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SYSTEMATIC REVIEW

A systematic review and practical considerations of stereotactic body radiotherapy in the treatment of head and neck cancer

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Objectives: Stereotactic radiotherapy (SBRT) is gaining popularity although its use in head and neck cancer (HNC) is not well defined. The primary objective was to review the published evidence regarding the use of stereotactic radiotherapy in HNC.
Methods: A literature search was performed by using MEDLINE and EMBASE databases for eligible studies from 2000 to 2019 and 26 relevant studies were identified.
Results: Literature demonstrates a heterogeneous use of this technique with regards to patient population, primary or salvage treatment, dose fractionation regimens, outcomes and follow-up protocols. Carotid blow out syndrome is a risk as with other forms of reirradiation but alternative treatment regimens may reduce this risk.
Conclusion: At present there is a lack of evidence regarding SBRT as a primary treatment option for HNC and definitive answers regarding efficacy and tolerability cannot be provided but there is growing evidence that SBRT reirradiation regimens are safe and effective. In lieu of evidence from large Phase III trials, we define appropriate organ at risk constraints and prescription doses, with accurate plan summation approaches. Prospective randomised trials are warranted to validate improved treatment outcomes and acceptable treatment morbidity.
Advances in knowledge: This article provides a comprehensive review of evidence of use of stereotactic radiotherapy in HNC site (either as a primary treatment or as reirradiation). We also provide an evidence-based approach to the implementation and practical consideration of stereotactic radiotherapy in HNC.

INTRODUCTION

Head and neck cancer (HNC) is the sixth most common malignancy worldwide.[1] A combination of surgery, radiotherapy ± systemic therapy is used to control locally advanced disease. Despite technological improvements in surgery and delivery of radiotherapy, locoregional recurrence remains a significant problem. In 20–30% of locally advanced cases, the disease recurs after primary treatment.[2,3] Locoregional relapse is more common than distant relapse; it represents 50–60% of first failures in both human papilloma virus (HPV) positive and HPV negative squamous cell HNC.[4] As locoregional progression is the most common cause of death, retreatment with radical dose to achieve local control (LC) has the potential to impact survival.[5]

Retreatment of unresectable recurrent HNC or a second primary cancer which develops in a previously irradiated area always represents a clinical challenge. Historically, the rate of reirradiation has been low because of unsatisfactory outcome and significant toxicity.[6–8] However, the use of modern treatment technologies is likely to improve treatment outcome, decrease toxicity and improve quality of life in a selected group of patients.

Stereotactic ablative body radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), is a method to

accurately deliver high dose external beam radiotherapy in a few fractions to a small, well-defined target.[9–11] SBRT is the standard of care (level one evidence) in medically inoperable early stage non-small cell lung cancer[12] and has also gained popularity in other disease sites; early stage prostate cancer (level two evidence)[13,14] and oligometastatic disease from other primary sites (level two evidence).[15,16]

However, the use of SBRT in HNC has not been well studied and there is paucity of such data in literature. This article reviews the current status of SBRT in the management of HNC and discusses the practical aspects of implementing SBRT for HNC.

METHODS

Literature search

A literature search was performed by a professional librarian using MEDLINE and Embase databases for eligible studies from January 2000 to November 2019. The search was performed using the terms 'head and neck', 'stereotactic radiotherapy', 'SABR', 'SBRT'. Studies were also considered and added manually after reference checking, if meeting the inclusion criteria. Duplicating or overlapping studies were removed. Search methodology has been added to the Supplementary Material 1. At the time of data collection, checks were made to ensure that there was no existing or ongoing systematic review of this topic.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies encompassing stereotactic radiotherapy in HNC and (2) studies published in English language.

Exclusion criteria included: (1) studies which reported exclusively SBRT use as a boost to the primary external beam radiotherapy in HNC were excluded.

Data extraction & quality assessment

As part of our review, two authors (MSI and NSW) independently evaluated the quality of the studies according to the National Institute of Health tool.[17] Grey literature was included.

The protocol for our review is in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[18] A flowchart of the search is shown in Figure 1 and a full protocol of this systematic review is available on application to the corresponding author.

RESULTS

The literature search yielded a total of 1236 records (552 from Medline; 684 from Embase). A further 20 studies were manually added after reference checking. Out of the total 1256 studies, 1175 were excluded after the exclusion criteria limits were applied based on titles and abstracts. After applying the inclusion criteria and removing duplicate or overlapping studies, a further 55 were removed. This left 26 studies; 5 studies relating to SBRT in primary HNC and 21 studies to SBRT as a reirradiation treatment for recurrent HNC.

The selected studies (n = 26; Tables 1 and 2) were heterogeneous in terms of patient population, dose regimens, outcome parameters, measurement of toxicity and length of follow-up. With the current data, a meta-analysis was not possible, therefore a descriptive data synthesis was performed through a narrative and tabulated approach.

