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Long-Term Results of Radiation Therapy Oncology Group 9903: A Randomized Phase 3 Trial to Assess the Effect of Erythropoietin on Local-Regional Control in Anemic Patients Treated With Radiation Therapy for Squamous Cell Carcinoma of the Head and Neck

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Abstract

Purpose—This paper reports long-term results of RTOG 9903, to determine whether the addition of erythropoietin (EPO) would improve the outcomes of radiation therapy (RT) in mildly to moderately anemic patients with head and neck squamous cell carcinoma (HNSCCa).

Methods and Materials—The trial included HNSCCa patients treated with definitive RT. Patients with stage III or IV disease received concomitant chemoradiation therapy or accelerated fractionation. Pretreatment hemoglobin levels were required to be between 9.0 and 13.5 g/dL (12.5 g/dL for females). EPO, 40,000 U, was administered weekly starting 7 to 10 days before RT was initiated in the RT + EPO arm.

Results—A total of 141 of 148 enrolled patients were evaluable. The baseline median hemoglobin level was 12.1 g/dL. In the RT + EPO arm, the mean hemoglobin level at 4 weeks

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increased by 1.66 g/dL, whereas it decreased by 0.24 g/dL in the RT arm. With a median follow-up of 7.95 years (range: 1.66-10.08 years) for surviving patients and 3.33 years for all patients (range: 0.03-10.08 years), the 5-year estimate of local-regional failure was 46.2% versus 39.4% ($P = .42$), local-regional progression-free survival was 31.5% versus 37.6% ($P = .20$), and overall survival was 36.9% versus 38.2% ($P = .54$) for the RT + EPO and RT arms, respectively. Late toxicity was not different between the 2 arms.

Conclusions—This long-term analysis confirmed that despite the ability of EPO to raise hemoglobin levels in anemic patients with HNSCCa, it did not improve outcomes when added to RT. The possibility of a detrimental effect of EPO could not be ruled out.

Introduction

Anemia is one of multiple contributing mechanisms responsible for the complex phenomenon of tumor hypoxia, which poorly influences the outcomes of anemic patients treated with radiation therapy (1). Initial attempts to reverse anemia used blood transfusions and, recently, erythropoietin (EPO) (2, 3). Although clinical trials showed reductions of anemia and fatigue with EPO addition (4, 5), many phase 3 studies have demonstrated that the addition of EPO has a detrimental effect on local-regional control (LRC) and disease-free survival (6, 7).

Machtay et al (8, 9) reported results of the Radiation Therapy Oncology Group (RTOG) clinical trial 9903, investigating radiation therapy with EPO (RT + EPO) and without (RT alone) for anemic patients with head and neck squamous cell carcinoma (HNSCCa). The analysis showed no improvement of LRC or survival, despite improvement in hemoglobin levels in RT + EPO patients. Another study, by Henke et al (7), showed that, although EPO corrected the anemia, it did not improve survival and lower disease control in erythropoietin receptors (EPORs) + RT patients compared to RT alone. A secondary analysis of the study demonstrated that the negative impact of EPO occurred more frequently in patients whose tumor expressed EPORs (10). Similar unexpected negative effects of EPO in phase 3 randomized trials were reported in metastatic breast cancer (6) and in non-small cell lung cancer (11).

Both basic in vitro and in vivo animal models (12-16) demonstrated that EPO has multifaceted biological activities with pro-angiogenic and anti-apoptotic properties that are not limited to cellular proliferation and differentiation of the erythroid lineage but also extend to normal and cancer cells. Belenkov et al (17) reported that EPO induces cancer cell resistance to irradiation and to cisplatin through a JAK-2-dependent mechanism.

