Prognostic Factors After Definitive Radio(Chemo)Therapy of Locally Advanced Head and Neck Cancer

DANIEL SEIDL[1], STEFAN JANSSEN[1,2], PRIMOZ STROJAN[3], AMIRA BAJROVIC[4], STEVEN E. SCHILD[5] and DIRK RADES[1]

[1]*Department of Radiation Oncology, 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;*
[4]*Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany;*
[5]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Aim: To identify predictors of locoregional control (LRC) and overall survival (OS) after definitive radio(chemo)therapy for squamous cell carcinoma of the head and neck (SCCHN). Patients and Methods: Two hundred and seventy-five patients were evaluated; 261 patients received radiochemotherapy with 30-40 mg/m^2 of cisplatin weekly, three courses of cisplatin 100 mg/m^2, two courses of cisplatin 5x20 mg/m^2 or two courses of cisplatin 5×20 mg/m^{2}plus 5-fluorouracil. Ten characteristics were analyzed: Pre-radiotherapy hemoglobin, T-/N-category, Karnofsky performance-score (KPS), gender, age, chemotherapy type, tumor site, grading and radiation dose. Results: On multivariate analyses, hemoglobin 12-14 g/dl (p=0.040), lower T-category (p=0.010), lower N-category (p=0.042) and female gender (p=0.006) were predictive of LRC. Hemoglobin >12 g/dl (p=0.020), lower N-category (p<0.001), KPS ≥80 (p<0.001), female gender (p=0.024) and cisplatin 100 mg/m^2 or 5×20 mg/m^2 (p<0.001) were predictors of improved OS. Conclusion: Predictors of LRC and OS were identified that can improve personalization of treatment. Since chemotherapy type was associated with OS, studies comparing different regimens are warranted.*

The most common treatments for locally advanced squamous cell carcinoma of the head and neck (SCCHN) include surgical resection followed by radio(chemo)therapy and definitive radio(chemo)therapy (1). The preference of treatment approaches depends on local expertise, national and institutional standards. Often, patients receiving definitive radio(chemo)therapy have large unresectable primary tumors, extensive lymphadenopathy, poorer performance and higher comorbidity than patients considered suitable for resection. Therefore, many patients treated with definitive radio(chemo)therapy for locally advanced SCCHN have a poor prognosis, requiring further research. In addition to modern radiation techniques and novel anticancer drugs, the use of more individualized treatment approaches can lead to better outcomes after definitive radio(chemo) therapy for patients with SCCHN (2-4). Besides age, comorbidity, personal situation and treatment preference, individualized therapeutic approaches should take into account the expected outcomes of treatment, such as locoregional control (LRC) and overall survival (OS). Both LRC and OS can be estimated with profound knowledge of independent prognostic factors. Furthermore, the most appropriate radiation dose and type of concurrent chemotherapy are critical to understand. This study analyzed the prognostic role of radiation dose, different dosing regimens of cisplatin-based chemotherapy and additional potential prognostic factors on LRC and OS in patients receiving definitive radio(chemo)therapy for locally advanced SCCHN.

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

Key Words: Locally advanced SCCHN, definitive radio(chemo) therapy, prognostic factors, locoregional control, overall survival.

Patients and Methods

Two hundred and seventy-five patients who received definitive radio(chemo)therapy for locally advanced SCCHN were evaluated for LRC and OS in this retrospective study. Irradiation was performed as conventionally fractionated (2.0 Gy per weekday) three-dimensional conformal radiotherapy. Total radiation doses administered to the primary tumor and the involved lymph nodes ranged between 60 Gy and 70 Gy. Doses given to non-involved intermediate-risk and high-risk lymph nodes were 50 Gy and 60 Gy, respectively. All but 14 patients received simultaneous chemotherapy in addition to radiotherapy, either with cisplatin weekly (30-40 mg/m^2 each week),

three courses of cisplatin 100 mg/m^2 (days 1, 22 and 43), two courses of cisplatin 20 mg/m^2 (days 1-5 and 29-33) or two courses of cisplatin 20 mg/m^2 supplemented by 600/1,000 mg/m^2 5-fluorouracil (5-FU) (days 1-5 and 29-33).

