TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2018;33(1):38–41
doi: 10.5505/tjo.2018.1753

REWIEW

Stereotactic Re-irradiation for Recurrent or Second Primary Head-and-Neck Cancer

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SUMMARY

Local recurrence after definitive radiotherapy for advanced head-and-neck cancer is observed in 30%–60% of the patients. Surgical resection is possible in only about 25% of the cases. Re-irradiation for local recurrence is most of the times the only local treatment option. However, it is highly morbid with a poor success rate. Stereotactic radiotherapy is a highly conformal radiotherapy technique, usually with hypofractionation. Most of the authors use 5–6 fractions by 6–8 Gy. Median OS rates vary between 12 and 24.5 months. Concomitant use of cetuximab may also have some beneficial effects. Recent multicentric RPA analysis from North America suggested the classification of patients into prognostic groups and advised selection of treatment protocols according to the RPA class of the patients. The authors also compared IMRT with SBRT for re-irradiation. They could not show any significant difference between the treatment techniques. Carotid artery blowout syndrome is one of the lethal toxicities of re-irradiation. Limiting radiation dose to the carotid artery is important for the prevention of such toxicities. However, there is currently no consensus pertaining to carotid artery doses in the literature.

Keywords: Head and neck cancer; reirradiation; SBRT.

Introduction

Re-irradiation, SBRT, Head-and-Neck Cancer

Treatment of head-and-neck cancer (HNC) is performed by surgery, radiotherapy, and chemotherapy modalities alone or together. Nonetheless, 30%–60% of patients develop local recurrence or secondary cancer in the irradiated field.[1]

Re-irradiation is a potentially curative treatment option for some patients with unresectable disease. However, increased risk of severe or life-threatening treatment-related toxicity and tumor radioresistance pose challenges to re-irradiation. Because locoregional progression is the most common cause of death in patients with HNC, obtaining local control may effect the survival of patients with locoregionally failed disease. In addition, local tumor progression may affect morbidity due to disfigurement in appearance, uncontrollable pain, cancer bleeding, infection, and impairment of speech and swallowing, thus resulting in a poor quality of life. Patients with recurrent or second primary HNC having a history of irradiation comprise a challenging heterogeneous group. Published data include diverse recurrent or second primary tumors in the extent and location, prior radiotherapy (RT) parameters, elapsed time since prior treatment, and extent and severity of normal tissue sequelae. Data in current literature on acute and late normal tissue recovery from prior treatment are not available. Lack of data pertaining to re-irradiation tolerance poses significant challenges or even

Received: March 12, 2018
Accepted: March 12, 2018
Online: March 16, 2018

Accessible online at:
www.onkder.org

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leads to fear pertaining to meeting these patients daily in the clinic. Recently, high precision RT, including intensity-modulated radiotherapy (IMRT), has demonstrated the ability to reduce toxicity and improve disease control. Novel systemic agents and radiotherapy techniques, including stereotactic body RT (SBRT) and proton therapy, are also being actively explored.[2]

Salvage surgery is the standard for patients suitable for surgery, but it can be successfully performed only in 25% of patients. In a Phase II multicenter randomized trial (Radiation Therapy Oncology Group [RTOG] 99-01), the outcome of chemotherapy treatment with post-surgical re-irradiation in recurrent disease was evaluated.[3] Overall, 130 patients who underwent salvage surgery were randomized to the observation and chemoradiotherapy arms. Local control and disease-free survival were increased in the chemoradiotherapy arm.[4,5]

Chang et al showed that age, Charlson comorbidity index score, clinical stage at first diagnosis, and recurrence-free interval were significant independent prognostic factors for overall survival (OS) of patients with recurrent head-and-neck squamous cell carcinoma (HNSCC). Regardless of the recurrence stage or site, salvage surgery is the recommended procedure. Re-RT alone and concurrent chemoradiotherapy are more suitable for inoperable recurrent HNSCCs.[6]

The use of SBRT with re-irradiation in recurrent disease has demonstrated the advantages of better protection of organs at risk and higher doses in the target volume. The duration of treatment is shortened in patients with poor prognosis due to hypofractionation.
Unger et al reported the outcome of 65 patients treated with median 30 Gy (21-35) SBRT in 2–5 fractions (33 patients received concomitant chemotherapy). Median OS for all patients was 12 months, and 2-year OS and locoregional control (LRC) rates were 41% and 30%, respectively. Complete response, partial response, and progressive disease rates were 54%, 27% and 20%, respectively. Higher total dose, surgical resection, and nasopharynx site were significantly associated with improved LRC; surgical resection and non-squamous histology were associated with improved OS.[7] In a retrospective analysis of 46 patients in whom Cengiz et al performed a median 30 Gy (18–35 Gy) SBRT in 1–5 fractions, the OS at 1 year was 46%. Complete response, partial response, and stable disease rates were 27%, 30%, and 27%, respectively.[8] Treatment responses were similar to those observed in other studies, but the late grade 4 toxicity rate was high. Of the 8 patients with late carotid blowout, 7 died due to carotid hemorrhage.[9]

