Review

Evolving role of stereotactic body radiation therapy for head and neck cancer: where do we stand?

Issa Mohamad , Irene Karam , Ahmed Elsehemy , Ibrahim Abu Gheida , Akram Al-Ibraheem , Hossam AL-Assaf , Mohammed Aldehaim , Majed Alghamdi , Ibrahim Alotain , May Ashour , Ahmad Bushehri , Mostafa Elhaddad , Ali Hosni *

Posted Date: 30 August 2023

doi: 10.20944/preprints202308.2011.v1

Keywords: Head and neck cancer, SBRT, Hypofractionation

Review

Evolving Role of Stereotactic Body Radiation Therapy for Head and Neck Cancer: Where Do We Stand?

Running title: SBRT for HNC

Issa Mohamad [1], Irene Karam [2], Ahmed Elsehemy [3], Ibrahim Abu-Gheida [4,5], Akram Al-Ibraheem [6], Hossam AL-Assaf [7], Mohammed Aldehaim [8], Majed Alghamdi [9,10], Ibrahim Alotain [11], May Ashour [12], Ahmad Bushehri [13], Mostafa ElHaddad [14] and Ali Hosni [15]

[1] Department of Radiation Oncology, King Hussein Cancer Center, Amman, Jordan
[2] Department of Radiation Oncology, Odette Cancer Centre, University of Toronto, Toronto, Ontario, Canada
[3] Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.
[4] Department of Radiation Oncology, Burjeel Medical City, Abu Dhabi, United Arab Emirates
[5] Emirates Oncology Society, Dubai, United Arab Emirates
[6] Department of Nuclear Medicine, King Hussein Cancer Center, Amman, Jordan
[7] Department of Radiation Oncology, Comprehensive Cancer Center, King Fahad Medical City , Riyadh , Saudi Arabia
[8] Department of Radiation Oncology, King Faisal Specialist Hospital and Research Center Riyadh, Saudi Arabia
[9] Radiation Oncology, Princess Noorah Oncology Center, King Abdulaziz Medical City, Ministry of National Guard Health Affairs-Western Region, Jeddah, Kingdom of Saudi Arabia
[10] College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[11] Department of Radiation Oncology, King Fahad Specialist, Dammam, Saudi Arabia
[12] Department of Radiation Oncology, National Cancer Institute, Cairo University, Egypt
[13] Department of Radiation Oncology, Kuwait Cancer Control Center, Kuwait.
[14] Clinical Oncology Department, Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine, Kasr Al-Ainy School of Medicine, Cairo University.
[15] Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada
* Ali Hosni, Princess Margaret Cancer Centre, 610 University Ave. Toronto, Ontario, Canada. M5G 2M9,Tel: (+1) 416-946-2124. Fax: (+1) 416-946-6566, Ali.Hosni@uhn.on.ca.

Abstract Stereotactic body radiation therapy (SBRT) is a precise and conformal radiation therapy (RT) that aims to deliver a high dose of radiation to the tumor with sparing surrounding normal tissue, making it an attractive option for head and neck cancer (HNC) patients who are not suitable for traditional long course of RT with comprehensive RT target volume. Definitive SBRT for HNC has been investigated in different settings, including early stage glottis cancer, and as alternative to brachytherapy boost after external beam RT. It also used as a primary treatment option for elderly or medically unfit patients. More recently, SBRT combination with immunotherapy in the neoadjuvant setting for HNC showed promising results. Salvage or adjuvant SBRT for HNC can be used in appropriately selected cases. Future studies are warranted to determine the optimum dose and fractionation schedules in any of these indications.

Keywords: head and neck cancer; SBRT; Hypofractionation

Introduction

Head and neck cancers (HNCs) constitute about 6% of global malignancies, with approximately 650,000 new cases and 350,000 annual deaths[1]. They often originate from different anatomical sub-sites in the head and neck (HN) region[1], primarily being squamous cell carcinoma (SCC)[2]. Second

 doi:10.20944/preprints202308.2011.v1

primary HNC occurs at rate of 3-5%[3]. HNCs are increasingly prevalent, especially in men, typically diagnosed in the early 60s[4–8]. Treatment options generally includes surgery, radiation therapy (RT), systemic therapy, or combination of any of these according to the overall stage and type of cancer, preference and medical/general condition of the patient, and the intent of treatment [9–11]. RT or chemoradiotherapy (CRT) is routinely used in the majority of advanced HNC, lasting usually for 6-7 weeks, as a primary or post-operative therapy[6]. However, some patients cannot tolerate prolonged RT/CRT course due to age, comorbidities, travel challenges, or lack of social support[12].

Stereotactic body radiation therapy (SBRT) is a precise HN treatment targeting specific areas with high-doses of radiation delivered in 1 to 5 fractions of ≥5 Gy per fraction using image guidance[12–17]. It destroys tumor blood vessels, leading to endothelial cell death [18]. New evidence indicates that SBRT maintains radiation-induced cellular death pathways and possibly enhances antitumor immunity with high fractional doses[19].

The utilization of SBRT in real-world practice varies between 0-10%[12,20–24]. SBRT is increasingly being used in treating a variety of cancers. However, the SBRT indications for HNC, dose, fractionation schedules, and HN organs-at-risk (OARs) dose constraints lack uniform consensus[25]. The data regarding oncologic and toxicity outcomes associated with SBRT for HNC are sparse[21–23]. This review aims to summarize the literature for SBRT to HNC in the definitive, neoadjuvant, salvage and adjuvant settings from clinical and technical perspectives.

Definitive SBRT for primary HNC

In general, SBRT is used in the palliative setting for HNC patients who are unable to attend standard long courses of RT (e.g., social and logistic challenges), and when omission or significant reduction of elective target volume is clinically acceptable. This includes the following clinical scenarios: 1) SBRT for elderly/medically unfit patients aiming to maximize locoregional control (LRC) and decrease the disease burden for HNC, 2) SBRT for early glottis cancer, or 3) SBRT boost to gross tumor volume (GTV) after definitive external beam radiation therapy (EBRT) as an alternative option to brachytherapy boost.

Definitive SBRT in elderly or medically unfit HNC patients

The ultimate goal of SBRT in elderly or medically unfit HNC patients is to achieve an acceptable balance between LRC, cancer-associated disease burden and RT-related toxicity[14,16,20–23,26,27]. SBRT demonstrated acceptable local control (LC) rates with minimal side effects compared to conventional fractionation RT with standard comprehensive target volume[15]. The literature included single-institution studies varied in number of included patient (3-106 patients), primary tumor sites and SBRT doses and fractionation schedules (15-22 Gy in single fraction to 30-50 Gy in five or six fractions [BED_{10} range between 32.17 and 91.65 Gy_{10}])[24]. The one-year LC and overall survival (OS) rates ranged from 69% to 87% and 60% to 85% respectively[12,14,16,20–23,26–28]. Acute or late grade 3 toxicities included osteoradionecrosis, pain, dermatitis, ulceration, and cataracts[12,20,22,27,28] (See Table 1).

A meta-analysis evaluated SBRT for de novo HNC in elderly patients who could not undergo aggressive CRT or altered fractionation RT (median age: 76 years). SBRT dose ranged from 25 to 59.5 Gy in 3 to 17 fractions, with a median BED_{10} ranged from 42.63 to 82.72 Gy_{10} and equivalent dose in 2Gy fractions ($\alpha/\beta = 10$) between 35.53 and 68.93 Gy. The 3-year LC rate was acceptable (73.5%), and the 3-year OS was approximately 50%, indicating that the focus might have been on optimizing the LC rather than OS due to comorbidities and old age of those patients. The late grade 5 toxicity rate was 0.1%[29].

Table 1. Summary of retrospective SBRT studies for primary head and neck cancer.

Author (Year)/design/subsite	n	Median age (range), y	Median target volume	Elective nodal	RT dose (Gy)/Fraction	EQD_2 (Gy) ($\alpha/\beta = 10$)	BED_{10} (Gy) ($\alpha/\beta = 10$)	BED_3 (Gy) ($\alpha/\beta = 3$)	Median follow up (months)	LC (%)	OS (%)	Toxicity

