Altered Fractionation for Non-Small Cell Carcinoma of the Lung

Rationale for the Prospective Trials of the Radiation Therapy Oncology Group

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The size and frequency of individual treatments or "fractions" and the total dose administered are the most important decisions available to the radiation oncologist; they are equalled only by determination of the treatment volume. Fractionation regimens in common practice for cancer of the lung vary considerably from one nation to another, and among institutions within a country. Large fractions, e.g., 3-6 Gy, and low total doses (30-40 Gy) are common when the primary aim is palliation; smaller-sized fractions, e.g., 1.8-2.5 Gy and higher total doses (50-60 Gy) are common if longer survival is the aim.

Recently, better understanding of acute and late effects of radiations on normal tissues and appreciation of tumor cell kinetics during treatment have led to new enthusiasm for departures from common fractionation. "Altered fractionation" is, therefore, considered anew as a promising means to increase local-regional control and survival in cancer of the lung.

Prospective clinical trials of altered fractionation for cancer of the lung have been conducted by the Radiation Therapy Oncology Group (RTOG) for more than 15 years. Early trials in non-small cell carcinoma of the lung were aimed at the most cost effective palliation; they used large fractions and low total doses. The most important early study, however, investigated the question of dose response with 2.0 Gy per fraction. This study (RTOG Protocol 73-01) demonstrated a dose-response relationship for control of tumors within the irradiated volume for patients with inoperable, stage 3 (MO) non-small cell carcinomas. RTOG investigators entered nearly 500 patients into these early trials, which demonstrated a dose-response relationship not just for control within the irradiated volume but also for survival. As a result, the standard for RTOG studies of sensitzers, biologic response modifiers, and other adjuncts became 60 Gy in 30 fractions of 2.0 Gy in 6 weeks.

Laboratory and clinical data subsequently became available that suggested potential advantages of standard or smaller-sized fractions administered more often and/or with a smaller interval than 24 h between fractions. Hyperfractionation (HFX) uses smaller-sized fractions (than common fractionation), which permits an increase in total dose in the same amount of time as with standard fractionation, without a corresponding increase in late effects in normal tissues. Accelerated fractionation (AFX) uses common or standard fraction sizes given more frequently to deliver approximately the same total dose as standard, but in a much shorter time.

Recent data have suggested that accelerated proliferation or repopulation may occur in tumors in humans as well as laboratory animals, as a result of the triggering of more rapid division of surviving clonogens as the tumor shrinks following the first irradiation or other insult with any cytotoxic agent. While HFX and AFX both exploit reassortment of cells into more radiosensitive phases of the cell cycle and reoxygation within tumors, HFX overcomes accelerated proliferation by an increase in total dose over the usual treatment time, and AFX avoids much of the accelerated proliferation by completing delivery of the total dose in a reduced period of time.

Recently, the RTOG has accrued nearly 1,000 patients to prospective trials seeking the upper limits of total dose with HFX. The most recent trial is termed "phase 1/2," but it differs profoundly from chemotherapy trials with similar appellations by virtue of an emphasis on late effects end points: this type of evaluation requires that larger numbers of patients be entered into trials to have a sufficient sample of patients for an accurate assessment of late effects, at least at 12-18 months.

Five total doses have been studied with HFX, 60.0-79.2 Gy, delivered as 1.2 Gy twice daily, 10 fractions per week. These trials have been closed, and results are expected which will indicate the most effective total dose. AFX is being explored with three regimens using 1.8 Gy via concomitant boost: a large field is treated 5 times per week.
Hyperthermia in the Management of Lung Cancer

The Current Situation

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Hyperthermia has attracted considerable attention recently as an additional treatment modality. Despite much research work over the past decade, its role in clinical practice remains uncertain. The difficulties in applying the biologic promise of hyperthermia relate to the physical difficulties associated with the delivery of heat and the measurement of temperature. These problems are evident in the treatment of tumors centrally placed in the chest, such as lung cancer. This brief review will detail some aspects of this subject and is essentially an update of previous reviews presented at the International Association for the Study of Lung Cancer Meetings.1,4

Hyperthermia in the temperature range of 40°C-46°C may have several potential biologic advantages in the treatment of cancer. Cell killing by heat is related to both the magnitude of the temperature rise and its duration. The biologic response may differ between different tumors and tissues. Thus, we have studied the thermal response of five small cell (SCLC) and five non-small cell (NSCLC) lung cancer cell lines in which there are very marked differences in their heat sensitivities. Collectively, the NSCLC lines are more easily killed by heat than the SCLC lines.

Heat enhances the cytotoxicity of radiotherapy and potentiates the action of some chemotherapeutic drugs such as the alkylating agents, nitrosores, and some antitumor antibiotics. In man studies have demonstrated the potential advantages of adding hyperthermia to radical radiation in superficial tumors such as cervical lymph nodes involved with metastatic squamous carcinoma.3 There are no similar unequivocal studies on tumors in the chest, and this relates to difficulties in heating at that site.

Heating Methods

It is relatively simple to heat superficial tumors up to a depth of 4-5 cm using the energy deposited by ultrasound or by 0.5-30 MHz radiofrequency (RF), or 300-2,450 MHz microwave (MW) beams. Treatment of tumors at depth presents more problems, although techniques employing 8-27 MHz RF with single, paired, or annular electrodes have been reported.** Intermittent implantation of MW antennas* or ferromagnetic seeds which can be excited by external RF fields** are also being developed. Thermometry remains a problem, as all present techniques are invasive, requiring implantation of fine detectors, usually thermocouples or thermistors.

Whole body heating gets over some of the above problems, but the core and tumor temperature can only be raised to around 41.5°C. Various techniques have been developed to achieve whole body heating either by external heat transfer

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References