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CLINICAL INVESTIGATION **Esophagus**

EPOETIN ALFA IMPROVES SURVIVAL AFTER CHEMORADIATION FOR STAGE III ESOPHAGEAL CANCER: FINAL RESULTS OF A PROSPECTIVE OBSERVATIONAL STUDY

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Purpose: This prospective, nonrandomized study evaluates the effectiveness of epoetin alfa to maintain the hemoglobin levels at 12 to14 g/dL (optimal range for tumor oxygenation) during chemoradiation for Stage III esophageal cancer and its impact on overall survival (OS), metastatic-free survival (MFS), and locoregional control (LC).

Methods and Materials: Ninety-six patients were included. Forty-two patients received epoetin alfa (150 IU/kg, 3 times a week) during radiotherapy, which was started at hemoglobin less than 13 g/dL and stopped at 14 g/dL or higher. Hemoglobin levels were measured weekly during RT.

Results: Both groups were balanced for age, sex, performance status, tumor length/location, histology, grading, T-stage/N-stage, chemotherapy, treatment schedule, and hemoglobin before RT. Median change of hemoglobin was +0.3 g/dL/wk with epoetin alfa and −0.5 g/dL/wk without epoetin alfa. At least 60% of hemoglobin levels were 12 to 14 g/dL in 64% and 17% of the patients, respectively ($p < 0.001$). Patients who received epoetin alfa had better OS (32% vs. 8% at 2 years, $p = 0.009$) and LC (67% vs. 15% at 2 years, $p = 0.001$). MFS was not significantly different (42% vs. 18% at 2 years, $p = 0.09$).

Conclusions: The findings suggest that epoetin alfa when used to maintain the hemoglobin levels at 12 to 14 g/dL can improve OS and LC of Stage III esophageal cancer patients. © 2006 Elsevier Inc.

Esophageal cancer, Chemoradiation, Epoetin alfa, Locoregional control, Survival.

INTRODUCTION

Esophageal cancer carries a poor prognosis, with 41% 1-year, disease-specific survival in patients with Stage III disease (1). Considerable controversy exists regarding the optimal treatment, especially for locally advanced esophageal tumors with lymph node involvement. Prognostic factors are very important, as they can help to select the appropriate treatment for the individual patients. Various potential prognostic factors for esophageal cancer have been reported, such as age, performance status, tumor length, T-stage, N-stage, UICC-stage, and the hemoglobin level before radiotherapy (RT) (2–7). The prognostic impact of the hemoglobin level during RT on treatment outcome has also been described for endometrial carcinoma and cervix cancer (8, 9). The hemoglobin level is associated with tumor oxygenation, which plays an important role with respect to the treatment effect of irradiation. Radiobiological data suggest tumor hypoxia to be associated with an increased resistance to radiation-induced tumor cell kill because lower production of cytotoxic free radicals results in less DNA damage (10). Thus, tumor hypoxia results in a worse treatment outcome. Tumor oxygenation can be affected by the oxygen-carrying capacity of the blood, which is represented by the hemoglobin level. Tumor oxygenation can be reduced by anemia. Contrary to intuition, an excessively high hemoglobin level is also associated with a drop in nutritive perfusion because of an increase in viscous resistance to flow that decreases tumor oxygenation. The Danish Head and Neck Cancer Study (DAHANCA) demonstrated that the hemoglobin level has to be considered an important prognostic parameter for treatment outcome in head-and-

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neck cancer patients and that hemoglobin levels higher than the normal range had a negative impact on outcome (11, 12).

Hemoglobin levels of 12 to 14 g/dL appear optimal for tumor oxygenation (13). Thus, the patients' prognosis may be improved by maintenance of the hemoglobin levels within this optimal range.