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

				irradiation								
Voruganti et al. (2021)/retrospective/skin [27]	106	86 (56-102).	(GTV)=31 cm^3 (range: 17-56 cm^3).	Yes	32-50/4-6	48-76.38	57.6-91.65	117.3-188.83	8	1 yr 78%	1 yr 53%	Acute: Grade 3: 31 dermatitis Late grade ≥ 3: 7 fibrosis, 1 ORN and 1 grade 4 skin ulceration
Al-Assaf et al. (2020)/retrospective/mixed [12]	48	81 (25- 102)	Median GTV volume = 33.2 cc (range, 1.9–368.6 cc)	Yes	35-50 /4–6	54.69-76.38	65.63–91.65	137-189	10.5	85.5 %	-	Acute: Grade 4:1 (Mucosal ulceration) Late : Grade 4:1 (ORN and skin ulceration)
Gogineni et al. (2020)/ retrospective /mixed [28]	66	80 (47-99)	Median PTV volume = 82 cc	Yes	35–40/5	49.58–60	59.5–72	116.67-146.67	15 (3–88)	1 yr 73%	1 yr 64%	Acute: Grade 3:2 Late: Grade ≥ 3:0
Khan et al. (2015)/ retrospective /mixed[14]	17	87 (25-103)	Median Maximum Diameter = 3.7 cm (1–10 cm)	Yes	35–48/5–6	49.58–72	59.5–86.4	116.67-176	8	1 yr 87%	1 yr 60%	Grade 3:0
Amini et al. (2014)/ retrospective /mixed [16]	3	82(72-88)	Tumor volume cc= 15-36.7cc	Yes	25–36/ 5	31.25–51.6	37.5–61.92	66.67-122.4	8	100 (crude rate)	33	Grade 3 = 0
Vargo et al. (2014)/ retrospective /mixed[17]	12	88(79-98)	Median = 42.1 cc (15.1–247.9 cc)	No	20–44/1–5	50–68.93	60–82.72	155.33-173.07	6 (0.5–29	1 yr 69%	1 yr 64%	Acute: Grade 3:1 Late: Grade 3:1
Kawaguchi et al. (2012)/ retrospective /mixed[22]	14	73(64-93)	-	No	35–42/3–5	63.18–64.4	75.81–77.28	171-77.28	36 (14–40)	Mean 71.4	Mean 78.6	Late: Grade 3:1 (ORN) (after 2nd SRS)
Karam et al./retrospective/ parotid[26]	13	80(34–99)	PTV= 13.3-195.3cc	Yes	25-40/5-7	31.25-52.37	37.5-62.84	66.67-116.13	14(0–59)	2 yr LRC 84%	2 yr 46%	Acute: G5: 1 Sepsis secondary to

 doi:10.20944/preprints202308.2011.v1

												aspiration pneumonia
Kodani et al. (2011)/ retrospective /mixed[21]	13	66(17-88)	Median GTV volume = 22 cc (0.7–78 cc)	No	19.5–42/ 3–8	26.81–53.38	32.17–64.05	61.75-115.5	16 (3–51)	CR:38% PR:46%	85%	Grade 3:0
Siddiqui et al. (2009)/ retrospective /mixed[20]	10	73.5(37-89)	Median GTV 15.5 cc (1.7–155 cc)	No	30–48/5–6	40–72	48–86.4	90-176	32 (7–53.4)	1 yr 83.3 %	1 yr 70%	Acute: Grade 3:1 (Pain) Late: Grade 3:1 (Cataract)

Abbreviations: RT: Radiotherapy, EQD2: Equivalent dose at 2 Gy/fraction, BED_{10}: Biologically effective dose (α/β = 10); BED_3: Biologically effective dose (α/β = 3) LC: local control, OS: Overall survival, GTV: Gross tumor volume, PTV: Planning target volume, CR: Complete response, PR: Partial response, ORN: Osteoradionecrosis.

Summary and recommendation

There is limited evidence supporting the use of definitive SBRT for elderly or medically unfit HNC patients who cannot tolerate standard long course of RT. A wide SBRT dose range was used (15 to 22 Gy in 1 fraction to 30 to 50 Gy in 5-6 fractions). Further studies are warranted to establish the optimal SBRT dose, fractionation, and criteria for selecting patients with primary HNC for definitive SBRT.

Definitive SBRT for early-stage glottis cancer

The use of SBRT is considered an attractive treatment option for early-stage glottis cancer given the shorter overall treatment time associated with SBRT that could potentially improve the LC. In addition, there is no need to treat un-involved contralateral vocal cord or elective nodal target volume which allows higher dose per fraction without possibly significant late morbidity[3031–33].

A phase I trial from the University of Texas Southwestern Medical Center investigated 3 dose levels (50 Gy/15 fractions, 45 Gy/10 fractions, and 42.5 Gy in 5 fractions) for 29 patients with early (Tis-T2) glottis cancer (median follow up: 39.2 months). Two patients had dose-limiting toxicity: one with cT2 cancer received 45 Gy in 10 fractions, who developed grade 4 laryngeal edema and grade 3 dysphagia at 5 months post-RT, and another patient with cT2 disease treated with 42.5 Gy in 5 fractions developed grade 3 laryngeal necrosis and grade 3 dysphagia at 7 months post-RT[34]. The voice handicap index improved in all groups. Five patients developed recurrence (no recurrence was observed in the 42.5 Gy group). Although there were 2 dose-limiting toxicities; these results were the foundation of an ongoing phase II trial (NCT03548285) investigating two SBRT schedules based on risk groups: low-risk (PTV <10cc and no smoking within 1 month from registration: SBRT with 42.5Gy/5fractions) and moderate-risk (PTV >10cc, or smoking history within 1 month from the registration [≤1 pack/day]: RT with 58.08/16 fractions)[35].

Another phase I trial for early glottis cancers evaluated 59.5 Gy/17 fractions and 55 Gy/11 fractions. Initial report showed satisfactory toxicity levels and favorable voice/quality of life (QoL) outcomes[36]. However, Kang et al.'s update led to trial closure due to toxicity in the 55 Gy group (arytenoids necrosis at 5 months post-SBRT, and vocal cord ulcer at 15 months post-SBRT), following predefined stopping rules[37]. Authors concluded SBRT is not feasible for early glottis cancer[37].

Summary and recommendation

Two phase I trials evaluated SBRT for early glottis cancer and showed the development of pre-defined dose limiting toxicities. An ongoing phase II trial is evaluating the potential use of risk-adaptive SBRT dose selection in the setting of SBRT for early glottis cancer. SBRT twice a week for

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

T1/T2 lesions is an interesting option, acknowledging the risk of severe late toxicity, including chondronecrosis, which may be dependent on pre-existing infiltration of the laryngeal framework.

Definitive SBRT as boost after EBRT (alternative to brachytherapy boost)

In 2008, Hara et al. updated results from Tate et al. (1999)[38] and Lee et al. (2003)[39] on SBRT boost for 82 patients (47 had stage IV nasopharynx cancer). SBRT boost of 7–15 Gy was given 2–6 weeks after EBRT. At 5 years, local failure, regional failure, DM rates and OS were 2%, 17%, 32% and 69% respectively. The late toxicities included radiation-induced retinopathy (n=3), carotid aneurysm (n=1) and temporal lobe necrosis (n=10)[40]. Chen et al. also reported outcomes and toxicity of SBRT boost (12-15 Gy in 4-5fractions) to nasopharynx cancer (n=64). The 3-year LC rate was 93.1%. Three patients had fatal nasal bleeding 6–7 months after SBRT boost[41].

Uno et al. investigated the feasibility of SBRT boost (9-16 Gy in 1-3 fractions) for various HNC sites in 10 patients [42]; 60% had complete response (CR), 40% had partial response (PR), with no grade ≥3 toxicities attributable to SBRT. In a Japanese series of 25 HNC patients, treated with SBRT boost (12-35 Gy in 1-5 fractions), 18 patients had CR, 6 patients had PR and one patient with disease progression (DP), resulted in 96% (24/25) overall response rate (ORR). The 2-year LC and OS rates were 89% and 70% respectively. Small SBRT planning target volume (PTV) boost (≤20 cm^3) and good initial response to RT predicted favorable outcomes in terms of LC and OS[43].

Lee et al. evaluated the long-term outcomes and toxicity of SBRT boost (10-25 Gy in 2-5 fractions) in 26 HNC patients. Major response rate was 100% (21 CR). Nine patients experienced grade ≥3 toxicities, of whom, 5 patients with late grade 3 (including pontine necrosis, temporal lobe necrosis (n= 2), radiation retinopathy, neovascular glaucoma, and optic neuropathy), 4 patients with late grade 4 toxicity (including soft tissue necrosis in the left base of the skull bone, mucosal ulcer and necrosis, soft tissue necrosis in the left nasopharyngeal wall, and an unhealed mucosal ulcer with bleeding), and 1 patient with grade 5 pontine necrosis. SBRT boost volume (median 47.7 cc) predicted late complications[44].

Almamgani et al. prospectively evaluated SBRT boost (16.5 Gy in 3 fractions) for 51 patients with stage I-IVb oropharyngeal carcinoma (OPC), not suitable for standard brachytherapy boost[45]. The 2 year LC and OS were 86% and 82% respectively, with acceptable toxicity including feeding tube dependency (n=1) and grade 3 xerostomia (n=2). Subsequently, the same group adopted the above treatment for T1-2 and small T3, N0-N2 OPC. They reported the pattern of failure, outcome and long term toxicity in a cohort of 195 patients treated between 2009 and 2016[46,47]. The 5 year LC and regional control (RC) were 90% and 93% respectively. By location of the center of the recurrent disease, 76% of failures were within the treated volume and 24% were outside the treated volume, significantly higher than what was reported in literature, attributed to highly conformal dose intensification[46]. At a median follow up of 4.3 years, the 5 year disease specific survival and OS were 85% and 67% respectively. Grade ≥3 toxicity was observed in 28% patients, the commonest being mucosal ulceration or soft tissue necrosis, dysphagia or weight loss and osteoradionecrosis[48].

