


Chemotherapy as an Adjuvant to Radiotherapy

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The rationale of combining a chemotherapeutic agent with radiation therapy can be on one of two hypotheses:

1. Agents like 5-fluorouracil (5-FU) or 5-bromodeoxyuridine (5-BUdR) have been shown to be radiation sensitizers (Bagshaw, 1961; Berry and Andrews, 1962; Bosch et al., 1958; Djordjevic and Szybalski, 1960, Kaplan et al., 1961, 1962; Vermund, 1961). The limiting factor in the effectiveness of such a sensitizing agent is the fraction of cells which can be affected by the agent. Furthermore, as the agent also sensitizes normal cells, clinical usefulness depends on the fraction of tumor cells which are sensitized versus the fraction of normal cells sensitized in the volume of tissue irradiated.

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2. Alkylating agents or antimetabolites like methotrexate are cytotoxic agents producing shrinkage of tumors but are not radiation sensitizers. The rationale of the combination of chemotherapy with such an agent prior to irradiation is based on the following radiobiological facts.

Survival fraction studies have shown that the dose necessary to control a tumor permanently is a function of the number of malignant cells. It has also been proven in tissue culture and solid animal tumor systems that a fraction of cells are hypoxic or anoxic and therefore more radioresistant. As normal oxygenation of a tumor depends on the vascularization of the tumor, it is likely that the larger the tumor the more areas of hypoxic cells are present therefore diminishing considerably the likelihood of permanent control (Powers, 1965).

The preliminary administration of a cytotoxic agent producing shrinkage of a tumor would then have the double advantage, as the tumor would be of smaller size at the inception of radiation therapy, of lessening the number of cells to be sterilized and there ought to be fewer hypoxic cells.

**Timing of the Combined Therapy**

When one uses a cytotoxic agent which is not a radiation sensitizer, chemotherapy should be administered prior to radiation therapy which should not be initiated until maximum regression has been obtained.

With 5-FU which produces shrinkage of the tumor and is also a radiation sensitizer there is a rationale to use 5-FU either prior to, or concomitantly with, radiation therapy.

**Clinical Material**

The squamous cell carcinomas of the upper respiratory and digestive tracts provide suitable material for the evaluation of combined chemotherapy and radiotherapy because results on the primary lesion and on the metastatic nodes to the neck can be assessed accurately by inspection and palpation.

At the M. D. Anderson Hospital background information was available because, for years, both normal tissue reactions and regression rates had been plotted for lesions of the various anatomical sites of the oropharynx by stage of the primary lesion. This staging was not identical but along lines similar to those recommended by the International Union Against Cancer (Table I). The percentage of permanent control of the primary lesions was known for the various anatomical sites according to this T staging. The best local control was obtained in the lesions of the tonsillar area and soft palate. Advanced lesions of the pharyngeal walls had the worst local control.

A pilot study was initiated giving a total of 60 mg/kg of 5-FU in five injections prior to radiation therapy. Radiation therapy was started on the day after the last injection. Originally additional biweekly injections of 10.5 mg/kg of 5-FU were done until toxicity developed, but were abandoned because the