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Hyperfractionated or Accelerated Hyperfractionated Re-irradiation with ≥42 Gy in Combination with Paclitaxel for Secondary/Recurrent Head-and-Neck Cancer

DIRK RADES[1], TOBIAS BARTSCHT[2], CHRISTIAN IDEL[1,3], STEVEN E. SCHILD[4] and SAMER G. HAKIM[5]

Departments of [1]Radiation Oncology, [2]Hematology and Medical Oncology, [3]Oto-Rhino-Laryngology and Head and Neck Surgery and [5]Oral and Maxillofacial Surgery, University of Lübeck, Lübeck, Germany; [4]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Background/Aim: Patients with secondary/ recurrent squamous cell head and neck cancer (SCCHN) have poor prognoses. Outcomes of re-irradiation with ≥42 Gy plus paclitaxel for secondary/recurrent SCCHN are herein presented. Patients and Methods: Two patients re-irradiated for secondary/recurrent SCCHN were evaluated. Patients received 44.4 Gy (2×1.2 Gy/day) or 42.0 Gy (2×1.5 Gy/day), respectively, plus concurrent paclitaxel (35 mg/m^2 weekly or 20 mg/m^2 twice per week). Results: One patient developed a locoregional recurrence and additional metastases at 12 months after re-irradiation and died at 13 months. The other patient developed multiple bone metastases at 103 months and died at 104 months. Acute toxicities included grade 2 anemia and mucositis in both patients. Radiation dermatitis was grade 2 in one patient and grade 3 in the other. Conclusion: Re-irradiation with 42.0-44.4 Gy given twice daily plus paclitaxel was well tolerated and achieved a favorable response. The results need to be confirmed in a prospective trial.*

Many patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) receive radiotherapy or chemoradiation, either as a definitive approach or following surgery (1-6). Depending on the situation (no surgery, complete resection, microscopically or macroscopically incomplete resection), total radiation doses mostly range between 60 and 70 Gy (7, 8). When patients irradiated with these high doses develop a locoregional recurrence of SCCHN or a secondary SCCHN, they again would require doses of 60-70 Gy as definitive or postoperative treatment to achieve optimal tumor control. However, re-irradiation (second course of radiotherapy in the same region) with such a high dose is generally risky, because the cumulative dose of the first and the second courses of radiotherapy is above the tolerance doses of the surrounding normal tissues and organs (9). Therefore, lower doses are often administered for re-irradiation. Whenever possible, re-irradiation should be accompanied by concurrent chemotherapy because of findings from a randomized trial of 384 patients with SCCHN demonstrated that the addition of concurrent chemotherapy resulted in significantly better local control, and progression-free and overall survival when compared to escalation of the radiation dose by 10% (10). Another important variable of re-irradiation is the dose-fractionation regimen. Giving doses per fraction of less than 1.8 Gy, twice daily, can reduce the risk of late toxicities because in contrast to tumor cells, normal tissues are able to recover within 6-8 hours following irradiation (11). Thus, re-irradiation of SCCHN should ideally include radiotherapy with two daily fractions of less than 1.8 Gy and concurrent chemotherapy. Many patients with SCCHN requiring a second course of radiotherapy cannot receive platin-based chemotherapy, which is the most common chemotherapy approach for SCCHN, because of significant potential toxicities, particularly those patients who had previously received platin-based chemotherapy (12). The most appropriate alternative single-agent or combination chemotherapy should take into account the patient's age, performance status and co-morbidities. For selected patients, taxane monotherapy is a reasonable option shown to be effective for SCCHN (13-17). In two previous studies of re-irradiation of recurrent SCCHN, we combined paclitaxel

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 4515003324, e-mail: rades.dirk@gmx.net

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Table I. *Patient characteristics and results of treatment for secondary/recurrent tumors.*

Characteristic	Patient 1	Patient 2
Age at the time of the primary tumor	56 Years	37 Years
Site of primary tumor	Base of tongue	Larynx + hypopharynx
Treatment of primary tumor	Complete resection + 66 Gy	Complete resection + 60 Gy
Interval between both courses of radiotherapy	111 Months	311 Months
Site of secondary/recurrent tumor	Hypopharynx	Oropharynx + hypopharynx
Stage of secondary/recurrent tumor	T4 N3 M1 (LYM, OSS)	T4 N0 M0
Age at the time of secondary/recurrent tumor	67 years	63 years
Treatment of secondary/recurrent tumor prior to re-irradiation	Complete resection (1 year earlier)	Macroscopicacally incomplete resection (1 month earlier)
Total dose of re-irradiation	42.0 Gy	44.4 Gy
Fractionation of re-irradiation	2×1.5 Gy per day on 5 days per week	2×1.2 Gy per day on 5 days per week
Concurrent paclitaxel	35 mg/m^2 weekly	20 mg/m^2 twice per week
Locoregional recurrence	None	None
Distant metastasis	At 12 months	At 103 months
Death	At 13 months	At 104 months

with either 30 or 36 Gy (1.5 Gy twice daily) of radiotherapy (16, 17). However, 36 Gy may be too low to achieve long-term disease control. Therefore, in the present study, the total dose of re-irradiation was further escalated to ≥42 Gy.

Patients and Methods

From our database of more than 750 patients irradiated for SCCHN, two were identified who had received a second course of radiotherapy with a total dose of >40 Gy in combination with concurrent paclitaxel for a secondary/recurrent SCCHN.

