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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Decrease in Hemoglobin Levels Following Surgery Influences the Outcome in Head and Neck Cancer Patients Treated with Accelerated Postoperative Radiotherapy

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ABSTRACT

Aim. To assess the influence of hemoglobin (Hb) levels in locally advanced head and neck cancer (LAHNC) patients treated with surgery and postoperative radiotherapy (PORT).

Material and Methods. Pre- and postoperative Hb levels were collected in 79 patients treated with surgery followed by accelerated PORT for LAHNC. Median follow-up was 52 months (range 12–95 months).

Results and Discussion. Four-year overall survival (OS) rate was 51%. Neither pre- nor postoperative Hb level (<120 or 130 g/l in women or men, respectively) influenced the outcome. However, when Hb decrease between pre- and postoperative Hb values was taken into account, 4-year OS was significantly higher in patients with Hb difference less than 38 g/l (quartile value) compared with those with Hb decrease 38 g/l or more (61% versus 16%, $P = 0.008$).

Conclusion. Decrease in Hb level by more than 38 g/l after surgery secondary to blood loss influences the outcome when postoperative RT is indicated.

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Despite the various strategies tried to improve the outcome, locoregional failure is still high in locally advanced head and neck cancer patients (LAHNC). Tumor stage, lymph node involvement, and extranodal extension (ENE) are well-known prognostic factors. Moreover, numerous studies pointed out that low hemoglobin (Hb) levels before and during radiation therapy (RT) were associated with worse local control and survival in the various types of cancer.[1–3]

Head and neck cancer patients are at high risk for developing anemia. Extensive radical surgery, being one of the important reasons, may cause high intraoperative blood loss. Furthermore, multimodality therapy such as concomitant chemo- and RT, which improve patient survival, can worsen debilitating anemia. Direct association between tumor hypoxia and anemia is unclear, but anemia leads to decreased cell oxygenation and has been shown to contribute to tumor resistance to RT or chemotherapy via deprivation of the oxygen essential for the cytotoxic actions of these agents.[4] Most studies report on the prognostic importance of the Hb level after primary RT with or without chemotherapy.[5–7] However, there is no published study assessing the role of decreasing Hb because of blood loss during surgery on the outcome when postoperative RT (PORT) is indicated.

Herein, we report the influence of pre- and postoperative Hb levels, and the amount of its decrease, in LAHNC patients treated with surgery and PORT.

PATIENTS AND METHODS

Between December 1997 and June 2002, 79 consecutive patients treated with curative surgery followed by

accelerated PORT were included in this retrospective study. Inclusion criteria consisted of nonmetastatic head and neck cancer classified pT1–pT4 and/or pN0–pN3, age 18 years or older, no previous history of cancer other than nonmelanoma skin cancer or in situ cervix cancer, and good performance status World Health Organization (WHO) scale 0–1 Patients with gross residual disease after surgery, previous RT with or without systemic chemotherapy, metastatic disease or known cause of anemia were excluded. The majority of patients were male (male-to-female ratio 62/17). Median age was 60 years (range 36–81 years). Patient characteristics are listed in Table 1.

All patients were seen and discussed at our multidisciplinary tumor board, and the treatment recommendation was made jointly by head and neck surgeon, radiation oncologist, and medical oncologist with advice from the pathologist, diagnostic radiologist, nursing staff, nutritionists, and dentists. Percutaneous endoscopic gastrostomy (PEG) was placed before or at the beginning of treatment in 24 of 79 patients (30%), and 6 patients (8%) required nasogastric feeding tube during their treatment.

TABLE 1 Characteristics of 79 patients

	Number	%
Tumor site		
Oral cavity	23	29
Oropharynx	23	29
Hypopharynx	17	21
Larynx	6	8
Other	10	13
RT indications		
ENE with PSM	29	37
ENE without PSM	25	31
PSM	18	23
Positive LN ≥3	4	5
pT4	3	4
PT-classification		
0	5	6
1	10	13
2	30	38
3	15	19
4	19	24
PN-classification		
0	11	14
1	15	19
2a	11	14
2b	27	34
2c	5	6
3	10	13

ENE extracapsular nodal extension, *PSM* positive surgical margin, *LN* lymph nodes

