (PTV) margin, thus, improving the therapeutic ratio.[36] Adaptive radiation therapy further revolutionized the RERT approach by exactly painting the planned dose over target volume via adopting dose distribution as per tumor response adaptation as well as target and normal structures shifting adaptation, thus, allowing dose escalation with sparing of critical structures. De Crevoisier *et al*. showed a strong correlation between PTV and OS.[22]

Recently, hypofractionated regimens were also explored with evolving technologies such as stereotactic body radiotherapy (SBRT), high dose brachytherapy, and intraoperative brachytherapy.

Reradiation Studies with Stereotactic Body Radiotherapy

SBRT came as a rescue when full dose retreatment >60 Gy is not feasible even with IMRT because of proximity to the spinal cord or other critical structures. SBRT allows precise delivery of high biological doses to limited volume in shorter duration with minimum acute toxicity. There is no systemic or hematologic toxicity. It can be safely used for patients with poor general condition. However, there is concern regarding late toxicity, tight margin, lack of reoxygenation in HNSCC with a high alpha-beta ratio similar to acutely responding tissues.

Roh *et al*. and other investigators have reported overall response rate of 70–80% and 2-year OS of approximately 30% with cyber knife reradiation.[37]

A phase I dose escalation study by Heron *et al*. showed the safety of SBRT in excess of 44 Gy/5 fractions with significantly improved clinical outcomes associated with SBRT >35 Gy, tumor volume <25 mL, and re-irradiation

intervals >24 months. No grade 4 or 5 treatment-related toxicities including carotid blowout were observed.[38]

Similarly, retrospective data showed improved local control and OS for concurrent cetuximab + SBRTm.[39] Finally, longitudinal prospective assessments of patient-reported quality of life outcomes after SBRT showed significant improvements, especially for patients surviving >1 year.[40] With hypofractionated SRT, there is 10–15% risk of carotid blowout reported in the literature. These studies reported that, this fatal event occurred only in patients with tumors surrounding carotid arteries, and they received the full dose. Incidence is more with a single fraction. Results are encouraging but preliminary with limited follow-up. SBRT should be explored further for RERT in HNC.

Patient with tumor recurrences in close proximity to critical normal structures like the base of the skull may be benefited by charged particle therapy. A sharp dose gradient at the end range of charged particles, called the Bragg peak, theoretically allows high-dose delivery at depth without exit dose.

Dose Response in Reradiation

It has been established via multiple studies that higher radiation dose results in improved DFS and OS.

A study by Haraf *et al*. showed 2 years survival of 35% in patients receiving >58 Gy versus 8% for those receiving <58 Gy. A direct correlation was observed between radiation dose and survival.[21]

Salama *et al*. reported a 3 years LRC, PFS, and OS of 56%, 38%, 30%, respectively, for those patient who received dose more 58 Gy compared to 33%, 21%, and 6% among those who received <58 Gy. On multivariate analysis, RERT dose was found to be the most important prognostic factor for survival.[26]

Namogram by Riaz *et al*. showed dose more than 50 Gy was independently associated with improved LRC.[35]

In SBRT series, also a dose of 35 Gy or more had a better LRC.

Adverse Events and Prognostic Factors for Survival in Reradiation

Dysphagia requiring a feeding tube or gastrostomy has been reported in 10–40% of patients. Other chronic adverse effects were ORN, cervical fibrosis, trismus, aspiration, and hormonal dysfunction.

The risk of severe late complication was reported as 20–40% and was related to prior radiotherapy dose to tumor and normal tissues, primary site, site of recurrence, proximity to critical structures, RERT dose and fractionation, radiation technique, and treatment volume.

One of the most feared but, fortunately, rare consequence of RERT is delayed neurologic toxicity. This may be due in part to mandate cumulative dose limits of 50 Gy to the spinal cord in most of the studies. Investigators at the University of Chicago identified only 1 patient with myelopathy and at Institute Gustavo–Roussy 1 patient with brachial plexopathy after receiving a cumulative radiation dose of 130 Gy. Brain necrosis and cranial nerve palsy are extremely rare complications observed in recurrences close to the base of the skull.

