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REWIEW

# Current Status and Future Aspects of Stereotactic Body Radiotherapy and Immunotherapy in the Management of Recurrent Head and Neck Cancer

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**SUMMARY**

The rate of loco-regional recurrence and secondary primary tumors is high in patients with head and neck cancer (HNC). Although surgery is very effective in the management of these patients, total resection is rarely possible due to anatomic and functional constraints. In patients not amenable to surgery, chemoradiotherapy plays a major role and stereotactic body radiotherapy (SBRT) is the treatment of choice based on its advantage of high therapeutic ratio. Recent advances in immunotherapeutic agents also provide promising results in many tumor sites and may have advantages in the treatment of recurrent HNC. Concurrent use of these agents with SBRT is still being investigated.

**Keywords:** Head and neck cancer; immunotherapy; radiotherapy; recurrent; stereotactic body radiotherapy.



## Introduction

The incidence of loco-regional recurrence (LRR) in patients with head and neck cancer (HNC) following definitive treatment has been reported as 15-50%.[1,2] The risk of second primary HNC was reported as high as 40% in patients with previously treated HNC.[3] It was shown that surgery is the most effective treatment for previously irradiated locally-recurrent or second primary HNC; however, the applicability of surgery remains <20% due to anatomical and functional constraints.[4] In patients that cannot undergo salvage surgery, concurrent chemoradiotherapy (CRT) is the treatment of choice. The prognosis is poor when chemotherapy (CT) alone is administered, with a median survival of 7.4 months.[2,5] Prior irradiation is an independently poor prognostic factor for CT in recurrent HNC.[2,6] Based on these data, in patients who are not candidates for salvage surgery, a potentially curative option is re-irradiation. However, re-irradiation for HNC is a clinical challenge due to the increased risk of morbidity and even mortality. Besides, the radio-resistant tumor cells lead to a high failure rate despite aggressive treatment. The 2-year overall survival (OS) rates range between 17% and 26% with high rates of grade ≥3 late toxicity.[7,8] Using 2-dimensional (2-D) and 3-D conformal RT led to LRR rates up to 50% and treatment-related mortality rates up to 20%.[9,10] Considering these results, highly conformal re-irradiation techniques have been given considerable attention with an aim to increase the therapeutic ratio.

Among the highly conformal RT techniques, such as intensity-modulated radiotherapy (IMRT) and proton RT, stereotactic body radiotherapy (SBRT) allows delivering higher doses besides better preserving the organs at risk, which are usually very close to the target in HNC. These techniques have been shown to improve the rates of local control (LC) and survival compared to traditional RT techniques.[11,12]

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It has been shown that concurrent CT sensitizes the effects of RT. Given the high rates of toxicity and still under-desired response rates, immunotherapy opens as a secret door to higher efficacy with less toxicity. The aim of this review is to present the recent data on the results of SBRT and immunotherapy in the treatment of recurrent HNC.

**1. SBRT in Recurrent HNC**

The critical organs are in close proximity to the target volume, and the response of these organs to irradiation differs from the response of the main tumor in HNC. Using SBRT, a very steep dose gradient is achieved, allowing a higher chance of tumor control without increasing toxicity. The shorter overall treatment time increases the LC rate by preventing the accelerated repopulation of tumor clonogens.[13] However, hypofractionation may also impair the sublethal damage repair leading to an increased rate of late toxicity. Therefore, it is crucial to identify the target volume with high conformality and precision. SBRT typically delivers 1-5 fractions, and it has several advantages over conventional fractionation, such as shorter overall treatment duration and lower resource burden, as well as improved patient convenience and a shorter interval to systemic therapy.

Different dose and fractionation schemes have been used in the studies of SBRT in recurrent HNC, ranging from 30-36 Gy in 6 fractions to 44-50 Gy in 5 fractions with a biologically equivalent dose given in 2-Gy fractions (EQD2) between 40 Gy and 101.1 Gy. Studies on SBRT in recurrent HNC are mostly retrospective and single-institution reports. The retrospective studies with >20 patients are summarized in Table 1. Table 2 shows the prospective studies on SBRT in recurrent HNC. The rate of 1-year LC and OS ranges between 37% and 79%, and 38% and 83%, respectively, in these studies.