Accrual of subjects to RTOG 9903 started in June 2000. Because of information received from Ortho Biotech about possible association between EPO and higher risk of thromboembolism and subsequent to the publication of results by Henke et al (7), the Data Monitoring Committee (DMC) reviewed data from the 148 patients enrolled. The analysis showed no differences in outcomes between the 2 arms; however, because of the incomplete sample size and moderately elevated hazard ratios (HR), a potential detrimental effect of EPO administration could not be ruled out. The accrual was closed on November 19, 2003. Results were presented at the American Society for Radiation Oncology meeting in 2004 (9).

as an abstract and as an article by Machtay et al (8). Here, we report the long-term results of the study. This longer follow-up of 8 years, versus 3 years for the initial report, ensures that there are no new or unexpectedly delayed failures, second primaries, and/or toxicities with longer follow-up. In addition, we performed an exploratory analysis of treatment effect by baseline hemoglobin levels for local-regional failure (LRF), local-regional progression-free survival (LRPFS), and overall survival (OS).

Methods and Materials

The purpose of this trial was to determine whether the addition of EPO to RT or chemoradiation would improve LRC and/or survival for patients with inoperable non-metastatic HNSCCa with baseline hemoglobin concentrations of ≥ 13.5 g/dL for males and ≥ 12.5 g/dL for females. The study was sponsored by RTOG with support from the US National Cancer Institute. Ortho Biotech provided financial and logistic support but was not involved in the design, analysis, or preparation of the manuscript.

All institutional Internal Review Boards (IRB) of participating institutions and the American College of Radiology IRB reviewed and approved the study. Registration and randomization were performed centrally at the RTOG headquarters.

Eligibility and exclusion criteria

Patients were eligible if they had HNSCCa of the oral cavity, oropharynx, hypopharynx, or larynx, had a Zubrod performance status of 0 to 2, and planned to receive radical primary RT. Eligible patients had a hemoglobin level of ≥ 13.5 g/dL for males and ≥ 12.5 g/dL for females. Patients with a hemoglobin level of <9 g/dL were not eligible. Patients with stage III and IV (M0) cancer received concomitant chemoradiation or accelerated RT. Pregnant women were not allowed on study, and women with childbearing potential were requested to use contraception. Exclusion criteria were described in detail in a previous publication (8). Patients were able to sign a study-specific IRB-approved written consent form.

Treatment and methods

Pretreatment evaluation included complete blood count, anemia workup, biochemistry, chest x-ray or computed tomography (CT) scan, and CT scan or magnetic resonance imaging (MRI) of the head and neck. Pregnancy tests were performed on all females of childbearing potential.

Patients received RT with or without EPO in an open-label randomized trial. Stratification was done by stage (stage I and II vs stage III and IV without chemotherapy vs stage III and IV with chemotherapy), hemoglobin levels at study entry (<11.5 vs ≥ 11.5 g/dL), and sex. All patients were treated with curative intent. Radiation therapy was delivered as a continuous course with no planned interruptions. Only conventional 2- or 3-dimensional RT techniques were allowed. Radiation therapy treatment volumes, dose specifications, field arrangements, and RT quality assurance (reviewed by M.M.) were described in details in a previous article (8).

Any one of the following concurrent chemotherapy regimens was accepted: high-dose cisplatin (80 mg/m² every 3 weeks), weekly cisplatin (30 mg/m² per week), weekly cisplatin and paclitaxel (20 mg/m²/week and 30 mg/m²/week, respectively), or weekly carboplatin and paclitaxel (area under the curve [AUC] = 1 and 30 mg/m/week, respectively).

Erythropoietin was supplied as epoetin- α (Procrit) by Ortho Biotech, and administration was started 7 to 10 days before the start of RT. A weekly EPO dose of 40,000 U was administered by subcutaneous injection throughout RT, except when hemoglobin levels exceeded 16 g/dL for males or 14 g/dL for females and was resumed when hemoglobin levels dropped to 13.5 g/dL for males or 12 g/dL for females. If hemoglobin levels did not increase 1 g/dL after 4 EPO injections, the dosage was increased to 60,000 U weekly (8, 9). Only patients randomized to receive EPO were encouraged to take iron supplementation. Blood transfusion was discouraged after registration. Patients who received transfusions prior to enrollment were eligible. Patients who received a transfusion(s) during treatment remained on study. If a patient in the EPO + RT arm required transfusion, epoetin- α was continued.

A post-RT lymph node dissection was allowed on protocol for patients with positive neck nodes. Post-RT chemotherapy was not allowed on study.

