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Impact of Anemia in Patients With Head and Neck Cancer

PARVESH KUMAR
Department of Radiation Oncology, UMDNJ/Robert Wood Johnson Medical School, Cancer Institute of New Jersey, St. Peter’s University Hospital, New Brunswick, New Jersey, USA

Key Words. Tumor hypoxia · Radiotherapy · Local control · Survival · Anemia

ABSTRACT
Head and neck squamous cell carcinoma, which is comprised of a heterogeneous group of tumors arising from the epithelial lining of the oral cavity, pharynx, and larynx, is a locoregional disease. Tumor hypoxia and anemia are known to adversely affect the efficacy of radiation therapy, a local treatment modality. Therefore, head and neck cancers represent an ideal model for assessing the impact of anemia following treatment with radiation therapy. Various treatment strategies aimed at increasing tumor oxygenation in head and neck cancer patients (including hyperbaric oxygen and hypoxic cell radiosensitizers) have been studied. These studies have been fueled by evidence that hypoxia adversely affects the radiosensitivity of cells. Although the exact mechanism of action of the oxygen effect is not known, in vitro studies with conventional photon radiation therapy under normoxic conditions have shown an effectiveness of 2.5-3.0 times greater than that achieved under anoxic conditions. Recent studies, including large retrospective analyses, have demonstrated the dramatic adverse impact of anemia upon locoregional tumor control and survival. These studies, which have revealed hemoglobin levels as a powerful prognostic factor, provide compelling evidence for the value of reversing anemia and hence tumor hypoxia in head and neck cancer patients. The Oncologist 2000;5(suppl 2): 13-18

INTRODUCTION
Head and neck squamous cell carcinoma is comprised of a heterogeneous group of tumors arising from the epithelial lining of the oral cavity, pharynx, and larynx. It constitutes approximately 4% of all cancers in the United States; more than 40,000 cases are estimated to be diagnosed in 2000 [1, 2]. Despite their heterogeneity, head and neck tumors share several features that make them an ideal model for assessing the impact of anemia and tumor hypoxia following treatment with radiation therapy. First, head and neck tumors are predominantly locoregional in nature, thus providing a therapeutic opportunity in which improvements in local control are likely to directly improve survival. In addition, a substantial body of evidence suggests that tumor hypoxia is common in head and neck tumors, whether large or small. Studies have also shown a correlation between hypoxia in head and neck tumors and anemia in patients who present with these tumors. The accumulated evidence of the adverse impact of low hemoglobin levels on locoregional tumor control and survival provides compelling evidence of the value of anemia management in head and neck cancer patients.

EFFECTS OF HYPOXIA: HISTORICAL PERSPECTIVES ON RADIOSensitivity and the Oxygen Enhancement Ratio
As initially described by Schwartz in 1909 [3], hypoxia has an adverse effect on the radiosensitivity of cells. The precise nature of the oxygen effect is unknown, but it is believed that oxygen enhances the efficacy of radiotherapy by making DNA damage caused by radiation-induced free radicals less repairable [4]. The process of biologic damage induced by ionizing photon radiation (x-rays or gamma rays) is mostly understood: DNA-damaging hydroxyl radicals are produced by the interaction of recoil (Compton) electrons and water. These hydroxyl radicals cause either single-standed (sub-lethal event) or...
double-stranded (lethal event) DNA damage. The presence of oxygen during radiation exposure, appears to “fix” the hydroxyl radical-mediated DNA damage, thereby decreasing the ability of the cell to repair sublethal (i.e., single-strand) damage.

To exert a radiosensitizing effect, oxygen must be present during radiation exposure at the tumor site. The condition of the vascular ecosystem surrounding a tumor can therefore greatly influence the efficacy of ionizing radiation therapy. Classically, cancer cells nearest to the arterial oxygen supply are the most sensitive to ionizing radiation, whereas cells further from the vascular bed tend to be more hypoxic and therefore more resistant to the effects of ionizing radiation. Tumor size can also affect oxygenation and tumor response to radiotherapy. The larger the tumor, the further the center of the tumor lies from the arterial oxygen supply and the greater the proportion of hypoxic cells that are present within the tumor.

In 1951, Hollaender and associates observed that Escherichia coli treated under anoxic conditions needed threefold higher radiation doses to obtain the same biologic effect when compared with cultures treated under normoxic conditions [5]. This discovery led to the development of the oxygen enhancement ratio (OER) for photons (x-rays), neutrons, and heavy ions. The OER is defined as a ratio of the radiation dose necessary to achieve a specified degree of cell survival under hypoxic conditions divided by the dose necessary to achieve the same degree of cell survival under aerated conditions (Fig. 1). The OER for conventional radiation therapy with photons (in vitro) has been determined to be approximately 2.5 to 3 [6, 7]. In other words, photon radiation is 2.5 to 3 times more effective at killing cancer cells under normoxic conditions as compared with anoxic conditions, or only one-third as effective under anoxic conditions (Fig. 2).