The definition of gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) vary in the published studies. While some authors did not add any margin to the GTV to create CTV and PTV,[14,15] Roh et al.[16] added 2-3 mm, and Unger et al.[17] added 2-10 mm to the GTV to create CTV. Wang et al.[14] recommended a 5-mm margin to the GTV to adequately cover the microscopic disease after evaluating the areas under high risk for recurrence. The authors reported that more than 60% of the recurrences occurred as overlapped or marginal to the PTV, whereas only <20% occurred inside the PTV.

Compared to traditional RT techniques, re-irradiation using SBRT provides improved LC and reduced toxicity. The predominant pattern of failure is local or marginal.[11,18] Local recurrence (LR) often develops inside the RT field, which constitutes a clear proof that recurrent parts of tumors are radio-resistant.[11] Another pattern is a marginal recurrence, which arises from a geometric miss. LR usually develops as multi-centric and multifocal sites, with mostly undifferentiated histopathology. Therefore, the more precise the RT delivery is, the more successful the treatment concludes. Thus, elective nodal irradiation is not recommended unless the neck is involved.

The total prescription dose varies widely among studies. The study of Rwigema et al.[19] is the only SBRT study to show a higher rate of loco-regional control (LRC) with a higher dose. In this study, the 2-year LRC rate was found 58% with doses 40-50 Gy compared to 32% with 15-36 Gy. In addition, Heron et al.[20] reported a higher OS with >40 Gy SBRT compared to doses ≤40 Gy. Based on these studies, SBRT doses of ≥40 Gy can be recommended in the treatment of recurrent HNC to obtain better survival and LC.

In addition to the total dose, tumor volume is also important for the outcomes of SBRT. The smaller the tumor volume is, the higher the LRC and OS rates have been reported. However, the threshold of the GTV varies between <15 and 25 $cm^3$ [19,21-23], and the PTV is ≤40 $cm^3$ in SBRT studies.[24] On the other hand, increased toxicity is inevitable with increased tumor volumes.[22,23]

**Toxicity of SBRT**

As expected, the re-irradiation of HNC comes with a price. The most common acute toxicities include mucositis, nausea, fatigue, dermatitis and odynophagia.[25] Studies on SBRT in HNC have reported ≥grade 3 late toxicity rates up to 25%, and grade 5 late toxicity rates up to 15%, predominantly due to carotid blow-out syndrome (CBOS). Other common late toxicities include fibrosis, fistula formation, aspiration, dysphagia, permanent feeding tubes, trismus, osteoradionecrosis, bone or soft tissue necrosis, otitis media, cranial nerve palsies, and brain necrosis.[25,26] The reason for the high rates of serious late toxicity is the close proximity of critical structures to the target. Prior RT dose, re-irradiation dose, treatment volume, and re-irradiation technique also affect the risk of severe late complications.

Although recent IMRT series have reported the rate of CBOS 0-3%, the rate increases to 9-18% in SBRT studies. The risk factors for CBOS were reported as tumor encasing ≥180° around the carotid artery, total dose to the carotid artery, presence of ulceration, and lymph node irradiation.[15,21,24] A simple strategy to decrease the rate of grade 5 CBOS is to administer RT every other day and to keep the carotid artery dose below 34 Gy.[27]