SBRT in primary HNC treatment

The evidence of use of SBRT in primary HNC is scarce; there are very few reports (Table 1) on the use of SBRT as a primary treatment for patients deemed unfit for standard radical dose fractionation. In general, patients considered unfit for standard radical treatment are typically treated with less effective

Figure 1. The flowchart of systematic search

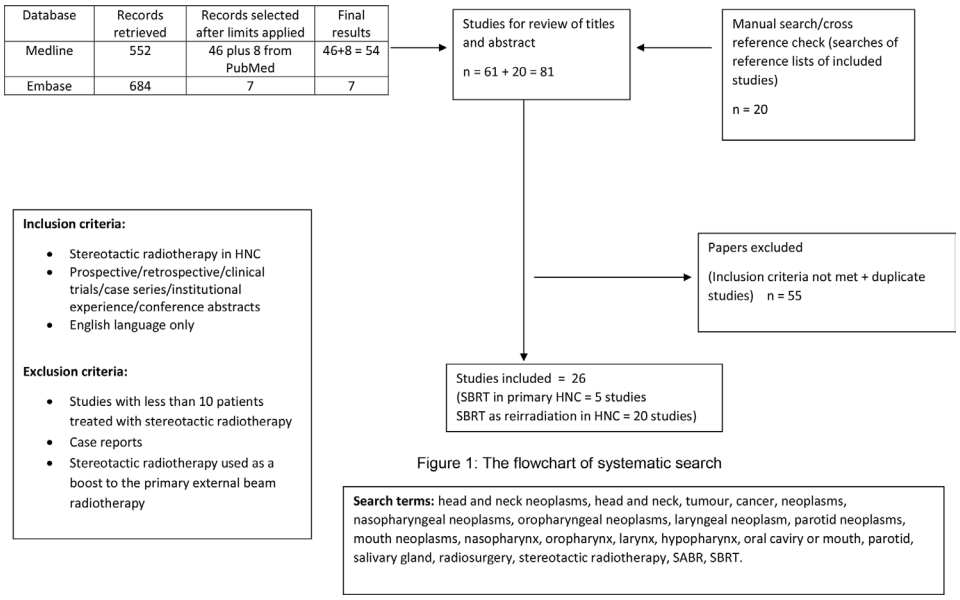


Table 1. A summary table of studies involving SBRT in primary HNC (in chronological order—year of publication)

Study [year of publication]	Type of study	Number of patients	SBRT dose	Outcome	Toxicity	Study Quality rating**
Gogineni et al 2019[19]	Case series	66	40 Gy in 5 f	At med f/u of 15m, LCR 68% Med time to LF 28.3m	G3 toxicity 3% No G4-5 toxicity	Fair
*Schwatz et al 2017[20]	Phase one trial	20 (early glottic cancer only)	50 Gy in 15 f 45 Gy in 10 f 42.5 Gy in 5 f	1-y local DFS for the full cohort was 82%. OS 100% at last follow-up.	Maximum acute toxicity: G2 hoarseness and dysphagia one late toxicity—required tracheostomy	Good
Vargo and Ferris et al 2014[21]	Case series	12	44 Gy in 5 f	1-y PFS and OS were 69 and 64%	Acute G3 dysphagia 8% Late G3 mucositis 8%	Poor
Kawaguchi et al 2012[22]	Case series	14	35–42 Gy in 3–5 f	CR = 36%, PR = 74% At med f/u of 36m, LCR 71.4% and OS 78.6%	No acute $G \geq 3$ toxicity	Fair
Siddiqui et al 2008[23]	Case series	10 primary HNC	13–18 Gy in 1 f Or 36–48 Gy in 5–8 f	1-y tumour control rate 83.3%. 1-y OS 70%; 2-y OS 50%	G3 cataract = 1 G3 pain = 1	Fair

DFS, disease free survival; G, grade; HNC, head and neck cancer; LCR, local control rate; LF, local failure; OS, overall survival; PFS, progression free survival; SBRT, stereotactic body radiation therapy; *f*, fractions; f/u, follow up; *m*, months; med, median.

[a]feasibility study of hypofractionated SBRT for early-stage glottis cancer cTis-T2N0M0. (In the table, there is asteric* but here in the footnote, it is a. Please keep consistency)

[b]Quality rating using study quality assessment tools NIH.[17] (In the table, there is double asteric ** but here in the footnote, it is b. Please keep consistency. Thanks)

palliative regimens; the reported median overall survival (OS) is only 6 months in this patient population.[34]

Recently, Gogineni et al[19] presented their experience of treating 66 medically unfit patients with HNC treated with SBRT. Median age of the patient cohort was 80 years with a median Charlson Comorbidity Index score of 12% and median geriatric assessment (G8) score was 11, representing a vulnerable group of patients. Median planning target volume (PTV) was 82 cm^3, with 40 Gy delivered in five biweekly fractions to the gross tumour volume (GTV), with 30 Gy to the clinical target volume (CTV). Nearly half of patient population (48%) also received concurrent cetuximab or chemotherapy. With a median follow-up of 15 months (range 3–88 months), LC was 68% with a median time to local failure of 28.3 months. Regional and distant control rates were 73 and 76% respectively. One-third (32%) developed infield failures and four patients had marginal failures. 26 patients had at least 1 year follow-up, and disease free survival was 88% in these patients. The treatment was well tolerated as there was no case of grade 4/5 toxicity and only two patients (3%) developed grade 3 toxicity. These outcomes with such low incidence of significant toxicity are quite promising in this medically unfit patient population.

In a geriatric oncology study published by Vargo et al,[21] primary SBRT was employed in medically inoperable elderly patients (median age 88 years). 12 patients were treated with 44 Gy in 5 fractions delivered on alternating days with concurrent cetuximab. PTVs were relatively small with volumes ranging from 15 to 248 cm^3 and a median of 41 cm^3. The outcome was very promising with acceptable toxicity. Compliance was good with 10 patients out of 12 completing the treatment as prescribed. The 1-year actuarial local progression free survival (PFS) and OS were 69 and 64% respectively. One patient experienced acute grade 3 dysphagia and one patient developed late grade 3 mucositis; there were no grade 4/5 toxicities. The authors concluded that SBRT provided encouraging survival with low toxicity in elderly patients.