A decrease of the hemoglobin levels during RT below 12 g/dL may be improved by the administration of recombinant human erythropoietin (14). Whether the effect of erythropoietin on the hemoglobin levels is associated with an improvement of tumor control and patient survival is controversial. Some reports, including our preliminary data, suggested a beneficial effect for erythropoietin with respect to outcome (15–19), whereas a prospective study from Germany in head-and-neck cancer patients suggested a poorer outcome for patients who received erythropoietin (20). However, that study has been criticized because of methodologic problems, which may have confounded the results. Many patients of the treatment group had hemoglobin levels greater than 14 g/dL during RT, which may have resulted in lower tumor oxygenation and, thus, a poorer prognosis. The patients of the control group had more favorable hemoglobin levels during RT than did the patients of the treatment group.

The administration of erythropoietin should be stopped if a hemoglobin level of 14 g/dL is reached, as has been done in our study (on-and-off administration when indicated). Thus, the potential effect of properly administered erythropoietin on treatment outcome in cancer patients still needs to be clarified.

Our prospective study evaluates the impact of on-and-off administration of epoetin alfa (ERYPO 10000;Janssen-Cilag, Neuss, Germany) during radiochemotherapy (RCT) on overall survival, metastatic-free survival, and locoregional control in Stage III esophageal cancer patients. Our preliminary report suggested that the administration of epoetin alfa was associated with significantly better locoregional control (18). The major goal of the study presented here was to evaluate whether the administration of epoetin may also improve overall survival.

METHODS AND MATERIALS

Ninety-six patients, 27 females and 69 males, who were treated with RCT for Stage III esophageal cancer between January 2001 and August 2005, were included in this prospective, nonrandomized study. Forty-three patients (45%) had T3N1M0 tumors, 14 patients (15%) had T4N0M0 tumors, and 39 patients (41%) had T4N1M0 tumors. The major goals of this prospective observational study were to evaluate the effectiveness of epoetin alfa in maintaining the hemoglobin levels at 12 to 14 g/dL (optimal range for tumor oxygenation) and to determine whether the administration of epoetin alfa can improve locoregional control and overall survival during RCT for Stage III esophageal cancer. Further endpoints investigated in this study were the impact of the administration of epoetin alfa on metastatic-free survival and on the median weekly change of hemoglobin levels during RCT.

Forty-two patients had received recombinant human erythropoietin (epoetin alfa) after informed consent to avoid hemoglobin levels less than 12 g/dL during radiotherapy. Fifty-four patients did not receive epoetin alfa. This control group was composed of patients who received chemotherapy in other institutions or who refused administration of epoetin alfa. The trial was performed after approval by the local ethics committee.

Blood transfusions were given if the hemoglobin level fell below 9 g/dL. Five patients with epoetin alfa and 9 patients without epoetin alfa received 2 to 4 transfusions during RCT.

Epoetin alfa in isotonic NaCl solution was administered s.c. (150 IU/kg) 3 times per week. Epoetin alfa treatment was started after the hemoglobin level became less than 13 g/dL, and epoetin alfa administration was stopped after the hemoglobin level reached 14 g/dL. Iron was administered orally (200 to 300 mg/day) if the ferritin was below 100 ng/mL or if the ferritin saturation was below 20%.

Radiotherapy was delivered by administration of 6-MV to 16-MV photons, with a daily dose of 1.8 Gy or 2.0 Gy, 5 days per week. Total radiation dose was 45 Gy to 50.4 Gy in 27 patients and 59.4 to 66 Gy in 69 patients. Nineteen patients were treated with 45 to 50.4 Gy plus surgery, and 8 patients were treated with 50 to 50.4 Gy alone. The initial RT fields (up to a dose of 50 to 50.4 Gy) had superior and inferior margins of 5 cm beyond the primary gross tumor volume. The lateral, anterior, and posterior margins were a minimum of 2 cm beyond the primary gross-tumor volume. Regional lymph nodes were included. After irradiation of the initial fields, a boost dose (9 to 16 Gy) was delivered to the primary tumor, with 2-cm margins, and to enlarged lymph nodes, with a minimum margin of 1 cm.