All patients had a complete blood count (CBC) test and were assessed on a weekly basis for toxicity from RT, chemotherapy, and EPO according to Common Toxicity Criteria for Adverse Events version 2.0 for toxicities related to chemotherapy and/or EPO at any time or related to RT within 90 days from the start of RT. Radiation toxicities appearing or persisting beyond 90 days from the start of RT were evaluated using the RTOG Late Radiation Morbidity Scoring Scheme.

Patients were seen at 2 and 4 weeks after completion of RT, then every 3 months for the first 2 years and every 6 months thereafter for 3 years, and annually thereafter. Baseline post-RT imaging of the head and neck was encouraged at 6 to 8 weeks and then every 6 to 12 months thereafter. CBC was obtained at 2 and 4 weeks after completion of RT. Subsequently, CBC was obtained only as needed, except for patients receiving concurrent chemotherapy. Chest radiography was performed yearly.

Collection of quality of life data was originally designed as a substudy of the protocol. Because of the premature closure of the study, quality of life data collection was discontinued.

Statistical considerations

The primary objective of the study was to test whether the addition of EPO to RT would reduce the LRF rate by at least 33%. The target accrual goal was 372 patients, using initially a 1-sided test with a .05 significance level and 0.85 statistical power. However, in light of the data from other studies, there was a possible adverse effect due to EPO. As such, all tests and confidence intervals (CIs) presented are 2-sided.

The secondary objectives of the trial were to determine whether the addition of EPO to RT or chemoradiation therapy would improve LRPFS and survival. Other end-points included change in the patterns of failure, toxicity, and change in hemoglobin levels.

LRF was defined as failure to obtain a complete response after RT or the reappearance of local and/or regional cancer after a complete response. Details about the definition of this and other secondary endpoints can be found in the initial report (8). Death without LRF was considered a competing risk. LRF rates were estimated by the cumulative incidence method, and groups were compared by using a 2-sided Gray test.

For LRPFS and OS, survival rates were estimated by the Kaplan-Meier method, and groups were compared by 2-sided log-rank test. HR were estimated by Cox proportional hazards models. Multivariate Cox models were used to test for a treatment effect after adjusting for study stratification factors. Analyses of these endpoints included only eligible patients. However, patients who did not complete therapy and/or had minor or major protocol violations were included in all analyses according to the intent-to-treat principle.

Results

Patient characteristics

The trial accrued 148 patients between June 30, 2000, and November 19, 2003, from 54 sites (71 in the RT arm and 77 in the EPO + RT arm). Withdrawal of consent occurred with 3 patients, and 4 patients were ineligible after review. Therefore, 141 patients were analyzable, 69 in the RT group and 72 in the EPO + RT group, as shown in Figure 1. Patient and tumor characteristics are shown in Table 1.

Compliance with protocol treatment

RT treatment was delivered according to protocol or with minor deviations in 88.4% and 88.9% of patients in RT and EPO + RT arms, respectively. Major RT treatment deviations were noted in 4% of patients in each arm. Each arm had 5 patients with incomplete or nonevaluable RT.

Erythropoietin was administered according to protocol in 56.9% and with acceptable minor deviations in 38.9% of patients. Three patients (4.2%) had major deviations: 1 who did not receive EPO and 2 who continued EPO therapy with hemoglobin concentrations >14 g/dL.

Chemoradiation therapy was used in 31.9% of patients in the RT arm versus 27.8% in the EPO + RT arm, with single-agent cisplatin being the most frequently used.

Local-regional control

With a median follow-up of 7.95 years (range: 1.66-10.08 years) for the surviving patients, there were 28 LRFs in the RT arm and 34 in the RT + EPO arm. At 5 years, the estimates of LRFs in RT + EPO arm were 46.2% (95% CI: 34.5-58.0) versus 39.4% in the RT arm (95% CI: 27.7-51.1). The HR was 1.27 (95% CI: 0.77-2.10) for the RT + EPO versus RT arms on univariate analysis ($P = .42$) and HR of 1.40 (95% CI: 0.84-2.33) on multivariate analysis (P

= .19). Curves of time to LRF are shown in Figure 2. LRFs were pathologically documented in 38.2% and 35.7% of patients in the RT + EPO and RT arms, respectively.