**Table 1** Retrospective studies of re-irradiation via SBRT in recurrent HNC

| Study | N of patients | Median FU (months) | Median total dose (range)/N of fractions | LC (%) | OS (%) | Toxicity |
|---|---|---|---|---|---|---|
| Roh et al., 2009 [16] | 36 (44 sites) | 17.3 | 30 Gy (18-40)/3-5 | 1y: 61<br>2y: 52 | 1y: 52<br>2y: 31 | G4-5: 9%<br>G5: 3% |
| Siddiqui et al., 2009 [58] | 44 (21 re-RT for 29 sites) | 6.7 | 36-48 Gy /6-8 or 14-18 Gy/1 | 1y: 61<br>2y: 40 | 1y: 38<br>2y: 14 | G3-4: 24% |
| Kawaguchi et al., 2010 [59] | 22 | 24 | 20-42 Gy/2-5 | CR: 64%<br>PR: 7% | 55 | ≥G3:0% |
| Unger et al., 2010 [17] | 65 | 16 (survivors) | 30 Gy (21-35/2-5 | 2y: 30 | 2y: 41 | G4: 9% |
| Ozyigit et al., 2011 [28] | 24 | 23 | 30 Gy/5 | 2y: 82 | 2y**: 64 | ≥G3:21%<br>G5: 12.5% |
| Rwigema et al., 2011 [19] | 96 | 14 | 35 Gy (20-50)/5 | For ≥40 Gy<br>1y: 79<br>2y: 58<br>For <40 Gy<br>1y: 52<br>2y: 32 | 1y: 59<br>2y: 28 | G3: 3%<br>G4-5: 0% |
| Cengiz et al., 2011 [15] | 46 | 11.9 | 30 Gy (25-30)/5 | CR: 27%<br>PR: 30% | 1y: 47 | G5 CBOS: 15% |
| Kodani et al., 2011 [21] | 34 (21 reRT) | 16 | 30 Gy (19.5-42)/3-8 | For ReRT<br>CR: 29%<br>PR: 33% | 1y: 71<br>2y: 58 | ≥G3:18%<br>G5: 6%<br>CBOS: 6% |
| Heron et al., 2011 [20] | 70 (35 and 35)* | 21.3 and 24.8* | 40 Gy (20-44)/5 | NA | 1y: 53 and 66*<br>2y: 21 and 53* | G3: 4%<br>≥G4: 0% |
| Vargo et al., 2014 [23] | 132 | 6 | 44 Gy (35-50)/5 | 1y: 48 | 1y: 38 | ≥G3:7% |
| Dizman et al., 2014 [60] | 24 | 19.5 | 30 Gy (24-30)/4-6 | 1y: 64<br>2y: 38<br>3y: 21 | 1y: 83<br>2y: 43<br>3y: 31 | ≥G3:8% |
| Kress et al., 2015 [61] | 85 | 17.3 (survivors) | 30 Gy (16-41)/5 | 1y: 58<br>2y: 28 | 1y: 51<br>2y: 24 | G3-4: 6% |
| Yamazaki et al., 2016 [24] | 107 | 15 | 30 Gy (25-37)/5 | 2y: 64 | 1y: 55<br>2y: 35 | ≥G3:22%<br>G5 CBOS: 8% |

HNC: Head and neck cancer; SBRT: Stereotactic body radiation therapy; N: Number; FU: Follow-up; LC: Local control; OS: Overall survival; CR: Complete response; PR: Partial response; CBOS: Carotid blow-out syndrome; RT: Radiotherapy; NA: Not applicable; G: Grade; *without and with concurrent cetuximab, respectively; **cancer-specific survival

**Hacettepe University Experience of SBRT in Recurrent HNC**

We, as Hacettepe University Department of Radiation Oncology, have a more than 10-year experience of re-irradiation of HNC using SBRT. In 2011, we compared our treatment results in 51 patients with recurrent nasopharyngeal cancer that were re-irradiated using SBRT and 3-D conformal RT with or without brachytherapy.[28] The median re-irradiation dose was 30 Gy in 5 fractions, and 57 Gy in 2 Gy/day, respectively. After a median follow-up of 24 months, the rate of 2-year cancer-specific survival was 64% and 47%, and actuarial LC was 82% and 80%, respectively. Although the LC and survival rates were similar, the rate of ≥ grade 3 late toxicity was significantly higher in the 3-D conformal RT arm (48% vs. 21%). Upon these results, we recommended using SBRT in the treatment of recurrent HNC if the patient was already irradiated.

We also presented our results of re-irradiation in 46 patients with recurrent HNC treated using Cyberknife (Accuray, Sunnyvale, CA, USA).[15] The median SBRT dose was 30 Gy (18–35 Gy) in a median of 5 (1-5) fractions. At the last follow-up, 10 patients had a complete response, 11 had a partial response, and 10 had stable disease with an actual LC rate of 83.8%. We found the median OS 11.93 months and the median progression-free survival (PFS) 10.5 months. The rate of 1-year OS and PFS was 46 % and 41%, respectively, with a rate of

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**Table 2** Prospective studies of re-irradiation via SBRT in recurrent HNC

| | N of patients | Median FU (months) | Median total dose (range)/N of fractions | LC (%) | OS (%) | Toxicity |
|---|---|---|---|---|---|---|
| Heron et al., 2009 [62] | 25 | NA | 40 Gy (25-44)/5 | CR: 4% PR: 12% | Median: 6 months | G3: 2.8% and 5.6%* |
| Comet et al., 2012 [44] | 40 | 25.6 | 36 Gy/6 | CR: 38% PR: 30% | 1y: 58 2y: 24 | G3: 10% ≥G4: 0% |
| Lartigau et al., 2013 [43] | 56 | 11.4 | 36 Gy/6 | CR: 49% PR: 20% | 1y: 48 | ≥G3:32% G5: 2% |
| Vargo et al., 2014 [22] | 48 | 18 (survivors) | 40-44 Gy/5 | 1y: 37 | 1y: 40 | G3: 6% ≥G4: 0% |

