Hemoglobin as a factor influencing the outcome in inoperable oropharyngeal carcinoma treated by concomitant radiochemotherapy

I. Oblak[1], P. Strojan[1*], B. Zakotnik[2], M. Budihna[1], L. Šmid[3]

[1]Department of Radiation Oncology, e-mail: pstrojan@onko-i.si, and [2]Department of Medical Oncology, Institute of Oncology, SI-1000 Ljubljana, Slovenia; [3]Department of Otorhinolaryngology and Cervicofacial Surgery, University Clinical Centre, Ljubljana, Slovenia

Received April 9, 2003

The aim of the study was to analyze the prognostic significance of hemoglobin (Hb) concentration for loco-regional control and survival of patients with inoperable carcinoma of the oropharynx. Seventy patients with inoperable squamous cell carcinoma of the oropharynx were prospectively treated by concomitant regimen of conventional radiotherapy and chemotherapy with Mitomycin C and Bleomycin. The prognostic value of Hb concentration before the therapy (Hb-S) and at the end of the therapy (Hb-E), the difference between both (ΔHb), and the average Hb concentration (Hb-Av) were analyzed. Hb concentration was falling significantly (median values, from 139 g/L to $p<0.0001$) during the first three weeks of the therapy; after that, it reached a plateau. In the last week of therapy, a slight increase ($p=0.08$) in Hb concentration was recorded. Significant correlation ($p<0.0001$) was found between Hb-S and other Hb-related parameters. The median follow-up of the patients alive on close-out date was 5.7 years (range 4–10.5 years). Longer disease-free survival (DFS) and disease-specific survival (DSS) correlated with higher values of Hb-S ($p=0.0005$, $p=0.008$) and Hb-E ($p=0.02$, $p=0.02$), while the Hb-Av was predictive for DFS only ($p=0.004$). The most significant difference between low- and high-Hb groups was calculated at cut-off concentrations of 122 (Hb-S), 116 (Hb-E), and 120 (Hb-Av) g/L. Only Hb-S was tested in multivariate model where its independent value for predicting both, DFS ($p=0.002$; RR 3.6) and DSS ($p=0.01$; RR 2.9), was confirmed. In our patients, Hb-S was proved to be an independent prognostic factor in predicting DFS and DSS. We believe that the concentration of Hb ≥120 g/L should be maintained during radiotherapy course.

Key words: Oropharyngeal cancer, concomitant therapy, radiotherapy, chemotherapy, hemoglobin, prognostic factor.

Anemia is a common finding in cancer. It is often present in the patients with the disease in the advanced stage and those with poor performance status, both being unfavorable prognostic factors for survival *per se*. In the patients with anemia, the supply of cells, including tumor cells, with oxygen is low because of the reduced concentration of hemoglobin (Hb) in the blood and, consequently, the reduced oxygen capacity of the blood [15]. On the other hand, the oxygenation status of the tissue is one of the key factors determining its radiosensibility [12]. A complete absence of oxygen at the time of irradiation can increase the cellular resistance by a dose-modifying factor of 3 [5].

An unfavorable effect of low Hb concentration on radiotherapy results has been documented in head neck cancer, respiratory tract malignancies, pelvic malignancies and genitourinary cancers [15]. In a view of the discrepancy of the opinions appearing in the literature, a series of questions remains unanswered: 1) which of the Hb parameters is of prognostic value, *viz.* the Hb concentration before irradiation, after its completion, the difference between these two values, or the average Hb concentration during the therapy; 2) which of the concentrations should be referred to as cut-off concentration, i.e. the concentration that makes the most clear distinction between the patients with favorable prognosis and those with unfavorable one that require the correction of their Hb status; and 3) does Hb concentration affect exclusively locoregional control of the disease, the survival of patients, or both.

The objective of our study was to analyze the prognostic

*Author to whom correspondence should be sent.

value of Hb concentration in a homogenous group of patients with the inoperable oropharyngeal carcinoma who were treated by concomitant radiochemotherapy with Mitomycin C and Bleomycin in the light of above listed questions and dilemmas.

Material and methods

Patients. Between December 1990 and August 1997, 70 patients with histologically confirmed inoperable squamous cell carcinoma of the oropharynx were treated by concomitant radiochemotherapy with Mitomycin C and Bleomycin at the Institute of Oncology, Ljubljana, Slovenia [21, 26]. Criteria for inoperability were as defined by Fu et al [9]. Entry criteria were as follows: World Health Organization (WHO) performance status <3, no distant metastases and severe pulmonary or hepatic diseases, no history of other malignancy except cured skin carcinoma, and Hb concentration >100 g/L [21, 26].