A feasibility study by Siddiqui et al,[23] evaluated the role of either single fraction of 13–18 Gy or 5–8 fractions of 36–48 Gy radiotherapy in a heterogeneous population of patients including primary, recurrent or metastatic HNC. Tumour control rates at 1 year follow-up were 83.3, 60.6 and 75% in the primary, recurrent and metastatic groups respectively. Median OS was 28.7 months for primary cancers, 6.7 months for recurrent and 5.6 months for the metastatic group. In this study, 10 patients with primary HNC were treated with 18–48 Gy in 1–8 fractions of SBRT. 1-year LC was 83% and 1-year OS was 70%. There was only one instance of grade 3 cataract and one instance of grade 3 pain.

Table 2. A summary table of studies involving SBRT in reirradiation of HNC (in chronological order—year of publication)

Prospective studies and early phase trials						
Study [year of publication]	**Type of study**	**N (received SBRT)**	**SBRT dose**	**Outcome**	**Toxicity**	**Study Quality rating****
Mesko 2019 et al[24]	Case series	54	Mean reirradiation (there shouldnt be a line underneath. This is continuous)	1-y PFS 48% & OS 84% (There shouldnt be a line underneath. It should be continuous)	Overall G3/4 toxicity 2% with SBRT (this was much less as compared to 28% with IMRT & 38% with PT; $p < 0.001$)	Fair
			BED (α/β 10) was 76.6_8.7 Gy (patients treated with SBRT, IMRT or PT) Again there shouldnt be a line underneeth this.	2-y PFS 27% & OS 72% Again no line underneath this. This is all continuous		
				No significant difference in outcomes with SBRT, IMRT or PT		
Vargo et al 2015[25]	Phase II trial	50	40–44 Gy in 5 f	Med OS 10m There shouldnt a line underneath. It gives a wrong impression of differnt category.	G3 mucositis 2%; G3 skin 2% No line underneath this either.	Good
				1-y local PFS 60%; 2-y PFS was 37%	G3 dysphagia 2%; Late G3 6%	
Lartigau et al 2013[26]	Phase II trial	60	36 Gy in 6 f	CR 49%; PR 20.4%; SD 22.5% No line underneath	G3 skin 12% No line underneath please	Good
				Med PFS 7.1m & OS 11.8m; 1-y OS 47.5%	G5 = 1.6%	
Heron et al 2009[1]	Phase I trial	25	five dose tiers up to (NO line underneath)	OR 17%; SD 48%	No G3/4 DLT	Good
			44 Gy in 5 f	Med OS 6m		
Retrospective studies						

(Continued)

Table 2. (Continued)

Orlandi et al 2019[27]	Case series	38	29–30 Gy in 5.8–9 Gy per f	1:2-y OS 64.1% (95% CI, 49.6–82.9%) (No line underneath)	No separate toxicity information on SBRT patients	Good
				5–y OS 23.3% (95% CI, 10.8–50.2%)		
Vargo and Ward et al 2018[28]	Case control	197	Med 40 Gy (range 16–50) in med 5f (range 1-8)	2-y OS 16.3% No line underneath please	New acute $G \geq 3$ 11.7% No line underneath	Good
				Med OS 7.8m	Acute $G \geq 4$ 0.5% No line underneath	
					G5 0.5%	
Ling et al 2016[29]	Case series	291	Med 44 Gy (16–52.8)	No information available	Acute $G \geq 3$=11.3% No line underneath please	Fair
					Late $G \geq 3$ 18.9%. G5 CBOS 1.3%	
Teckie et al 2016[30]	Case series	48	Med 30 Gy in 5 f (32% received ≥ 8 Gy per f)	CR 10%; PR 69%; SD 16%; PD 3% No line underneath	G3 = 2% No line underneath please	Fair
				1-y local PFS 50%. Med OS 7.2m	Late G3 = 3%	
Yamazaki et al 2016[31]	Case control	25	32 Gy in 5 f	1-y LCR 63.8% No line underneath	$G \geq 3$=24% No line underneath	Fair
				1-y OS 36.3%	G5 8%	
Quan et al 2016[32]	Case series	18	40–44 Gy in 5 f	No information available	No G4 toxicity No line underneath	Poor
					G3 mucositis 6%	
Kress et al 2015[33]	Case series	85	Med 30 Gy ([16–28,30–41]) in med of 5 f (3 – 5)	CR 36%; PR 33%; SD 9% No line underneath	G3 2.4%. No G4 toxicity No line underneath	Fair
				Med PFS 8.6m & OS 12.2m; 1-y OS 51.1%: 2-y OS 24%	Late $G \geq 3$ 5.9%	

(Continued)

Table 2. (Continued)

