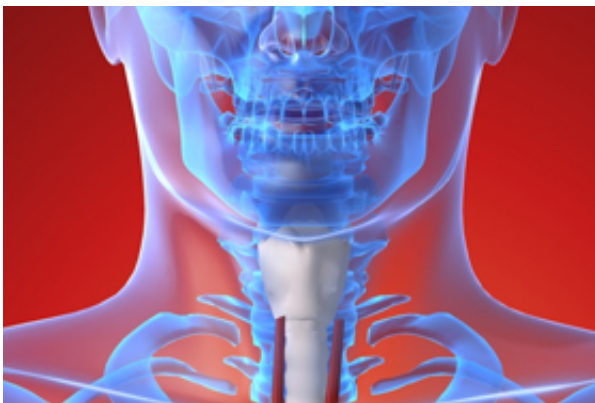


erythropoietin combined with radiation therapy does not improve local-regional control in anemic patients

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Long-term analysis of Radiation Therapy Oncology Group (RTOG) 9903 demonstrates that the addition of erythropoietin (EPO) did not improve local-regional control for anemic patients with head and neck squamous cell carcinoma (HNSCCa) who receive radiation therapy or chemoradiation, according to a study published in the April 1, 2015 issue of the International Journal of Radiation Oncology • Biology • Physics (Red Journal), the official scientific journal of the American Society for Radiation Oncology (ASTRO). This study is a long-term analysis of RTOG 9903, originally published in 2007¹, to determine if there were additional failures, second primaries and/or toxicities at a longer follow-up of eight years.

RTOG 9903, an open-label, Phase 3 randomized trial, examined if the addition of EPO, which stimulates the body's bone marrow to increase red blood cell production to prevent and to treat anemia, to radiation therapy would improve disease control in anemic [patients](#) with HNSCCa. The study accrued 148 patients from June 2000 to November 19, 2003, and fifty-four cancer centers participated in the trial. Eligible patients had HNSCCa of the oral cavity, oropharynx, hypopharynx or larynx; had a Zubrod performance status of zero to two (the Zubrod score indicates a patient's health status from zero to four, with zero indicating a patient is "fully active, able to carry on all pre-disease activities without restriction" and four indicating a patient is "completely disabled, cannot carry on any self-care, totally confined to bed or chair"); and [hemoglobin levels](#) ≤ 13.5 g/dL for males and ≤ 12.5 g/dL for females. After enrollment in the study, four patients were considered ineligible, and three patients withdrew from the trial.

Of the 141 patients included in the study, 69 were randomized to receive radiation therapy or chemotherapy plus radiation, and 72 were randomized to receive radiation therapy or chemotherapy plus radiation with EPO. Patients randomized to receive EPO received the first dose seven to 10 days prior to beginning radiation therapy, and then received EPO in a weekly dose of 40,000 units throughout treatment, unless hemoglobin levels exceeded 16 g/dL for males or 14 g/dL for females. Patients whose hemoglobin levels did not increase ≥ 1 g/dL after four doses of EPO received a dose increase to 60,000 units.

During treatment, patients were evaluated weekly for toxicities and review of their complete blood count. Follow-up was conducted at two and four weeks after treatment was completed, then every three months for the first two years post-treatment, every six months for the next three years and annually thereafter. For this long-term analysis, the median follow-up for surviving patients was 7.95 years (range 1.66 to 10.08 years) and 3.33 years for all patients (range 0.03 to 10.08 years).

This new analysis of RTOG 9903 found that at five-year follow-up, the local-regional failure rate was 39.4 percent for patients who received [radiation therapy](#) or chemoradiation without EPO and 46.2 percent for patients who received EPO (Hazard Ratio (HR) 1.27 on univariate analysis and 1.40 on multivariate analysis). The five-year local-regional progression-free survival rate was 37.6 percent for patients who did not receive EPO and 31.5 percent for patients who received EPO (HR 1.28 on univariate analysis and 1.39 on multivariate analysis). The five-year overall survival rate was 38.2 percent for patients who did not receive EPO and 36.9 percent for patients who received EPO (HR 1.13 on univariate analysis and 1.23 on multivariate analysis). The five-year distant metastases rate was 14.5 percent for patients who did not receive EPO and 15.6 percent for patients who received EPO (HR 1.03 on univariate analysis and 1.07 on multivariate analysis). The confidence interval for all measures was 95 percent. None of the differences were statistically significant; however, the HR in this long-term follow-up demonstrated improved outcomes for the patients who did not receive EPO.

"It is well-known that cancer patients with anemia (low hemoglobin) have lower cure rates than patients with normal hemoglobin levels. RTOG 9903 was aimed at improving the outcomes of anemic patients with head and neck [squamous cell carcinoma](#) by restoring their hemoglobin levels to normal," said George Shenouda, MD, lead author of the study and an associate professor of oncology and otolaryngology at McGill University Health Centre in Montréal. "The initial analysis of the results was unexpected and led to the study's early closure because of a possible detrimental effect of EPO. While EPO improved hemoglobin levels, the control rates were not similarly improved. This long-term analysis confirms that EPO is not the appropriate treatment option for our anemic HNSCCa cancer patients. It is important for us to be aware that EPO is a growth factor and as such, may stimulate the growth of cancer cells, resulting in decreased tumor control. Carefully designed

clinical trials are required to address how to treat anemia in our [cancer patients](#)."

An accompanying editorial from Todd A. Aguilera, MD, PhD, and Amato J. Giaccia, PhD, also published in the April 1 issue of the Red Journal, examines the implications of the study and the need to address tumor hypoxia in future clinical trials.

More information: [1] 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.

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