Chemotherapy with 5-FU (1,000 mg/m^2/day) was administered as a continuous infusion for 120 hours (Days 1 to 5 of each course) every fourth week. Cisplatin, at 75 mg/m^2, was administered as an i.v. bolus over 60 min on Day 1 of each course. The standard regimen was the administration of 2 chemotherapy courses concurrently with RT. In case of a large waiting list for the patients, 1 to 2 additional courses was administered before RT. In case of severe chemotherapy-related toxicity with the first course, a second course of chemotherapy was omitted.

Surgery for tumors of the upper third ($n = 3$) and middle third ($n = 9$) of the esophagus was performed with radical en-bloc resection of the esophagus and 2-field lymphadenectomy. The main parts of the 3 upper-third tumors were situated close to the middle third and did not involve the cervical esophagus, which allowed the application of surgery. For tumors of the lower third ($n = 7$), a transhiatal esophagectomy was performed. Esophageal continuity was restored by gastric tube. Preferentially, the route via the posterior mediastinum was taken.

The following potential prognostic factors were investigated with respect to OS, MFS, and LC: age ($\leq$60 years vs. $>$60 years), Eastern Cooperative Oncology Group (ECOG) performance status (1 vs. 2 to 3), tumor length ($<$7 cm vs. $\geq$7 cm, according to endoscopy), histology (squamous cell carcinoma [= SCC] vs. adenocarcinoma), histologic grade (G1 to G2 vs. G3), T-stage (T3 vs. T4, according to endoscopic ultrasound and computed tomography), N-Stage (N0 vs. N+ , according to endoscopic ultrasound and computed tomography), chemotherapy courses (1 course vs. 2 to 3 courses), treatment approach (45 to 50.4 Gy plus surgery vs. 50 to 50.4 Gy alone vs. 59.5 to 66 Gy alone), hemoglobin before RT ($<$12 g/dL vs. 12 to 14 g/dL and $>$14 g/dL), and application of epoetin alfa during RT (yes vs. no).

The hemoglobin levels were monitored weekly during therapy. Both treatment groups (patients who received epoetin alfa vs.

patients who did not receive epoetin alfa) were compared with respect to the proportion of patients who maintained at least 60% of their hemoglobin values in the optimal range of 12 to 14 g/dL during RT.

This trial was designed as a nonrandomized Phase II trial that compared the outcome of those who did vs. those who did not receive epoetin alfa. The calculation of the required sample size was performed with the Stata statistical software (StataCorp LP, College Station, TX), on the basis of previous findings with respect to locoregional control and survival at 2 years (18). According to those findings, the 2-year locoregional control rate was 66% in patients with epoetin alfa and 27% in patients without epoetin alfa. The 2-year survival rates were 44% and 12%, respectively. To achieve a statistical power of at least 90% (level of significance = 5%) for both 2-year LC and 2-year OS, a total number of 92 patients (at least 40 patients per group) was required.

Locoregional control was defined as absence of locoregional progression on the basis of findings of endospcopy, endoscopic ultrasound, and computed tomography, which were performed at regular intervals. OS, MFS, and LC were calculated for each potential prognostic factor by the Kaplan-Meier method (21) and measured from the first day of RT. Differences between the Kaplan-Meier curves were evaluated by use of the log-rank test. Results were considered significant if $p < 0.05$.

Potential prognostic factors found to be significant in the univariate analysis were evaluated in a multivariate analysis. The multivariate analysis was performed by application of the Cox proportional-hazard model.

RESULTS

Both treatment groups were well balanced for patient characteristics and for the investigated potential prognostic factors (Table 1). The results of the univariate analysis with respect to OS, MFS, and LC at 2 years related to the potential prognostic factors are summarized in Table 2. The ECOG performance status achieved significance for OS; the tumor length achieved significance for MFS and OS; the number of chemotherapy courses achieved significance for LC, MFS and OS; and the hemoglobin before RT achieved significance for LC and OS. The administration of epoetin alfa was significantly associated with OS ($p = 0.009$ [Fig. 1]) and with LC ($p = 0.001$ [Fig. 2]) but not with MFS ($p = 0.09$ [Fig. 3]).