Karam et al 2012[42]	Case series	18	Med 30 Gy in 5 f	Med OS, PFS & LRC were 11.5, 3.5 & 5.5m. No line underneath	*G* ≥ 4 aspiration pneumonia 3% No line underneath	Fair
				2-y OS, PFS and LRC were 39%, 24% & 53%	Late severe soft tissue necrosis 22%	
Iwata et al 2012[35]	Case series	51	med 35 Gy (20–41.5) in 1–5 f	Med LRC 9.5m & OS 14.5m No line underneath	*G* ≥ 3 23% No line underneath	Fair
				1-y LCR & OS were 62% & 67%	G4 4%	
Comet et al 2012[36]	Feasibility study	40	36 Gy in 6 f	CR 44%; PR 35%; SD 20.6% No line underneath	G3 10.3%	Good
				Med OS 13.6m; 1-y OS 58%; 2-y OS 24%		
Cengiz et al 2011[43]	Case series	46	Med 30 Gy ([18–28,30–35]) in med 5 f (1 – 5)	CR 27%; PR 29.8%; SD 27% No line underneath	Acute G3 dermatitis 2.2% No line underneath	Good
				Med OS 11.9m; 1-y PFS & OS were 41% & 46%	G3 mucositis 2.2%; CBOS 17.3%*	
Unger et al 2010[37]	Case series	65	Med 30 Gy ([20–28,30–33,35]) in 2–5 f	CR 54%: PR 27%: No response 20% NO line underneath	Acute ≥ G3 11% No line underneath	Good
				Med OS 12m	Late G4 9%	
Rwigema et al 2010[38]	Case series	85	Med 35 Gy ([15–28,30–41,44–46])	CR 34%; PR 34%; SD 20%; PD 12% No line underneath	G3 xerostomia = 2%; G3 pain = 1% No line underneath	Fair
				2-y LRC & OS were 48.5% & 16.1%; Med OS 11.5m	G3 dysgeusia = 1%	
Seo et al 2009[47]	Case series	35	med 33 Gy ([20,24–28,30–33,35–41,44–46,48]) in 3–5 f	CR 72%; PR 16%; SD 3% No line underneath	Late *G* ≥ 4=14% No line underneath	Fair
				5-y PFS 74%; 5-y OS 60%	G5 = 6%	

(Continued)

Table 2. (Continued)

Roh et al 2008[49]	Case series	36	18–40 Gy (med 30 Gy) in 3–5 f	CR 42.9%; PR 37.1%; SD 8.6%; PD 11.4%	G3 36% NO line underneath	Good
					1 G5 soft tissue & skull base necrosis	
Wu et al 2007[39]	Case series	90	18 Gy in 3 f or 48 Gy in 6 f	1, 2 & 3-y DSS and PFS were 82.6%, 74.8%, 57.5 and 72.9%, 60.4%, 54.5% respectively	*G* ≥ 3 19%; Mucosal necrosis 9% No line underneath	Good
					G5 bleeding 2%; Brainstem necrosis 3%	
Voynov et al 2006[40]	Case series	24	Med 24 Gy ([10–28,30–36]) in med 5 f (3-16)	Med duration of LC 12m. NO line underneath	G3 mucositis = 4% No line underneath	Fair
				Med OS 12m; 2-y LC & OS 26% & 22%	No G4-5 toxicity	

CBOS, carotid blow out syndrome; CR, complete response; DLT, dose limiting toxicity; DSS, disease specific survival; G, grade; IMRT, intensity modulated radiotherapy; LC, local control; LRC, locoregional control; OR, objective response; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; PT, proton therapy; SD, stable disease; f, fraction(s); m, months; med, median; n, number of patients with SBRT; y, year.

[a]fatal CBOS occurred only in those patients where tumour was surrounding carotid arteries (CA) and CA received full prescribed dose. (Again, in the table, there are asteric * and ** but here these are a and b. Please correct. Thanks)

[b]Quality rating using study quality assessment tools NIH[17]

Kawaguchi et al[22] published their experience of treating 14 patients with HNC with SBRT. Median age of the patient cohort was 73 years. Radiation dose fractionation was 35–42 Gy in 3 to 5 fractions. Five patients had complete responses and in the remaining nine patients, there was partial response. With a mean follow-up of 36 months, LC was 71.4% and OS 78.6%. There was no incidence of acute grade ≥ 3 toxicity. One patient developed grade 3 osteoradionecrosis, 6 months after treatment (patient had reirradiation after local recurrence).

A small feasibility study of utilising SBRT for early-stage glottic cancer involving 20 patients showed that 42.5 Gy in 5 fractions yielded comparable results as compared to standard conventional radiotherapy, 50 Gy in 15 fractions.[20]

Summary and limitations of SBRT in primary HNC

There is lack of evidence of use of stereotactic radiotherapy in primary HNC and therefore cannot be recommended as standard of care. The previous studies have been small case series and a phase 1 trial with inherent methodological weaknesses (Table 1).

SBRT as reirradiation in HNC

The main evidence for the role of SBRT in HNC is the context of reirradiation. Table 2 summarises the findings of studies involving SBRT in reirradiation of HNC.

Prospective studies and early phase trials

In a phase 1 trial by Heron et al,[1] 25 patients were treated in 5 dose tiers up to 44 Gy in 5 fractions in 2 weeks. There was no grade ≥3 dose limiting toxicity and the median time to disease progression was 4 months, with a median OS of 6 months.

Two phase 2 trials[25,26] treated a total 110 patients with recurrent HNC. In both trials, concomitant cetuximab was also given. SBRT was given in 5–6 fractions on alternate days with doses ranging between 36 and 44 Gy. The median OS was 10 and 11.8 months; 1 year OS was 40 and 47.5%. Vargo et al[25] reported quite a low incidence of acute and late grade ≥3 toxicities which included one patient each with grade 3 mucositis/skin, grade 3 dysphagia, and grade 3 late dysphagia and 2 aerodigestive fistulas. Lartigau et al[26] reported one toxic death from haemorrhage and malnutrition. Grade ≥ 3 toxicities were as follows: cutaneous 10%, mucositis 7%, dysphagia 5%, xerostomia 3%, oral cavity fistula 1% and dysgeusia 2%. Overall, these two trials showed promising results with acceptable toxicities, especially considering that in both of these trials, concomitant cetuximab was also given which is prone to cause cutaneous toxicities.