Ten characteristics were analyzed for potential associations with LRC and OS, including pre-radiotherapy hemoglobin level (<12 g/dl *versus* 12-14 g/dl *vs*. >14 g/dl), T-category (T1/T2 *versus* T3/T4), N-category (N0/N1/N2a *vs*. N2b/N2c/N3), Karnofsky performance-score (≤70 *versus* ≥80), gender, age (≤57 years *versus* ≥58 years, median age=57 years), type of chemotherapy (none *versus* cisplatin weekly *versus* cisplatin 100 mg/m^2 *versus* cisplatin 20 mg/m^2 *versus* cisplatin 20 mg/m^2 plus 5-FU), primary tumor site (oropharynx *versus* hypopharynx *versus* larynx *versus* oral cavity/floor of mouth), histologic grading (G1/G2 *versus* G3) and total radiation dose (60-66 Gy *versus* 70 Gy).

The Kaplan-Meier method plus the log-rank test were applied for univariate analyses of LRC and OS (5). Characteristics showing a significant association ($p<0.05$) with LRC or OS were also included in a multivariate analysis performed with the Cox proportional hazards model.

Results

The LRC rates in the entire series were 73%, 60% and 58%, respectively, after 1, 3 and 5 years following irradiation. On univariate analyses, LRC was positively associated with a pre-radiotherapy hemoglobin level of 12-14 g/dl ($p=0.003$), lower T-category ($p=0.029$), lower N-category ($p=0.020$) and female gender ($p=0.009$). Results of the univariate analyses of LRC are shown in Table I. On the multivariate analysis, pre-radiotherapy hemoglobin level ($p=0.040$), T-category ($p=0.010$), N-category ($p=0.042$) and gender ($p=0.006$) proved to be independent predictors of LRC (Table II).

OS rates after 1, 3 and 5 years were 76%, 50% and 36%, respectively. In the univariate analyses, OS was positively associated with pre-radiotherapy hemoglobin levels of 12-14 g/dl and >14 g/dl ($p=0.019$), lower N-category ($p<0.001$), a KPS of ≥80 ($p<0.001$), female gender ($p=0.045$), chemotherapy with three courses of cisplatin 100 mg/m^2 or two courses of cisplatin 20 mg/m^2 ($p=0.009$) and larynx or oropharynx cancer ($p<0.001$). The results of the univariate analyses of OS are summarized in Table III. In the multivariate analysis of OS, pre-radiotherapy hemoglobin level ($p=0.020$), N-category ($p<0.001$), KPS ($p<0.001$), gender ($p=0.024$) and type of simultaneous chemotherapy ($p<0.001$) were significant predictors, whereas the primary tumor site did not achieve significance ($p=0.57$). The complete results of multivariate analyses of OS are shown in Table IV.

Table I. *Univariate analysis of locoregional control.*

	At 1 year (%)	At 3 years (%)	At 5 years (%)	*p*-Value
Pre-radiotherapy hemoglobin level				
<12 g/dl (n=94)	61	48	48	
12-14 g/dl (n=109)	83	69	69	
>14 g/dl (n=72)	73	61	54	0.003
T-category				
T1/T2 (n=38)	95	72	72	
T3/T4 (n=237)	69	58	56	0.029
N-category				
N0/N1/N2a (n=116)	81	67	63	
N2b/N2c//N3 (n=159)	67	54	54	0.020
Karnofsky performance-score				
≤70 (n=66)	65	52	52	
≥80 (n=209)	75	63	60	0.055
Gender				
Female (n=56)	91	72	72	
Male (n=219)	68	57	54	0.009
Age				
≤57 years (n=141)	72	57	57	
≥58 years (n=134)	73	62	58	0.59
Simultaneous chemotherapy				
No chemotherapy (n=14)	75	47	n/a	
Cisplatin weekly (n=70)	65	53	49	
Cisplatin 100 mg/m^2 (n=47)	87	72	72	
Cisplatin 20 mg/m^2 (n=72)	71	61	61	
Cisplatin 20 mg/m^2 + 5-FU (n=72)	73	56	56	0.15
Primary tumor site*				
Oropharynx (n=135)	75	62	60	
Hypopharynx (n=41)	54	50	50	
Larynx (n=57)	78	66	62	
Oral cavity/Floor of mouth (n=39)	72	53	53	0.21
Histologic grading				
G1/G2 (n=165)	73	62	58	
G3 (n=110)	72	58	58	0.89
Total radiation dose				
60-66 Gy (n=38)	75	63	63	
70 Gy (n=237)	73	59	57	0.92

n/a=Not available, *not clearly defined in 3 patients.

