Importance of Chemotherapy and Radiation Dose After Microscopically Incomplete Resection of Stage III/IV Head and Neck Cancer

DANIEL SEIDL[1], STEFAN JANSSEN[1,2], PRIMOZ STROJAN[3], SAMER G. HAKIM[4], BARBARA WOLLENBERG[5], STEVEN E. SCHILD[6] and DIRK RADES[1]

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

Abstract. *Aim: To investigate the importance of chemotherapy and radiation dose after R1 resection of squamous cell carcinoma of the head-and-neck (SCCHN). Patients and Methods: One hundred and twenty-two patients receiving radiotherapy alone or with concurrent chemotherapy [cisplatin or cisplatin/5-fluorouracil (5-FU)] were retrospectively analyzed. Results: On multivariate analysis, chemotherapy was significantly associated with improved locoregional control (p=0.048). Three-year locoregional control rates were 61% for those treated without chemotherapy, 83% for those treated with cisplatin and 77% for those treated with cisplatin/5-FU. Radiation doses of 66 and 70 Gy were non-significantly superior to 60-64 Gy (p=0.18). On multivariate analysis, chemotherapy showed a trend for improving survival (p=0.055). Three-year OS rates were 51% for those without chemotherapy, 65% for those treated with cisplatin and 57% for those treated with cisplatin/5-FU. Radiation doses of 66 Gy (3-year survival=61%) and 70 Gy (70%) were superior to 60-64 Gy (25%) (p=0.021). Conclusion: Concurrent chemotherapy and a radiation dose of 66 Gy resulted in better outcomes. Cisplatin and cisplatin/5-FU were similarly effective. Radiation doses >66 Gy appear not to be necessary.*

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

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Patients with locally advanced (stage III/IV) squamous cell carcinoma of the head and neck region (SCCHN) have a comparably poor prognosis (1). Many patients undergo resection of the primary tumor and regional lymph nodes followed by radiotherapy or radiochemotherapy (2). Microscopically incomplete resection (R1 resection) is considered a risk factor for worse treatment outcomes (3). A re-analysis of two randomized trials suggested that patients in whom an R1 resection was performed benefited from the addition of chemotherapy to postoperative irradiation (4). Despite these randomized trials, two questions remain unanswered. One question relates to the chemotherapy regimen. Both randomized trials used an aggressive regimen consisting of 100 mg/m^2 cisplatin alone given on days 1, 22 and 43 during the radiation course (5, 6). However, many centers worldwide use 5-fluorouracil (5-FU) in addition to cisplatin. The question is whether patients undergoing R1 resection would also benefit from cisplatin/5-FU. Another question relates to the most appropriate radiation dose. In one of the two randomized trials, all patients received 66 Gy (4), and in the other trial, 60 Gy or 66 Gy (5). Some centers also use 70 Gy. The present study investigated chemotherapy and compared no chemotherapy, cisplatin alone and cisplatin plus 5-FU. Additionally, three radiation dose levels were compared with respect to locoregional control and survival after R1 resection of non-metastatic stage III/IV SCCHN.

Patients and Methods

Data of 122 patients who received radiotherapy alone (n=45) or in combination with concurrent cisplatin-based chemotherapy (n=77) following R1 resection of locally advanced SCCHN were retrospectively analyzed for locoregional control and survival. Patients received radiotherapy of 2.0 Gy once daily on five days per week. Total doses ranged from 60-70 Gy (median dose=66 Gy) to

the R1-resected former primary tumor. Higher-risk and intermediate-risk lymph nodes received 60 Gy and 50 Gy, respectively. When concurrent chemotherapy was administered, it included cisplatin alone (30-40 mg/m^2 weekly, 20 mg/m^2 on days 1-5+29-33, or 100 mg/m^2 on days 1, 22 and 43) or cisplatin (20 mg/m^2 on days 1-5+29-33) plus 600/1000 mg/m^2 5-FU on days 1-5 and 29-33.

The impact of the following potential prognostic factors on locoregional control and survival was evaluated: Age (≤60 *vs.* >60 years), gender, pre-radiotherapy Karnofsky performance score (80-100 *vs.* ≤70), site of SCCHN (oropharynx *vs.* hypopharynx *vs.* larynx *vs.* oral cavity/floor of mouth), T-stage (T1/T2 *vs.* T3/T4), N-stage (N0/N1 *vs.* N2/N3), histological grade (G1/G2 *vs.* G3), pre-radiotherapy hemoglobin (<12 *vs.* ≤12 g/dl), radiotherapy dose (60-64 Gy *vs.* 66 Gy *vs.* 70 Gy) and concurrent chemotherapy (none *vs.* cisplatin alone *vs.* cisplatin/5-FU).