At the 2019 ASTRO meeting, preliminary clinical outcomes of prospective registry were presented[24], treating 167 patients with either IMRT (n = 67), SBRT (n = 54) or proton therapy, PT (n = 44). There was no significant difference in patient demographics in these three groups. Overall median follow-up was 18.2 months. The median time to locoregional failure and PFS were 23.2 months (95% CI:13.3–33.1) and 13.6 months (95% CI:9.2–18.0), respectively, and there was no significant differences noted in three groups. The incidence of overall acute grade 3–4 toxicity rates were 19% (28% IMRT, 2% SBRT, 38% PT; $p < 0.001$). Late grade 3–4 toxicity occurred in 9% of patients. In this study, PT failed to show superiority over photon therapy, and the incidence of toxicity was less with SBRT. [Reference not required now. Already provided, ref number 27]

Retrospective studies

Table 2 summarises all included studies. Here, we describe select studies that offer the most insight. Orlandi et al[27] presented long-term results of AIRO, a multi-institutional study of reirradiation for recurrent or second primary HNC. Of total 159 patients, 38 (24%) were treated with SBRT (a total dose of 29–30 Gy; 5.8–9 Gy per fraction). There were survival differences noted in patients treated with different radiotherapy techniques; 1:2- and 5–year OS estimates were 83.5% (95% CI, 74.6–93.4%) and 64.3% (95% CI, 51.8–80.0%) in patients treated with IMRT, and 64.1% (95% CI, 49.6–82.9%) and 23.3% (95% CI, 10.8–50.2%) in patients treated with SBRT, respectively. However the authors did admit that their SBRT doses were less than those suggested by other reports which allude to possible dose–response relationships.

Vargo et al[28] published retrospective multi-institutional analysis on 414 patients (217 treated with IMRT and 197 with SBRT) from 8 institutions. The 2 year OS rate was 35.4% (95% CI, 29.3–42.8%) for IMRT and 16.3% (95% CI, 11.7–22.7%) for SBRT ($p < 0.01$). The authors performed subset analysis and IMRT was associated with improved OS in recursive partitioning analysis (RPA) Class II. However, while taking known prognostic factors of tumour bulk and SBRT dose into account, on further analysis there was no significant difference in OS between patients with small tumours treated with IMRT or SBRT dose ≥35 Gy. There was less incidence of acute grade ≥4 toxicity with SBRT than with IMRT (0.5% *vs* 5.1%, $p < 0.01$).

Kress et al[33] reported outcomes on 85 patients treated with a median dose of 30 Gy (range:16–41 Gy) in median 5 fractions (range: 3–5). The median interval from previous radiation was 32 months. Complete response was achieved in 36% and partial response in further 33% of patients. The median PFS and OS were 8.6 and 12.2 months respectively. 1-year OS was 51.1% and 2 year OS was 24%. The incidence of acute grade 3 toxicity was 2.4% and late grade ≥3 toxicity was 5.9%. Time interval from previous radiation to SBRT of ≥2 years was associated with improved OS.

SUMMARY AND LIMITATIONS OF SBRT AS REIRRADIATION IN HNC

Although there is no phase 3 randomised control trial of the use of SBRT as reirradiation in HNC, however there are phase 2 trials and large collaborative observational studies that indicate a role for SBRT in light of few other treatment options. Also to note that majority of these studies carry inherent methodological weaknesses given the retrospective nature. In light of some positive results, a phase 3 trial is warrented.

Toxicity of SBRT as reirradiation in HNC

Irrespective of reirradiation technique, radiotherapy in a previously irradiated field in head and neck region is associated with potentially significant toxicity, and therefore this merits separate discussion. One of the largest retrospective studies involving 291

patients by Ling et al[29] reported 1 patient dying as a result of acute toxicity and 2 patients developing grade 4 toxicities. In absence of active disease, three patients (1.3%) died of late carotid blow out syndrome. Acute grade ≥3 toxicities rate was seen in 11.3% and late grade ≥3 toxicities identified in 18.9%.

Toxicity: carotid blow out syndrome (CBOS)

CBOS is a fatal complication and is a concern in irradiation in particular with SBRT. In a recently published study, Gebhardt et al[44] described the risk of CBOS. In a patient population of 75 with reirradiation of HNC (median reirradiation interval was 20 months, and prior median radiation dose was 70 Gy), there were a total of 4 bleeding events (5.3%) within a median follow-up of 8 months (range:1–19 months). Two patients had mucosal bleeds which required embolisation of carotid artery branches but the other two patients died from complications from CBOS. Dosimetrically, radiotherapy dose to 1 cm^3, 2 cm^3 or median dose to the carotid artery was not found to be significantly associated with bleeding events. It was important to note that there was no case of CBOS when maximum dose (D0.1cm^3) to carotid artery was less than 47.6 Gy though there was a trend towards increased risk of bleeding and radiotherapy dose to 0.1 cm^3 of the carotid artery ($p = 0.080$).