Pretreatment assessment consisted of physical examination, endoscopy with biopsy, chest X-ray, ultrasonography of the neck and abdomen, diffusion for CO, complete blood count and blood biochemistry. The tumors were staged according to the American Joint Committee on Cancer (AJCC) staging system [1]. The patient and tumor characteristics are shown in Table 1.

Treatment. All patients were treated with curative intent, with the regimen of concomitant radiochemotherapy.

Table 1. Patient data and tumor parameters (n=70)

Patients
- Age: 50 (37–70)[a]
- Sex
  - females, 3 (4%)
  - males, 67 (96%)
- Performance status:
  - WHO 0, 61 (87%)
  - WHO 1, 9 (13%)

Tumors
- Site: oropharynx
- Histology: squamous cell carcinoma
- TNM-classification:

	N0	N1	N2a	N2b	N2c	N3	Total
T1	–	–	–	–	1	–	1
T2	–	–	–	–	–	3	3
T3	4	8	2	7	7	3	31
T4	8	6	–	6	9	6	35
Total	12	14	2	13	17	12	70

- Stage:
  - stage III, 12 (17%)
  - stage IV, 58 (83%)

[a]Median (range), in years.

Radiotherapy was delivered using megavoltage Co-60 or 5 MV linear accelerator photon beams to the tumor dose of 64–70 Gy (median, 68 Gy) in 1.8–2 Gy (median, 2 Gy) daily fractions. The median duration of treatment was 49 days (range, 41–64 days). The area of the primary tumor and regional lymph nodes was included in the irradiation field and the technique of two opposing lateral beams was used. The distance of 100% isodose was at least 1.5 cm from the tumor margins. To cover the lower neck and supraclavicular nodes, one anterior field was used. After 40 Gy, irradiation field was reduced for the spinal cord protection. Sites of suspected sub-clinical deposits were electively irradiated to the dose of 50 Gy.

After delivery of 10 Gy of irradiation, Mitomycin C was applied intravenously in a dose of 15 mg/m^2. Three patients, two for hepatopathy and one for hemorrhage from the primary tumor, did not receive Mitomycin C, but Bleomycin only. In 11 patients one more dose of Mitomycin C of 10 mg/cm^2 were given on the last day of irradiation. On the day of the first application of Mitomycin C, patients were treated with two fractions of 1.8 Gy or 2 Gy, with an interval of ≥8 h in between.

The regimen of Bleomycin application was 5 mg intramuscularly, twice a week, to a planned total dose of 70 mg. When radiomucositis of WHO grade 3 or 4 developed [25], the application of Bleomycin was temporary discontinued, until local recovery. The median total dose of Bleomycin received by our patients was 25 mg (range, 5–70 mg). Four patients were not treated with Bleomycin because of abnormal results of diffusion test for CO.

Throughout the duration of therapy, patients were receiving Nicotinamide (650 mg/day, p.o.), and, in addition to Bleomycin application, Chlorpromazine (200 mg, p.o.). On the evening and morning before Mitomycin C, they were given also Dicumarol (300 mg, p.o.). Nine patients (13%) received blood transfusion for the correction of anemia that occurred because of the bleeding from primary tumor.

Follow-up of the patients. During the therapy, patients were weekly examined for the assessment of treatment response and acute toxicity that were defined according to WHO criteria [25]. In addition, patient's performance status, body weight, blood count and biochemistry were registered. Late toxicity was graded according to the criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) [18].

The median follow-up of all patients was 1.8 years (range, 0.2 to 10.5 years), and those alive on the last follow up examination was 5.7 years (range, 4–10.5 years; 62% of patients were followed ≥5 years).

Statistical analysis. The aim of the analysis was to assess the prognostic value of Hb concentration. Four different Hb parameters were used as a variable: the Hb concentration at

the beginning of the therapy (Hb-S), at the end of the therapy (HbE), the difference between the two concentrations (ΔHb), and the average Hb concentration during the therapy (Hb-Av). The difference among median Hb concentrations as measured on weekly follow-up examinations during the therapy was calculated by Wilcoxon signed rank test. The relationship between different Hb parameters was established by Spearman's rank correlation.