HNC: Head and neck cancer; SBRT: Stereotactic body radiation therapy; N: Number; FU: Follow-up; LC: Local control; OS: Overall survival; CR: Complete response; PR: Partial response; NA: Not applicable; *without and with concurrent cetuximab, respectively

13.3% ≥ grade 2 late toxicity. CBOS was observed in 8 (17.3%) patients, and 7 of them were succumbed to this complication. When we evaluated further, we discovered that death was observed only when the tumor was surrounding the carotid artery and the carotid artery received 100% of the prescribed dose.

Based on the high rate of CBOS, we changed our treatment policy and started to irradiate recurrent HNC patients every other day, and published the results in 2013.[27] We compared the results of 43 patients irradiated on consecutive days with the results of 32 patients irradiated every other day. Median OS was 11 months and 23 months, respectively (p=0.006). CBOS was observed in a total of 11 patients with a mortality of 86% in consecutive treatment and 50% in the every-other-day treatment. The median CBOS-free OS was nine months and 23 months, respectively (p=0.002). The threshold dose for CBOS was detected 34 Gy, with no patients developing CBOS when received under this dose. Based on these studies, we have been treating recurrent HNC patients every other day since 2013, and trying to keep the maximum dose to the carotid artery <34 Gy.

**2. Immunotherapy in Recurrent HNC**

It has been shown that concurrent systemic therapy sensitizes the effects of radiation in the treatment of primary HNC at the expense of increased toxicity rate. However, to our knowledge, there are no prospective trials on the comparison of re-irradiation with and without concurrent systemic therapy, although a retrospective study on re-irradiation of HNC using SBRT reported increased serious toxicity with concurrent chemotherapy.[23] The use of concurrent targeted agents, such as cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, has been shown to improve the outcomes without increasing toxicity in the primary treatment of HNC.[29-31]

Cetuximab is the first targeted agent used in the treatment of HNC. Dysregulation of the EGFR pathway is common in HNC, and it has been shown that high EGFR expression leads to worse outcomes.[32] Cetuximab inhibits the proliferation of tumor cells and stimulates the pro-apoptotic pathways within these cells by preventing the ligand-mediated activation and dimerization of EGFR.[33-35] It also limits the translocation of EGFR into the nucleus and prevents the activation of the deoxyribonucleic acid (DNA)-dependent protein kinase resulting in the inhibition of the repair of double-strand DNA break which may also affect the pathways of distant metastasis (DM).[36,37] Another mechanism is the induction of antibody-dependent cell-mediated cytotoxicity (ADCC), which targets and kills the cells coated in immunoglobulin (Ig)-G1 and other antibodies and maximizes antitumor effects using natural killer (NK) cells.[33,34,38] The stimulation of ADCC is the main mechanism that makes cetuximab adequate for the treatment of recurrent HNC, which differentiates it from panitumumab, an IgG2 antibody with lower clinical activity in recurrent HNC.[39,40] In the first-line treatment of recurrent and metastatic HNC, adding cetuximab to cisplatin/carboplatin and 5-fluorouracil followed by maintenance cetuximab (the EXTREME regimen) resulted in better outcomes concerning overall response rate, OS, and PFS compared to the chemotherapy-only-arm, independent from the human papillomavirus (HPV) status.[30,41] The addition of cetuximab also resulted in improved social functioning and quality of life.[42] However, the 80% rate of grade 3-4 toxicity in both arms of this study should not be overlooked.

There are data on the positive effects of adding concurrent cetuximab on LC and survival compared to re-irradiation via SBRT alone.[20,22,43,44] Heron et al.[20] retrospectively observed a complete response in

34% and 46% of patients that underwent SBRT alone and SBRT with concurrent cetuximab, respectively, with similar toxicity rates. This study led the way to prospective trials on the use of cetuximab in the re-irradiation of recurrent HNC. In a phase I trial, Comet et al.[44] showed the feasibility of cetuximab concurrent with SBRT in recurrent HNC with a response rate of 75% and mild toxicity. In the phase II trial of Vargo et al.[22], concurrent cetuximab with SBRT resulted in a 1-year OS 40%, local PFS 60%, loco-regional PFS 37%, and distant PFS 71% with a late grade 3 toxicity of 6%. In another phase II trial, Lartigau et al.[43] administered concurrent cetuximab with an SBRT dose of 36 Gy in 6 fractions and reported the 1-year OS rate 47.5%, LC rate 92%, and grade 3 toxicity 30%.