A retrospective study by Cengiz et al[43] reported CBOS in 17.3% and out of these, seven patients (15.2%) died of bleeding. This fatal carotid bleeding occurred only in those patients where tumour surrounded carotid arteries and the carotid arteries received full prescribed radiotherapy dose. Later on, Yazici et al[45] from the same centre, looked at the rates of CBOS in two different SBRT protocols, sequentially and on alternate days. This study reported median radiation dose in cases of CBOS rather than the maximum dose to the carotids. The authors found that the median dose received by the carotid artery in patients who developed CBOS was 36.5 Gy (range:34–42.8 Gy) as compared to the median dose of 34.7 Gy (range:0–44 Gy) in the patients who didn't develop CBOS ($p = 0.15$). The incidence of developing CBOS from SBRT fractions on alternate days was significantly lower than SBRT daily fractions. It was also noted that CBOS didn't occur in any of 75 patients with a maximum carotid artery radiation dose <34 Gy in 5 fractions.

A Japanese multi-institutional matched-cohort study showed 12 cases of CBOS per 60 cases without CBOS cases.[46] The median SBRT dose regimen was 30 Gy in 5 fractions (range:15–39 Gy in 3–8 fractions). The significant finding was that only patients with carotid artery invasion of >180°, *i.e.* tumour invasion of more than a half semicircle around the carotid artery developed CBOS (12/50, 24%). There was not a single incidence of CBOS in patients <180° carotid invasion (0/22, 0%, $p = 0.03$). It was also noted that presence of ulceration and lymph nodal radiotherapy were risk factors of developing CBOS. Based on their findings, the authors developed a CBOS risk classification system based on risk factors; carotid invasion more than 180°, presence of ulceration and lymph node area irradiation.

In a recently presented abstract by Sari et al[48] in ASTRO 2019 meeting, the incidence of CBOS was 15% with a SBRT dose ranging 15–65 Gy. The risk of CBOS development was significantly higher in patients with a median maximum carotid dose of more than 33 Gy ($p = 0.02$), and in those patients where the carotid circumference receiving at least 30 Gy was more than 180° ($p = 0.03$).

Other toxicities

In regard to severe late toxicities beyond CBOS, the literature is sparse but risks can be extrapolated from reirradiation studies in HNC. Ward et al[50] published a toxicity prediction tool. They conclude that even though severe late toxicity is a potential concern, evidence suggests that locoregional and distant progression and death even without failure or toxicity are far larger concerns than the incidence of severe late toxicities (all below 5%).

PATIENT REPORTED OUTCOMES WITH SBRT IN HNC

Gogineni et al[51] published patient reported outcomes following SBRT in previously irradiated HNC. The radiation dose fractionation was 40 Gy in 5 fractions for definitive treatment and 35 Gy in 5 fractions as a post-operative treatment. The median volume treated was 61 cm^3. Quality of life (QOL) data were reported as per MD Anderson Dysphagia Inventory (MDADI), Symptom Inventory head and neck (MDASI-HN) and Xerostomia questionnaire. QOL data showed that patients with reirradiation to the skull base, maintained stable MDADI scores. However, in patients where the reirradiation site was the aerodigestive tract, a reduction in MDADI score was seen. MDASI-HN scores showed an increase in patient-reported symptoms in acute settings after treatment in the skull base treatment group, and in the aerodigestive tract group there was delay before symptoms developed. Almost all patients demonstrated increase in xerostomia scores after treatment; however, there was a trend for an improvement in xerostomia scores in patients with skull base tumours during the long-term follow-up.

PRACTICAL CONSIDERATIONS OF IMPLEMENTATION OF SBRT IN HNC

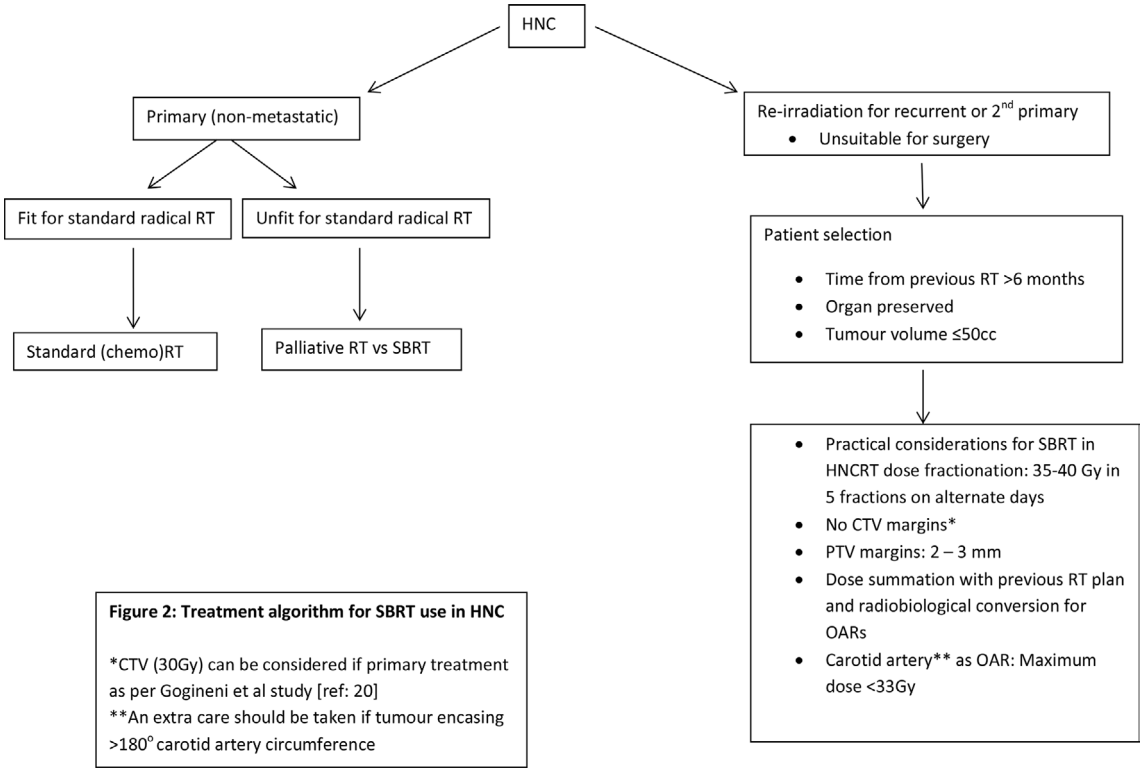
Latest NCCN Guidelines® on HNC state, "When using SBRT techniques for reirradiation, careful selection of patients is advised. The best outcomes are seen in patients with smaller tumours and no skin involvement. Caution should be exercised in cases of circumferential carotid artery involvement.".[52]