Survival was calculated from the first day of therapy. The disease-free survival (DFS, local and/or regional failure considered as event), disease-specific survival (DSS, deaths from disease-unrelated causes censored) and overall survival (OS, all deaths considered as events) were calculated using KAPLAN-MEIER product limit method [14]. The differences between various prognostic groups were compared with the log rank test [19]. For the survival analysis, Hb concentrations were dichotomized using the criterion of optimal cut-off concentration. The latter was determined among the measured (Hb-S, Hb-E) or calculated (ΔHb, Hb-Av) concentrations on the basis of maximal difference in the survival rates between the low and high Hb groups.

The same tests were used to assess the effect of other patient-, disease- and treatment-related variables on the survival. Those variables that statistically significantly influenced the survival on univariate analysis were included into multivariate Cox proportional hazard model to test their independent prognostic value [4].

All tests were two-sided and the results were considered statistically significant at the probability level of 0.05.

Results

During observation period, the disease recurrence was established in 43/70 patients (61%): above the clavicles and in distant sites it occurred in 28 and in 8 patients, respectively, while both, local and/or regional failure and systemic dissemination, developed in 7 patients. Of 70 patients, 49 died (70%): in 41 patients, the cause of death was disease-related, whereas 8 patients died of intercurrent diseases. Five-year DFS, DSS and OS were 45%, 40% and 32%, respectively (Fig. 1). No significant difference was observed in the survival of the transfused or non-transfused patients.

Dynamics of Hb concentration changes during the therapy and its effect on survival. The values of Hb-S, Hb-E, ΔHb and Hb-Av are given in Table 2. Figure 2 shows a statistically significant drop in Hb concentration during the first three weeks of therapy ($p<0.0001$); after that it reached a plateau and, in the last week of therapy, Hb concentration even increased, though insignificantly ($p=0.08$). A significant correlation ($p<0.0001$) was found between Hb-S and all the other Hb-related parameters under the study, i.e. Hb-E ($S_R=0.49$), ΔHb ($S_R=0.50$), and Hb-Av ($S_R=0.75$).

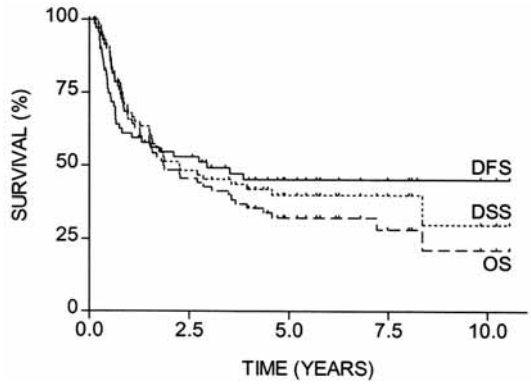

Figure 1. Actuarial survial of patients with inoperable oropharyngeal carcinoma treated with concomitant radiochemotherapy with Mitomycin C and Bleomycin (n=70).
DFS – disease-free survival, DSS – disease-specific survival; OS – overall survival.

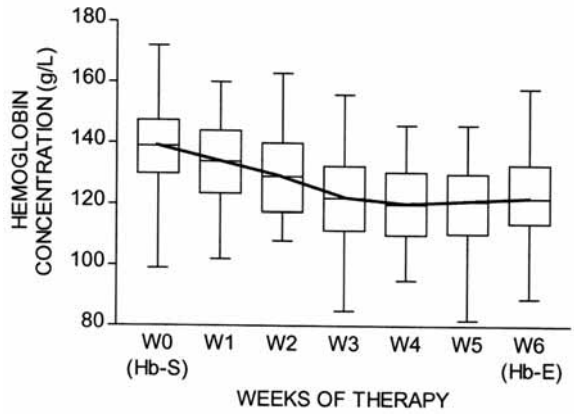

Figure 2. Dynamics of alteration in median hemoglobin concentration during therapy. The top and the bottom of the box represent the 25th and 75th percentile, respectively, and the ends of the bars represent the range. The line in the box is the median value.

Table 2. Hemoglobin concentrations (n=70)

Variable	Median (range)[a]	Mean ± SD[a]
Hb-S	139 (99–172)	138.9 ± 14.35
Hb-E	122 (89–158)	122.3 ± 13.83
Hb-Av	126 (105–153)	125.6 ± 12.20
ΔHb	16 (–14–50)	16.6 ± 15.00

[a]Gram per liter (g/L).