The univariate analyses of locoregional control and survival were performed using the Kaplan–Meier analysis supplemented by the log-rank test. Potential prognostic factors achieving significance ($p<0.05$) or a trend ($p<0.08$) on univariate analyses were additionally evaluated in a multivariate manner with the Cox regression model.

Results

Patients were followed up until death or for a median of 28 months (range=5-76 months) in those alive at the last follow-up. For the entire cohort, the locoregional control rates at 3 and 4 years were 73% and 66%, respectively. Of all investigated factors, only chemotherapy was found to have a significant association with locoregional control (Table I). The 3- and 4-year rates were 61% and 33%, respectively, for patients who did not receive chemotherapy; 83% and 83% respectively, after radiochemotherapy with cisplatin alone; and 77% and 77%, respectively, after radiochemotherapy with cisplatin/5-FU ($p=0.010$, Figure 1). On the Cox regression analysis, the addition of chemotherapy to radiotherapy was also significant (risk ratio=1.64, 95% confidence interval=1.01-2.77; $p=0.048$).

The 3- and 4-year survival rates for the whole patient cohort were 58% and 54%, respectively. On univariate analyses, lower N-stage ($p=0.006$), lower histological grade (*i.e.* better differentiated tumors) ($p=0.021$) and pre-radiotherapy hemoglobin levels of ≥12 g/dl ($p=0.002$) were significantly associated with improved survival (Table II). In addition, lower T-stage ($p=0.053$) and RT doses of 66 Gy or 70 Gy ($p=0.076$) showed a trend for association with better survival. These five factors plus chemotherapy were included in the Cox regression analysis. In that analysis, T-stage ($p=0.018$), N-stage ($p=0.011$), pre-radiotherapy hemoglobin level ($p=0.003$) and the radiotherapy dose ($p=0.021$) achieved significance. Histological grade ($p=0.078$) and chemotherapy ($p=0.055$) showed a trend. The complete results of the Cox regression analysis are summarized in Table III.

Table I. *Locoregional control rates at 3 and 4 years (univariate analysis).*

	At 3 years (%)	At 4 years (%)	*p*-Value
Age			
≤60 years (n=72)	73	73	
>60 years (n=50)	72	55	0.90
Gender			
Female (n=29)	70	70	
Male (n=93)	74	65	0.84
Karnofsky performance score			
80-100 (n=80)	73	65	
≤70 (n=42)	74	74	0.75
Tumor site			
Oropharynx (n=60)	78	74	
Hypopharynx (n=20)	69	69	
Larynx (n=25)	80	0	
Oral cavity/floor of mouth (n=17)	46	n/a	0.15
T-Stage			
T1/T2 (n=48)	79	73	
T3/T4 (n=74)	70	60	0.17
N-Stage			
N0/N1 (n=43)	75	68	
N2/N3 (n=79)	73	67	0.46
Histological grade			
G1/G2 (n=71)	80	74	
G3 (n=51)	63	54	0.19
Pre-radiotherapy hemoglobin			
<12 g/dl (n=49)	71	71	
≥12 g/dl (n=73)	75	66	0.49
Radiotherapy dose			
60-64 Gy (n=15)	32	n/a	
66 Gy (n=97)	77	69	
70 Gy (n=10)	80	n/a	0.18
Concurrent chemotherapy			
None (n=45)	61	33	
Cisplatin alone (n=44)	83	83	
Cisplatin/5-FU (n=33)	77	77	0.010

n/a: Not available.

Discussion

Patients with metastatic SCCHN have a very poor prognosis (7, 8). Patients with locally advanced non-metastatic disease have a better expected outcome (1). In many patients with resectable stage III/IV SCCHN, the final pathological evaluation reveals that the tumor has not been removed completely microscopically. The question is whether a second surgery should be performed. A re-resection is often not possible or refused by patients. There is general agreement that patients undergoing resection of stage III/IV tumors should receive postoperative radiotherapy (3, 9). Since two randomized trials and their re-analysis demonstrated 10 years ago that patients in whom only R1 resection was performed benefited from the addition of concurrent chemotherapy, this

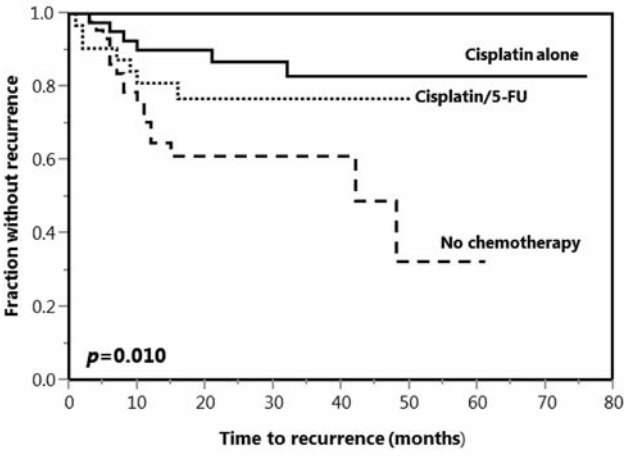

Figure 1. *Locoregional control of the groups with no chemotherapy treated with cisplatin alone and treated with cisplatin/5-fluorouracil (5-FU).*