The rate of LRF between the RT + EPO and RT arms was unaffected by the administration of chemotherapy: HR of 1.40 (95% CI: 0.78-2.50) for patients who did not receive chemotherapy versus 0.93 (95% CI: 0.34-2.58) for patients who did (P value for interaction = .50).

Local-regional progression-free survival

There were no statistically significant differences in LRPFS rates when the 2 arms of the study were compared (Fig. 3). At 5 years, the LRPFS rate was 31.5% (95% CI: 20.4-42.6) in the RT + EPO arm versus 37.6% (95% CI: 25.9-49.4) in the RT arm. The HR between the RT + EPO arm and the RT arm was 1.28 (95% CI: 0.87-1.87; P = .20) on univariate analysis and 1.39 (95% CI: 0.94-2.05; P = .09) on multi-variate analysis.

LRPFS rates were not statistically different between patients who received concurrent chemotherapy and those who did not, with an HR of 0.74 (95% CI: 0.36-1.53) for the chemotherapy group versus 1.59 (95% CI: 1.01-2.50) for the group without chemotherapy (P value for interaction = 0.08). Although this suggests a differential effect of EPO depending on whether the patients received concurrent chemotherapy with RT, the effect was not statistically significant.

Overall survival

At the time of the analysis, 53 patients died in the RT + EPO arm versus 49 in the RT arm. There were 15.3% of the patients alive with no evidence of disease in the RT + EPO arm versus 24.6% in the RT arm.

The 5-year OS rate for the RT + EPO arm was 36.9% (95% CI: 25.4-48.4) versus 38.2% (95% CI: 26.3-50.1) in the RT arm, with an HR of 1.13 (95% CI: 0.77-1.67) on univariate analysis (P = .54) and an HR of 1.23 (95% CI: 0.83-1.82; P = .31) on multivariate analysis. Figure 4 shows the Kaplan-Meier OS estimates for the 2 groups.

Distant metastases and second cancers

At 5 years, the RT + EPO arm had a 15.6% (95% CI: 7.0-24.2) distant metastases rate versus 14.5% (95% CI: 6.1-22.9) for the RT arm, with an HR of 1.03 (95% CI: 0.44-2.37) on univariate analysis (P = .95) and an HR of 1.07 (95% CI: 0.46-2.50; P = .88) on multivariate analysis.

Both head and neck and non-head and neck cancer secondary primary tumors were observed in 16.6% of patients in the RT + EPO arm and in 14.5% of patients in the RT arm.

Toxicity

Two patients died of grade 5 acute toxicity in each arm of the study, as shown in Table 2. The deaths of the 2 patients in the RT arm who died of pneumonia were considered possibly related to RT (aspiration). In the RT + EPO arm, the first patient died of pulmonary

embolism; however, on detailed evaluation, the death was considered unrelated to study treatment. The second patient died of sepsis, which was attributed to chemotherapy toxicity.

Effect of baseline hemoglobin levels

We defined “high” hemoglobin concentration as greater than the median for the patient's sex and evaluated the interaction between treatment assignment (RT + EPO vs RT) and baseline hemoglobin level (“high” vs “low”). In this trial, the median baseline hemoglobin for males was 12.3 g/dL compared to 11.7 for females.

For each of the LRF and LRPFS endpoints, the HRs associated with the interaction between treatment assignment and baseline hemoglobin levels were 1.96 ($P = .19$) for LRF and 1.71 ($P = .17$) for LRPFS. Although statistically nonsignificant, the results may suggest a potential harmful effect of EPO in patients with high baseline hemoglobin. For LRF, the estimated treatment effect in the “low” group was HR = 0.91 (95% CI 0.46-1.80), whereas the estimated treatment effect in the high group was HR = 1.78 (95% CI: 0.85-3.73); similarly, for LRPFS, the estimated treatment effect in the low group was HR = 0.97 (95% CI: 0.58-1.62), whereas the estimated treatment effect in the high group was HR = 1.65 (95% CI: 0.94-2.90).