The potential prognostic factors that achieved significance in the univariate analysis were included in the multivariate analysis. Administration of epoetin alfa and the number of chemotherapy courses maintained significance for LC. Tumor length and the number of chemotherapy courses maintained significance for MFS. Regarding OS, the administration of epoetin alfa, the tumor length, and the number of chemotherapy courses maintained significance. The ECOG performance status was of borderline significance. The results of the multivariate analysis are summarized in Table 3.

In 27 of 42 patients (64%) who received epoetin alfa and in 9 of 54 patients (17%) who did not receive epoetin alfa, at least 60% of the hemoglobin levels during RCT were within the optimal range of 12 to 14 g/dL ($p < 0.001$). The comparison of both groups for median changes of hemoglobin per week, related to the total number of weeks of RT, to the weeks with concurrent chemotherapy, and to the weeks without chemotherapy, is demonstrated in Table 4. Epoetin alfa−related adverse effects were not observed in the patients who received it.

Table 1. Patient characteristics related to the two treatment groups

Potential prognostic factor	Patients with epoetin alfa (%)	Patients without epoetin alfa (%)	*p*
Age			
≤60 years	21 (50)	29 (54)	
>60 years	21 (50)	25 (46)	0.89
ECOG performance status			
1	19 (45)	28 (52)	
2–3	23 (55)	26 (48)	0.75
Tumor location			
Upper/middle third	36 (86)	47 (87)	
Lower third	6 (14)	7 (13)	0.97
Tumor length			
<7 cm	19 (45)	22 (41)	
≥7 cm	23 (55)	32 (59)	0.89
Histology			
SCC	36 (86)	47 (87)	
Adenocarcinoma	6 (14)	7 (13)	0.98
Histologic grade			
G1–2	24 (57)	27 (50)	
G3	18 (43)	27 (50)	0.74
T-stage			
T3	20 (48)	23 (43)	
T4	22 (52)	31 (57)	0.84
N-stage			
N0	6 (14)	8 (15)	
N+	36 (86)	46 (85)	0.99
Chemotherapy courses			
0–1	9 (21)	10 (19)	
2–4	33 (79)	44 (81)	0.94
Treatment approach			
45–50.4 Gy plus resection	10 (24)	9 (17)	
50–50.4 Gy alone	4 (9)	4 (7)	
59.4–66 Gy alone	28 (67)	41 (76)	0.80
Hemoglobin prior to RT			
<12 g/dL	15 (36)	24 (44)	
12–14 g/dL	18 (43)	22 (41)	
>14 g/dL	9 (21)	8 (15)	0.79

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy; SCC = squamous cell carcinoma.

DISCUSSION

The prognosis of patients with locally advanced esophageal is poor. RT and RCT are common modalities in the treatment of esophageal cancer. The effect of RT is dependent on the tumor oxygenation, which is represented by the hemoglobin level. Hemoglobin levels of 12 to 14 g/dL during RT or RCT are considered optimal for tumor oxygenation (13). Thus, keeping the hemoglobin levels within