Table II. *Survival rates at 3 and 4 years (univariate analysis).*

	At 3 years (%)	At 4 years (%)	p-Value
Age			
≤60 years (n=72)	60	57	
>60 years (n=50)	55	50	0.81
Gender			
Female (n=29)	65	65	
Male (n=93)	57	51	0.33
Karnofsky performance score			
80-100 (n=80)	62	5	
≤70 (n=42)	50	50	0.25
Tumor site			
Oropharynx (n=60)	64	60	
Hypopharynx (n=20)	36	36	
Larynx (n=25)	67	56	
Oral cavity/floor of mouth (n=17)	41	n/a	0.11
T-Stage			
T1/T2 (n=48)	72	64	
T3/T4 (n=74)	47	47	0.053
N-Stage			
N0/N1 (n=43)	76	65	
N2/N3 (n=79)	48	48	0.006
Histological grade			
G1/G2 (n=71)	66	60	
G3 (n=51)	48	38	0.021
Pre-radiotherapy hemoglobin			
<12 g/dl (n=49)	42	42	
≥12 g/dl (n=73)	69	62	0.002
Radiotherapy dose			
60-64 Gy (n=15)	25	0	
66 Gy (n=97)	61	59	
70 Gy (n=10)	70	n/a	0.076
Concurrent chemotherapy			
None (n=45)	51	44	
Cisplatin alone (n=44)	65	61	
Cisplatin/5-FU (n=33)	57	57	0.21

n/a: Not available.

approach became the standard procedure in many centers worldwide (4-6). However, radiochemotherapy after R1 resection is not performed everywhere. When concurrent chemotherapy is administered, the most appropriate chemotherapy protocol is still controversial. In the two randomized trials, an aggressive protocol with three courses of 100 mg/m^2 of cisplatin was used. This regimen is the standard in many countries, including the United States. Since this regimen is fairly toxic and the patients require substantial supportive care, other centers, particularly in Europe, have explored alternatives. One alternative is a regimen including two courses of 20 mg/m2 cisplatin given for five days in the first and fifth week of radiotherapy (10). This regimen has been shown to be much better tolerated than three courses of 100 mg/m^2 of cisplatin (11). However, since the cumulative cisplatin dose of two courses of 20 mg/m^2 cisplatin is only two-thirds that of three times 100 mg/m^2, many centers added two courses of 5-FU (either 600 or 1,000 mg/m^2) over five days in the first and fifth week of radiotherapy to cisplatin at 20 mg/m^2. To our knowledge, it has not yet been shown that after R1 resection, patients benefit from radiochemotherapy with cisplatin/5-FU.

In this study, radiochemotherapy either with cisplatin alone or cisplatin/5-FU was superior to radiotherapy alone. Cisplatin/5-FU resulted in similar locoregional control and survival rates as different cisplatin alone regimens. Moreover, the outcomes were similar to those found in the two previous randomized trials using high-dose cisplatin (three courses of 100 mg/m^2). In order to better define the optimal chemotherapy regimen for radiochemotherapy of R1-resected SCCHN, additional studies directly comparing these regimens are warranted. Novel approaches including induction chemotherapy and 5-FU pro-drugs may be reasonable (12, 13).

Another important question addresses the most appropriate total radiation dose. One of the previous randomized trials used 66 Gy for all patients, the other trial either 60 Gy or 66 Gy. In the latter trial, a separate analysis of the separate dose groups was not performed. Thus, the optimal dose is unclear. Is 60 Gy sufficient or should the dose be 66 Gy or even greater? In the present study, 66 Gy was clearly superior to 60-64 Gy, as was a dose of 70 Gy. However, an escalation of the radiation dose beyond 66 Gy did not appear to further improve outcomes significantly. Thus, 66 Gy appears to be appropriate.

In addition to concurrent chemotherapy and the radiation dose, T-stage, N-stage and pre-radiotherapy hemoglobin were significantly associated with survival. Histological grade showed a trend towards such an association. These findings agree with previously reported

Table III. *Multivariate analysis (Cox regression model) of survival.*

Variable	Risk ratio	95% Confidence interval	*p*-Value
T-Stage (T1/T2 *vs.* T3/T4)	1.44	1.06-1.99	0.018
N-Stage (N0/N1 *vs.* N2/N3)	2.50	1.23-5.51	0.011
Histological grade (G1/G2 *vs.* G3)	1.31	0.97-1.78	0.078
Pre-radiotherapy hemoglobin (≥12 g/dl *vs.* <12 g/dl)	2.56	1.38-4.78	0.003
Radiotherapy dose (70 Gy *vs.* 66 Gy *vs.* 60-64 Gy)	2.49	1.15-5.15	0.021
Concurrent chemotherapy (Cisplatin alone *vs.* Cisplatin/5-FU *vs.* none)	1.44	0.99-2.12	0.055

data, which reveals some consistency of the results of the present study (14-17). However, its retrospective nature should be taken into account when interpreting the data. Prospective randomized trials focusing on R1-resected SCCHN are desirable but may not be practical, since R1 resection is less common due to improved surgical procedures and standards.