The OS results do not show the same pattern. The HR associated with the interaction was 1.13 ($P = .76$), suggesting no differential treatment effect by baseline hemoglobin level for this endpoint.

Treatment effect by hemoglobin response

There could be a differential treatment effect on LRF between patients with any increase in their hemoglobin levels (responders) from baseline to 4 weeks from the start of the treatment (HR = 1.47) and nonresponders (HR = 0.87) when the RT + EPO and RT arms were compared; however, the result of a formal test of interaction was not significant ($P = .54$). Similarly, for overall survival, the HR was 1.32 (95% CI: 0.71-2.45) for responders versus an HR of 1.91 (95% CI: 0.78-4.70) for the nonresponders, with a P value of .51 for interaction.

Discussion

Long-term versus early reports

Results were updated in February 2012 in order to ensure a complete and long-term reporting of the RTOG 9903 trial since previous reporting in 2007 (9).

Currently, the median follow-up was 7.95 years (range: 1.66-10.08 years) for surviving and 3.33 years for all patients (range: 0.03-10.08 years), compared to 3.1 years for surviving and 2.5 years for all patients (range: 0.03-5.0 years) as previously reported. The 2- and 5-year estimates of LRF were 40% and 46% for RT + EPO, respectively, and 36% and 39% for RT alone, respectively. Similar tendencies were observed in a comparison of the 2- and 5-year estimates for LRPFS and OS. Thus, the initial observation of a tendency for a better outcome with regard to LRF rates for RT alone was maintained.

There were no statistically significant differences between the 2 arms for rates of LRF, LRPFS, or OS, either in univariate or multivariate analysis; however, the HR estimates favored the RT-alone arm for all endpoints and confirmed the fact that any potential improvement by the addition of EPO to RT could be ruled out. Therefore, a detrimental effect of EPO is more likely than a small positive impact on outcome.

Similar to efficacy endpoints, the current updated toxicity rate is not different from the one previously reported, with similar rates of grade 3 to 4 dysphagia and mucositis in the 2 arms of the study and acute skin toxicity more frequent but not statistically significantly different between the RT + EPO and RT groups. The initial incidence of secondary primary tumors remained similar and equal between the 2 arms.

Comparison with the German study

The RTOG study included 148 patients versus 351 patients in the study by Henke et al (7). Only patients with intact HNSCCa were treated with definitive RT in the RTOG study with altered fractionation schedules and/or chemoradiation for stage III and IV, whereas the study by Henke et al (7) included patients with intact primaries as well as patients who had undergone initial R0 and R1 surgery and used conventional RT schedules only. Two-thirds of the patients in the RTOG study had American Joint Committee on Cancer stage III or IV cancer, with <10% with hypopharyngeal cancers, in contrast to the study by Henke et al (7) in which >95% of the patients had an initial stage III or IV and >25% hypopharyngeal cancers. Epoetin- α was started 7 to 10 days before RT, whereas epoetin- β was administered 10 to 14 days prior to RT in the study by Henke et al (7). On subgroup analysis of the German trial, the detrimental effect of EPO appeared to be limited to patients with intact or incompletely resected tumors.

Biological explanations

Intact EPORs are functionally activated by EPO in cancer cells (18-23), resulting in the activation of many cellular pathways leading to increased cell survival and resistance to apoptosis. The addition of EPO to cancer cell lines induces a JAK-2 kinase-dependent resistance to ionizing radiation and chemotherapeutic agents (17, 22, 23, 24). Although statistically nonsignificant, the results obtained from an exploratory analysis of our data suggest that the detrimental effect of EPO may be more pronounced in patients with baseline hemoglobin levels higher than the median. The authors recognize that the interaction between baseline hemoglobin and EPO did not reach statistical significance and is only hypothesis-generating. Vaupel et al (25) suggested that attempt to increase the hemoglobin levels to >12 g/dL reduces microcirculation and paradoxically increases hypoxia and subsequent induction of radioresistance. More recently, breast cancer stem cells showed in vivo increased chemoresistance when EPO was added in an animal model (26).