Here, we summarise the practical considerations of SBRT implementation in HNC; the level of evidence (LoE) was determined using the Centre for Evidence-Based Medicine, University of Oxford, criteria.[53] We propose here a suggested SBRT algorithm based on our literature review (Figure 2).

1. Patient selection [LoE=4]

Ward et al[54] described the American Multi Institutional ReIrradiation (MIRI) collaborative approach towards refinement of patient selection for reirradiation in HNC based on RPA. Their RPA resulted in three distinct categories; Class I consisted of those patients where the time period was more than 2 years from

Figure 2. Treatment algorithm for SBRT use in HNC. HNC, head and neck cancer; SBRT, stereotactic body radiation therapy.



the first treatment with resected tumour (2 year OS 61.9% with 95% CI 51.9–73.9%), Class II consisted of patients with more than 2 years from the first treatment but unresected tumour or time period of less than 2 years but with organ preserved (2 year OS 40.0% with 95% CI:33.9–47.2%) and Class III represented the patients with time period of less than 2 years from their first treatment along with organ dysfunction (2 year OS 16.8%; 95% CI 10.0–28.1%). This prognostic RPA classification was validated on a subsequent comparative study between IMRT and SBRT 30 (This should be reference number 30)]. This collaborative group has also published a nomogram to predict severe late toxicities in HNC reirradiation in general, not specific to SBRT technique. The nomogram was based on patient's six characteristics at the time of reirradiation; 1) dose of radiotherapy during first course, 2) organ dysfunction, 3) any surgery, 4) tumour site, 5) age, 6) recurrence or second primary. The authors reported that the risk of disease progression or death is approximately four times more likely than late toxicity, indicating that this model should be used to guide consent for the intervention, and recommended against deintensification of reirradiation dosage, which may compromise survival further.[41]

Based on this analysis, and our interpretation of the literature, the patients suited for SBRT are:

- Ideally >2 years from the first treatment but certainly >6 months from previous treatment
- Resected tumour
- If unresected tumour, functional, preserved organ

2. Optimal radiation volume [LoE = 4]

A few studies have described a cut-off value of PTV volume as a prognostic factor. Vargo et al[55] found that the tumour volume >25 cm^3 remained a significant predictor of inferior survival and tumour control. It was also associated with significantly more acute toxicity ($p = 0.017$) but no difference in late toxicity. Sari et al[48] reported that patients with smaller GTV size (≤50 cm^3) had significantly better survival outcome in a 162 patient cohort who received reirradiation.

3. Dose fractionation [LoE = 4]

A report of the American Association of Physicists in Medicine Working Group produced recommendations on optimal dose fractions of SBRT for locally recurrent previously irradiated HNC. The authors suggested that there was a dose–response relationship with superior outcome for doses of 35–45 Gy in five fractions compared with <30 Gy.[56] Orlandi et al[27] showed that SBRT with doses 29–30 Gy in five fractions was associated with less survival as compared to IMRT (45–70 Gy). Similarly, Rwigema et al[38] also showed that there was significantly lower locoregional control with <35 Gy than with ≥35 Gy ($p = 0.014$). Vargo et al[55] documented that treatment duration <14 days was associated with significantly improved recurrence-free survival but it was at the expense of increased late toxicity ($p = 0.029$).

Based on these studies, we suggest dose fractionation 35–40 Gy in 5 fractions, either twice a week or on alternative days.

4. Radiotherapy voluming/margins [LoE=4]

It is recommended that only involved disease be irradiated with no elective nodal treatment during reirradiation.[57,58] No CTV was added in AIRO study.[27] A prospective study by Mesko et al[59] reported data on 405 treatment fractions of HNC SBRT reirradiation in 79 patients. The authors reported that in order to determine PTV margins, the location of radiation should be taken into consideration, *e.g.* PTV margins of 1.5–2.0 mm may be sufficient in the skull base region while PTV margins of 2–2.5 mm may be necessary for neck and mucosal targets. Bearing in mind, this recommendation was based on daily cone beam CT (CBCT) and ExacTract for positioning agreement. Based on institutional experience, an isotropic PTV margin of 3 mm can be justified or reduced to account for critical OARs in proximity.