On univariate analysis, Hb-S and Hb-E significantly influenced both, DFS and DSS, and Hb-Av correlated with DFS only (Tab. 3). While at the median cut-off values 139 g/L (Hb-S), 122 g/L (Hb-E) and 126 g/L (Hb-Av), the difference in survival between the two groups with Hb concentrations above and below these values was not significant, it became explicitly significant with subsequent lowering of

Table 3. Univariate analysis for disease-free survival and disease-specific survival

Variable	*n*	Disease-free survival % at 5 years	p-value	Disease-specific survival % at 5 years	p-value
Hb-S					
< *vs.*≥ 122 g/L	8/62	0 *vs.* 52	0.0005	13 *vs.* 44	0.008
Hb-E					
< *vs.*≥ 116 g/L	19/51	24 *vs.* 53	0.02	22 *vs.* 46	0.02
Hb-Av					
< *vs.*≥ 120 g/L	22/48	19 *vs.* 58	0.004	23 *vs.* 48	0.07
*Δ*Hb					
< *vs.*≥ 7 g/L	17/53	26 *vs.* 52	0.06	30 *vs.* 44	NS
Age					
< *vs.*≥ 50 years	33/37	44 *vs.* 47	NS	38 *vs.* 42	NS
Performance status (WHO)					
< *vs.*≥ grade 1	61/9	53 *vs.* 0	0.0005	46 *vs.* 0	0.01
Weight loss					
≤ *vs.* > 10%	35/35	46 *vs.* 45	NS	41 *vs.* 39	NS
T-stage					
T_{1-3} *vs.* T_4	35/35	55 *vs.* 36	NS	50 *vs.* 30	NS
N-stage					
N_{0+1} *vs.* N_{2+3}	26/44	67 *vs.* 32	0.02	58 *vs.*29	0.03
Treatment time					
≤ *vs.*> 49 days	37/33	48 *vs.* 44	NS	42 *vs.* 37	NS
Tumor dose					
≤ *vs.*> 68 Gy	37/33	42 *vs.* 47	NS	37 *vs.* 43	NS

n – number of patients, NS – not significant.

Table 4. Multivariate analysis for disease-free survival and disease-specific survival

Variable	Disease-free survival			Disease-specific survival		
	p-value	RR	95% CI	p-value	RR	95% CI
Performance status (WHO)	0.002	3.6	1.6–8.2	0.02	2.6	1.2–5.8
N-stage	0.04	2.3	1.0–5.1	0.08	1.9	0.9–3.8
Hb-S	0.002	3.6	1.6–8.1	0.01	2.9	1.3–6.6

RR – risk ratio; CI – confidence interval.

these cut-off values (Fig. 3). In all cases, higher Hb concentrations were prognostically advantageous.

Influence of other variables. In addition to assess the prognostic value of Hb concentration, the univariate analysis was used also for determining the prognostic impact of the following variables: patient's age, performance status and loss of body weight during therapy, T- and N-stage of the disease, the radiotherapy duration and tumor dose. Only patient's performance status and N-stage of the disease were found to correlate significantly with DFS and DSS (Tab. 3).

Multivariate analysis. In addition to other variables that proved to be statistically significant on univariate analysis, of the studied Hb-related parameters only Hb-S was included in multivariate model: Hb-S is the only parameter known at the beginning of therapy and has the potential to affect the value of all the other Hb parameters. The results are shown in Table 4. Hb-S proved its independent prognostic value in relation to both, DFS as well as DSS.

Discussion

In the present study, the prognostic value of Hb concentration was evaluated in a group of patients with inoperable squamous cell carcinoma of the oropharynx treated by concomitant radiochemotherapy with Mitomycin C and Bleomycin. Of all Hb-related parameters tested, Hb-S turned out to be the most significant and independent predictor for both, DFS and DSS.