Pretreatment evaluation included a medical history, physical examination, panendoscopy and biopsy, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck region in all cases. Additional diagnostic procedures for distant metastases, including CT scan of the chest, liver ultrasound, bone scintigraphy, and/or, more recently, positron emission tomography were only performed if clinically indicated. T- and N-classification were assigned according to the staging system of the International Union against Cancer (UICC) 2002.[8]

Statistical Methods

Overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS) rates as well as actuarial locoregional control (LRC) rates were calculated using the product-limit method.[9] Time to any event was measured from the date of pathological diagnosis. The events were death (all causes) for OS, head and neck cancer-related mortality for CSS, and death (all causes) or relapse for DFS. For the LRC rate, the event consisted of local and/or regional relapse. Confidence intervals (CI) were calculated from standard errors. Differences between groups were assessed using the log-rank test.[10] Multivariate analyses were done using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor.[11]

RESULTS

All patients underwent primary curative surgery. PORT was indicated for positive surgical margins ($n = 18$) or for pT4 tumors ($n = 3$) in 21 (27%) patients, or because of extranodal infiltration with ($n = 29$) or without ($n = 25$) positive surgical margins in 54 (68%) patients. Four patients (5%) with three or more positive nodes were also included. Total dose to the spinal cord was limited to 46 Gy. Median RT duration was 39 days (range 35–59 days). The interval between surgery and radiotherapy was ≤42 days in 51 patients (65%) and >42 days in 28 patients (35%).

Conformal three-dimensional (3D)-RT planning was used in all patients. Patient immobilization was accomplished with individualized thermoplastic masks. The boost volume (66 Gy) consisted of the clinical target volume (CTV1), which was defined according to the presurgical location of the primary tumor and its nodal extension including the entire surgical bed; and the planning target volume (PTV1) included a 5-mm margin around the CTV1 in three dimensions. This volume was treated every Friday afternoon during the first 5 weeks, and daily during the first 3 days of the sixth week. The initial treatment volume

(PTV2; 50 Gy), which was treated once daily during the first 5 weeks, consisted of the boost volume and all nodal areas at risk of subclinical malignant disease (CTV2) including a 5-mm margin around the CTV2 in three dimensions. The irradiation source was either a telecobalt unit or a linear accelerator using 6-MV photons and electrons.

Pre- and postoperative Hb levels were collected in all patients. While no information was available concerning the amount of blood loss during surgery, none of the patients required blood transfusion due to surgery. In this study, Hb cut-off value was considered <120 g/l in women and <130 g/l in men. The median Hb level before surgery was 138 g/l (range 98–174 g/l), and after surgery 109 g/l (range 74–161 g/l). The distribution of the Hb value according to gender is shown in Table 2. A median decrease of 24 g/l of Hb (quartile values 9 and 38 g/l) was observed between pre- and postoperative Hb levels (range −44–68 g/l).

After median follow-up period of 52 months (range 12–95 months), 39 of 79 patients were alive with ($n = 1$) or without ($n = 38$) evidence of disease. Median time to locoregional relapse ($n = 16$) was 14 months (range 4–68 months). Median time to distant metastases ($n = 19$) was 16 months (range 3–48 months).

The 2- and 4-year OS, CSS, and DFS rates were 65% (95% CI: 54–76%) and 51% (95% CI: 39–63%), 71% (95% CI: 60–82%), and 60% (95% CI: 48–72%), and 61% (95% CI: 49–73%) and 48% (95% CI: 35–60%), respectively (Fig. 1). The 2- and 4-year actuarial LRC probability was 94% (95% CI: 88–100%) and 79% (95% CI: 69–89%), respectively. Distant metastases were observed in 19 (24%) patients, with the probability of being without distant metastases at 2 and 4 years being 79% (95% CI: 69–89%) and 67% (95% CI: 55–79%), respectively.

In univariate analyses, gender, age, tumor site, Hb values before and after surgery, pT- and pN-classification, presence of ENE, interval between surgery and PORT, total RT time, and amount of Hb decrease were analyzed.