Discussion

The prognoses of patients with SCCHN presenting with distant metastases or locally advanced unresectable disease are generally poor and require improvement (1-3, 6-8). For locally advanced disease, modern techniques of head-and-neck surgery and radiotherapy have already led to improved outcomes, which may be further enhanced with new chemotherapy approaches (9, 10). The application of personalized treatment programs may also result in better outcomes. Such programs should consider an individual patient's specific situation, including his prognosis. Therefore, the identification of prognostic factors is important. In this study, several potential predictors for LRC and OS were analyzed. In the multivariate analysis of LRC, pre-radiotherapy hemoglobin levels of 12-14 g/dl, lower T-category, lower N-category and female gender were independent prognostic factors. In the multivariate analysis of

Table II. *Multivariate analysis of locoregional control.*

	Risk ratio	95% confidence interval	*p*-Value
Pre-radiotherapy hemoglobin level	1.33	1.01-1.77	0.040
T-category	1.53	1.10-2.30	0.010
N-category	1.54	1.02-2.38	0.042
Gender	2.24	1.24-4.46	0.006

Table III. *Univariate analysis of survival.*

	At 1 year (%)	At 3 years (%)	At 5 years (%)	p-Value
Pre-radiotherapy hemoglobin level				
<12 g/dl (n=94)	64	41	35	
12-14 g/dl (n=109)	84	54	39	
>14 g/dl (n=72)	81	57	37	0.019
T-category				
T1/T2 (n=38)	84	67	43	
T3/T4 (n=237)	75	47	35	0.13
N-category				
N0/N1/N2a (n=116)	85	63	46	
N2b/N2c//N3 (n=159)	70	40	28	<0.001
Karnofsky performance-score				
≤70 (n=66)	62	25	25	
≥80 (n=209)	81	58	41	<0.001
Gender				
Female (n=56)	84	66	40	
Male (n=219)	74	46	35	0.045
Age				
≤57 years (n=141)	77	51	33	
≥58 years (n=134)	76	49	39	0.98
Simultaneous chemotherapy				
No chemotherapy (n=14)	64	21	n/a	
Cisplatin weekly (n=70)	70	46	31	
Cisplatin 100 mg/m^2 (n=47)	87	67	45	
Cisplatin 20 mg/m^2 (n=72)	79	62	48	
Cisplatin 20 mg/m^2 + 5-FU (n=72)	75	34	34	0.009
Primary tumor site*				
Oropharynx (n=135)	76	52	38	
Hypopharynx (n=41)	61	33	13	
Larynx (n=57)	88	61	48	
Oral cavity/Floor of mouth (n=39)	74	42	34	<0.001
Histologic grading				
G1/G2 (n=165)	81	49	39	
G3 (n=110)	70	52	32	0.38
Total radiation dose				
60-66 Gy (n=38)	66	40	40	
70 Gy (n=237)	78	52	35	0.38

n/a=Not available, *not clearly defined in 3 patients.