Two characteristics of the study should be exposed: the homogeneity in respect to patient population and treatment regimen, and the maturity of survival results, which are comparable to those of other series dealing with poor-risk

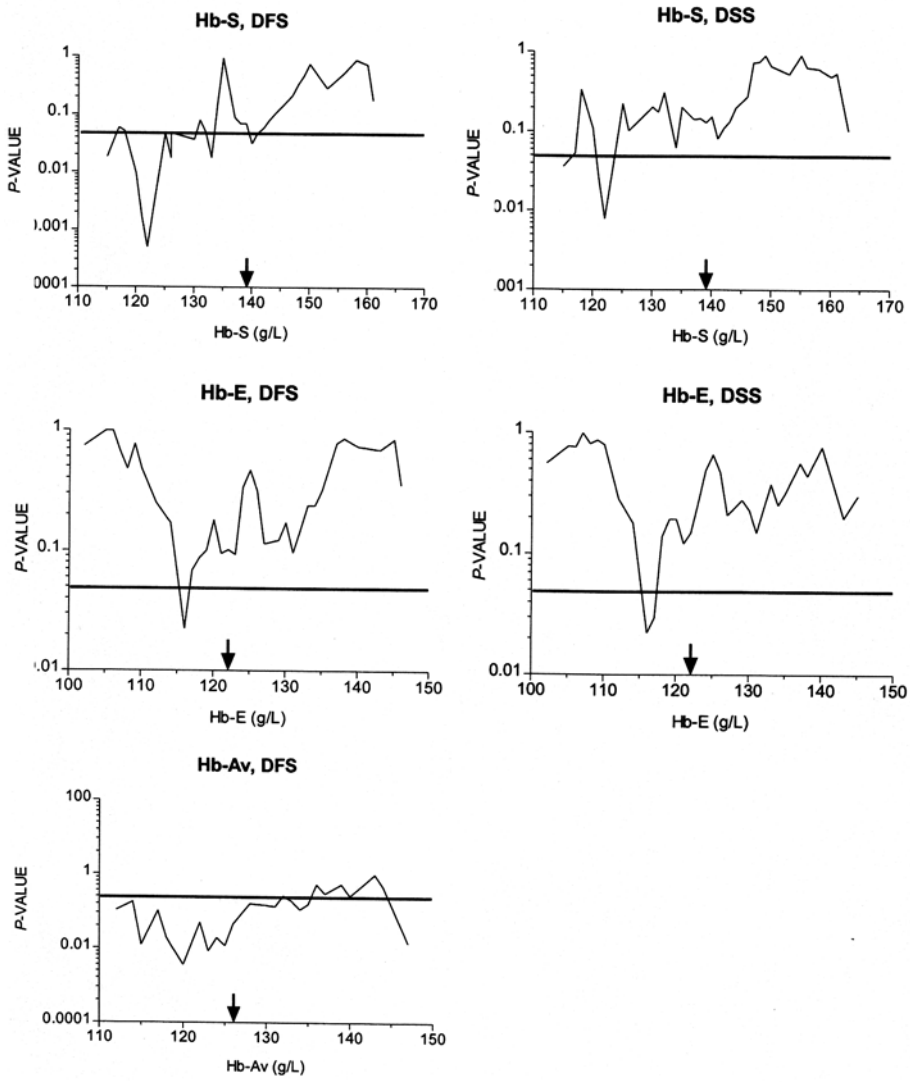

Figure 3. Dynamics of P-value alteration according to possible cut-off hemoglobin concentrations. The arrow represents the median hemoglobin concentration; the horizontal line is the p-value of 0.05. DFS – disease-free survival, DSS – disease-specific survival.

patients and concomitant radiochemotherapy [2]. There is, however, still a window of opportunity for improving the survival: more sophisticated radiotherapy techniques (three-dimensional radiotherapy, intensity-modulated radiotherapy), advanced fractionation regimens (acceleration, hyperfractionation), new drugs and combinations, and modulation of certain important radiobiological parameters, tumor oxygenation status being one of them. Hypoxia was determined directly by means of polarographic pO_2 measurements in different human tumors and it seems that it correlates with poor tumor response to irradiation [13]. Though no clear answer has been given to the question to what extent hypoxia in the tumor depends on Hb concentration in the blood, the findings of numerous clinical studies support the view that anemia has an unfavorable effect on the outcome of the treatment with irradiation [15].

When reviewing the literature on the head and neck cancer, both the Hb-S [3, 6–8, 10, 11, 16, 20, 24] and Hb-E [22, 23] were recognized as independent prognostic factors on multivariate setting. In the present study, the prognostic significance of ΔHb and Hb-Av was also tested and the results were positive for three out of four Hb-related parameters, i.e. Hb-S, Hb-E and Hb-Av. From clinical point of view, however, the most usable parameter is Hb-S. As a rule, this parameter is known before treatment and, according to our findings, it pre-determines the value of the remaining three Hb parameters. Therefore, with correction of anemia before the beginning of radiotherapy, it is possible to influence indirectly the Hb-E and Hb-Av in individual patients.