5. Dose prescription [LoE=5]

As with all SBRT techniques reduced treatment margins and high conformity are paramount to minimise normal tissue damage, this is usually accompanied by prescriptions to 95% of the PTV volume with increased hotspots, commonly >120% within the GTV. Our literature review uncovered little detail alluding to optimal prescription. Mesko et al recommended that at least 100% of the target be covered by 95% of the prescription dose, normalising to 95% or 90% isodose depending on target location.[59]

6. Dose summation in reirradiation and OAR dose constraints [LoE=5]

Optimal dose constraints for OARs are unknown in reirradiation for SBRT HNC. To ensure previously delivered doses are properly accounted for, radiobiological conversion and summation should be carried out. Gogineni et al[51] reported dose constraints with SABR reirradiation for what they termed $OAR_{extreme}$, defined as organs that approached their maximal radiation tolerance after the initial course of radiation (although explicit values were not provided). 60 patients were treated with these constraints and demonstrated low levels of toxicity.

(Table 3)provides indicative maximum cumulative BED and EQD2 values received by these patients (using an α/β ratio of 3 Gy). In reality, actual cumulative doses will likely have been lower, as the initial OAR doses will in most cases would not have received the full tolerance dose but approaching it.

The spinal cord tolerance used by Gogineni et al[51] seems conservative as the spinal cord is known to demonstrate recovery of initial radiation damage. Nieder et al[60] suggest a cumulative BED tolerance of 135 Gy for standard retreatments (using α/β of 2 Gy) presents a relatively low risk. This corresponds to a cumulative EQD2 of 67.5 Gy_2. However, the spinal cord has been shown to have a strong dependence on dose per fraction (α/β of 0.87 Gy[61]). This is an additional consideration if the cord receives high dose per fraction from a SABR retreatment.

Table 3. Maximum cumulative BED and EQD_2values (using an α/β ratio of 3Gy). These calculations are based on 65 Gy in 30daily fractions as a primary treatment and 35-40 Gy in 5 fractions as SBRTreirradiation.

			Primary treatment		Reirradiation			
Organ at Risk	**DVH Parameter**	**α/β**	**Prescription dose (Gy)**	**Fractions**	**Constraint dose [Gy]**	**Fractions**	**Constraint BED [Gy3]**	**Constraint EQD2 [Gy3]**
Carotid artery	Maximum dose	3	65.0	30	32.5	5	214.9	128.9
Lens	Maximum dose	3	10.0	30	5	5	17.8	10.7
Mandible	Maximum dose	3	65.0	30	20	5	158.6	95.2
Optic chiasm	Maximum dose	3	50.0	30	25	5	144.4	86.7
Optic nerves	Maximum dose	3	50.0	30	25	5	144.4	86.7
Larynx	Mean Dose	3	54.0	30	15	5	116.4	69.8
Cochlea	Mean Dose	3	45.0	30	15	5	97.5	58.5
Retina	Mean Dose	3	45.0	30	15	5	97.5	58.5
Temporal tips	Mean Dose	3	54.0	30	5	5	93.1	55.8
Skin	D10cc	3	65.0	30	39.5	5	255.5	153.3
Thyroid lamina	Maximum dose	3	65.0	30	30	5	201.9	121.2
Spinal cord								54.0
Brainstem								54.0

Based on these calculations, Gogineni et al[51] allowed accumulative EQD2 of 86.7Gy3 for the optics; this seems high if conventional recovery is assumed and this would exceed tolerances for standard head and neck retreatments.

Ideally, radiobiological summation would account for relative dose distributions; using a deformable registration to propagate the primary EQD_2 dose on to the new planning CT allows an approximate accumulation with the planned SBRT EQD_2 dose. This would reduce the uncertainties and limitations associated with manually calculating combined dose; however, as with any deformable registration to propagate information, results must be carefully assessed.

7. Daily matching on treatment [LoE = 5]

Daily CBCT and kV imaging is recommended before treatment and mid-treatment, to reduce interfractional variation.[51] The use of ExacTrac (BrainLab AG, Feldkirchen, Germany) has demonstrated reduced intrafactional uncertainites although in good agreement with CBCT.[59]

FUTURE DIRECTIONS

Recently, with the introduction of immunotherapy targeting immune system has led to a paradigm shift in many cancer sites including HNC in palliative settings[62]. These immune checkpoint inhibitors are being combined with radiotherapy to explore synergistic effect. Currently an RTOG Phase II study is exploring SBRT ± pembrolizumab in patients with locoregionally recurrent or second primary HNC [ClinicalTrials.gov Identifier: NCT03546582]. Another observational study is in progress looking at proton-based SBRT 35–40 Gy in 5 fractions with Nivolumab immunotherapy for recurrent/progressive locoregional or metastatic HNC [ClinicalTrials.gov Identifier: NCT03539198].

CONCLUSION

SBRT is a feasible treatment option in recurrent HNC but patients do need to be specifically counselled about the risk of carotid blow out. Based on heterogeneous evidence available and the challenges associated with accurate dose summation, it is difficult to recommend a definitive dose fractionation regime, although prescribing between 35 and 40 Gy in 5 fractions on alternative days appears to be a safe and effective regimen. Keeping the maximum dose to carotid artery below 33 Gy appears to reduce the risk of CBOS and extra care should be taken with tumours in close proximity to the carotid artery circumference; >180°circumference of the carotid artery receiving at least 30 Gy significantly increases the risk of CBOS. Otherwise, the technique is relatively safe with manageable toxicity. At present, there is not enough evidence to advocate its use as a primary treatment option for HNC; however, it represents an option in patients with low volume disease, otherwise not fit for radical treatment, demonstrating improved outcome as compared to palliative-intent radiotherapy. Potential selection bias and limited follow-up in retrospective studies suggests a phase 3 trial is warranted.

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