TABLE 2 Hemoglobin status in 79 patients

	Preoperative	Postoperative
Median (g/l)	138	109
Range (g/l)	98–174	74–161
	Number (%)	Number (%)
Men (g/l)		
<130	21 (27)	48 (61)
≥130	41 (52)	14 (18)
Women (g/l)		
<120	4 (5)	11 (14)
≥120	13 (16)	6 (7)

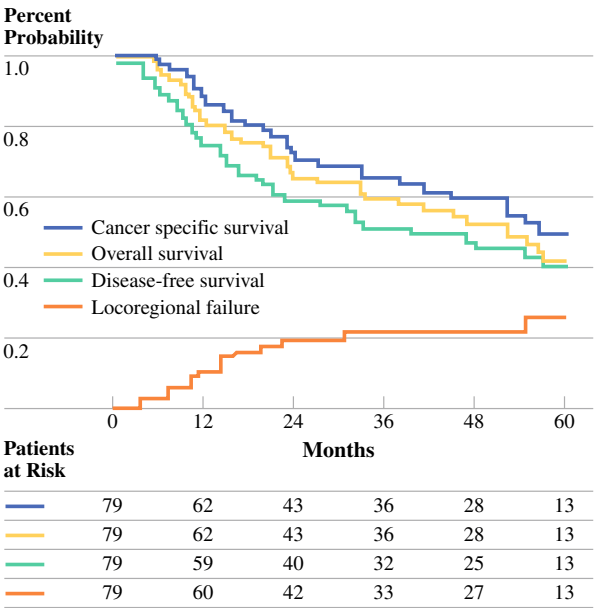

FIG. 1 Probability of cancer-specific survival (dashed line), overall survival (solid line), disease-free survival (dotted line), and locoregional failure (dashed/dotted line) in 79 patients treated with accelerated postoperative radiotherapy

T-classification, ENE, and decreasing Hb more than 38 g/l were statistically significant prognosticators on univariate analyses (Table 3; Fig. 2). T-classification and ENE remained independently significant in multivariate analyses (Table 4) for OS, DFS, and CSS. Hb decrease more than 38 g/l was also an independent factor influencing the CSS (Table 4). No factor influencing the LRC was found in either univariate or multivariate analyses.

There was no correlation between T- or N-classification and the amount of Hb decrease following surgery (9 of 45 patients with T1–T2 tumors and Hb decrease ≤38 g/l versus 9 of 34 patients with T3–T4 tumors and Hb decrease>38 g/l, $P = 0.50$; and 9 of 26 patients with N0–N1 disease and Hb decrease ≤38 g/l versus 9 of 53 with N2–N3 disease and Hb decrease>38 g/l, $P = 0.09$).

DISCUSSION

Locoregional control is currently the most important issue in the treatment of LAHNC, and locoregional recurrence translates directly into poor overall survival.[12,13] Several treatment-specific factors (e.g., total radiation dose, overall treatment time, interval between surgery, and RT) and patient-specific characteristics (e.g., age, sex, performance status, anemia, stage, ENE, and surgical margin) are known to influence the probability of local tumor control by RT alone or with surgery. Patients with positive surgical margins, perineural invasion, lymph node involvement, presence of ENE constitute a subgroup of patients with