As suggested by the data from our study, Hb-S was the most powerful prognosticator of all Hb parameters in univariate analysis, with an independent prognostic value proved also on multivariate setting. In the latter, Hb-S was analysed as a categorical variable and was dichotomized on the basis of the optimal cut-off concentration, determined by the criterion of maximal difference in the survival rates between low- and high-Hb groups. For routine clinical practice, the exact definition of threshold Hb concentration is of crucial importance: only that way the prognostically important states of Hb deficiency calling for intervention could be identified and corrected in time.

Unfortunately, as the series dealing with the prognostic value of Hb-S in the head and neck cancer are extremely heterogeneous in respect to both, the patient selection and treatment parameters, it is not surprising that the cut-off concentrations of Hb-S as reported in the literature vary substantially, from 125 g/L to 145 g/L [3, 6, 7, 10, 11, 16]. According to our data, it is the concentration ≤122 g/L that calls for correction, and is bellow the range determined by other authors. This difference is mainly due to the fact that the categorization of patients into low- and high-risk groups was, in other studies, based on the arbitrarily defined cut-off

concentrations, whereas in our study, the categorization was based on the so-called optimal cut-off concentration.

On the other hand, the numbers obtained from the analyses using Hb as continuous variable do not provide clear information on which Hb-S concentration is critical and need to be corrected. However, the information from these studies on the changes in tumor control and/or in patients' survival that occur with the decrease in Hb concentration by one unit (1 g/L) is highly indicative and emphasizes the importance of maintaining the Hb status inside of predefined normal range [8, 20, 24].

Another dilemma arising from the literature is whether Hb-S has the potential to predict the tumor control, patients' survival, or both. The results from the reports in which multivariate analysis was performed are inconclusive. Namely, the majority of studies generally had only one objective [3, 10, 20, 24], or the Hb-S correlated with only one end-point (with tumor control, Ref. 11; with patients' survival, Refs. 6, 7), with both [8, 16], or with none [17]. In the present series, Hb-S has turned out to be independent prognosticator for both, the DFS and DSS, with the degree of statistical significance comparable to that of two other classical prognostic factors in the head and neck cancer, i.e. performance status and N-stage of disease.

On the basis of the presented results, the urge for Hb correction is obvious in routine clinical practice. However, the optimal way how to perform it is yet to be defined. The issue of blood transfusion given to low-Hb patients was addressed prospectively in DAHANCA 5–85 study [17]. Despite the fact that almost half of the anemic patients received blood transfusion, a significant difference in locoregional control was observed between low- and high-Hb groups. On the other hand, the treatment outcome of transfused and non-transfused patients in low-Hb group was the same. In our study, 13% of patients were transfused, which may not suffice to assess the effect of blood transfusion on the outcome of treatment or prognosis. The other possibility of improving Hb status is to stimulate erythropoiesis by using recombinant erythropoietin. The first results of its implementation in radiotherapy protocols are encouraging [10]. However, the question whether this is the procedure of choice is yet to be resolved.

Based on the results of our analyses, we may conclude that Hb-S is an independent prognostic factor for DFS and DSS of the patients treated with concomitant radiochemotherapy for inoperable carcinoma of the oropharynx. We recommend that, throughout radiotherapy course, Hb concentration be maintained within the range of ≥120 g/L.

References

[1] American Joint Committee on Cancer. AJCC manual for staging of cancer. 4th edition. Philadelphia: JB Lippincott, 1992.

[2] Brockstein BE, Vokes EE. Chemoradiotherapy for head and neck cancer. PPO updates. 1996; 10: 1–19.

[3] Bryne M, Eide GE, Lilleng R, Langmark F, Thrane PS, Dabelsteen E. A multivariate study of the prognosis of oral squamous cell carcinomas: are blood group and hemoglobin new prognostic factors? Cancer 1991; 68: 1994–1998.

[4] Cox DR. Regression models and life tables. J R Stat Soc 1972; 187: 187–220.

[5] Denekamp J, Joiner MC. The potential benefit from a perfect radiosensitizer and its dependence on reoxygenation. Br J Radiol 1982; 55: 657–663.