Current role of EPO in oncology

Because of several reports of a detrimental effect of EPO on cancer control, administration of EPO to patients with malignancies treated with curative intent is currently not indicated. In addition, the use of EPO is associated with an increase of thromboembolism.

Conclusions

The long-term review of the RTOG 9903 clinical trial confirms the initial results, indicating that a detrimental effect due to the use of EPO cannot be ruled out in mildly to moderately anemic patients with HNSCCa treated with RT, despite an increase of hemoglobin levels from baseline.

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References

1. Grau, C.; Overgaard, J. Significance of Hemoglobin Concentration For Treatment Outcome. New York: Springer; 2000.
2. Abels RI. Recombinant human erythropoietin in the treatment of the anemia of cancer. *Acta Haematol.* 1992; 87(suppl 1):4–11. [PubMed: 1574966]
3. Case DC Jr, Bukowski RM, Carey RW, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *J Natl Cancer Inst.* 1993; 85:801–806. [PubMed: 8487324]
4. Crawford J, Cella D, Cleeland CS, et al. Relationship between change in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer.* 2002; 95:888–895. [PubMed: 12209734]
5. Jones M, Schenkel B, Just J, et al. Epoetin alfa improves quality of life in patients with cancer: Results of metanalysis. *Cancer.* 2004; 101:1720–1732. [PubMed: 15386341]
6. Leyland-Jones B, Semiglavov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. *J Clin Oncol.* 2005; 23:5960–5972. [PubMed: 16087945]
7. Henke M, Lasig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anemia undergoing radiotherapy: Randomized, double-blind placebo-controlled trial. *Lancet.* 2004; 362:1255–1260. [PubMed: 14575968]
8. Machtay M, Pajak T, Suntharalingam M, et al. Radiotherapy with or without erythropoietin for anemic patients with head and neck cancer: A randomized trial of the Radiation Therapy Oncology Group (RTOG 9903). *Int J Rad Oncol Biol Phys.* 2007; 69:1008–1017.
9. Machtay M, Pajak T, Suntharalingam M, et al. Definitive radiotherapy with or without erythropoietin for squamous cell carcinoma of the head and neck: Preliminary report of RTOG 9903. *Int J Rad Oncol Biol Phys.* 2004; 60(suppl 1):S132.
10. Henke M, Mattern D, Pepe M, et al. Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol.* 2006; 24:4708–4713. [PubMed: 17028293]
11. Wright JR, Ung YC, Julian JA, et al. Randomized double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol.* 2007; 25:1027–1032. [PubMed: 17312332]
12. Arcasoy MO, Amin K, Chou SC, et al. Erythropoietin and erythropoietin receptors expression in head and neck cancer: Relationship to tumor hypoxia. *Clin Cancer Res.* 2005; 11:20–27. [PubMed: 15671524]
13. Kjellen E, Sasaki Y, Kjellstrom J, et al. Recombinant erythropoietin beta enhances growth of xenografted human squamous cell carcinoma of the head and neck after surgical trauma. *Acta Otolaryngol.* 2006; 126:545–547. [PubMed: 16698707]
14. Ribatti D, Presta M, Vacca A, et al. Human erythropoietin induces a pro-angiogenic phenotype in cultured endothelial cells and stimulates neovascularization in vivo. *Blood.* 1999; 93:2627–2636. [PubMed: 10194442]