In a phase I trial of dose-escalated SBRT boost to residual gross tumor of 8 or 10 Gy in a single fraction, or 10 Gy in 2 fractions, after 60-66 Gy/30-33 fractions with concurrent cisplatin for unfavorable intermediate- or high-risk OPC. The LC rate was 85.3% at 4.3 years. Four patients with tumor necrosis had grade 3 dysphagia, and three patients had grade 4 pharyngeal hemorrhage requiring surgical intervention[49]. The outcome, patterns of failure and toxicity profile of various SBRT boost studies are described in Table 2.

Table 2. Summary of SBRT boost studies in head and neck cancer.

Author (year)/subsite/design	Sample size (n)	Median follow	EBRT dose/fraction	Boost dose (Gy)/ Fraction	GTV (cc) or boost volume (range)	EQD2 (Gy) (α/β = 10) (Total)	BED10 (Gy) (α/β = 10) (Total)	Margins for stereotactic	LC (%)	OS (%)	Initial site of Failure (N)	Toxicity (N)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

		up(months)						boost (PTV)				
Tate et al. (1999)/retrospective/nasopahrynx[38]	23	21 (2–64)	64.8 Gy-70 Gy (Median 66 Gy/33frs)	7–15 Gy /1#frs Median 12 Gy	Not reported	Median 88	Median 105.6	Not reported	100%	Not reported	Local: 0 Regional:2 Distant: 7	As expected for EBRT
Le et al. (2003)/ retrospective/nasopahrynx[39]	45	31	66 Gy /33frs	7–15 Gy/ 1frs	Not reported	88	105.6	Not reported	3 yr LC: 100%	3 yr OS: 75%	Local: 0 Regional:3 Distant: 14	CN weakness:4 Retinopathy:1 Asymptomatic TLN: 3
Chen HH et al. (2006) retrospective/nasopahrynx[41]	64	31 (22–54)	64.8 Gy-68.4 Gy/ 36–38frs	12–15 Gy /4–5frs	Mean GTV 62.6 (21.1–145.3)	76.72–83.51	92.06–100.2	CTV + 2–3 mm	3 yr LC: 93.1%	3 yr OS: 84.9%	Local:4 Regional:7 Distant: 7	Late Grade 4: None Note: 3 fatal nasal bleeding could be not related to SBRT boost
Hara et al. (2008)/ retrospective/nasopahrynx[40]	82	40.7 (6.5–144.2)	66 Gy/ 33frs	7–15 Gy /1frs	Median GTV 34.2 (6.4–102.2)	88	105.6	Not reported	5 yr LC: 98%	5 yr OS: 69%	Local:1 Regional:5 Distant: 27	Retinopathy: 3 Asymptomatic TLN:8 Symptomatic: 2
Uno T et al. (2010))/ retrospective/mixed[42]	10	16 (6–24)	40 Gy-60 Gy/ 20–30frs	9–16 Gy/ 1–3frs	Not reported	54.22–80.44	65.1–96.53	CTV + 0-5mm	CR:60% PR:40%	Not reported	Local:3 Distant: 1	≥ Grade 3: None
Lee DS et al. (2012) retrospective/mixed[44]	26	56 (27.6–80.2)	39.6 Gy-70.2 Gy (Median 50.4 Gy/ 28frs)	10–25 Gy/ 2–5frs Median 21 Gy/5frs	NPC median GTV 45.3 (21.3–69.4) Non-NPC Median GTV 19.4 (6.9–66.8)	Median 74.41	Median 89.29	GTV + 1- mm	1 yr LRRFR: 91.4% 2 yr LRRFR: 86.3%	2 yr OS: 61.5% 5 yr OS: 46.2%	Local:2 Regional:1 Distant: 5	≥ Grade 3: 9
Al-Mamgani et al. (2012)/retro	51	18 (6–65)	46 Gy/ 23frs	16.5 Gy/3frs	Not reported	67.31	80.78	CTV + 3 mm	2 yr LC: 86% 3 yr LC: 70%	2 yr OS: 82% 3 yr OS: 54%	Local:5 Regional:1 Distant: 1	≥ Grade 3:2 1 feeding tube dependence

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

spective/oropharynx [45]												
Yamazaki H et al. (2014) retrospective/mixed[43]	25	28 (7–128)	35 Gy –70 Gy (Median 50 Gy/25frs)	12–35 Gy/1–5frs Median 15 Gy/3frs	Not reported	Median 68.75	Median 82.5		2 yr LC: 89% 5 yr LC: 71%	2 yr OS: 83% 5 yr OS: 70%	-	≥ Grade 3: None
Karam et al., (2014)/ retrospective/ salivary gland[26]	10	29(12-120)	Median 64.8, range(50–75.6)	Median17.5, range (10–30)/3-6frs	Not reported	87.82(61.11-113.1)	92.5(75.91-102.3)	Definitive= GTV + 15–20 mm Post-op CTV + 10–20 mm	1-yr LC: 90% 2-yr LC: 80%	1 yr: 100%	Local: 1 Distant: 1	≥ Grade 3: None
Kataria et al., (2015) / retrospective/mixed[77]	9	8 (6–19)	54 (50–60)/ (25–30)	15 (10–25)/2-5frs	Median GTV 16.3 (7–47)	72.7 (62.5–91.2)	87.3 (75–109.5)	GTV +3–5 mm	CR: 55%	Not reported	Distant: 1	≥ Grade 3: None
Diaz-Martinez et al., (2018)/ retrospective/ Sinonasal/ nasopharynx[78]	9	13.3 (4–32)	64.3 (54–70)/ (27–35)	13 (12–20)/1fr	Mean GTV 4.5 (1.17–8.2)	89.2 (76–120)	107.1 (91.2–144)	Not reported	1-yr LC: 100%	Not reported	Distant: 3	≥ Grade 3: None
Baker S et al. (2018)/ retrospective/oropharynx Baker S et al. (2019)b retrospective/oropharynx[46]	195	42.8 (2.1–98.6)	46 Gy /23frs	16.5 Gy/3frs	Not reported	67.31	80.78	CTV + 3 mm	5 yr LC: 90%	5 yr OS:66.7%	Local:18 Regional:12 Distant: 11	≥ Grade 3: 47

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

Vempati et al., (2020)/prospective/oropharynx[79]	34	50	60–66/30frs	8–10/1-2frs	Mean GTVp 70 Mean boost volume 54 (13–185)	72–79.6	86.4–95.5	CTV = GTV + 7 mm PTV = CTV + 3 mm	Median follow up of 50 months LC: 85.3%	Median follow up of 50 months OS: 85.3%	Local:1 Regional:2Distant: 4	≥ Grade 3: 4 Dysphagia: 1 Pharyngeal hemorrhage: 3

Summary and recommendation

Despite acceptable oncologic outcome of SBRT boost after EBRT for HNC, severe treatment-related toxicities have been reported. As such, the use of SBRT boost for HNC as an alternative to brachytherapy boost is recommended only in the investigational setting.

Neoadjuvant SBRT (with immunotherapy) for HNC

Immunotherapeutic approaches are effective in recurrent/metastatic HNC[50] and enhance treatment when combined with other modalities[51]. SBRT can overcome immunotherapy resistance and sensitize cancer cells[52]. Neoadjuvant immunoradiation could potentially improve the oncologic and functional outcomes by shortening the overall treatment time, limiting radiation target volumes, and facilitating less extensive surgery through downsizing the tumor[53].

A phase Ib/II trial included 19 patients (phase Ib: 6; phase II: 13) with untreated locally advanced HPV-related OPC. Patients received neoadjuvant durvalumab±tremelimumab for 2 doses (durvalumab only [n=3]; durvalumab+tremelimumab [n=16]), with concurrent SBRT of 25 Gy in 5 fractions to gross disease only, followed by transoral robotic surgery with adjuvant durvalumab for up to 4 cycles. Median follow-up was 12.7 months. No safety signals were reported. Eighteen out of 19 patients (95%) achieved a clinical/pathological downsizing, of whom 9 (47%) had pathologic complete response (pCR). Five patients (26%) developed locoregional failure (LRR), with a median time to recurrence of 3 months. Failing to achieve pCR was significantly associated with LRR (p=0.03). Caution against omitting elective volume irradiation is warranted even in favorable prognosis HPV-related OPC in the neoadjuvant setting with SBRT and immunotherapy[54].

In a phase Ib trial, locally advanced p16-positive and p16-negative head and neck squamous cell carcinoma (HNSCC) patients were treated with neoadjuvant SBRT over 1 week with nivolumab (240 mg intravenous q2 week's ×3 cycles) before surgery. Cohort-I included 5 patients who received 40 Gy in 5 fractions; cohort-II included 5 patients who received 24 Gy in 3 fractions. After assessment of the toxicity, 2 expansion cohorts were added: cohort-III which included 6 patients who received SBRT alone (24 Gy in 3 fractions) for stages I-III HPV-related HNSCC and cohort-IV included 5 patients who received nivolumab + SBRT (24 Gy in 3 fractions) for stages III-IVA p16-negative HNSCC. Surgery was scheduled 5 weeks post SBRT, followed by adjuvant nivolumab 480 mg intravenous q4 weeks for 3 doses starting 4 weeks after surgery in all cohorts. All 21 patients completed neoadjuvant treatment without dose-limiting toxicity. In the entire study group, the major pathological response (mPR) and pCR rates were 86% and 67% respectively. Among the 10 HPV-related HNSCC patients who underwent treatment with nivolumab and SBRT, the pCR rate was 90% (cohort-I =5/5; cohort-II =4/5) and mPR rate was 100%. In HPV-related HNC patients treated with neoadjuvant SBRT alone (cohort-III), the pCR rate was 50% (n=3). In HPV-negative patients (cohort-IV), the pCR and mPR rates were 20% (n=1) and 60% (n=3) respectively[53].

