Re-irradiation of Head and Neck Cancer–Impact of Total Dose on Outcome

S. JANSSEN[1*], M. BAUMGARTNER[1*], M. BREMER[1], A. WARSZAWSKI[1], M. STIEVE[2], A. ECKARDT[3], J.-H. KARSTENS[1] and A. MEYER[1]

Departments of [1]Radiation Oncology, [2]Otolaryngology and [3]Oral and Maxillofacial Surgery, Medical School Hannover, Hannover, Germany

Abstract. *Aim: To evaluate the outcome of re-irradiation and to define favourable pre-treatment characteristics. Patients and Methods: seventy-five patients with locally recurrent head and neck cancer were treated with re-irradiation, either postoperatively or as definitive treatment, with and without chemotherapy. Mean time period between first and second series of irradiation was 19 months. Mean overall dose of re-irradiation was 46 Gy. Median follow-up was 8.7 months. Results: Overall survival, loco-regional disease-free survival and metastasis-free survival after two years were 23%, 24% and 77%, respectively. Higher overall doses of re-irradiation gave a statistically significant better outcome with regard to overall survival (p=0.018). Conclusion: For patients with locally recurrent head and neck cancer, re-irradiation is a feasible therapeutic option. The total dose at re-irradiation improves overall survival. Therefore, re-irradiation with curative intent should only be applied if a sufficient total dose of ≥46 Gy can be given.*

Local recurrence of head and neck cancer is the major cause of treatment failure (1, 2). For patients with loco-regional recurrence, treatment options are limited and include salvage surgery, chemotherapy, re-irradiation with or without chemotherapy and supportive care. Surgery as the treatment of first choice is often not feasible due to the extent and location of tumour, co-morbidities and reduced clinical condition of health. A supportive care treatment has poor median survival rates between 3 and 5 months; even with chemotherapy as a palliative treatment, the median survival rates only rise to between 5 and 9 months (3). In the past, re-irradiation held problems as tolerance doses of organs at risks had been exploited in the first radiation series. Regarding acute and especially chronic complications, this was the main factor limiting the possibility of delivering a sufficient total dose. Our goal was to examine re-irradiation treatment strategies of recurrent head and neck cancer in terms of loco-regional control, metastasis-free survival and overall survival.

Patients and Methods

From 1987-2009, 75 patients (female n=18, male n=57) with locally recurrent head and neck cancer were treated in our institution with re-irradiation, either postoperatively or as definitive treatment with or without chemotherapy. Clinical data were obtained retrospectively by evaluation of all patients' follow-up data. All patients alive at the time of the data analysis (n=14) were contacted by telephone; additional information was obtained from the general practitioner/otolaryngologist following the patient. The patients' characteristics and clinical details are summarised in Tables I and II. All different primaries were histologically proven by biopsy and are summarized in Table IV.

For re-irradiation, all patients underwent CT-based treatment planning and were treated with 3D conformal therapy. For immobilisation a thermoplastic mask fixation was used. The minimum target volume included all gross disease plus a safety margin to account for setup uncertainty. The cumulative dose to the cervical spinal cord was kept below 70 Gy. Recurrence had to be located at least ≥50% in the pre-irradiated field.

Statistical analysis was performed using a commercially available software package (SPSS 15.0 for Windows, 2006 SPSS Inc.). All events were measured from the end of the re-irradiation treatment. The following end-points were analysed: loco-regional disease-free survival, metastasis-free survival and overall survival. The endpoints were compared between the following subgroups: Age (>60 *vs.* <60 years), overal dose of re-irradiation (<45 *vs.* >45 Gy), simultaneous application of chemotherapy, gender, time intervall between irradiation treatments (>19 *vs.* <19 months) and surgical resection. The actuarial rates were calculated by the product-limit method of Kaplan and Meier, differences were compared using the log-rank test. Differences between the subgroups were tested for significance using the chi-square test for categorical factors (two to four categories) and the one-way ANOVA test for continuous variables. A *p*-value of less than 0.05

*The Authors contributed equally to this study.

Correspondence to: Stefan Janssen, MD, Department of Radiation Oncology, Medical School Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Tel: +49 5115323591, Fax: +49 5115329797, e-mail: janssen.stefan@mh-hannover.de

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was considered as statistically significant. A multivariate step-wise Cox proportional regression analysis was used to identify significant prognostic factors for the clinical end points analysed.