OS, pre-radiotherapy hemoglobin levels of >12 g/dl, lower N-category, KPS ≥80, female gender and the type of the concurrent chemotherapy were independent predictors. These results widely agree with those of previous studies of treatment of SCCHN demonstrating consistency of the results of this study (11-13). An impact of the tumor stage on outcomes was already shown for patients with locally advanced SCCHN. The prognostic role of the pre-radiotherapy hemoglobin was also reported before, for which two interpretations exist. The hemoglobin level may be a surrogate marker for more advanced underlying disease. However, it has also been suggested that hemoglobin levels are important for tumor oxygenation, which is important for the efficacy of radiation therapy (14, 15). The effect of irradiation widely depends on the induction of oxygen free radicals that lead to damage of the tumor cell DNA and, subsequently, the tumor cell itself. It is well-recognized that anemia, which is associated with a reduced oxygen-carrier capacity, has a detrimental effect on tumor cell oxygenation (14). In addition, it has been suggested that high concentrations of hemoglobin may also have a negative impact on tumor cell oxygenation due to a reduced perfusion of the small capillaries (16). Hemoglobin levels of 12-14 g/dl or 13-15 g/dl have been considered optimal for tumor oxygenation. Indeed, in the present study, hemoglobin levels of 12-14 g/dl were associated with a better LRC than levels >14 g/dl and <12 g/dl. This result supports the idea of an optimal range of hemoglobin levels in the light of tumor cell oxygenation. With respect to OS, both hemoglobin levels of 12-14 g/dl and >14 g/dl were superior to levels <12 g/dl, while the OS rates for 12-14 g/dl and >14 g/dl were similar. Thus, in addition to the aspect of tumor cell oxygenation, the hemoglobin level may also be a surrogate marker for advanced disease.

In the present study, the radiochemotherapy protocols, including three courses of 100 mg/m^2 cisplatin (on days 1, 22 and 43) or two courses of 20 mg/m^2 cisplatin (on days 1-5 and 29-33), resulted in better OS than the protocols that included weekly administration of cisplatin or cisplatin plus 5-FU. However, the retrospective design of the current study must be taken into account when using these findings to recommend a chemotherapy regimen. Additional (matched-pair) studies should be performed directly comparing two radiochemotherapy programs.

In contrast to other significant predictors, the total radiation dose (70 Gy *vs*. 60-66 Gy) had no significant impact on LRC or OS. This finding may be due to the relatively small number of patients (n=38) who received doses of 60-66 Gy. However, it may also be true that a total dose of 66 Gy is sufficient for definitive radio(chemo)therapy of advanced SCCHN when administered with chemotherapy. A randomized trial comparing 66 Gy to 70 Gy for definitive treatment of SCCHN is recommended.

In conclusion, this study demonstrated the prognostic significance of the pre-radiotherapy hemoglobin levels for

Table IV. *Multivariate analysis of survival.*

	Risk ratio	95% confidence interval	*p*-Value
Pre-radiotherapy hemoglobin level	1.32	1.04-1.68	0.020
N-category	2.02	1.39-2.98	<0.001
Karnofsky performance score	2.05	1.39-3.01	<0.001
Gender	1.67	1.07-2.74	0.024
Type of simultaneous chemotherapy	1.22	1.12-1.34	<0.001
Primary tumor site	1.04	0.91-1.17	0.57

definitive treatment of SCCHN. Furthermore, concurrent chemotherapy is mandatory to achieve optimal results. Cisplatin alone with three courses of 100 mg/m^2 (on days 1, 22 and 43) or two courses of 20 mg/m^2 (on days 1-5 and 29-33) appear most effective. However, further studies are required to identify the optimal chemotherapy program. A total radiation dose of 70 Gy may not be superior to lower doses, which needs to be properly investigated in a future randomized trial. These findings, regarding prognostic factors, can aid treatment recommendations and stratification of groups when designing prospective trials.

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 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.

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 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.

5 Kaplan EL and Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.

6 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.

7 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.

8 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.

9 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.

10 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.

11 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.

12 Leemans CR, Tiwari R, Nauta JJ, van der Waal I and Snow GB: Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer *71*: 452-456, 1993.

13 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.

14 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.

15 Becker A, Stadler P, Lavay RS, Hänsgen G, Kuhnt T, Lautenschläger C, Feldmann HJ, Molls M and Dunst J: Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys *46*: 459-466, 2000.

16 Vaupel P, Mayer A and Höckel M: Impact of hemoglobin levels on tumor oxygenation: the higher, the better? Strahlenther Onkol *182*: 63-71, 2006.

Received March 10, 2016
Revised April 11, 2016
Accepted April 13, 2016