A phase I/Ib trial was conducted to evaluate the safety of administering both SBRT and a single dose of durvalumab as neoadjuvant treatment for 21 patients with HPV-unrelated locally advanced HNSCC[55]. Patients received neoadjuvant durvalumab (1500 mg) and SBRT approximately 3-6 weeks before surgery. The starting SBRT dose level was 6 Gy for 2 fractions (12 Gy total) every other day to gross disease. If the dose was tolerated, the dose was increased to 6 Gy for 3 fractions (18 Gy total)

 doi:10.20944/preprints202308.2011.v1

for the next 3 patients then 6 Gy for 4 fractions (24 Gy total). Adjuvant therapy was used based on a standard of care indications for the first enrolled 8 patients, and all patients received adjuvant durvalumab to be initiated approximately 6–12 weeks post-surgery. It was given as 1500 mg intravenously once every 4 weeks for a maximum of six doses, or until disease progression, unacceptable toxicity or withdrawal from the study. The protocol was updated after the 8th enrolled patient to omit adjuvant RT for patients with pCR or mPR, but all patients still received adjuvant durvalumab. The safety endpoint was met. With a median follow-up of 16 months, OS was 80.1%, LRC and PFS were 75.8%, and mPR was 75%. For patients treated with 24 Gy in 4 fraction, mPR rate was 89%. Radiation dose and time from SBRT to surgery correlated with mPR. One patient, treated below the maximum tolerated dose, recurred out of the SBRT volume, despite having received adjuvant RT and durvalumab. Two other patients failed in the SBRT volume, of whom one refused adjuvant RT but received adjuvant durvalumab[55].

Shen et al. retrospectively studied 30 locally advanced oral cavity SCC patients treated with neoadjuvant nivolumab plus SBRT (median dose: 24 Gy, range, 14–48 Gy) with 56.6% of patients received adjuvant RT +/- chemotherapy. Treatment was well-tolerated with no serious adverse events. R0 resection was achieved in 90% of patients, with 16.7% of patients' experienced procedure-associated complications. Response rates were: CR 10%, PR 46.7%, and SD 43.3%. The mPR and pCR rates were 60.0% and 33.3% respectively. Median follow-up was 13.5 months. The 2-year disease-free survival (DFS) and OS were 70.4% and 76.4% respectively for 26 patients with surgical resection. Patients with mPR and CR showed significantly better DFS and OS ($p<0.05$)[56].

Summary and recommendation

Neoadjuvant SBRT with immunotherapy is a safe treatment for locoregionally advanced HNSCC, potentially resulting in relatively high rates of mPR with subsequent favorable outcomes. Commonly used SBRT regimen in the neoadjuvant setting is 24Gy/3 fractions and 25-40Gy in 5 fractions. Omitting elective nodal irradiation during neoadjuvant SBRT has a higher risk of regional nodal recurrence even in favorable HPV-related OPC despite the use of immunotherapy. Futures studies are warranted to further confirm the efficacy of this stratgey[53–56].

Salvage SBRT for recurrent unresectable or second primary HNC

Salvage SBRT for unresectable recurrent and second primary HNC in a previously irradiated volume is challenging. While studies consistently demonstrate improved LC with re-irradiation, the accumulation of high cumulative doses may result in severe side effects, such as the potentially fatal carotid blowout syndrome. Hence, it is crucial to carefully select patients and appropriate RT techniques.[17,20,57–65].

Heron et al. conducted a phase I dose-escalation trial with salvage SBRT for recurrent HNC. Twenty five participants received escalating SBRT doses, starting at 5 Gy per fraction that was escalated to 8.8 Gy per fraction for 5 fractions delivered over 2 weeks. The maximum tolerated dose was 44 Gy in 5 fractions, with no associated grade ≥3 acute toxicities, and an ORR of 17%, a median duration of response of 4 months, and a median OS of 6 months[66]. An updated report included 85 patients showed that SBRT doses ≥35 Gy resulted in improved LC (71% vs. 59%, $p = 0.01$). The 1-year and 2-year LC and OS rates were 51.2% and 30.7%, and 48.5% and 16.1% respectively[65].

A retrospective-matched case-control study investigated concurrent cetuximab with SBRT (n=35) vs. SBRT alone (n=35) for unresectable recurrent HNSCC. Both study arms received a median SBRT dose of 40 Gy (range, 20–44 Gy). Concurrent cetuximab showed improved OS (median 24.5 vs. 14.8 months, $p = 0.03$)[67]. In 2014, an updated retrospective review included 132 patients who were treated with salvage SBRT for recurrent HNC, with a median dose of 44 Gy in 5 fractions (range, 35–50 Gy), and median follow-up of 6 months[17]. The 1-year OS and LRC rates were 38% and 48% respectively. Overall, toxicity rates were acceptable; 16 patients (12%) and 6 patients (7%) experienced grade ≥3 acute and late toxicity respectively (with the majority of toxicity related to mucosal and skin reactions)[17]. Treatment duration <14 days improved recurrence-free survival but

 doi:10.20944/preprints202308.2011.v1

increased late toxicity (p = 0.03). This study found that tumor volume >25 cc predicted inferior survival, poor tumor control, and more acute toxicity (p = 0.02) but no difference in late toxicity[17].

Comet et al. performed a feasibility study of salvage SBRT with or without cetuximab for locally recurrent or new primary HNC[62]. In this phase I trial, 40 patients with 43 lesions were treated to a total dose of 36 Gy in 6 fractions, of whom; 15 (37.5%) were treated with concurrent cetuximab, and 1 was treated with concurrent cisplatin[62]. Half of the patients had HNSCC. The 1-year OS rate was 58%. Of the 34 study patients who were evaluable for response, 15 (44%) had CR, 12 (35%) had PR, and 7 (21%) had SD. For the 14 patients with concurrent cetuximab, 75% had an overall objective response[62]. Following these results, Lartigau et al. conducted a phase II multi-institutional trial to assess re-irradiation using salvage SBRT with concurrent cetuximab in 56 patients with recurrent or new primary HNSCC who were treated with 36 Gy in 6 fractions for 11 to 12 days[63]. The 1-year OS was 47.5%[63]. Of the 49 evaluable study participants, the ORR was 69%; CR was seen in 24 (49%), PR in 10 (20%), and SD in 11 (23%). Eighteen study patients (32%) experienced toxicities of grade ≥3 and 1 patient died from arterial rupture[63]. These results were comparable with those seen in the study conducted by Heron et al.[67], Lartigau et al[63] attributed the low rate of carotid blowout to the careful selection of patients without tumor encasement of less than one-third of the carotid artery.

Cengiz et al. retrospectively analyzed 46 patients with locally recurrent HNC (65% had HNSCC) treated with re-irradiation using SBRT (median dose: 30 Gy, range: 18-35 Gy, 1 to 5 fractions)[61]. The 1-year OS rate was 46%[61]. A total of 10 of 37 evaluable study patients (27%) had CR, 11 (30%) had PR, and 10 (27%) had SD. Despite the comparable survival outcome with other studies[62,63], the late-grade ≥4 toxicity rate was higher; 8 patients (17%) experienced late carotid blowout, of whom 7 died from carotid hemorrhage[61]. It has been suggested that the relatively high rate of late toxicity in this study was a result of daily SBRT fractionation, rather than an every- other-day fractionation scheme, as seen in other studies[17].

Unger et al. reviewed 65 patients treated with SBRT for recurrent HNC. The study included 27 patients (42%) with metastatic disease or untreated local disease, 11 (17%) with non-squamous histologies, 19 (29%) treated with surgery prior to re-irradiation, and 21 (32%) treated with CRT. The SBRT dose ranged from 21 to 35 Gy in 2 to 5 fractions[68]. The group reported an ORR of 80%; CR rate of 54%, and PR rate of 27%. The median OS was 12 months and the 2-year OS rate for patients with non-metastatic cancer at the time of treatment was 41%. Seven patients (11%) experienced late toxicities related to SBRT, and 1 patient died due to treatment[68]. Roh et al.'s reviewed 36 patients (44 lesions) who were treated for locally recurrent HNC using SBRT with 18 to 40 Gy (median, 30 Gy) in 3 to 5 fractions[69]. More than half of the lesions were SCC. Median OS was 16 months, with CR rate of 43%, PR rate of 37%, and SD in 9%. Grade 3 acute complications affected 36% of participants, and late complications affected 8%. The study reported a high rate of late grade ≥4 toxicities, which some attributed to daily radiation rather than every-other-day delivery[17,69].