In patients receiving definitive radiotherapy for SCCHN, radiation oncologists aim to keep the overall treatment time short to improve outcomes. This can be achieved with hyperfractionated radiotherapy (*e.g.* 2×1.2 Gy per day on 5 days per week) or accelerated-hyperfractionated radiotherapy (*e.g.* 2×1.5 Gy per day on 5 days per week) instead of conventionally fractionated radiotherapy (1×1.8 Gy or 1×2.0 Gy per day on 5 days per week). In the present study, one patient received re-irradiation with 44.4 Gy (2×1.2 Gy per day) for a locoregional recurrence plus a metastasis in the sternum 1 year after complete resection of a secondary SCCHN and 9.5 years following his first SCCHN treated with resection plus 66 Gy. The other patient received postoperative radiotherapy with 42.0 Gy (2×1.5 Gy per day) one month after macroscopically incomplete resection of the secondary/recurrent SCCHN and 26 years following resection plus 60 Gy for his first SCCHN.

The biological effective doses for tumor cell kill given by the equivalent dose in 2-Gy fractions were 45.9 Gy and 45.5 Gy, respectively. The EQD2s with respect to late radiation-related toxicity were 37.3 Gy and 37.8 Gy, respectively. Since both fractionation regimens were similarly effective, both patients were included in this study. Re-irradiation was performed in 2008 and 2010, respectively, with 3D-conformal radiotherapy following computed tomography-based treatment planning. Both patients received concurrent paclitaxel (35 mg/m^2 weekly and 20 mg/m^2 twice per week, respectively). Prior to each application of paclitaxel, the patients received intravenously administration of 2 mg clemastine, 1 mg granisetron and 8 mg dexamethasone. Patient characteristics are shown in Table I.

Investigated endpoints included acute toxicity and treatment outcomes in terms of locoregional control, metastasis and death. Treatment outcomes were referenced from the day of presentation to a radiation oncologist for re-irradiation. The assessment of acute toxicities was performed according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0 (18).

Results

One patient already had mediastinal lymph node metastases and bone metastasis in the sternum at the time of the secondary SCCHN. He developed both a locoregional recurrence and additional metastases at 12 months and died at 13 months after presentation for re-irradiation of the secondary SCCHN. The other patient had not developed locoregional recurrence during the period of follow-up but developed multiple bone metastases at 103 months and died at 104 months after presentation for re-irradiation. Treatment results are included in Table I. Acute toxicities included grade 2 anemia and grade 2 oral mucositis in both patients. Radiation dermatitis was grade 2 and grade 3, respectively. Both patients received the treatment for the secondary SCCHN as planned.

Discussion

Many patients with SCCHN who experience locoregional recurrence or a secondary SCCHN receive a second course of irradiation combined with concurrent chemotherapy (16,

17, 20). Taking into account the tolerance doses of the organs at risk and the fact that such patients had already received total doses of 60-70 Gy as part of the treatment of the primary SCCHN, it is not particularly safe to deliver a second course of radiotherapy with 60 Gy or higher doses (11). The risk of late toxicities can potentially be reduced, if doses per fraction of less than 1.8 Gy are given twice daily with an interval of 6-8 hours between the two daily fractions (11). This approach gives the cells of the organs at risk time to recover from the previous radiation fraction. In contrast, tumor cells are far less able to recover between two fractions. The effect of radiotherapy on SCCHN can be increased probably by at least 15% with the addition of concurrent radiosensitizing chemotherapy (10). In two very small retrospective studies, we combined 30 Gy and 36 Gy (1.5 Gy per fraction given twice daily), respectively, with paclitaxel (16, 17). In both studies, this approach appeared effective and quite feasible. However, the total doses given as EQD2 were 32.5 Gy and 39.0 Gy, respectively. Adding 15% for concurrent chemotherapy would mean that the biological effect of the treatment may be considered comparable to doses of 37.4 Gy and 44.9 Gy, respectively, which are still well below 60 Gy (10, 11). Therefore, we investigated a further escalation of the radiation dose. The EQD2 of the two regimens used in this study were 45.5 Gy and 45.9 Gy, respectively. After adding 15% for concurrent chemotherapy, the doses may be considered comparable to 52.3 Gy and 52.8 Gy, respectively, which are closer to 60 Gy and are likely minimally required to eradicate local disease. Given the advanced stage at the time of re-irradiation, both our patients benefited from the treatment in terms of local control and overall survival. Moreover, the treatment with escalated dose of re-irradiation plus concurrent paclitaxel appeared feasible. Hematotoxicity and oral mucositis did not exceed grade 2, and grade 3 dermatitis, which occurred in one patient, was managed without problems. Both patients received the entire treatment as planned. The outcomes in terms of overall survival and locoregional control in the present study appeared quite favorable, particularly when compared to the outcomes of previous studies in patients with recurrent SCCHN using modern radiation techniques (21-26). The 1-year overall survival rates in the previous studies ranged from 33% to 77%, and the 1-year locoregional control rates ranged between 44% and 80% (21-26). Regarding acute toxicities, one patient in the present study developed grade 3 radiation dermatitis. In our two previous studies, acute toxicities did not exceed grade 2 (16, 17). In other studies, grade 3 or more toxicities were observed in up to 36% of patients, and even treatment-related death occurred in up to 12% of the patients (21-26). In order to properly judge the feasibility and the efficacy of re-irradiation with doses ≥42.0 Gy plus paclitaxel, a prospective phase I trial is required, followed by a randomized phase II or phase III trial.

In conclusion, re-irradiation with 42.0-44.4 Gy (1.2-1.5 Gy per fraction twice daily) plus paclitaxel led to favorable results in these two patients. However, given the retrospective study design and the very limited number of patients, the results are anecdotal and need to be confirmed in a prospective trial before this regimen can be introduced into clinical routine.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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