Haraf *et al*., reported 5 treatment-related death. One due to carotid blowout, one due to respiratory arrest, one nasopharynx case died due to brain necrosis, and two died due to neutropenic sepsis.[21]

In a study by De Crevoisier *et al*. thirteen patients had long-term DFS of 42 months. Eleven patients developed ORN of the mandible, and 5 patients had carotid blowout. Other late toxicities were cervical fibrosis in 41%, trismus 30%, and mucosal necrosis in 21%. On multivariate analysis, the only 2 factors that correlated with death were the surface area and volume of the second RT course. Patients reradiated with a surface area of <125 cm^2 or a volume of <650 cc had significantly greater OS.[22]

In a study by Salama *et al*. triple agent chemotherapy was associated with improved LRC, OS, and freedom from distant metastasis.[18] However, these results were not applicable to inoperable recurrences. In this study, 19 patients died during treatment. Fifteen patients had carotid blowout. Eighteen patients required surgery for ORN.[26]

In RTOG-9610 study grade, 5 toxicity occurred in 6 (7.6%) patients. Four patients died due to bleeding and 2 due to neutropenia. Grade 3 toxicity occurred in 19.4% and grade 4 toxicity in 3% of patients. Time interval since prior radiation came out to be a significant prognostic factor for survival in this study. 1-year survival for patients treated within 3 years of prior radiotherapy was 35% compared with 48% for patients treated for >3 years. Patients who were treated within 1-year of their therapy had a median survival of 6.5 months versus 15 months for those who were treated 24 months or more after the first radiation. One year survival rate and median survival for patients with SPM were 54% and 19.8 months, respectively, compared with 38% and 7.7 months, respectively, for recurrent cancer in this study similar to a study by

Spencer *et al*. who reported a local control rate of 27% and 5-year actuarial survival of 17% in recurrent HNC compared with 37% and 60%, respectively, for SPM with RERT. Prognosis of SPM is better than the recurrent disease.[27]

Thereafter, Langer *et al*. reported a succeeding RTOG-9911 trial. Eight patients died due to treatment-related toxicity, 2 due to neutropenic sepsis, 1 due to pneumonitis, 1 due to dehydration, 1 due to cerebrovascular accident, 2 due to carotid blowout, and 1 due to orocutaneous fistula.[28]

A secondary analysis of RTOG 9610 and RTOG 9911 trials predicts prognostic namogram for toxicity and survival. Body surface area, nutritional status, stage of recurrent disease, and largest recurrent tumor diameter were independent predictors of acute toxicity. Age, interval between two radiation treatment, prior RT dose to index tumor, anatomical location, and stage of the lesion were predictors of OS.[41]

Ohizumi *et al*. treated 44 such patients with cumulative radiation dose (prior RT DOSE + RERT DOSE) >80 Gy and found 5 years OS of 6%. Site of disease and overlapping field of <40 cm^2 were found to be significant prognostic factors for survival on multivariate analysis. Nasopharynx, larynx, and oropharynx were the favorable sites whereas the oral cavity, nasal cavity, and hypopharynx were the unfavorable sites. Severe late complications occurred in 11% of cases.[23]

A study by Wang and McIntyre reported excellent salvage outcomes by RERT in recurrent laryngeal cancer. The 5-year actuarial local control and survival rates were 60 and 93%, respectively. The majority of the survivors had relatively normal and functional larynx. Those who failed locally had total laryngectomy without significant postoperative complications.[42]

Tanvetyanon *et al*. examined a large single institution experience of 103 patients treated with RERT; patient with both comorbidity and organ dysfunction had the worst median OS (5.5 months) and those who had neither fared the best (59.6 months).[43]

Nagar *et al*. reported lower response rate, DFS, and OS in patients who received chemoradiotherapy as their first treatment versus radiotherapy alone. This finding suggests that there is development of chemoresistance also due to prior exposure to platinum-based concurrent chemo-radiotherapy and along with RERT dose escalation, modification in chemotherapy is also required.[24] Platinum-based CRERT does not significantly affect the outcome in various IMRT Series.[30,31,33]

Taxanes and targeted therapy have the potential to improve outcome in the platinum-resistant tumor, but further research is warranted.