Vargo et al. studied 414 patients with unresectable recurrent or second primary HNC treated with intensity-modulated radiation therapy (IMRT, n=217 patients) or SBRT (197 patients). The OS was similar for IMRT and SBRT with dose ≥35 Gy for small tumor volumes (25 cc), however dose <35 Gy resulted in significantly worse 2-year OS of 14%[15]. Another study with 45 patients showed higher 1-year OS of 68% with ≥40 Gy in 5 fractions, compared to 24% with lower doses[70].

Summary and recommendation

Salvage SBRT for recurrent (or 2nd primary) HNC in previously irradiated volume showed acceptable survival (Table 3)[17,58–64,68]. Rate of carotid blowout is relatively low with appropriate patient selection, target volume definition, and every other day treatment delivery. However, differences in patient selection criteria, tumor histology, and salvage SBRT doses make direct comparisons challenging. Therefore, a large, multi-institutional trial for re-irradiation using SBRT is warranted.

Table 3. Salvage SBRT studies for unresectable recurrent or second primary head and neck cancer.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

Author (Year)/design/subsite	Sample size (n)	Treatment	rRT dose (Gy)/Fraction	Radiotherapy treatment duration	rRT Tumor volume (cm3), median (range)	Median follow up (Months)	LC/LRC	Median Survival Rate, months	Overall Survival Rate, %	Grade 4/5 Late Toxicity, %
Heron et al. (2009)/phase I/Mixed[66]	25	SBRT	25-44Gy/5frs	2 weeks	44.8 (4.2–217)		-	6	-	0
Rwigema et al. (2010)/Retrospective/Mixed[65]	85	SBRT	15-44Gy/1-5frs	1-38 days	25.1(2.5-162)	6	1-y LC: 51.2 2-y LC: 30.7	11.5	1-y OS: 48.5 2-y OS: 16.1	0
Heron et al. (2011)/Retrospective/Mixed[67]	70	SBRT +/- cetuximab	20-44Gy/5frs	9-14 days	29(4.8-86.8)	21.3	SBRT alone: 1-y LC: 53.8 2-y LC: 33.6. SBRT + Cetuximab: 1-y LC: 78.6 2-y LC: 49.2	SBRT alone: 14.8 SBRT + Cetuximab: 24.5	SBRT alone: 1-y OS: 52.7 2-y OS: 21.1. SBRT + Cetuximab: 1-y OS: 66 2-y OS: 53.3	0
Comet et al. (2011)/Retrospective/Mixed[62]	40	SBRT +/- cetuximab	36Gy/6frs	11-12 days	29.5 (8-85)	25.6	-	13.6	1-y OS: 58 2-y OS: 24	0
Lartigau et al. (2011)/Phase II/Mixed[63]	56	SBRT + cetuximab	36Gy/6frs	11-12 days	-	11.4	3 months LC: 91.7	11.8	1-y OS: 47.5	Grade 5:2 patients: (hemorrhage and denutrition)
Cengiz et al. (2011)/Retrospective/Mixed[61]	46	SBRT	18-35Gy/1-5frs	Daily	45(3-206)	7	Median PFS: 10.5	1.9	1-y OS: 47	Grade 5:8 patients, 17.8%): carotid blowout
Vargo et al. (2014)/Retrospective/Mixed[17]	132	SBRT + cetuximab	35-40Gy/5frs	7-14 days	30.9 (4.4–192.4)	6	1-y LRC: 48	7	1-y OS:38	0
Unger et al. (2010)/Retrospective/Mixed[57]	65	SBRT	21-35Gy/2-5frs	Daily	-	16	2-y LRC: 30	12	2-y OS: 41	Grade 4/5 late Toxicity: (6 patients, 9%) arterial bleeding, soft tissue necrosis, fistula formation, and dysphagia requiring hospitalization.

Roh et al. (2009)/Retrospective/Mixed[69]	36	SBRT	18-40Gy/3-5frs	Daily	22.6(.2-114.9)	17.3	1-y LRFS: 61 2-y LRFS: 52.2	16.2	1-y OS: 52.1 2-y OS: 30.9	Grade 4/5 late Toxicity: (3 patients, 6.8%) (1 bone necrosis, 2 soft tissue necrosis)
[15] et al. (2018)/Retrospective/Mixed	197	SBRT	16-50Gy/1-8frs	Every other day	30 (1-427)	24	2-y cumulative LRF: 57	7.8	2-y OS: 16.3	Grade 4/5 late Toxicity: (5% of patients developed carotid blowout syndrome, fistula, and intensive care unit admission)
Ansinelli et al. (2018)/Retrospective/Mixed[70]	45	SBRT	20-42.5Gy/5frs	Every other day	34.09 (1.00 - 258.12)	8.78	1-y LC: 49.6	9.23	1-y OS: 37.7	0

Abbreviations: rRT = re-irradiation, LC= local control, LRC= locoregional control, SBRT = stereotactic body radiotherapy, PFS: Progression free survival, Fr = fraction.

Adjuvant SBRT for recurrent HNC

An ongoing multi-center phase II trial (STEREO POSTOP, NCT03401840) evaluates post-operative SBRT (36 Gy in 6 fractions over 11-13 day) for pT1-2 N0-1 oral cavity SCC and OPC with compromised resection margins (with no pathologic extranodal extension) [72]. The study hypothesize that postoperative SBRT's safety and efficacy will be similar to conventional RT schedule[73,74].

Vargo et al.[71] conducted a retrospective study on 28 patients who had high-risk features (involved resection margin[s] or pathologic extranodal extension) following salvage surgery with gross total resection (i.e. R0/R1) followed by adjuvant SBRT with (7/28 patients) or without (11/28) cetuximab. The SBRT dose was 40 to 44 Gy in 5 fractions over 1-2 weeks. All patients had previously received RT (median dose of initial RT was 70 Gy; range, 54-99 Gy), with a median time to re-irradiation (from original RT) of 25 months (range, 6-156 months). Median follow-up was 14 months (range, 2-69 months). The 1-year LRC, distant control, DFS, and OS rates were 51%, 90%, 49%, and 64% respectively. The rates of acute and late severe (grade ≥3) toxicity were 0% and 8%, respectively[71]. At six months follow-up, 56% of patients reported improved or stable overall QoL scores[71].

Practical and technical aspects of SBRT for HNC

Target volume definition for SBRT

Majority of institutions use a cut off size and/or volume constraint for primary tumor (e.g., 3–5 cm/ 25–30 cc) and nodal disease (4–5 cm/ <50 cc)[24]. Contouring protocols varied across studies with different approaches taken.At the time of simulation, the use of intravenous contrast (whenever possible) and magnetic resonance imaging (MRI) diagnostic or simulation scans (whenever available) facilitate accurate gross tumor delineation. The commonly used strategy is centered on contouring the GTV with 0 mm margin expansion to create the clinical target volume (CTV). An elective dose CTV to include a concentric expansion of the GTV or to encompass a limited elective nodal volume

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

is at the discretion of the treating radiation oncologist. The PTV is a uniform expansion of 3 to 5 mm from the GTV/CTV based on institutional practice [12].

SBRT dose and fractionation

Dose prescription varied across institutions and ranged from 12-22 Gy single fraction, 24–25 Gy/2 fractions, 24–27 Gy/3fractions, 24–30 Gy/4 fractions and 30-50 Gy/5 fractions, with BED_{10} range from 26.4-100Gy_{10}. The most common variables altering the choice of fractionation regimens include tumor size/volume, location of tumor, prior dose delivery and indication for SBRT[24]. Treatment was often delivered either every other day or twice weekly 2 days apart.

Target objectives and OAR constraints

Plan normalization should provide coverage of ≥95% of the PTV. Planning optimization uses conformity indices, D95%, D99%, near-minimum dose (D98%) and near-maximum dose (D2%)[24]. Critical OARs are the spinal cord, brain, brainstem, optic chiasm, optic nerves and eyes. Table 4 summarizes dose constraints for various SBRT fractionation regimens. Patients are to be planned and treated using IMRT or VMAT planning (ideally with ≤5mm leaf width of the multi-leaf collimator). Maximum point dose up to 115% of the prescription dose is acceptable within the PTV and the prescription dose outside of the PTV should be avoided. Aim to achieve a conformality index (CI) < 1.1. Daily cone beam computed tomography (CBCT) should be performed with pre- and post-shifts, with physician present at day 1 of SBRT treatment.

Table 4. Oragns-at-risk constaints among different different head and neck SBRT regimen.