Median follow-up time was 8.7 months with a range of 0.03 to 94 months. The short follow up of 0.03 months is explained by a single patient dying shortly after treatment due to tumour symptoms. The mean age at time of re-irradiation was 59 years (range 30-89 years). Fifty-seven patients were male and 18 were female. Twenty-nine patients were treated with definitive re-irradiation, 26 patients with definitive re-irradiation and simultaneous application of chemotherapy and 20 patients were treated postoperatively with or without chemotherapy. Altogether, 33 patients received simultaneous application of chemotherapy: cisplatin was used in 10 patients, carboplatin/taxol in 10 patients, cetuximab in 7 patients, cisplatin/5-fluorouracil in 4 patients, 5-fluorouracil as a bolus in 1 patient and gemcitabine in 1 patient. The mean total dose of first irradiation was 60 Gy (range: 26.9-70.6 Gy), the mean total dose of re-irradiation treatment was 46 Gy (range 20-75 Gy). 75 Gy was delivered to one patient with brachytherapy in combination with external re-radiation. Mean cumulative dose of both treatment sessions amounted to 106.8 Gy (range: 70.1-138.4 Gy). Mean time interval between the two irradiation treatments was 19.4 months (range 4.8 -198.9 months).

Results

Fifty-four patients developed a loco-regional recurrent tumor after a mean time period of 12.2 months and 9 patients developed distant metastasis after a mean time period of 15.9 months. Sixty-one patients (75 %) were dead at the end of the time of the follow-up.

For all patients actuarial loco-regional disease free survival was 50%, 35% and 24% after 6 months, 1 year and 2 years, respectively. The metastasis-free survival rates at 6 months, 1 year and 2 years were 93%, 90% and 77%, respectively. The overall survival after 6 months, 1 year and 2 years was 60%, 41% and 23%, respectively.

Dividing the study population into subgroups depending on the treatment schedule, loco-regional disease-free survival after 6 months, 1 year and 2 years were 34%, 21% and 13% for definitive treatment, 73%, 51% and 43% for a combined radiochemotherapy and 49%, 35% and 21% for postoperative treatment, respectively. Metastasis-free survival for 6 months, 1 year and 2 years for definitive treatment was 92%, 80% and 66%, for combined radiochemotherapy 95%, 95% and 82%, and for postoperative treatment and 94%, 94% and 80%, respectively. The rates for overall survival after 6 months, 1 year and 2 years were 43%, 23% and 16% for definitive radiotherapy, 64%, 48% and 30% for combined radiochemotherapy and 79%, 55% and 24% for postoperative treatment, respectively.

No statistically significant differences were seen in loco-regional disease free survival, metastasis free survival and overall survival in univariate analysis according to gender, age, definitive vs. postoperative treatment, simultaneous application of chemotherapy and time period between irradiation treatments, respectively. Comparing the cohort with regard to the mean total dose of re-irradiation (≤46 Gy (n=31) *vs.* >46 Gy (n=44)), no statistically significant differences were seen in loco-regional disease-free survival and metastasis-free survival, whereas that for overall survival was statistically significant (p=0.018, Figure 1). The results are summarized in Table II. In multivariate analysis, total dose of re-irradiation remained statistically significant for overall survival (p=0.020, Table III).

Regarding the toxicity of the second series of radiotherapy, one out of 75 re-irradiated patients (1.4%) developed an osteoradionecrosis according to a CTCAE grade IV late side-effect. Twenty-seven (36%) and 7 (9%) patients developed acute grade II and III dermatitis/mucositis, respectively. No grade IV acute side effects were seen.

Table I. *Patient and treatment related parameters.*

Mean age at time of re-irradiation, range (years)	59 (30-89)
Mean overall dose first irradiation treatment, range (Gy)	60 (26.9-70.6)
Mean overall dose second irradiation treatment, range (Gy)	46 (20-75)
Mean cumulative dose of both treatments, range (Gy)	106.8 (70.1-138.4)
Mean time period between both irradiation treatments, range (months)	19.4 (4.8-198.9)
Median follow-up, range (months)	8.7 (0.03-94)

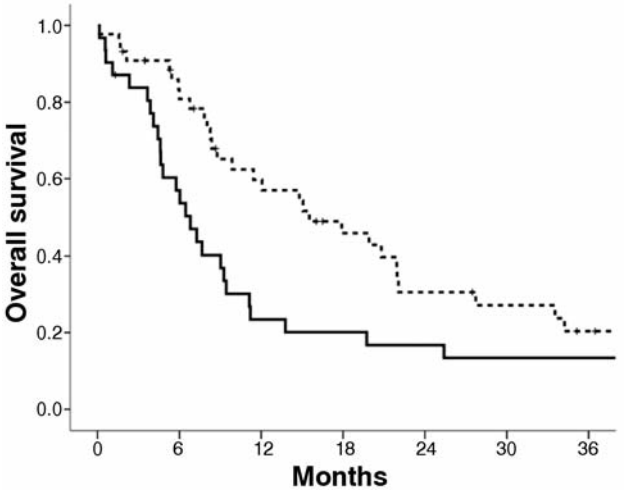

Figure 1. *Overall survival of patients with ≤46 Gy (solid line, n=31) vs. >46 Gy (broken line, n=44) overall dose at re-irradiation, calculated by Kaplan-Meier (log-rank test, p=0.018).*