In conclusion, this study supported the importance of concurrent chemotherapy when added to radiotherapy for R1-resected SCCHN. Cisplatin alone and cisplatin/5-FU appeared to be similarly efficacious. The optimal chemotherapy regimen needs to be defined. 66 Gy appears to be an appropriate radiation dose.

Conflicts of Interest

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

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin *65*: 5-29, 2015.

2 Chen LY, Huang CC, Tsou YA, Bau DT and Tsai MH: Prognostic factor of severe complications in patients with hypopharyngeal cancer with primary concurrent chemoradiotherapy. Anticancer Res *35*: 1735-1741, 2015.

3 Rades D, Fehlauer F, Wroblesky J, Albers D, Schild SE and Schmidt R: Prognostic factors in head-and-neck cancer patients treated with surgery followed by intensity-modulated radiotherapy (IMRT), 3D-conformal radiotherapy, or conventional radiotherapy. Oral Oncol *43*: 535-543, 2007.

4 Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK and Lefèbvre JL. 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 *27*: 843-850, 2005.

5 Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A and van Glabbeke M: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med *350*: 1945-1952, 2004.

6 Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N and Fu KK: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med *350*: 1937-1944, 2015.

7 Rades D, Schild SE, Karstens JH and Hakim SG: Predicting survival of patients with metastatic epidural spinal cord compression from cancer of the head-and-neck. Anticancer Res *35*: 385-388, 2015.

8 Rades D, Dziggel L, Hakim SG, Rudat V, Janssen S, Trang NT, Khoa MT and Bartscht T: Predicting survival after irradiation for brain metastases from head and neck cancer. In Vivo *29*: 525-528, 2015.

9 Song JH, Jeong BK, Choi HS, Jeong H, Kang MH, Kang JH, Kim JP, Park JJ, Woo SH, Jang HS, Choi BO and Kang KM: Comparison of failure patterns between conventional and intensity-modulated radiotherapy for stage III and IV head and neck squamous cell carcinoma. Anticancer Res *35*: 6833-6840, 2015.

10 Tribius S, Kronemann S, Kilic Y, Schroeder U, Hakim S, Schild SE and Rades D: Radiochemotherapy including cisplatin alone versus cisplatin + 5-fluorouracil for locally advanced unresectable stage IV squamous cell carcinoma of the head and neck. Strahlenther Onkol *185*: 675-681, 2009.

11 Rades D, Kronemann S, Meyners T, Bohlen G, Tribius S, Kazic N, Schroeder U, Hakim SG, Schild SE and Dunst J: Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys *80*: 1037-1044, 2011.

12 Franco P, Potenza I, Schena M, Riva G, Pecorari G, Demo PG, Fasolis M, Moretto F, Garzaro M, Di Muzio J, Melano M, Airoldi M, Ragona R, Rampino M and Ricardi U: Induction chemotherapy and sequential concomitant chemo-radiation in locally advanced head and neck cancers: How induction-phase intensity and treatment breaks may impact on clinical outcomes. Anticancer Res *35*: 6247-6254, 2015.

13 Fujimoto Y, Kato S, Itoh Y, Naganawa S and Nakashima T: A phase I study of concurrent chemoradiotherapy using oral s-1 for head and neck cancer. Anticancer Res *34*: 209-213, 2014.

14 Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE and Dunst J: Locally advanced stage IV squamous cell carcinoma of

the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys *70*: 1108-1114, 2008.

15 Rades D, Seibold ND, Gebhard MP, Noack F, Schild SE and Thorns C: Prognostic factors (including HPV status) for irradiation of locally advanced squamous cell carcinoma of the head and neck (SCCHN). Strahlenther Onkol *187*: 626-632, 2011.

16 Vaupel P, Kelleher DK and Höckel M: Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. Semin Oncol *28(2 Suppl 8)*: 29-35, 2001.

17 Noble AR, Greskovich JF, Han J, Reddy CA, Nwizu TI, Khan MF, Scharpf J, Adelstein DJ, Burkey BB and Koyfman SA: Risk factors associated with disease recurrence in patients with stage III/IV squamous cell carcinoma of the oral cavity treated with surgery and postoperative radiotherapy. Anticancer Res *36*: 785-792, 2016.

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