OAR constraint	Constraint for 1 fx		Constraint for 2 fx		Constraint for 3 fx		Constraint for 4 fx		Constraint for 5 fx		Endpoint ≥ grade 3	
	Primary disease	Re-RT	Primary disease	Re-RT	Primary disease	Re-RT	Primary disease	Re-RT	Primary disease	Re-RT	Primary disease	Re-RT
Spinal cord and medulla_PRV	Dmax 14 Gy (D0.035 cc), V10 (<0.35cc) [80–83]	Dmax 9 Gy[80,84]	Dmax 17-19.3 Gy (D0.035cc), V13 (<0.35cc)[84,84]	Dmax 12.2 Gy[80,84]	Dmax 20.3-22.5 Gy (D0.035cc), V15.9 (<0.35 cc)[80,81,83]	Dmax 14.5 Gy[80,84]	Dmax 23-25.6 Gy (D0.035cc), V19.2(<0.35 cc)[80,83]	Dmax 16.2 Gy[80,84]	Dmax 25.3-30 Gy (D0.035cc), V22 (<0.35 cc)[80,81,83]	Dmax 18 Gy[80,84]	Myelitis[83] Sahgal et al. [80]: Radiation myelopathy (1-5% risk for 1-5 fractions)	Myelitis[84]
Optic pathway	Dmax 10 Gy, V8(<0.2 cc)[83]	Dmax 8 Gy[24]	Dmax 17.3 Gy, V11.7 (<0.2 cc)[83]	-	Dmax 17.4 Gy, V15.3(<0.2cc)[83]	Dmax Gy, V15 < 0.2cc (Optic nerves)[24]	Dmax 21.2 Gy, V19.2(<0.2 cc)[83]	-	Dmax 25 Gy, V23 (<0.2 cc)[83]	Dmax 10 Gy[24]	Neuritis[83]	-
Cochlea	Dmax 10 Gy [83], Dmax 4-12 Gy[24]	Dmax 12 Gy[24]	Dmax 13.7 Gy [83]	-	Dmax 17.4 Gy [83], Dmax 20 Gy[24]	Dmax 24 Gy[24]	Dmax 21.2 Gy [83]	-	Dmax 22 Gy [83], Dmax 25-30 Gy[24]	Dmax 20-27.5 Gy[24]	Hearing loss[83]	-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 August 2023 doi:10.20944/preprints202308.2011.v1

Brain stem (not medulla)	Dmax 15 Gy, V10(<0.5 cc)[83]	Dmax 10-15 Gy, V10<1cc[24]	Dmax 17.3, V13 Gy (<0.5 cc)[83]	-	Dmax 23.1 Gy, V15.9 (<0.5 cc)[83]	Dmax 23 Gy, V18<1cc[24]	Dmax 27.2 Gy, V20.8 (<0.5 cc)[83]	-	Dmax 31 Gy, V23(<0.5 cc)[83]	Dmax 9-15 Gy[24]	Cranial neuropathy[83]	-
Esophagus	Dmax 24 Gy, V20 (< 5 cc)[83], Dmax 19 Gy[24]	Dmax 10 Gy[24]	Dmax 28.3 Gy, V24.3 (<5 cc) [83]	-	Dmax 32.4 Gy, V27.9(<5 cc) [83]	-	Dmax 35.6 Gy, V30.4(<30.4 cc)[83]	-	Dmax 38 Gy, V32.5(5 cc) [83], Dmax 27-35 Gy[24]	Dmax 20-25 Gy[24]	Esophagitis[83]	-
Brachial plexus	Dmax 16.4 Gy, V 13.6 (<3 cc)[83]	Dmax 10-16 Gy, V14.4 <3cc[24]	Dmax 20.8 Gy, V17.8 (<3 cc)[83]	-	Dmax 26 Gy, V22 (<3 cc)[83]	Dmax 23 Gy, V22.5 <3cc[24]	Dmax 29.6 Gy, V24.8 (24.8(3 cc)[83]	-	Dmax 32.5 Gy, V27 (3 cc)[83]	Dmax 20-32 Gy V30<3 cc[24]	Neuropathy[83]	-
Trachea	Dmax 30 Gy, V27.5(< 4 cc)[83]	-	Dmax 38 Gy, V 34.5(<4 cc)[83]	-	Dmax 43 Gy, V39<(5 cc)[83]	-	Dmax 47 Gy, V42.4(5 cc)[83]	-	Dmax 50Gy, V45(<5 cc)[83]	-	Stenosis[83]	-
Skin	Dmax 27.5 Gy, V25.5(10 cc)[83]	-	Dmax 30.3Gy. V28.3 (10cc)[83]	-	Dmax 33Gy, V31(10 cc)[83]	-	Dmax 54Gy, V33.6(10cc)[83]	-	Dmax 38.5Gy, V36.5(10 cc)[83]	Dmax 20 Gy[24]	Ulceration[83]	-
Brain	V12 Gy (10-15 cc)[85], Dmax 15-20 Gy V10<1cc[24]	Dmax 10 Gy[24]	-	-	20Gy (D20cc)[85], Dmax23 Gy V18<1cc[24]	-	-	-	24Gy (D20cc)[85], Dmax 10-25 Gy[24]	Dmax 20-23 Gy[24]	Milano et al.[85]: Symptomatic radiation necrosis (one fraction), oedema/necrosis (three and five fractions)	-
Carotid artery	-	Dmax 10 Gy[24]	-	-	-	-	-	-	Dmax 25–47 Gy[24]	Dmax 15–34 Gy < 50%	-	-

										gets PTV dose[24]		
Parotid	-	-	-	-	-	-	-	-	-	Dmax 20–25 Gy[24]	-	-
Lens	-	-	-	-	-	-	-	-	-	Dmax 6 Gy[24]	-	-
Larynx	-	-	-	-	-	-	-	-	Dmax 20 Gy[24]	Dmax 20 Gy[24]	-	-

Abbreviations: Dmax: Maximal dose; Fx: Fraction; OAR: Organ-at-risk; Re-RT: Re-irradiation.

Future directions

Recent advances in immunotherapeutic agents showed promising outcomes in the treatment of HNC. The combined application of these drugs alongside SBRT is currently under active research. For example, the RTOG 3507 phase II clinical trial, is exploring the use of re-irradiation with SBRT plus concurrent pembrolizumab for patients with recurrent HNSCC in a previously irradiated volume[75]. Furthermore, recent advances in RT technology such as magnetic resonance-guided radiation therapy (MRgRT) for HNCs allows precise treatment, facilitates tighter PTV margin/smaller irradiated volumes, evaluates tumor response with functional imaging i.e. DWI, with possibly response-adaptive RT. However, further research is required for evaluation of predictive MR imaging biomarkers, and the use of SBRT with MRgRT for patients with HNC who cannot tolerate long course RT[76]. Moreover, the impact of SBRT for HNC in the palliative setting aiming to improve HNC outcomes in patients who are unable to tolerate curative-intent RT is going to be investigated by the CCTG HN13 phase III randomized controlled trial (SBRT vs standard palliative RT).

Related: None declared

Unrelated: Ali Hosni: non-financial leadership (DSC) of liver TSG at ELEKTA MRL consortium

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/CAAC.21660
2. Gilyoma JM, Rambau PF, Masalu N, Kayange NM, Chalya PL. Head and neck cancers: a clinico-pathological profile and management challenges in a resource-limited setting. *BMC Res Notes*. 2015;8:772. doi:10.1186/s13104-015-1773-9
3. Khuri FR, Lee JJ, Lippman SM, et al. Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst*. 2006;98(7):441-450. doi:10.1093/JNCI/DJJ091
4. Vahl JM, Wigand MC, Denkinger M, et al. Increasing Mean Age of Head and Neck Cancer Patients at a German Tertiary Referral Center. Published online 2021. doi:10.3390/cancers13040832
5. Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer Survival and Incidence from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist*. 2003;8(6):541-552. doi:10.1634/THEONCOLOGIST.8-6-541
6. Lacas B, Carmel A, Landais C, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. *Radiother Oncol*. 2021;156:281. doi:10.1016/J.RADONC.2021.01.013
7. Shaikh H, Karivedu V, Wise-Draper TM. Managing Recurrent Metastatic Head and Neck Cancer. *Hematol Oncol Clin North Am*. 2021;35(5):1009-1020. doi:10.1016/J.HOC.2021.05.009
8. Peng KA, Grogan T, Wang MB. Otolaryngol Head Neck Surg. 2014;151(4):627-633. doi:10.1177/0194599814545747

9. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*. 2005;27(10):843-850. doi:10.1002/HED.20279
10. Weiss J, Sheth S, Deal AM, et al. Concurrent Definitive Immunoradiotherapy for Patients with Stage III-IV Head and Neck Cancer and Cisplatin Contraindication. *Clin Cancer Res*. 2020;26(16):4260-4267. doi:10.1158/1078-0432.CCR-20-0230
11. Mohamad I, Almousa A, Taqash A, et al. Primary radiation therapy for advanced-stage laryngeal cancer: A laryngo-esophageal dysfunction disease-free survival. Published online 2022. doi:10.1002/lio2.972
12. Al-Assaf H, Erler D, Karam I, et al. Stereotactic body radiotherapy for medically unfit patients with cancers to the head and neck. *Head Neck*. 2020;42(8):2050-2057. doi:10.1002/HED.26138
13. Russell JS, Brown JM. The irradiated tumor microenvironment: role of tumor-associated macrophages in vascular recovery. *Front Physiol*. 2013;4. doi:10.3389/FPHYS.2013.00157
14. Khan L, Tjong M, Raziee H, et al. Role of stereotactic body radiotherapy for symptom control in head and neck cancer patients. *Support Care Cancer*. 2015;23(4):1099-1103. doi:10.1007/S00520-014-2421-Y/FIGURES/2
15. Vargo JA, Ward MC, Caudell JJ, et al. A Multi-institutional Comparison of SBRT and IMRT for Definitive Reirradiation of Recurrent or Second Primary Head and Neck Cancer. *Int J Radiat Oncol Biol Phys*. 2018;100(3):595-605. doi:10.1016/J.IJROBP.2017.04.017
16. Amini A, McDermott JD, Gan G, et al. Stereotactic body radiotherapy as primary therapy for head and neck cancer in the elderly or patients with poor performance. *Front Oncol*. 2014;4(OCT). doi:10.3389/FONC.2014.00274
17. Vargo JA, Heron DE, Ferris RL, et al. Examining tumor control and toxicity after stereotactic body radiotherapy in locally recurrent previously irradiated head and neck cancers: implications of treatment duration and tumor volume. *Head Neck*. 2014;36(9):1349-1355. doi:10.1002/HED.23462
18. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science*. 2003;300(5622):1155-1159. doi:10.1126/SCIENCE.1082504
19. Brown JM, Carlson DJ, Brenner DJ. The Tumor Radiobiology of SRS and SBRT: Are More than the 5 R's Involved? *Int J Radiat Oncol Biol Phys*. 2014;88(2):254. doi:10.1016/J.IJROBP.2013.07.022
20. Siddiqui F, Patel M, Khan M, et al. Stereotactic body radiation therapy for primary, recurrent, and metastatic tumors in the head-and-neck region. *Int J Radiat Oncol Biol Phys*. 2009;74(4):1047-1053. doi:10.1016/J.IJROBP.2008.09.022
21. Kodani N, Yamazaki H, Tsubokura T, et al. Stereotactic body radiation therapy for head and neck tumor: disease control and morbidity outcomes. *J Radiat Res*. 2011;52(1):24-31. doi:10.1269/JRR.10086
22. Kawaguchi K, Sato K, Yamada H, et al. Stereotactic radiosurgery in combination with chemotherapy as primary treatment for head and neck cancer. *J Oral Maxillofac Surg*. 2012;70(2):461-472. doi:10.1016/J.JOMS.2011.02.063
23. Vargo JA, Ferris RL, Clump DA, Heron DE. Stereotactic body radiotherapy as primary treatment for elderly patients with medically inoperable head and neck cancer. *Front Oncol*. 2014;4. doi:10.3389/FONC.2014.00214
24. Karam I, Yao M, Heron DE, et al. Survey of current practices from the International Stereotactic Body Radiotherapy Consortium (ISBRTC) for head and neck cancers. *Future Oncol*. 2017;13(7):603-613. doi:10.2217/FON-2016-0403
25. Bisello S, Cilla S, Benini A, et al. Dose-Volume Constraints fOr oRganS At risk In Radiotherapy (CORSAIR): An "All-in-One" Multicenter-Multidisciplinary Practical Summary. *Curr Oncol*. 2022;29(10):7021-7050. doi:10.3390/CURRONCOL29100552
26. Sana D. Karam1*, James W. Snider1, Hongkun Wang2, Margaux Wooster1, Christopher Lominska3, John Deeken4, Kenneth Newkirk5 BD and KWH. Survival outcomes of patients treated with hypofractionated stereotactic body Radiation Therapy for Parotid Gland Tumors: a Retrospective Analysis. *Front Oncol*. 2(55).
27. Voruganti IS, Poon I, Husain ZA, et al. Stereotactic body radiotherapy for head and neck skin cancer. *Radiother Oncol*. 2021;165:1-7. doi:10.1016/J.RADONC.2021.10.004
28. Emile Gogineni 1, Zaker Rana 1, Prashant Vempati 1, Jessie Karten 1, Anurag Sharma 1, Peter Taylor 1, Lucio Pereira 2, Douglas Frank 2, Doru Paul 3, Nagashree Seetharamu 3 MG. Stereotactic body radiotherapy as primary treatment for elderly and medically inoperable patients with head and neck cancer. *Head Neck*. 42(10):2880-2886.
29. Malik NH, Kim MS, Chen H, et al. Stereotactic Radiation Therapy for De Novo Head and Neck Cancers: A Systematic Review and Meta-Analysis. *Adv Radiat Oncol*. 2021;6(1):100628. doi:10.1016/J.ADRO.2020.11.013
30. Le QTX, Fu KK, Kroll S, et al. Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys*. 1997;39(1):115-126. doi:10.1016/S0360-3016(97)00284-8
31. Dinshaw KA, Sharma V, Agarwal JP, Ghosh S, Havaldar R. Radiation therapy in T1-T2 glottic carcinoma: influence of various treatment parameters on local control/complications. *Int J Radiat Oncol Biol Phys*. 2000;48(3):723-735. doi:10.1016/S0360-3016(00)00635-0

32. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys*. 2006;64(1):77-82. doi:10.1016/J.IJROBP.2005.06.014
33. Garden AS, Forster K, Wong PF, Morrison WH, Schechter NR, Ang KK. Results of radiotherapy for T2N0 glottic carcinoma: Does the "2" stand for twice-daily treatment? *Int J Radiat Oncol Biol Phys*. 2003;55(2):322-328. doi:10.1016/S0360-3016(02)03938-X
34. Sher DJ, Timmerman RD, Nedzi L, et al. Phase 1 Fractional Dose-Escalation Study of Equipotent Stereotactic Radiation Therapy Regimens for Early-Stage Glottic Larynx Cancer. *Int J Radiat Oncol*. 2019;105(1):110-118. doi:10.1016/J.IJROBP.2019.03.010
35. Zhao B, Park YK, Gu X, Reynolds R, Timmerman R, Sher DJ. Surface guided motion management in glottic larynx stereotactic body radiation therapy. *Radiother Oncol*. 2020;153:236-242. doi:10.1016/J.RADONC.2020.08.027
36. Yu T, Wee CW, Choi N, et al. Study design and early result of a phase I study of SABR for early-stage glottic cancer. *Laryngoscope*. 2018;128(11):2560-2565. doi:10.1002/LARY.27226
37. Kang BH, Yu T, Kim JH, et al. Early Closure of a Phase 1 Clinical Trial for SABR in Early-Stage Glottic Cancer. *Int J Radiat Oncol Biol Phys*. 2019;105(1):104-109. doi:10.1016/J.IJROBP.2019.03.011
38. Tate DJ, Adler JR, Chang SD, et al. Stereotactic radiosurgical boost following radiotherapy in primary nasopharyngeal carcinoma: impact on local control. *Int J Radiat Oncol Biol Phys*. 1999;45(4):915-921. doi:10.1016/S0360-3016(99)00296-5
39. Le QT, Tate D, Koong A, et al. Improved local control with stereotactic radiosurgical boost in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2003;56(4):1046-1054. doi:10.1016/S0360-3016(03)00117-2
40. Hara W, Loo BW, Goffinet DR, et al. Excellent local control with stereotactic radiotherapy boost after external beam radiotherapy in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2008;71(2):393-400. doi:10.1016/J.IJROBP.2007.10.027
41. Chen HHW, Tsai ST, Wang MS, et al. Experience in fractionated stereotactic body radiation therapy boost for newly diagnosed nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;66(5):1408-1414. doi:10.1016/J.IJROBP.2006.07.1385
42. Uno T, Isobe K, Ueno N, et al. Fractionated stereotactic radiotherapy as a boost treatment for tumors in the head and neck region. *J Radiat Res*. 2010;51(4):449-454. doi:10.1269/JRR.10040
43. Hideya Yamazaki 1, Mikio Ogita 2, Kengo Himei 3, Satoaki Nakamura 4, Ken Yoshida 5, Tadayuki Kotsuma 5, Yuji Yamada 6, Masateru Fujiwara 7, Sungjae Baek 7 YY. Hypofractionated stereotactic radiotherapy using CyberKnife as a boost treatment for head and neck cancer, a multi-institutional survey: impact of planning target volume. *Anticancer Res*. 34(10):5755-9.
44. Lee DS, Kim YS, Cheon JS, et al. Long-term outcome and toxicity of hypofractionated stereotactic body radiotherapy as a boost treatment for head and neck cancer: the importance of boost volume assessment. *Radiat Oncol*. 2012;7(1). doi:10.1186/1748-717X-7-85
45. Al-Mamgani A, Tans L, Teguh DN, Van Rooij P, Zwijnenburg EM, Levendag PC. Stereotactic body radiotherapy: a promising treatment option for the boost of oropharyngeal cancers not suitable for brachytherapy: a single-institutional experience. *Int J Radiat Oncol Biol Phys*. 2012;82(4):1494-1500. doi:10.1016/J.IJROBP.2011.05.019
46. Baker S, Verduijn G, Petit S, et al. Locoregional failures and their relation to radiation fields following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. *Head Neck*. 2019;41(6):1622-1631. doi:10.1002/HED.25587
47. Baker S, Verduijn GM, Petit S, et al. Long-term outcomes following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. *Acta Oncol*. 2019;58(6):926-933. doi:10.1080/0284186X.2019.1581375
48. Sarah Baker 1, Gerda M Verduijn 1, Steven Petit 1, Aniel Sewnaik 2, Hetty Mast 3, Senada Koljenović 4, Joost J Nuyttens 1 WDH 1. Long-term outcomes following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. *Acta Oncol*. 58(6):926-933.
49. Vempati P, Halthore AN, Teckie S, et al. Phase I trial of dose-escalated stereotactic radiosurgery (SRS) boost for unfavorable locally advanced oropharyngeal cancer. *Radiat Oncol*. 2020;15(1). doi:10.1186/s13014-020-01718-w
50. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet (London, England)*. 2019;394(10212):1915-1928. doi:10.1016/S0140-6736(19)32591-7
51. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. doi:10.1038/s41577-020-0306-5