Single institution study by Riaz *et al*. with largest cohort of HNC patient treated with RERT (IMRT in 78%) clearly showed that long-term survival is feasible in this setting, but there is a significant risk of toxicity. Overall rate of any grade 3 or higher toxicity was 31.3%. In 3 grades, 5 toxicities occurred, 2 due to the carotid blowout and one due to ORN of clivus. 7% of patients require surgery for ORN of the mandible, 4% of patients had grade 3 or higher hearing loss, 2 patients developed esophageal fistulas requiring reconstructive surgery. One patient developed unilateral blindness. Hence, a namogram was formulated to predict LRC after RERT in HNC patient recurrent stage, nonoral cavity subsite, absent organ dysfunction, salvage surgery prior to RERT, and dose more than 50 Gy were independently associated with improved LRC.[35] Performance status of the patient, interval from previous RT, comorbidity, volume of overlap with previous RT field were the prognostic factors for survival in different RERT studies.

Carotid blowout is the most fatal toxicity. Reported incidence of carotid blowout was 2.6% among 1554 patients receiving salvage RERT with 76% of these events proving fatal in Review by McDonald *et al*.[29] Incidence is more with patient treated with accelerated hyper fractionation and hyper fractionation with 1.5 Gy twice a day as compared to conventional fractionation (4.5% vs. 1.3%). Other risk factors for Carotid Blowout are total high local dose, complication of uncontrolled diabetes, tumor recurrence, chronic infection, chronic inflammation, and consequences of surgery.

Composite dosimetric measures to evaluate dose to carotid arteries were done by Garg *et al*. in their RERT study. 1/50 patient developed carotid blowout and the 1 cc and V 100 values were 120 Gy and 3.64 cc, respectively, for this patient.[44]

With modern radiotherapy techniques, side effects are less. A comparison of three-dimensional conformal radiation therapy (3DCRT) and IMRT in 38 patients undergoing CRERT with weekly carboplatin (area under the curve 2) and paclitaxel (50 mg/m^2) showed significantly greater late toxicity with 3DCRT compared with IMRT (44% vs. 7%).[45] A study by Lee *et al*. reported only one case of grade 2 osteitis, decreased the incidence of ORN, and no incidence of carotid blowout. Several institutional reports of IMRT for RERT have demonstrated favorable disease control and toxicity profile when compared with historical standards. Toxicities observed are the combined effects of prior multimodality treatment, salvage surgery, and concurrent systemic therapies.

Role of Brachytherapy in Reradiation

Brachytherapy holds a distinct advantage by giving highly conformal doses to gross disease with sparing of normal surrounding structures due to rapid fall of doses from the center of the source. This is the highest form of conformal radiotherapy but requires good experience on the part of the radiation oncologist. It is important to keep needles/tubes and doses away from vascular structures such as carotids, bone and cartilage, and also from neurovascular bundles. Oropharyngeal malignancy and isolated small flap recurrence can be handled well with reasonably good results.

Here, also a careful selection of the patient, proper mapping with endoscopy, and radiological investigation holds the key for better outcomes. Careful planning and keeping the doses received earlier by the normal tissues and time elapsed from first radiation are essential to prescribe the optimum dose and fractionation to target volume. Image-guided brachytherapy integrating PET-CT/magnetic resonance imaging/CT SCANS and mapping of disease volume onto planning scan could help to exactly delineate the gross disease to which minimal margins may be given. The other advantage is that if "brachy only" was carefully done it does not give the toxicities as expected by external radiotherapy even with modern techniques but applicable for a small superficial circumscribed T1 lesion, whereas other would need external radiotherapy first followed by brachytherapy boost.