The 1-year OS rate was 47% for a Phase II multicenter study in which Lartigau et al used concomitant cetuximab with 36 Gy SBRT in 6 fractions between 11 and 12 days for the treatment of patients with recurrent or newly diagnosed HNC. Complete response, partial response, and stable disease rates were 49%, 20%, and 23%, respectively. Grade 3/4 toxicity was seen in 32% of patients. Only one patient died because of the choice of patients with the carotid artery wrapped around a fewer than third of the carotid artery, resulting in a carotid blowout.[10] Seventy patients in the Pittsburgh series were retrospectively matched and analyzed. Of these, 35 patients received concurrent cetuximab treatment with SBRT and the remaining patients received only SBRT. In the cetuximab group, OS was higher (24.5 vs. 14.8 months). Grade 3/4 toxicity was not different between the two groups.[11] Patient selection criteria, differences in tumor histology, radiotherapy fractionation, and dose differences make it difficult to compare studies. In conclusion, phase III multicenter trials are needed to demonstrate whether the 2-year median survival, particularly Heron et al.'s study, is reproducible.[12]

A multi-institutional study validated the recursive partitioning analysis (RPA) classification for patients with unresected recurrences treated with SBRT and compared outcomes of patients with unresected disease treated with IMRT.[13] Authors have analyzed 412 patients from 7 institutions in North America. RPA identified 3 prognostic subgroups: class I included patients >2 years from initial RT with resected tumors; class II included patients >2 years from initial RT with unresected tumors or those ≤2 years without feeding tube or tracheostomy dependence; and the remaining patients formed class III. The authors highlighted the differences between the cohorts, a reflection of the selection bias inherent in retrospective studies where treatment is typically selected based on the baseline characteristics. SBRT-treated patients had a shorter interval between RT courses (1.2 years vs. 3.1 years) and were more likely to have prior chemotherapy (64% vs. 46%) than IMRT-treated patients. After adjustment analysis, differences in OS and locoregional failure (LRF) between IMRT and SBRT were no longer statistically significant. In a second attempt to minimize bias introduced by baseline differences, a subgroup analysis by RPA class was performed. In the poor-prognosis class III group, the investigators observed a statistically insignificant difference in 2-year OS with IMRT than with SBRT (16.2% vs. 3.6%). Among class II patients, IMRT was associated with a statisti-

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cally significantly better 2-year OS rate compared with SBRT (39.1% vs. 18.6%, P < .001). This difference was attenuated substantially when further stratified by tumor size and SBRT dose. Specifically, patients with small tumors (≤25 cm3 or rT0-2) treated with ≥35 Gy of SBRT had a 2-year OS rate closer to that of patients treated with IMRT (38.5% vs. 50%). For patients with larger tumors treated with SBRT, the OS difference remained significantly worse than that in those treated with IMRT irrespective of the SBRT dose (28.2% with IMRT vs. 9.1% with SBRT <35 Gy or 8.8% with SBRT ≥35 Gy). The rate of LRF mirrored that of OS, which is no surprise because LRF is frequently the ultimate cause of death for recurrent HNC. In terms of toxicity trade-off, the rate of acute grade 4 or 5 toxicity was low, but such toxicity was more common with IMRT (5.1% vs 0.5%), and rates of grade >3 toxicity beyond 90 days were comparable after adjustment for competing risks of recurrence or death (12.4% with IMRT vs. 11.6% with SBRT). Although the toxicity of IMRT and SBRT re-irradiation appeared similar, the study demonstrated differences in outcome between IMRT and SBRT, particularly among class II patients with larger tumors, which need to be evaluated in a prospective setting. Patterns-of-failure analysis after SBRT would be helpful to determine whether failures are marginal to the treated gross tumor volume, particularly among larger tumors that may require a larger clinical target volume margin. Besides the standard clinical examination and imaging, other methods are needed to help clinicians decide when a tumor can be treated with a minimal margin and when a larger margin is needed to account for subclinical spread. In addition, dose and fractionation may play a role in the observed OS and LRF differences between SBRT and IMRT.[14]

Carotid blowout syndrome and spinal cord myelopathy are rare and are late lethal side effects of re-irradiation.[15] For re-irradiation of the full cord cross-section at 2 Gy per day after prior conventionally fractionated treatment, cord tolerance appears to increase at least by 25% 6 months after the initial course of RT based on animal and human studies. For partial cord irradiation as part of spine radiosurgery, a maximum cord dose of 13 Gy in a single fraction or 20 Gy in 3 fractions appears associated with a <1% risk of injury.[16] Carotid blowout syndrome was observed in patients who were treated more than once in the study by Yazici et al. and for whom the maximum carotid artery dose was below 34 Gy.[17] However, Gebhardt et al. reported no carotid blowout syndrome below 47.6 Gy maximum point dose to carotid artery.[18]

Conclusion

In conclusion, stereotactic body radiotherapy is a promising therapy that is still developing in the treatment of HNCs that cannot be resected locally after definitive radiotherapy. In general, the 1-year survival rates following treatment are similar in conventional radiotherapy groups only with chemotherapy and chemotherapy. Because of the small volume of treatment in SBRT, it is difficult to compare SBRT with other palliative treatment methods in terms of toxicity. SBRT is more advantageous than other palliative treatment methods with a shorter treatment duration.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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