52. Caressa Hui, 1 Brittney Chau, 2 Greg Gan, 3 William Stokes, 4 Sana D. Karam 5 and Arya Amini. Overcoming Resistance to Immunotherapy in Head and Neck Cancer Using Radiation: A Review. *Front Oncol*. 11: 592319.
53. Leidner R, Crittenden M, Young K, et al. Neoadjuvant immunoradiotherapy results in high rate of complete pathological response and clinical to pathological downstaging in locally advanced head and neck squamous cell carcinoma. *J Immunother Cancer*. 2021;9:2485. doi:10.1136/jitc-2021-002485
54. Ma TM, Wong DJ, Chai-Ho W, et al. High Recurrence For HPV-Positive Oropharyngeal Cancer With Neoadjuvant Radiotherapy To Gross Disease Plus Immunotherapy: Analysis From a Prospective Phase Ib/II Clinical Trial. *Int J Radiat Oncol*. Published online May 2, 2023. doi:10.1016/J.IJROBP.2023.04.029
55. Darragh LB, Knitz MM, Hu J, et al. A phase I/Ib trial and biological correlate analysis of neoadjuvant SBRT with single-dose durvalumab in HPV-unrelated locally advanced HNSCC Check for updates. *Nat Cancer* |. 2022;3:1300-1317. doi:10.1038/s43018-022-00450-6
56. Shen P, Qiao B, Jin N, Wang S. Neoadjuvant immunoradiotherapy in patients with locally advanced oral cavity squamous cell carcinoma: a retrospective study. *Invest New Drugs*. 2022;40(6):1282-1289. doi:10.1007/S10637-022-01293-9/METRICS
57. Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(5):1411-1419. doi:10.1016/j.ijrobp.2009.06.070
58. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359(11):1116-1127. doi:10.1056/NEJMOA0802656
59. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. *Head Neck*. 2008;30(3):281-288. doi:10.1002/HED.20697
60. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *J Clin Oncol*. 2007;25(30):4800-4805. doi:10.1200/JCO.2006.07.9194
61. Cengiz M, Özyiit G, Yazici G, et al. Salvage reirradiaton with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. *Int J Radiat Oncol Biol Phys*. 2011;81(1):104-109. doi:10.1016/J.IJROBP.2010.04.027
62. Comet B, Kramar A, Faivre-Pierret M, et al. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head-and-neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys*. 2012;84(1):203-209. doi:10.1016/J.IJROBP.2011.11.054
63. Lartigau EF, Tresch E, Thariat J, et al. Multi institutional phase II study of concomitant stereotactic reirradiation and cetuximab for recurrent head and neck cancer. *Radiother Oncol*. 2013;109(2):281-285. doi:10.1016/J.RADONC.2013.08.012
64. Roh KW, Jang JS, Kim MS, et al. Fractionated Stereotactic Radiotherapy as Reirradiation for Locally Recurrent Head and Neck Cancer. *Int J Radiat Oncol Biol Phys*. 2009;74(5):1348-1355. doi:10.1016/j.ijrobp.2008.10.013
65. Rwigema JC, Heron DE, Ferris RL, et al. Fractionated stereotactic body radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma: updated report of the University of Pittsburgh experience. *Am J Clin Oncol*. 2010;33(3):286-293. doi:10.1097/COC.0B013E3181AACBA5
66. Heron DE, Ferris RL, Karamouzis M, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1493-1500. doi:10.1016/J.IJROBP.2008.12.075
67. Heron DE, Rwigema JCM, Gibson MK, Burton SA, Quinn AE, Ferris RL. Concurrent cetuximab with stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: a single institution matched case-control study. *Am J Clin Oncol*. 2011;34(2):165-172. doi:10.1097/COC.0B013E3181DBB73E
68. Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(5):1411-1419. doi:10.1016/J.IJROBP.2009.06.070
69. Roh KW, Jang JS, Kim MS, et al. Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2009;74(5):1348-1355. doi:10.1016/J.IJROBP.2008.10.013
70. Ansinelli H, Singh R, Sharma DL, et al. Salvage Stereotactic Body Radiation Therapy for Locally Recurrent Previously Irradiated Head and Neck Squamous Cell Carcinoma: An Analysis from the RSSearch® Registry. Published online 2018. doi:10.7759/cureus.3237
71. Vargo JA, Kubicek GJ, Ferris RL, et al. Adjuvant stereotactic body radiotherapy±cetuximab following salvage surgery in previously irradiated head and neck cancer. *Laryngoscope*. 2014;124(7):1579-1584. doi:10.1002/LARY.24441
72. Biau J, Thivat E, Millardet C, et al. A multicenter prospective phase II study of postoperative hypofractionated stereotactic body radiotherapy (SBRT) in the treatment of early-stage oropharyngeal and

oral cavity cancers with high risk margins: the STEREO POSTOP GORTEC 2017-03 trial. *BMC Cancer*. 2020;20(1). doi:10.1186/S12885-020-07231-3

73. Collan J, Lundberg M, Vaalavirta L, et al. Acta Oncologica Patterns of relapse following surgery and postoperative intensity modulated radiotherapy for oral and oropharyngeal cancer. Published online 2011. doi:10.3109/0284186X.2010.549839
74. Chan AK, Huang SH, Le LW, et al. Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure. *Oral Oncol*. 2013;49(3):255-260. doi:10.1016/J.ORALONCOLOGY.2012.09.006
75. Wong S, Torres-Saavedra P, Le QT, et al. Safety of reRT with SBRT plus concurrent and adjuvant pembrolizumab in patients with recurrent or new second primary head and neck squamous cell cancer in a previously irradiated field: RTOG 3507 Foundation (KEYSTROKE). *Int J Radiat Oncol*. 2020;106(5):1224-1225. doi:10.1016/j.ijrobp.2020.02.010
76. Lavigne D, Ng SP, O'sullivan B, et al. Magnetic Resonance-Guided Radiation Therapy for Head and Neck Cancers. *Curr Oncol 2022, Vol 29, Pages 8302-8315*. 2022;29(11):8302-8315. doi:10.3390/CURRONCOL29110655
77. Kataria T, Basu T, Goyal S, et al. Preliminary results of CyberKnife stereotactic radiotherapy (SBRT) boost for primary head and neck cancers: is it the future direction? *J Radiother Pract*. 14(2):187-193.
78. Planned Gamma Knife Boost After Chemoradiotherapy for Selected Sinonasal and Nasopharyngeal Cancers. *World Neurosurg*. 119:e467-e474.
79. Vempati P, Halthore AN, Teckie S, et al. Phase I trial of dose-escalated stereotactic radiosurgery (SRS) boost for unfavorable locally advanced oropharyngeal cancer. Published online 2020. doi:10.1186/s13014-020-01718-w
80. Sahgal A, Chang JH, Ma L, et al. HyTEC Organ-Specific Paper: Spinal Cord Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy Radiation Oncology. *Int J Radiat Oncol Biol Phys*. 110(1):2021. doi:10.1016/j.ijrobp.2019.09.038
81. Stanley H Benedict 1, Kamil M Yenice, David Followill, James M Galvin, William Hinson, Brian Kavanagh, Paul Keall, Michael Lovelock, Sanford Meeks, Lech Papiez, Thomas Purdie, Ramaswamy Sadagopan, Michael C Schell, Bill Salter, David J Schlesinger, Almon FFY. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys*. 39(1):563.
82. Zhang Y, Chiu T, Dubas J, et al. Benchmarking techniques for stereotactic body radiotherapy for early-stage glottic laryngeal cancer: LINAC-based non-coplanar VMAT vs. Cyberknife planning. *Radiat Oncol*. 2019;14(1). doi:10.1186/S13014-019-1404-Z
83. Timmerman RD. A Story of Hypofractionation and the Table on the Wall. *Int J Radiat Oncol Biol Phys*. 2022;112(1):4-21.
84. Sahgal A, Ma L, Weinberg V, et al. Reirradiation Human Spinal Cord Tolerance for Stereotactic Body Radiotherapy. *Int J Radiat Oncol*. 2012;82(1):107-116. doi:10.1016/J.IJROBP.2010.08.021
85. Milano MT, Grimm J, Niemierko A, et al. Single and Multi-fraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain HHS Public Access. *Int J Radiat Oncol Biol Phys*. 2021;110(1):68-86. doi:10.1016/j.ijrobp.2020.08.013