Table 2. Univariate analysis

Potential prognostic factor	2-Year LC (%)	*p* for LC	2-Year MFS (%)	*p* for MFS	2-Year OS (%)	*p* for OS
Age						
≤60 years	35		31		18	
>60 years	36	0.94	28	0.76	16	0.83
ECOG performance status						
1	41		35		21	
2–3	31	0.07	28	0.12	10	0.049
Tumor length						
<7 cm	37		43		27	
≥7 cm	34	0.60	19	0.027	11	0.040
Histology						
SCC	33		29		19	
Adenocarcinoma	36	0.84	23	0.59	12	0.52
Histologic grade						
G1–2	40		31		24	
G3	18	0.39	29	0.98	12	0.30
T-stage						
T3	49		32		19	
T4	25	0.15	25	0.19	15	0.29
N-stage						
N0	40		29		20	
N+	0	0.14	25	0.62	11	0.19
Chemotherapy courses						
0–1	24		0		4	
2–4	37	0.042	34	0.009	22	0.013
Treatment approach						
45–50.4 Gy plus resection	46		47		21	
50–50.4 Gy alone	0		0		0	
59.4–66 Gy alone	37	0.50	27	0.13	11	0.13
Hemoglobin prior to RT						
<12 g/dL	19		24		13	
12–14 g/dL	53		36		23	
>14 g/dL	0	0.003	0	0.12	0	0.014

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LC = locoregional control; MFS = metastatic-free survival; OS = overall survival; RT = radiotherapy; SCC = squamous cell carcinoma.

Data are OS, MFS, and LC at 2 years and the *p* values obtained from the log-rank test, related to the potential prognostic factors.

this optimal range during RT appears to achieve the best treatment outcome.

This prospective study investigates whether keeping the hemoglobin levels within the optimal range can be achieved with administration of epoetin alfa and whether administration of epoetin alfa improves the outcome after RCT for Stage III esophageal cancer.

Our study demonstrates that epoetin alfa is effective in maintaining the hemoglobin levels during RCT within the optimal range of 12 to 14 g/dL. When compared with the patients who did not receive epoetin alfa, significantly more patients who received epoetin alfa had at least 60% of the hemoglobin levels within the optimal range. The course of the hemoglobin levels during RCT was much more favorable in patients who received epoetin alfa than in the

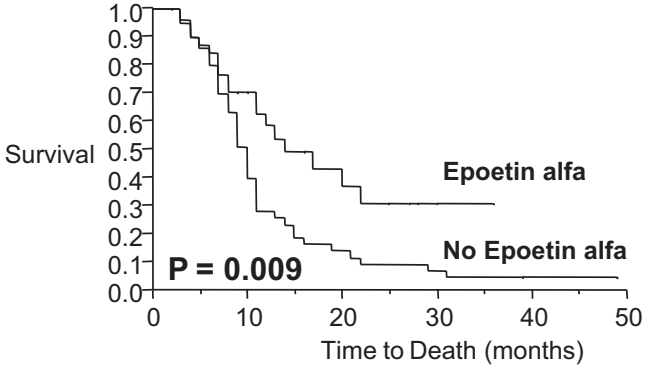

Fig. 1. Overall survival: Patients who received epoetin alfa vs. patients who did not receive epoetin alfa.

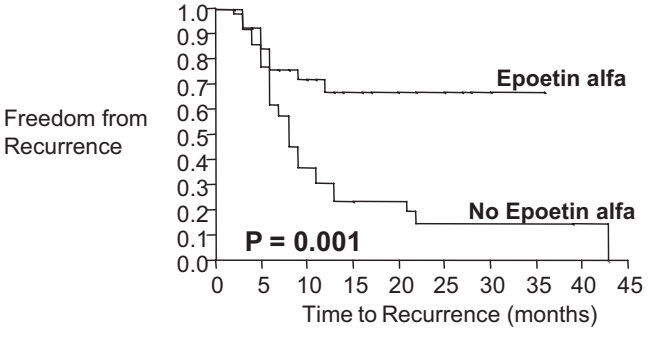

Fig. 2. Local control: Patients who received epoetin alfa vs. patients who did not receive epoetin alfa.