TABLE 3 Univariate analyses

	n	4-yr OS	95% CI	*P*-value	4-yr DFS	95% CI	*P*-value	4-yr CSS	95% CI	*P*-value	4-yr LRC	95% CI	*P*-value
All patients	79	51	39–63		48	35–60		60	48–72		79	69–89	
Gender													
Female	17	68	44–90	0.38	62	37–87	0.35	77	53–100	0.29	71	46–96	0.65
Male	62	48	34–62		44	30–58		56	42–70		81	70–92	
Age (years)													
<60	43	50	42–68	0.35	46	28–64	0.47	54	38–70	0.54	76	62–90	0.74
≥60	36	52	34–70		49	31–67		68	50–86		84	71–97	
Tumor site													
Oral cavity	23	59	39–79	0.93	47	25–69	0.86	65	45–85	0.99	86	71–100	0.57
Oropharynx	23	49	28–70		45	24–66		56	34–78		72	53–91	
Larynx/hypo.	23	50	25–75		50	27–73		57	31–83	7	3	49–97	
Other	10	50	15–85		50	15–85		57	20–94		83	53–100	
T-classification													
pT1–2	45	57	41–73	0.03	59	43–75	0.07	63	47–79	0.06	83	72–94	0.51
pT3–4	34	44	26–62		30	12–48		55	36–74		71	52–90	
N-classification													
pN0–1	26	55	33–77	0.35	46	24–68	0.44	69	50–88	0.40	75	57–93	0.62
pN2–3	53	49	35–63		48	34–52		55	39–71		81	69–93	
ENE													
No	26	73	54–92	0.03	57	35–79	0.04	87	73–100	0.01	87	73–100	0.16
Yes	53	40	26–54		38	23–53		45	29–61		74	60–88	
Surgery–RT interval (days)													
≤42 days	51	50	34–66	0.96	47	31–63	0.92	55	37–73	0.59	79	67–91	0.94
>42 days	28	53	37–69		49	30–68		68	48–88		79	62–96	
RT duration (days)													
≤39 days	54	49	35–63	0.58	43	29–57	0.46	54	38–70	0.15	76	63–89	0.58
>39 days	25	57	35–72		57	35–79		73	53–93		84	68–100	
Hb (g/l) before surgery													
Low[a]	25	56	34–78	0.95	53	31–75	0.97	65	42–88	0.75	86	68–100	0.33
High[b]	54	50	43–57		47	33–61		58	44–72		75	63–87	
Hb (g/l) after surgery													
Low[a]	59	53	39–67	0.89	47	33–61	0.89	60	56–74	0.78	79	67–91	0.95
High[b]	20	46	23–69		46	23–69		59	46–82		77	57–97	
Hb decrease (g/l)													
Median ≤24	43	60	44–76	0.15	56	40–72	0.32	72	56–88	0.04	80	66–94	0.94
>24	36	41	23–59		37	19–55		46	28–64		77	62–92	
Quartile ≤38	61	61	47–75	0.008	56	42–70	0.02	70	56–84	0.005	80	69–91	0.59
>38	18	16	0–36		17	0–36		24	0–50		74	52–96	

[a] Low <120 g/l in women and <130 g/l in men

[b] High ≥20 g/l in women and ≥130 g/l in men

OS overall survival, *DFS* disease-free survival, *CSS* cancer-specific survival, *LRC* locoregional control, *CI* confidence interval, *RT* radiotherapy, *ENE* extracapsular nodal extension

high risk of locoregional relapse.[14–18] Besides all of these prognostic factors, numerous reports have pointed out the prognostic value of anemia and the adverse effects of tumor hypoxia on the efficacy of anticancer treatments in recent years, indicating that decreased radiosensitivity resulting from tumor hypoxia was the most likely explanation.[1–4,19] Recently Rades et al. analyzed 153 LAHNC patients; they found performance status, stage, surgery,

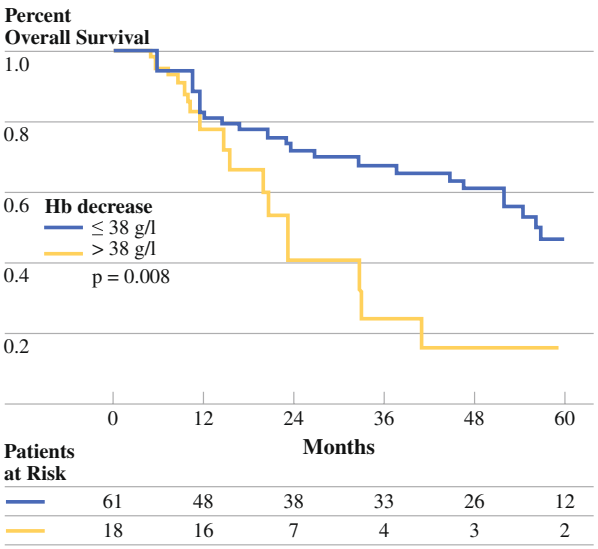

FIG. 2 Overall survival according to hemoglobin (Hb) decrease following surgery. Solid line represents patients with Hb decrease ≤38 g/l, and dashed line patients with Hb decrease>38 g/l (log-rank test, $P = 0.008$)

pre-radiotherapy Hb level, and interruptions during RT >1 week were important prognostic factors for outcome of radiochemotherapy treatment.[20] Three-year LRC was 46% and 75% in the Hb <12 g/dl and Hb ≥12 groups.