These discoveries ultimately lead clinicians to focus on the OER as a tool for intervention. Initial attempts to improve the OER and thus potentially enhance clinical outcomes for patients with head and neck tumors employed hyperbaric oxygen [8-10] or hypoxic cell radiosensitizers [11, 12]. These trials, however, have been largely unsuccessful. More recently, attempts to optimize the OER have attacked the problem of tumor hypoxia more directly by correcting anemia.

**Effects of Tumor Hypoxia and Anemia in Patients with Head and Neck Cancer**

Data suggest that most head and neck cancers contain a hypoxic cell subpopulation (Table 1). Evidence comes from

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\text{OER} = \frac{\text{Dose in hypoxic conditions}}{\text{Dose in aerated conditions}} \quad \text{to achieve same cell survival fraction}
\]

**Figure 1. The oxygen enhancement ratio (OER).**

**Figure 2. Survival curves for mammalian cells exposed to x-ray radiation under normoxic and hypoxic conditions illustrate the effects of oxygen [7].** Higher doses of radiation are required under hypoxic conditions as compared with normoxic conditions to achieve comparable degrees of target cell survival. In this example, the oxygen enhancement ratio (OER) is 2.5, indicating that radiation therapy is 2.5 times less efficient under hypoxic versus normoxic conditions. Adapted with permission [7].
direct measurements of oxygen tension within tumors and also from histologic and radiographic findings revealing the frequent presence of tumor necrosis in head and neck cancers. Biochemical findings of anaerobic glycolysis and misonidazole metabolite formation in patients with head and neck cancers provide additional, indirect evidence of tumor hypoxia. The hypoxic cell fraction in solid head and neck cancers varies from <1% to >50%. Many investigators have found that tumor hypoxia adversely effects clinical radiotherapy outcome (i.e., local control). Thus, numerous studies have assessed the impact of tumor hypoxia and anemia upon clinical outcome following radiation therapy.

One of the first studies to illustrate the impact of anemia on locoregional tumor control in head and neck cancer patients came from the Danish Head and Neck Cancer II Study (DAHANCA II) [12]. This study assessed the effect of a radiosensitizer (misonidazole) upon local tumor control following split-course radiotherapy in patients with invasive carcinoma of the larynx and pharynx. This double-blind multi-center study randomized 626 patients into two different split-course radiation regimens given either misonidazole or placebo. Overall, the study showed no significant benefit of misonidazole on local tumor control versus placebo. However, a strong correlation between the pretreatment hemoglobin levels and local control was noted in male patients with pharyngeal tumors. Male patients with pharynx cancer who were treated with misonidazole and had pretreatment hemoglobin levels of ≥14.5 g/dl had five-year local tumor control rate of 61% as compared with only 14% in the placebo-treated patients with pretreatment hemoglobin values <14.5 g/dl [12].

The DAHANCA II study was followed by numerous other studies illustrating the effects of anemia on radiotherapy outcome. Among these were retrospective clinical analyses of radiotherapy outcome in patients with early glottic laryngeal carcinoma. Fein et al. evaluated 109 patients with T1-2N0 carcinoma of the glottic larynx treated with definitive radiotherapy at the Fox Chase Cancer Center between June 1980 and November 1990 [13]. The results showed that patients who presented with hemoglobin values >13.0 g/dl had a significantly higher two-year locoregional tumor control rate of 95% and survival rate of 88% as compared with patients with hemoglobin values <13.0 g/dl, in whom the locoregional tumor control rate was 66% and the survival rate was 46% (p = 0.0018).

Similarly, in a much larger study of 735 patients with T1-2,N0 carcinoma of the glottic larynx performed by Warde et al. at the Princess Margaret Hospital in Canada between January 1981 and December 1989, pretherapy hemoglobin values were found to be an independent prognostic factor for locoregional tumor control [14]. On multivariate analysis, a patient with a hemoglobin value of 12.0 g/dl was found to be 1.8 times more likely to develop local relapse after radiation therapy as compared with a patient with a hemoglobin value of 15.0 g/dl (95% confidence interval, 1.2-2.5). Skladowksi et al. further refined the relationship between the pretreatment hemoglobin value and locoregional tumor control. This study included 235 patients with T1N0 carcinoma of the glottic larynx treated with radiation therapy at the Maria Sklodowska-Curie Memorial Institute Center of Oncology in Poland between 1980 and 1994 [15]. Various parameters were assessed for their impact upon local control using a mixed LQ/log-logistic model including pretreatment hemoglobin levels. As an example, their model predicted that a decrease in hemoglobin level from 13.8 to 12.8 g/dl would result in a 6% decrease in locoregional tumor control (p = 0.006).