[6] Dubray B, Mosseri V, Brunin F, Jaulerry C, Poncet P, Rodriguez J, Brugere J, Point D, Giraud P, Cosset JM. Anemia is associated with lower local-regional control and survival after radiation therapy for head and neck cancer: a prospective study. Radiology 1996; 201: 553–558.

[7] Fazekas JT, Scott C, Marcial V, Davis LW, Wasserman T, Cooper JS. The role of hemoglobin concentration in the outcome of misonidazole-sensitized radiotherapy of head and neck cancers: based on RTOG trial #79-15. Int J Radiat Oncol Biol Phys 1989; 17: 1177–1181.

[8] Fein DA, Lee WR, Hanlon AL, Ridge JA, Langer CJ, Curran WJ, Coia LR. Pretreatment hemoglobin level influences local control and survival of T1-2 squamous cell carcinomas of the glottic larynx. J Clin Oncol 1995; 13: 2077–2083.

[9] Fu KK, Phillips TL, Silverberg IJ, Jacobs C, Goffinet DR, Chun C, Friedman MA, Kohler M, McWhirter K, Carter SK. Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced inoperable head and neck cancer: update of Northern California oncology group randomized trial. J Clin Oncol 1987; 5: 1410–1418.

[10] Glaser CM. Millesi W, Kornek GV, Lang S, Schull B, Watzinger F, Selzer E, Lavey RS. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharynx. Int J Radiat Oncol Biol Phys 2001; 50: 705–715.

[11] Grant DG, Hussain A, Hurman D. Pre-treatment anemia alters outcome in early squamous cell carcinoma of the larynx treated by radical radiotherapy. J Laryngol Otol 1999; 13: 829–833.

[12] Gray LH, Conger AD, Ebert M, Hornsey S, Scott OCA. The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Br J Radiol 1953; 26: 638–648.

[13] Horsman MR. Measurement of tumor oxygenation. Int J Radiat Oncol Biol Phys 1998; 42: 701–704.

[14] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–481.

[15] Kumar P. Tumor hypoxia and anemia: impact on the efficacy of radiation therapy. Semin Hematol 2000; 37: 4–8.

[16] Lee WR, Berkey B, Marcial V, Fu KK, Cooper JS, Vikram B, Coia LR, Rotman M, Ortiz H. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. Int J Radiat Oncol Biol Phys 1998; 42: 1069–1075.

[17] Overgaard J, Hansen HS, Overgaard M, Bastholt L, Berthelsen A, Specht L, Lindelov B, Jorgensen K. A rando-

mized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol 1998; 46: 135–146.

[18] Perez CA, Brady LW. Overview. In: Perez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. 2nd edition. Philadelphia: JB Lippincott, 1992: 53.

[19] Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35: 1–39.

[20] Skladowski K, Tarnawski R, Maciejewski B, Wygoda A, Slosarek K. Clinical radiobiology of glottic T1 squamous cell carcinoma. Int J Radiat Oncol Biol Phys 1999; 43: 101–106.

[21] Smid L, Lesnicar H, Zakotnik B, Soba E, Budihna M, Furlan L, Zargi M, Rudolf Z. Radiotherapy, combined with simultaneous chemotherapy with Mitomycin C and Bleomycin for inoperable head and neck cancer – preliminary report. Int J Radiat Oncol Biol Phys 1995; 32: 769–775.

[22] Tarnawski R, Skladowski K, Maciejewski B. Prognostic value of hemoglobin concentration in radiotherapy for cancer of supraglottic larynx. Int J Radiat Oncol Biol Phys 1997; 38: 1007–1011.

[23] Van Acht MJJ, Hermans J, Boks DES, Leer JWH. The prognostic value of hemoglobin and a decrease in hemoglobin during radiotherapy in laryngeal carcinoma. Radiother Oncol 1992; 23: 229–235.

[24] Warde P, O'Sullivan B, Bristow RG, Panzarella T, Keane TJ, Gullane PJ, Witterick IP, Payne D, Liu FF, McLean M, Waldron J, Cummings BJ. T1/T2 glottic cancer managed by external beam radiotherapy: the influence of pretreatment hemoglobin on local control. Int J Radiat Oncol Biol Phys 1998; 41: 347–353.

[25] World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: WHO, 1979.

[26] Zakotnik B, Smid L, Budihna M, Lesnicar H, Soba E, Furlan L, Zargi M. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys 1998; 41: 1121–1127.