As reported in the literature, in this study univariate and multivariate analyses showed that tumor stage and ENE were significant prognostic factors for OS, DFS, and CSS (Table 3). Besides all of these factors, univariate analyses showed that Hb decrease more than 38 g/l during surgery was also a prognostic factor. Four-year DFS, OS, and CSS were 56%, 61%, and 70% in patients with Hb decreased 38 g/l or less compared with 16%, 16%, and 24% in patients with Hb decreased more than 38 g/l. However, presurgery or pre-RT Hb value did not show any significant influence on DFS, OS, or CCS (Table 3).

During major surgery, substantial blood loss is possible, varying between mean values of 500 and 1,500 ml, and amount of this loss may be depending on disease stage, tumor size, or any other surgical parameters.[2,21] In our study, neither tumor size nor nodal status was correlated with the Hb decrease. Twenty percent of patients with T1–T2 tumors had an Hb decrease of ≤38 g/l, whereas 26% of the patients with T3–T4 an Hb decrease of >38 g/l.

Confirming explanations might be based on radiobiological theories. Tumor hypoxia may induce proteomic and genomic changes, and they may result in clinically more aggressive tumors with increased potential of metastases through cellular process.[22] Hypoxia induces the expression of various angiogenic cytokines [vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin-8 (IL-8), tumor necrosis factor (TNF), etc.], responsible in the course of various signal transduction cascades for the proliferation, migration, and differentiation of the endothelial cells responsible for the development of neovasculature in a tumor.[23] Furthermore, hypoxia gives rise to inhibition of cellular proliferation by an accumulation of cells in phase G0 of the cell cycle. It reduces cytotoxicity, induces hypoxic stress proteins, lowers the apoptotic potential, and causes tissue acidosis.[24] All these factors released under hypoxic conditions may result in a malignant phenotype of residual tumor cells left after surgery; and may, therefore, lead to a more aggressive regrowth of these cells resulting in recurrences.

A number of clinical studies aimed to increase the outcome by increasing the Hb level by either blood transfusions or recombinant erythropoietin (rEPO). There is, currently, no clear evidence that correction of anemia improves prognosis. Henke and colleagues prospectively compared anemic head and neck cancer patients receiving definitive RT or PORT with or without rEPO treatment.[25] They reported that rEPO treatment corrected hemoglobin levels, however, had negative impact on locoregional cancer control and survival. Recently, Overgaard et al. presented the results of the DAHANCA 10 randomized trial.[26] In this study, 515 patients with Hb values below 9.0 mmol/l (14.0 g/dl) treated with definitive RT were randomized to receive darbopoietin together with accelerated RT. They observed a significant correction of the Hb level with darbopoietin in patients with LAHNC resulting, however, in a significantly poorer locoregional control after

TABLE 4 Multivariate analyses

Parameter	Overall survival		Disease-free survival		Cancer-specific survival		Locoregional control	
	RR	*P*-value	RR	*P*-value	RR	*P*-value	RR	*P*-value
T-classification (pT3–4 versus pT1–2)	1.47	0.02	1.38	0.05	1.49	0.04	NS	
Extranodal extension (yes versus no)	1.59	0.01	1.52	0.02	1.82	0.005	NS	
Hb decrease (g/l) (>38 versus ≤38)	1.39	0.07	1.35	0.09	1.49	0.05	NS	

RR risk ratio, *NS* not significant

RT (56% versus 69%, $P = 0.02$). The use of darbopoietin resulted in an increased Hb value in more than 91% of the patients. However, there was no significant difference in terms of overall survival (38% versus 51%, $P = 0.08$).

Primary surgery and PORT is a traditional approach for operable LAHNC patients. Success of the RT may be compromised by the presence of demonstrably unfavorable factors. Surgical procedures and reconstruction frequently result in high intraoperative blood loss. This study shows that perioperative Hb decrease may influence the outcome of the patients who are candidates for PORT. Given negative anemia-correction studies using rEPO, strategies to prevent perioperative Hb decrease should focus on limiting blood loss during surgery. Alternative intraoperative techniques to minimize bleeding, intraoperative or postoperative blood transfusion, and investigation of other pharmacologic agents are warranted.

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