In recent years, interest in immunotherapy has risen. Immune checkpoint inhibitors (ICI) interrupt the immunosuppressive pathways, which are called inhibitory checkpoints. These checkpoints are used by tumor cells to hide from the detection and elimination by the immune system of the host.[45,46] The molecular targets of ICIs on T cells include cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) receptor, and this PD-1's corresponding ligand, PD-L1, which is found on both tumor and immune cells.[45,46] The examples are ipilimumab and tremelimumab, which are anti-CTLA-4 antibodies, nivolumab and pembrolizumab, which are anti-PD-1 antibodies, and durvalumab and avelumab, which are anti-PD-L1 antibodies. The higher the levels of endogenous PD-L1 expression, the more successful these antibodies are.[45]

PD-1 inhibitors are shown to be effective in HNC patients with DM.[47-49] A randomized phase III trial compared nivolumab and standard systemic therapy in recurrent HNC and reported increased OS rate with nivolumab.[50] The KEYNOTE-028 trial on the effects of pembrolizumab in recurrent and metastatic nasopharyngeal cancer patients with ≥1 PD-L1 expression reported an overall response rate of 74.1%.[51] A phase I trial of pembrolizumab for recurrent and metastatic HNC in 56 patients with ≥1 PD-L1–positive staining reported a 20% overall response rate, regardless of HPV status.[52] However, the rate of long-term durable response and survival was achieved in <5% of the patients.

There is evidence that RT and ICI have synergistic effects in the treatment of HNC given that ICI can overcome the negative effects of RT on the tumor microenvironment.[53,54] Besides, the antigenic response to RT may also increase the effectiveness of ICI. In the ongoing CheckMate 651 trial, nivolumab and ipilimumab together are compared to the EXTREME regimen. In the KEYNOTE-048 trial, pembrolizumab is under investigation either alone and in combination with systemic chemotherapy. Durvalumab is also being examined either alone and in combination with in the KESTREL study. While waiting for the results of these trials, the use of ICIs as a first-line treatment in recurrent or metastatic HNC is not recommended outside of clinical trials.

The potential synergy between SBRT and concurrent systemic targeted and immunotherapeutic agents have been reported in lung cancer and melanoma patients.[55] The high dose-per-fraction in SBRT may affect as a potential immune stimulant and induce an abscopal effect in patients treated simultaneously with PD-1 checkpoint inhibitors by increasing T cell activity. As patients with recurrent HNC are at high risk for regional and DM, this may particularly be important in patients that will be re-irradiated with limited volumes. The KEYSTROKE trial (RTOG 3507) is currently ongoing to compare SBRT re-irradiation alone to SBRT re-irradiation and pembrolizumab.

There are several challenges regarding the timing of RT, timing of immune checkpoint blockade and RT, and optimal site for treatment in metastatic cases. In this context, Vanpouille-Box et al.[56] published a promising study showing that exonuclease TREX1 abrogated the immunogenicity of irradiated cancer cells by degrading interferon-stimulatory cytosolic double-strand DNA. TREX1 upregulation by radiation dose per fraction beyond a threshold of 10-12 Gy resulted in poor synergy with immune checkpoint blockers. They also showed that 24 Gy in three fractions seems to be stimulating the immune response more efficiently compared to lower doses, similar to one fraction-based schemes, such as 20 Gy in one fraction. Based on this preclinical study, we administered an SBRT dose of 24 Gy in three fractions and immunotherapy to our two patients with recurrent/metastatic sinonasal cancer.[57] We achieved excellent local responses in both cases without any significant side effects with such a low SBRT dose regimen. To our knowledge, those two cases are the first clinical proof supporting the findings of Vanpouille-Box et al.

## Conclusion

Many retrospective and prospective trials on SBRT in recurrent HNC have reported response rates over 50% with a not-so-negligible rate of serious toxicity. However, SBRT is an exquisite treatment option for patients with recurrent HNC, particularly when used concurrently with systemic antitumor agents. Recently popular ICI has been reported to be lead to impressive results. However, studies with ICI and concurrent SBRT are very few, and some studies are still ongoing. Clinicians should be aware of the toxicity profile of these treatments and should decide on a patient basis. The

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results of ongoing studies are likely to provide us more insightful information about the patient group that will best benefit from ICI.

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