Another set of studies assessing the effects of anemia on radiotherapy outcome was performed in patients with early and advanced-stage glottic laryngeal carcinoma (Table 2). van Acht et al. performed a retrospective analysis of 306 patients treated with primary radiation therapy at the Leiden University Hospital in the Netherlands between January 1971 and June 1985 [16]. The study found that glottic laryngeal carcinoma patients with hemoglobin values below normal at the start and/or at the end of therapy had significantly reduced disease-free survival (p = 0.09 and 0.0012, respectively) when compared with patients with normal hemoglobin concentrations. In patients with supraglottic carcinoma, only below-normal hemoglobin values at the end of therapy were predictive of disease-free survival (p = 0.05). Hemoglobin values were also found to be predictive of outcomes in a prospective study by Dubray et al. of 217 patients with head and neck cancer (including patients with oral cavity, oropharynx, hypopharynx, and larynx cancers) treated with radiation therapy between 1989 and December 1993 [17]. Univariate analysis showed anemia (defined as <13.5 g/dl for men and <12.0 g/dl for women) to be associated with lower rates of two-year

| Table 1. Clinical evidence of tumor hypoxia in patients with head and neck cancer |
|----------------------------------------|----------------------------------------|
| **Direct evidence**                  | **Indirect evidence**                  |
| • Histologic evidence → necrosis     | • pH (tumor venous blood × NL tissues) |
| • ↓ pO2 levels by O2 electrodes      | — Anaerobic glycolysis                 |
| • Tumors: metabolites of misonidazole | — “Hypoxic physiology”                |
| • Therapy evidence                  | — HBO → ↑ Local Control               |
| — HBO                                | — ↓ pO2 and Anemia → ↓ Local Control  |

...
locoregional tumor control (50% versus 76%, \( p < 0.00001 \)) and poorer two-year survival rates (49% versus 77%, \( p < 0.00001 \)). Multivariate analysis revealed a trend toward anemia being predictive of locoregional tumor control \( (p = 0.06) \).

Posttreatment hemoglobin concentrations have also been found to be highly predictive of local tumor control in a retrospective analysis of 847 cases of supraglottic larynx cancer treated with radiotherapy [18]. All patients had initial Karnofsky index scores \( \geq 70 \); the minimum follow-up time was three years in this study. Of the eight clinical variables studied (including T-stage, age, sex, total radiation dose, dose per fraction, and overall treatment time), post-treatment hemoglobin concentration was the strongest predictor of local tumor control \( (p < 0.001) \) using a stepwise logistic regression analysis.

Other studies using radiation therapy in conjunction with either hypoxic cell radiosensitizers or intra-arterial (IA) chemotherapy have also shown an association between pretreatment hemoglobin levels and outcome. In a secondary analysis of the Radiation Therapy Oncology Group (RTOG) protocol 85-27, Lee et al. reported that low hemoglobin levels (<14.5 g/dl for men and <13 g/dl for women) reduced survival and increased locoregional failure rates [19]. In this trial, 521 patients with stage III-IV head and neck cancer were randomly assigned to conventional radiation therapy with or without etanidazole. At five years, the survival rate was 36% in patients with normal hemoglobin levels as compared with 22% in anemic patients \( (p = 0.002) \). The estimated locoregional failure rate was 52% at 5 years in patients with normal Hgb level, versus 68% in anemic patients \( (p = 0.0003) \). Multivariate analysis revealed hemoglobin levels to be a significant predictor of overall survival (dichotomous variable, \( p = 0.001 \); continuous variable, \( p = 0.0007 \)) and locoregional tumor control (dichotomous variable, \( p = 0.003 \); continuous variable, \( p = 0.006 \)).