15. Tam BY, Wei K, Rudge JS, et al. VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. *Nat Med.* 2006; 12:793–800. [PubMed: 16799557]
16. Osterborg A, Aapro M, Cornes P, et al. Preclinical studies of erythropoietin receptor expression in tumor cells: Impact on clinical use of erythropoietin proteins to correct cancer-related anemia. *Eur J Cancer.* 2007; 43:510–519. [PubMed: 17150352]
17. Belenkov AL, Shenouda G, Rizhevskaya E, et al. Erythropoietin induces cancer cell resistance to ionizing radiation and to cisplatin. *Mol Cancer Ther.* 2004; 3:1525–1532. [PubMed: 15634645]
18. Acs G, Chen M, Xu X, et al. Autocrine erythropoietin signaling inhibits hypoxia-induced apoptosis in human breast carcinoma cells. *Cancer Lett.* 2004; 214:243–251. [PubMed: 15363551]
19. Acs G, Acs P, Beckwith SM, et al. Erythropoietin and erythropoietin receptor expression in human cancer. *Cancer Res.* 2001; 61:3561–3565. [PubMed: 11325818]
20. Westenfelder C, Baranowski RL. Erythropoietin stimulates proliferation of human renal carcinoma cells. *Kidney Int.* 2000; 58:647–657. [PubMed: 10916088]
21. Acs G, Zhang PJ, McGrath CM, et al. Hypoxia-inducible erythropoietin signaling in squamous dysplasia and squamous cell carcinoma of the uterine cervix and its potential role in cervical carcinogenesis and tumor progression. *Am J Pathol.* 2003; 162:1789–1806. [PubMed: 12759237]
22. Yasuda Y, Fujita Y, Matusuo T, et al. Erythropoietin regulates tumor growth of human malignancies. *Carcinogenesis.* 2003; 24:1021–1029. [PubMed: 12807756]
23. Shenouda G, Mehio A, Souhami L, et al. Erythropoietin receptor expression in biopsy specimens from patients with uterine cervix squamous cell carcinoma. *Int J Gyn Cancer.* 2006; 16:752–756.
24. Lai S, Childs EE, Xi S, et al. Erythropoietin-mediated activation of JAK-STAT signaling contributes to cellular invasion in head and neck squamous cell carcinoma. *Oncogene.* 2005; 24:4442–4449. [PubMed: 15856028]
25. Vaupel P, Mayer A, Hockel M, et al. Impact of hemoglobin levels on tumor oxygenation: The higher, the better? *Strahlenther Onkol.* 2006; 182:63–71. [PubMed: 16447012]
26. Todaro M, Turdo M, Bartucci M, et al. Erythropoietin activates cell survival pathways in breast cancer stem-cells to protect them from chemotherapy. *Cancer Res.* 2013; 73:6393–6400. [PubMed: 24008319]

Summary

Erythropoietin (EPO) is used to reverse anemia in cancer patients. Here, we report the long-term results of the RTOG 9903 protocol of radiation therapy (RT) with or without EPO in moderately anemic patients with head and neck squamous cell carcinoma. Analysis confirmed that despite raising the hemoglobin levels in anemic patients, the addition of EPO to RT did not improve outcomes. Moreover, the possibility of a detrimental effect of EPO could not be ruled out.

Fig. 1.
 Trial profile flow chart showing randomization and treatment.

Fig. 2.
Time to local-regional failure of the 2 arms of RTOG 9903 of radiation therapy (RT) versus RT plus erythropoietin (EPO).

Fig. 3.
Local-regional progression-free survival of the 2 arms of RTOG 9903, comparing radiation therapy (RT) versus RT plus erythropoietin (EPO).

Fig. 4. Overall survival of RTOG 9903 patients treated with radiation therapy (RT) versus RT plus erythropoietin (EPO).