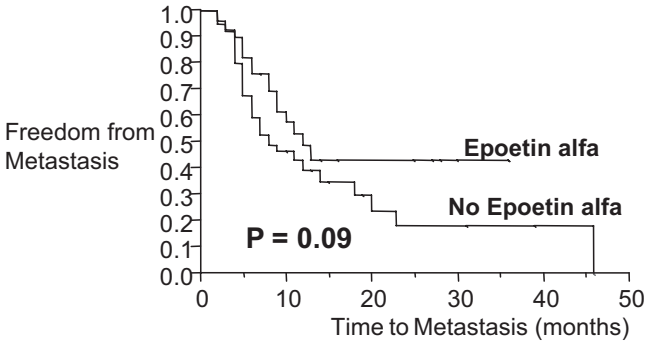

Fig. 3. Metastatic-free survival: Patients who received epoetin alfa vs. patients who did not receive epoetin alfa.

other patients, either during administration of RT with concurrent chemotherapy or during RT alone. The median weekly increase of the hemoglobin levels in our series was consistent with the data from the literature (22–24) that described an average increase of 0.4 to 0.7 g/dL in patients treated with RT alone, depending on the erythropoietin dose.

Furthermore, our study demonstrated that the administration of epoetin alfa is associated with a significant improvement in locoregional control and in overall survival. However, the potential benefit of epoetin alfa on outcome is controversial. Several studies have administered erythropoietin during RT to improve the prognosis of cancer patients. One retrospective analysis (15) and 2 randomized studies, recently published as abstracts (16, 17), suggested a benefit for erythropoietin with respect to LC, and another randomized study published in abstract form suggested an increase in overall survival with erythropoietin in myeloma patients (19).

On the other hand, a randomized study from Germany suggested a worse outcome for patients who received erythropoietin during RT (20). However, that study is heavily criticized because of methodologic problems that may have contributed to the results. The investigated groups were not balanced for relevant prognostic factors, about one third of the patients were not treated per protocol, and differences were no longer significant when the analysis was limited to patients treated according to the protocol. A major criticism was that the hemoglobin levels were more favorable in the placebo group than in the treatment group (mean values of 12.4 g/dL vs. 14.8 g/dL at 4 weeks and of 12.9 g/dL vs. 15.4 g/dL at 9 weeks), which is explained by an overtreatment with erythropoietin.

In contrast to that German study (21), we stopped the administration of epoetin alfa if a hemoglobin level of 14 g/dL was reached, in accordance with a philosophy of on-and-off administration. This strategy resulted in about two thirds our patients treated with epoetin alfa having the majority of their hemoglobin levels within the optimal range of 12 to 14 g/dL, which led to a significant improvement in locoregional control and survival.

Concerns have been raised regarding erythropoietin receptors that have been demonstrated in tumor cell lines *in vitro* (25). However, in most of these cell lines, they do not have a functional role, because of no effective downstream signaling, although increased proliferation of tumor cells has been described (26, 27). Erythropoietin receptors have also been described in *in vivo* models and in human tissue samples (28, 29). However, in animal models, the application of erythropoietin has not led to an increased tumor growth (30, 31). Our data suggest that the beneficial effect of epoetin alfa on tumor oxygenation is more important than this theoretical effect on tumor cell growth. This effect may be different for tumors other than esophageal cancer. Thus, more prospective studies are required to define the clinical relevance of erythropoietin receptors for cancer patients.

Furthermore, this study was not randomized, which may have introduced biases. In the present study, both treatment groups were well balanced with respect to the potential prognostic factors. Thus, a selection bias would be lessened, which would strengthen the results of our study.

When compared with other series from the literature, the 2-year OS of 17% in our study was worse than the 30% to 40% of the reported series (32–34). This difference can be explained by an imbalance with respect to the distribution of the tumor stages. In our series, 55% of the patients had T4 tumors, 85% had N+ tumors, and 40% had T4N+ tumors. In the series from the literature, less than 20% of the patients had T4 tumors, 10% to 65% of the patients had N+ tumors, and less than 10% had T4N+ tumors.