Discussion

Recurrent head and neck cancer in previously irradiated areas is a difficult therapeutic problem due to the high rates of local

Table II. *One-year survival rates of different subgroups divided by patient- and treatment-related parameters (p-values of univariate statistical analysis between subgroups).*

	Overall survival	Loco-regional disease-free survival	Metastasis-free survival
Mean age at time of re-irradiation	*p*=0.986	*p*=0.397	*p*=0.895
≤60 Years (n=38)	37%	24%	92%
>60 Years (n=37)	46%	47%	89%
Gender	*p*=0.440	*p*=0.668	*p*=0.284
Male (n=57)	44%	35%	93%
Female (n=18)	31%	32%	78%
Mean overall dose of second irradiation treatment	*p*=0.018	*p*=0.058	*p*=0.238
≤46 Gy (n= 31)	20%	20%	91%
>46 Gy (n=44)	57%	44%	90%
Simultaneous chemotherapy with irradiation treatment	p=0.508	*p*=0.076	*p*=0.630
With chemotherapy (n=33)	46%	43%	92%
Without chemotherapy (n=42)	37%	28%	88%
Operation before second irradiation treatment	*p*=0.271	*p*=0.911	*p*=0.430
With operation (n=21)	36%	35%	88%
Without operation (n= 54)	67%	44%	100%
Mean time period between irradiation treatments	*p*=0.246	*p*=0.136	*p*=0.846
≤19 Months (n=37)	32%	25%	94%
>19 Months (n=38)	50%	43%	89%

Table III. *Multivariate step-wise Cox proportional regression analysis for the different prognostic factors for the clinical endpoints analysed.*

	Overall survival	Loco-regional disease-free survival	Metastasis-free survival
Mean age at time of re-irradiation	*p*=0.695	*p*=0.397	*p*=0.895
Gender	*p*=0.940	*p*=0.669	*p*=0.284
Mean overall dose of second irradiation treatment	*p*=0.020	*p*=0.058	*p*=0.238
Simultaneous chemotherapy with irradiation treatment	*p*=0.933	*p*=0.077	*p*=0.630
Surgery before second irradiation treatment	*p*=0.130	*p*=0.911	*p*=0.430
Mean time period between irradiation treatments	*p*=0.749	*p*=0.137	*p*=0.846

recurrence (4-9). Surgical resection with curative intent is the therapy of choice for patients with limited disease progression and offers curative potential (10, 11). However, often high-risk pathological features such as positive margins, perineural invasion, lymphovascular invasion, and extranodal extension necessitate adjuvant treatment. As a consequence some patients with locally advanced tumours have been treated with radiotherapy before (3, 12). Re-irradiation has not been applied for decades because normal tissue, and especially the spinal cord, have been irradiated with the maximum tolerance doses in the initial series facing the risk of strongly enhanced late side effects (13).

Table IV. *Different tumour sites.*

Original tumour site	Number of patients (%)
Oropharyngeal carcinoma	20 (27%)
Oral cavity carcinoma	19 (25%)
Hypopharyngeal carcinoma	16 (21%)
Carcinoma of the paranasal sinuses/maxilla	8 (11%)
Nasopharyngeal carcinoma	7 (9%)
Laryngeal carcinoma	5 (7%)

However, there is a chance of recovery of previously irradiated tissue, especially if the interval between the two irradiation courses is long enough (14). The lifetime dose to the spinal cord of 50 Gy, which should not be exceeded during initial treatment, can be raised to a total dose of cumulative 70 Gy according to 140% of the tolerance dose (15, 16). Furthermore, the treatment volume of the re-irradiation strongly differs from that of the initial radiotherapy. Planning target volume (PTV) is limited to a small margin around the tumour or the surgical side. The prophylactic irradiation of

cervical lymph nodes that are clinically and radiographically inconspicious is a matter of controversy. Keeping this in mind, the irradiated volume can be minimized with the possibility of increasing the total dose by minimizing the exposure of critical normal tissues and enhancing the therapeutic ratio. However, if a tumour occurs again in a previously irradiated volume within 3-6 months after the first course of irradiation, the tumour cells may have radioresistant clones, limiting the therapeutic effect of a second treatment course.