Pretreatment hemoglobin levels significantly predicted various outcome measures in a retrospective analysis of more than 125 patients with stage III-IV head and neck cancer treated with conventional radiation therapy and IA high-dose cisplatin chemotherapy (150 mg/m\(^2\) weekly for four weeks) [20, 21]. In two separate model systems, one evaluating “pure” radiation therapy-related factors \( (n = 137) \) and one studying “other” nonradiation-related prognostic factors \( (n = 125) \), preirradiation hemoglobin levels were significantly prognostic for complete response rates at the primary site and nodal region using a logistic regression analysis, as well as locoregional failure-free survival and overall survival using a multivariate Cox regression analysis. In the latter model [20], the impact of T-stage, N-stage, disease site, pretreatment albumin levels (i.e., <3.2 or \( \geq 3.2 \)), and hemoglobin levels (i.e., for males <12 versus \( \geq 12 \) g/dl; for females <11 versus \( \geq 11 \) g/dl), on response rates (i.e., complete response [CR] versus less than CR), at the primary and lymph node sites was evaluated. Multivariate analysis was also performed to determine the impact of these factors upon overall survival. The primary site CR rate was only affected by pretreatment hemoglobin level \( (p = 0.003) \). Lymph node CR rate was prognosticated by N-stage \( (p = 0.03) \) and pretherapy hemoglobin levels \( (p = 0.01) \). Only N-stage affected overall survival \( (p = 0.005) \) (Table 3).

In the former model [21], the impact of radiation related factors upon complete response rates at primary and lymph node sites, local control, and overall survival was assessed. The factors analyzed were total radiation dose to primary site, total posterior neck dose to lymph nodes, dose/fraction to primary site, radiation related treatment interruptions, and pretherapy hemoglobin levels. The primary site response rate was affected by treatment interruptions \( (p = 0.04) \) and pretherapy hemoglobin levels \( (p = 0.004) \). The lymph node

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**Table 2.** Summary of results from clinical trials assessing the effect of anemia on local control and survival in patients with early or advanced stage head and neck cancer

<table>
<thead>
<tr>
<th>Author/institution</th>
<th>Patients</th>
<th>Stage</th>
<th>Sites</th>
<th>Impact of anemia* local control/survival ( (p &lt; 0.05) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Acht [16]</td>
<td>306</td>
<td>III-IV</td>
<td>glottic</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supraglottic</td>
<td>yes*</td>
</tr>
<tr>
<td>Dubray [17]</td>
<td>217</td>
<td>II-IV</td>
<td>all</td>
<td>yes/yes</td>
</tr>
<tr>
<td>Tarnawski [18]</td>
<td>847</td>
<td>T2-T4</td>
<td>supraglottic</td>
<td>yes*‡</td>
</tr>
<tr>
<td>Lee [19]</td>
<td>521</td>
<td>III-IV</td>
<td>all</td>
<td>yes/yes</td>
</tr>
</tbody>
</table>

*Pretreatment Hgb level
†Posttreatment Hgb Level
‡Change in Hgb level
response rate was only affected by pretreatment hemoglobin levels ($p = 0.001$). Locoregional failure-free survival ($p = 0.0005$) and overall survival ($p = 0.002$) were only affected by pretreatment hemoglobin levels (Table 4).

**Conclusions**

The data presented in this review, including clinical data on the adverse effects of anemia on radiotherapy efficacy, provide strong evidence for the negative impact of low hemoglobin levels upon response rates, local control, and survival in head and neck cancer patients treated with definitive radiation therapy. The correlation between anemia and these outcome measures was prevalent among many analyses revealing pretreatment or posttreatment hemoglobin levels to be a powerful, statistically significant prognostic factor. Based upon these clinical observations, the reversal of anemia should be strongly considered in head and neck cancer prior to the initiation of definitive radiation therapy.

**References**


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| Table 3. “Classical” prognostic factors for treatment response and survival on the RADPLAT protocol ($n = 125$) |
|---|---|
| **Endpoints** | **Statistically significant prognostic factor(s)”** |
| Response rates (CR [complete response] versus < CR) —Primary Site —Lymph Nodes | Pretreatment Hgb ($p = 0.003$) N-stage ($p = 0.03$), Hgb ($p = 0.01$) |
| Overall Survival | N-stage ($p = 0.05$) |
| *Significant in multivariate analyses. Adapted from [22]. |

| Table 4. Radiation-related prognostic factors for treatment response and survival on the RADPLAT protocol ($n = 137$) |
|---|---|
| **Endpoints** | **Statistically significant prognostic factor(s)”** |
| Response rates (CR [complete response] versus < CR) —Primary site —Lymph nodes | Treatment interruption ($p = 0.04$), Hgb ($p = 0.004$) Pretreatment Hgb ($p = 0.001$) |
| Locoregional failure-free survival | Pretreatment Hgb ($p = 0.005$) |
| Overall survival | Pretreatment Hgb ($p = 0.002$) |
| *Significant in multivariate analyses. Adapted from [21]. |

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Impact of Anemia


