
3. ROLE OF CARBOGEN IN THE TREATMENT OF HEAD AND NECK CANCER

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Because of rapid and uncontrolled neoplastic cell proliferation, solid tumor masses typically exhibit abnormal blood vessel networks that fail to provide adequate and homogeneous nutritional support to the tumor cells. Such spatial and temporal heterogeneity of the microcirculation within a tumor can result in an expansion of intercapillary space and a decrease in vessel density. These factors may consequently lead to increased oxygen-diffusion distances and oxygen-deficient or hypoxic regions in tumors. Areas of low oxygen tensions (pO_2) have been well documented using oxygen electrodes in both rodent and human tumors. Most critically, pO_2 distributions measured in malignancies generally have been found to be far lower than those in the surrounding normal tissues.¹

The importance of oxygen in modifying radiation response has been appreciated for more than 90 years. Cells irradiated in the presence of oxygen are approximately 2.5 to 3 times more sensitive than cells irradiated under conditions of severe hypoxia. As the level of oxygen increases, the sensitivity of cells rises rapidly to near maximal levels at a pO_2 of approximately 25 mm Hg, well below the value of 40 mm Hg that is typical of venous blood. Half-maximum sensitization is obtained with pO_2 values of approxi-

mately 3 to 4 mm Hg. Based on such observations, it was postulated that one possible cause for failure of radiation therapy was the existence within tumors of viable hypoxic cells of reduced radiosensitivity.² Indeed, a growing body of evidence strongly supports the hypothesis that hypoxic cells influence radiation response in at least some human tumors. Support for this notion has come primarily from two sources: (1) retrospective clinical studies in which pathophysiologic parameters were related to tumor control or patient survival and (2) prospective studies that employed regimens aimed at targeting hypoxic cells. For example, it has been well documented that in certain disease sites, patients with anemia do poorer when treated with radiation, and the outcome for such patients may be improved by transfusion.³

Improvement of survival and/or local control rates in some trials of hypoxic cell radiation sensitizers and hyperbaric oxygen also is taken as evidence that radioresistant hypoxic cells in some solid tumors can influence outcome. Meta-analysis of the randomized, prospective clinical trials of electron-affinic radiosensitizers has revealed the efficacy of this approach to be more significant than originally appreciated.⁴ Finally, several recent papers have

shown excellent correlation between tumor therapy outcome and the distribution of intratumor oxygen concentration measured with the Eppendorf oxygen electrode histogram.⁵ Evidence for a detrimental role of hypoxia is particularly strong in tumors of the head and neck.^{4,5}

Since normal tissues are presumed to be sufficiently well oxygenated to show maximum radiation sensitivity, numerous strategies are aimed at improving treatment outcome by increasing tumor oxygenation overcoming radioresistance and, hence, improving the likelihood of cure. One method being investigated is high-oxygen-content inhalation (specifically, carbogen: 95% O_2 plus 5% CO_2) during radiation therapy. Data indicate that carbogen alone or in combination with nicotinamide may improve the likelihood of local-regional control.^{6,9}

Beginning in November 1996, a prospective, randomized trial of carbogen breathing during hyperfractionated radiation therapy for head and neck cancer was initiated at the University of Florida. The primary endpoints of the study were local control and cause-specific survival. Secondary endpoints were toxicity and identification of parameters that might predict a benefit from carbogen breathing.

The volume of the primary tumor was calculated on pretreatment computed tomography (CT) or magnetic resonance imaging (MRI) in all patients. Hyperfractionated radiation therapy was employed because it may improve the likelihood of tumor control by decreasing overall treatment time, thus offsetting (to some degree) tumor repopulation during treatment.¹⁰ Patients eligible for the trial had previously untreated T2, T3, and T4 squamous cell carcinomas of the oropharynx, hypopharynx, and larynx (excluding T2 glottic larynx). Exclusion criteria included age under 18 years, pregnancy, nonsquamous histology, distant metastases, resection of the primary cancer as part of the treatment plan, and inability to tolerate carbogen breathing.

After signing an informed consent, patients underwent a carbogen breathing test for 10 minutes. If this was well tolerated, they were stratified according to site and T stage and were randomized to either radiation therapy alone or radiation therapy with carbogen breathing. Before beginning treatment, the patients were asked to fill out a questionnaire pertaining to their smoking history. Blood was obtained for arterial blood gases before and after carbogen breathing. Patients underwent CT simulation, and time-dose-volume data were prospectively calculated to correlate these parameters with the likelihood of late complications. The radiation therapy treatment schedule was 1.2 Gy per fraction twice daily, with a minimum 6-hour interfraction interval, to total

doses ranging from 74.4 Gy to 79.2 Gy. The radiation therapy schedule was identical in both arms with the exception that field size was reduced to exclude the spinal cord after 40.8 Gy in 34 fractions in the carbogen arm as opposed to 45.6 Gy in 38 fractions in the radiation therapy alone arm. Carbogen breathing was administered 6 to 8 minutes before and during each treatment to those patients receiving carbogen. Early in the study, patients who received induction adjuvant chemotherapy as a means of treatment selection (radiation therapy vs surgery plus postoperative radiation therapy) were included. After approximately 1 year, it was decided to limit the trial to patients treated with radiation therapy alone.

Between November 1996 and August 1999, 55 patients were entered into the trial. Breathing carbogen increased the median arterial oxygen tensions from approximately 85 mm Hg to approximately 375 mm Hg. The data on toxicity, tumor control, and survival were analyzed in January 1999. There was no difference in any of the end results between the two groups. Specifically, acute toxicity was comparable. Although there are no obvious differences in the rates of tumor control and survival, the number of patients treated is relatively small and the follow-up is short. The trial is ongoing.

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