In our retrospective study, 21 patients were treated with postoperative re-irradiation with or without simultaneous application of chemotherapy. This group demonstrated a loco-regional disease-free survival of 35% after 1 year and 22% after 3 years which was worse compared to other groups with local control rates of up to 74% after 3 years (17-19). A recently published prospectively conducted trial could have demonstrated the impact of postoperative re-irradiation on progression-free survival that unfortunately did not translate into enhanced local control nor overall survival rate (19). In fact, we observed a higher local control rate in patients treated with definitive than with postoperative treatment, but the number of patients treated postoperatively was small in comparison to the total cohort.

Many patients with locally advanced tumours are not amenable to surgery or are in poor general health condition. Therefore, for selected patients definitive re-irradiation with or without simultaneous application of chemotherapy offers an option in curative intention. With definitive re-irradiation, local control rates after 2 years of 20%-42% can be achieved (13, 20-24). In our retrospective series we demonstrated a comparable local control rate of 13% without and 43% with chemotherapy.

Several prognostic factors for overall survival and locoregional control could be evaluated in retrospective and prospective trials including time interval, second primary *vs*. recurrent tumour, postoperative irradiation *vs*. definitive irradiation, and total dose of second irradiation course (13, 20-31). A recently published study identified coexisting morbidities and organ dysfunction as important prognostic factors (13). However, heterogeneous patient populations described in literature constitute a major problem. Some series include patients with definitive re-irradiation alone, concomitant chemotherapy in various strategies as well as patients with resected disease.

Our study population also contained different treatment strategies. In the present analysis, no statistically significant differences were seen between improved outcome and gender, age, previously performed surgical resection, time period between irradiation treatments and simultaneous chemotherapy.

But as we demonstrated here, the main factor influencing the overall survival rate is the total dose to be given at re-irradiation. To gain a long-lasting therapeutic effect with curative intent, a total dose of more than 46-50 Gy should be applied (13, 15). Before starting re-irradiation a thorough examination and analysis of the initial treatment volume and dose distributions should be carried out in relation to the locoregional recurrent tumor to estimate the possible total dose that can be applied. Otherwise a re-irradiation with curative intent yields only limited response rates and enhanced risk of late side-effects leading to a diminshed therapeutic ratio. In contrast to other authors, we did not observe any benefits in receiving surgical treatment prior to re-irradiation or simultaneous application of chemotherapy, but this may be due to the heterogenous patient cohort with only small subgroups in our study.

To escalate the dose directly to the tumour while sparing organs at risk and surrounding normal structures, 3D-conformal radiotherapy, hyperfractionation, intensity modulated radiation therapy (IMRT), brachytherapy, intraoperative radiotherapy and stereotactic radiosurgery have been used (23, 31-35). To compensate for the constrained total dose of re-irradiation, some authors have shown an enhancement of the therapeutic effect using radiation sensitizers such as chemotherapy or targeted agents (23, 24). Unfortunately, we were unable to demonstrate a statistically significant effect on the local control rate using chemotherapy. But one has to keep in mind that the poor clinical condition of most patients at the time of the recurrent disease and the use of simultaneous chemotherapy increases the treatment-related toxicity and mortality.

A comparison of late toxicities with other published series is very difficult to carry out due to the heterogeneity of the different studies regarding fraction size, target volume, radiation technique, application of simultaneous chemotherapy and intervals between radiation series. The incidence of late toxicities observed in the two prospective trials RTOG 9610 and RTOG 9911 were up to 19% of grade 3 and 17% of grade 4 (23, 24). A recently published study dealing with the evaluation of potential prognostic factors for survival after re-irradiation, including comorbidity and pre-existing organ dysfunction, found an incidence of late toxicities of grade 3 or higher in 47.5% of the patients including mandibular fracture or necrosis in 6% and mucocutaneous fistula in 5% (13). Due to the retrospective nature of our series with 61 patients (75%) being dead at the end of the time of the follow-up the assessment of late toxicities is quite difficult. In our series, one out of 75 re-irradiated patients developed an osteoradionecrosis according to a CTCAE grade IV late side-effect.

In conclusion, re-irradiation with or without concomitant chemotherapy or sequentially operation is a feasible treatment option for patients with loco-regional recurrence of head and neck cancer. In contrast to palliative chemotherapy, this regime offers curative potential. Higher doses in re-irradiation improved local control leading to longer overall survival. Therefore re-irradiation with curative intent should only be performed when doses above 46 Gy are possible.

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