Regarding the impact of the investigated potential prognostic factors, the results of this study were in accordance with the data from the literature. The prognostic value of the tumor length as found in the present series has also been observed in other series (2, 4, 6). A survival benefit for simultaneous RCT when compared with RT alone as observed in our series is in accordance with the results of the INT 0121 (RTOG 85-01) study and the meta-analysis of the Cochrane Work Group (32, 33, 35). A prognostic impact for the performance status has been described by other authors (3, 4, 36). In the literature, a prognostic impact was also suggested for T-stage and N-stage (2, 4–6, 36). Although our data did not reveal a significant impact for T-stage and

Table 3. Results of the multivariate analysis with respect to OS, MFS, and LC

Potential prognostic factor	LC (p value)	MFS (p value)	OS (p value)
ECOG performance status	n.s.u.	n.s.u.	0.051
Tumor length	n.s.u.	0.008	0.017
Number of chemotherapy courses	0.027	0.006	0.049
Hemoglobin before RT	0.59	n.s.u.	0.39
Administration of epoetin alfa	0.035	n.s.u.	0.004

Abbreviations as in Tables 1 and 2.
The notation n.s.u. indicates not significant on univariate analysis.

Table 4. Median changes (decrease or increase) of hemoglobin levels, for the total number of weeks of RT, for the weeks with concurrent chemotherapy, and for the weeks without chemotherapy

Change of hemoglobin levels per week	Patients with epoetin alfa	Patients without epoetin alfa
Total number of weeks of RT	+0.3 g/dL (90% CI, −0.6 to +0.9) (range, −1.0 to +1.2 g/dL)	−0.5 g/dL (90% CI, −1.2 to +0.2) (range, −1.6 to +0.7 g/dL)
Weeks with concurrent chemotherapy	−0.4 g/dL (90% CI, −0.7 to +0.4) (range, −1.0 to +0.6 g/dL)	−0.8 g/dL (90% CI, −1.4 to −0.3) (range, −1.6 to +0.3 g/dL)
Weeks without concurrent chemotherapy	+0.4 g/dL (90% CI, −0.3 to +1.1) (range, −0.6 to +1.2 g/dL)	−0.3 g/dL (90% CI, −0.9 to +0.2) (range, −1.2 to +0.6 g/dL)

Abbreviations: CI = confidence interval; RT = radiotherapy.

N-stage, trends were observed between lower T- and N-stages and better outcomes. In the present series, age, histology, and histologic grade were not associated with outcome. With respect to histology and histologic grade, these findings are consistent with the data from the literature (2–4, 6). The prognostic value of age has not yet been clarified. Because some authors did not find a prognostic impact of age (3, 6), others suggested a worse prognosis for younger patients (2, 4). The hemoglobin level before RT achieved significance for LC and OS on univariate analysis, which is in accordance with the findings of our previous retrospective analysis (7). In the present study, the hemoglobin level before RT lost significance on multivariate analysis. However, the results of the multivariate analysis may be confounded by a correlation between hemoglobin levels before RT and during RT. On the other hand, optimal tumor oxygenation during RT has to be considered more important for production of cytotoxic free radicals and for treatment outcome than optimal tumor oxygenation before RT.

The question of whether blood transfusions might improve or impair the prognosis of anemic cancer patients, is still debated. Some retrospective analyses suggest a negative impact on survival of gastrointestinal cancer patients, whereas other studies suggest an improvement in survival for patients with cancer of the cervix uteri if anemia was corrected by administration of transfusions (37–39). The role of transfusions in cancer treatment needs to be further investigated. However, erythropoietin appears more effective in steadily increasing and stabilizing hemoglobin levels (40).

In conclusion, administration of epoetin alfa is effective in maintaining the hemoglobin levels during RCT within the range of 12 to 14 g/dL, which is considered optimal for the tumor oxygenation and for the treatment effect. The proper administration of epoetin alfa during RT, which should be stopped if a hemoglobin level of 14 g/dL is reached, appears to improve overall survival and locoregional control in Stage III esophageal cancer patients. Although this study suggests that epoetin alfa can improve the outcome of esophageal cancer patients when used in this manner, a Phase III trial would be required for definitive proof of this concept.

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