Table 1
Pretreatment characteristics

Characteristic	No. of patients (%) undergoing RT (n=69 patients)	No. of patients (%) RT + EPO (n=72 patients)
Age (years)		
Median	61	64
Range	42-86	29-90
Sex *		
Male	51 (73.9%)	53 (73.6%)
Female	18 (26.1%)	19 (26.4%)
Race		
White, not Hispanic origin	46 (66.7%)	46 (63.9%)
Hispanic	1 (1.4%)	0 (0.0%)
Black, not Hispanic origin	21 (30.4%)	24 (33.3%)
Asian	0 (0.0%)	2 (2.8%)
Other	1 (1.4%)	0 (0.0%)
Zubrod performance status		
0	32 (46.4%)	37 (51.4%)
1	29 (42.0%)	26 (36.1%)
2	8 (11.6%)	9 (12.5%)
Hemoglobin concentration (g/dL, all patients) *		
Median	12.1	12.0
Range	9.0-13.5	9.2-13.5
Hemoglobin concentration (g/dL, males only)	(n=51)	(n=53)
Median	12.4	12.3
Range	9.0-13.5	9.2-13.5
Hemoglobin concentration (g/dL, females only)	(n=18)	(n=19)
Median	11.8	11.7
Range	10.0-12.3	9.2-12.5
Feeding tube		
No	50 (72.5%)	55 (76.4%)
Yes	19 (27.5%)	17 (23.6%)
Cigarette pack-years	(n=52)	(n=61)
Median	35.0	35.0
Range	0.0-111.0	0.0-181.5
Primary site		
Oral cavity	6 (8.7%)	6 (8.3%)
Oropharynx	31 (44.9%)	34 (47.2%)
Hypopharynx	9 (13.0%)	4 (5.6%)
Larynx	23 (33.3%)	28 (38.9%)
T stage		
T1	15 (21.7%)	14 (19.4%)

Characteristic	No. of patients (%) undergoing RT (n=69 patients)	No. of patients (%) RT + EPO (n=72 patients)
T2	22 (31.9%)	25 (34.7%)
T3	14 (20.3%)	20 (27.8%)
T4	18 (26.1%)	13 (18.1%)
N stage		
N0	31 (44.9%)	39 (54.2%)
N1	10 (14.5%)	5 (6.9%)
N2a	2 (2.9%)	3 (4.2%)
N2b	13 (18.8%)	10 (13.9%)
N2c	7 (10.1%)	9 (12.5%)
N3	6 (8.7%)	6 (8.3%)
AJCC stage*		
Stage I/II	23 (33.3%)	27 (37.5%)
Stage III/IV without chemotherapy planned	24 (34.8%)	23 (31.9%)
Stage III/IV with chemotherapy planned	22 (31.9%)	22 (30.6%)

Abbreviations: AJCC = American Joint Committee on Cancer, 5th edition, 1997; EPO = erythropoietin; RT = radiation therapy.

* Stratification factor.

Table 2

Selected acute and chronic toxicities

Toxicity	RT toxicity grade					RT + EPO toxicity grade				
	1	2	3	4	5	1	2	3	4	5
Acute	n=68 patients					n=72 patients				
Cardiovascular	2	-	-	-	-	2	2	1	-	1*
Dysphagia	11	21	18	1	-	9	22	19	1	-
Dermatitis	26	26	3	1	-	22	27	12	-	-
Hematologic	5	6	4	1	-	8	4	7	-	-
Mucositis	11	21	20	1	-	11	17	24	1	-
Infection	-	5	1	-	-	-	2	1	1	1†
Respiratory	14	15	4	-	2‡	13	14	3	-	-
Constitutional	11	13	2	-	-	13	18	3	-	-
Worst acute toxicity per patient	4	22	34	6	2	6	19	36	4	2
Chronic	n=65					n=66				
Dysphagia	13	8	4	-	-	6	7	2	-	-
Xerostomia	19	22	1	-	-	11	20	2	-	-
Mucositis	7	10	2	-	-	12	7	1	-	-
Cutaneous	10	3	-	1	-	15	2	-	-	-
Subcutaneous	11	10	-	-	-	10	5	2	-	-
Larynx	12	8	1	-	-	14	4	2	-	-
Worst late RT toxicity per patient	15	23	8	3	1§	13	22	9	-	-

Abbreviations: EPO = erythropoietin; RT = radiation therapy.

Acute toxicities were graded according to NCI Common Terminology Criteria for Adverse Events version 2.0. Chronic toxicities were graded according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group late toxicity criteria. Chronic toxicity was caused by radiation therapy that occurred after or continued for >90 days from the start of radiation therapy.

* Patient died of pulmonary embolism that was considered possibly related to EPO.

† Patient died considered probably related to chemotherapy and unrelated to EPO.

‡ Two patients died of pneumonia; one death was considered possibly and the other death probably related to radiation therapy.

§ One patient died of pneumonia, considered possibly related to radiation therapy.

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