Hepel *et al*. reported their experience in 30 patients treated with high dose rate brachytherapy. 1 and 2-year survival was 56% and 37%, respectively. Grade 3 and 4 complications were occurred in 16% of patients.[46] Intraoperative radiotherapy has shown promising approach in salvage of neck recurrences.[47]

A study by Levendag *et al*. reported better LRC with a combination of external beam radiotherapy (EBRT) and brachytherapy than EBRT alone. Actuarial survival at 5 years was 20% in both groups. Severe side effects were experienced by 28% of patients, but no treatment-related deaths occurred.[19]

Role of Systemic Therapy in Reradiation

Role of concurrent systemic therapy remains uncertain and is an area of active research and investigations. As locoregional failure is the predominant mode of failure, systemic therapy is mainly used as a radiosensitizer. There is no direct comparison between RERT versus CRERT. A study from The Netherlands has shown similar results with RERT alone when compared with contemporary CRERT series.[25]

Role of systemic therapy as an induction chemotherapy (IC) is under investigation as a prognostic tool.[48] Those who respond well to IC also showed a good response to CRERT. IC can also be used in recurrences <6 months from prior RT.

Tumor hypoxia is known for radioresistance and due to prior intervention; recurrent tumor is more hypoxic than the primary tumor in HNC. In a phase II multi-institutional trial tirapazamine – a hypoxic cell sensitizer has shown promising result concurrent with cisplatin and RERT.[49,50]

Targeted agents such as cetuximab and erlotinib have shown promising results in phase I and II studies and further research is warranted in this direction.

Conclusion

Though RERT is challenging it is feasible with favorable outcome in carefully selected patients. With higher recurrence rates in loco regionally advanced cancers, selection of patient after being properly mapped the disease extent and investigation remains the key to optimize outcomes keeping prognostic factors in mind. Outcome of RERT is better when given as an adjuvant after surgical salvage with or without concurrent systemic therapy. Involved field radiotherapy with small margins is the way forward to address these patients who need to be carefully planned keeping the tight constraints for surrounding critical dose-limiting structures.

Image guided brachytherapy alone or with latest techniques like IMRT/IGRT holds the key for better results though good expertize, is required for this technique.

IMRT with adaptation and careful replanning to reduce dose to surrounding avoidance structures and IGRT to confirm reproducibility of the plan are required, as the margins are tight around gross disease with extremely tight constraints.

Role of chemotherapy is still not clear but can be used concurrently with "targeted agents" holding great promise. Outcomes can be improved further by involving multidisciplinary team along with a focus on pre, intra, and post treatment rehabilitation, nutrition, speech therapy and voice rehabilitation, prevent aspiration to improve functionality, and cosmesis. Psychosocial problems are other area to deal with which would hugely impact patients well-being, especially who are going to survive longer after RERT.

Future Direction

With most of the recurrences being locoregional much needs to be done with properly conducted trials to optimize results

and answer the unanswered questions regarding appropriate doses, hypoxia and radioresistance, role of radiosensitizers, integration with chemotherapy, and improving surgical techniques.

Functional imaging agents like 3'-deoxy-3'-[18F]-fluorothymidine or 18fluoro-misonidazole may lend insight into tumor biology and better define the r GTV via hypoxia imaging and these radioresistant hypoxic regions if boosted with additional dose could further improve LRC. Reradiation tolerance of normal tissue needs to be redefined in IGRT era.

Surgical outcomes also need relook in the era of robotics and minimally invasive surgery for better cosmetic and functional outcome. Good flaps taken allow reradiating better with higher doses, which in turn can improve outcomes. With salvage surgery definitely improving results followed by reradiation, telerobotic surgery with experienced surgeon anywhere in the world can remotely log into the local center and operation by robots is practically possible now and holds great promise for future.

Effective chemotherapy probably holds the key, which targets the recurrent tumor tissue only. This is one area requiring extensive research and trials since most of the refinements in surgery and radiotherapy have plateaued, and any further improvement from these modalities is going to contribute little to improve outcomes. Hence, the search for this effective targeted agent is long overdue which could be used for induction, concurrently or in adjuvant setting working both in hypoxic and radioresistant environment.

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Conflicts of interest
There are no conflicts of interest.

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