and a reduced field which encompasses all known tumor is treated on the same day as the large field two or three times per week (an interval of 4+ h is required between fractions) to total doses of 63-70.2 GY in 5-5½ weeks.

Acute and late reactions were found to be tolerated such that interruption of treatment ("split") was avoided with HFX. Data suggest that acute reactions were more marked than those seen with common fractionation; late effects were equivalent to those seen with common fractionation, and there was no suggestion of increased late effects with higher total doses. AFX has also been tolerated without interruption. Toxicity with the shortest AFX regimen and tumor control rates are still undergoing evaluation. Preliminary estimates of tumor control rates and progression-free survival rates suggest that these altered fractionation regimens are at least comparable to the best results obtained in previous prospective RTOG trials with common fractionation.

Definitive results in the phase 1/2 trials of HFX and AFX therapy require further observation, and comparisons with common or standard fractionation await the results of phase 3 trials. Altered fractionation schemes with systemic chemotherapeutic will be considered for future trials: such combinations hold promise for major advances in the treatment of locally advanced, nonmetastatic carcinomas of the lung.

REFERENCES


Hyperthermia in the Management of Lung Cancer*

The Current Situation

N. M. Bleehen, M.D.

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.1,2

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, nitrosoureas, 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.** Intrstitial 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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through the skin\textsuperscript{16-18,19} or by extracorporeal heat exchange with the blood.\textsuperscript{13-15} Recently a modified radiant heat system has been reported which is claimed to be safe and does not require general anesthesia.\textsuperscript{16}

**Clinical Results**

The assessment of the results of hyperthermia either alone or combined with radiotherapy or chemotherapy is fraught with difficulty. Only very advanced cases are treated and survival and other end points are ill defined.

**Local Hyperthermia (MW and RF)**

MW heating may be used for treating tumors to a depth of 4-5 cm, so that there are few reports of its use in lung cancer. In 1 patient with superficial accessible tumor on the chest wall, a partial response (PR) was obtained by combining heat and radiation.\textsuperscript{16} In another larger series of miscellaneous tumor, 5 patients with supraventricular node involvement from lung cancer received combined therapy; 12 or 24 evaluable patients achieved a complete response (CR), but the response of the 5 lung patients was not specified.\textsuperscript{16}

The majority of experience in lung cancer employs RF capacitive\textsuperscript{16,18} or magnetic loop techniques.\textsuperscript{9} Studies on temperature distribution in the thorax have been reported both in phantom material and sometimes in patients.\textsuperscript{5,10,12} These show very variable ability to heat central tumors. The capacitive techniques have a major problem of the preferential heating of superficial fat. This makes use of the Japanese 8 MHz Thermatron only suited to small, thin patients. The problems of power distribution are well illustrated by theoretic calculations in simulated thoracic cross sections.\textsuperscript{51} Even so, many reports of good heating of central tumors have been published.\textsuperscript{5,58,59} Thus, 2 of 4 patients treated with the Thermatron achieved tumor temperatures between 42-43°C.\textsuperscript{5} Of 35 patients heated using the 13.56 Magnetrode, only 6 tumors failed to achieve 40°C; 17 reached 40-41.9°C; 9 reached 42-44.9°C, and 2 developed temperatures of ≥45°C.\textsuperscript{5} Details of how many times and for how long these temperatures are maintained are rarely given. The significance of the effect of hyperthermia in these patients, also receiving radiotherapy, thus becomes difficult to assess.

**Table 1—Some Recent Results of RF Hyperthermia in Lung Cancer Patients, Usually as Part of a Combined Treatment with Fractionated Radiotherapy**

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Total Patients</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>34</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
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<td>1</td>
<td>7</td>
</tr>
<tr>
<td>28</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>29</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
<td>11</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 1 presents some recent reports in which conventional response rates (CR, PR) have been reported. Further reports, not providing response rates, still specify considerable symptomatic improvement by the patients.\textsuperscript{13} The question remains whether or not such patients would have achieved the same response rates (11% CR, 35% PR) with radiation alone.

**Whole Body Hyperthermia (WBH)**

The results of WBH, usually with chemotherapy, are also difficult to evaluate, as several authors have not defined tumor responses in conventional terms.\textsuperscript{5} Table 2 gives details of 104 patients in whom objective response rates have been recorded (CR 20%, PR 44%). The hyperthermia was usually combined with a wide variety of chemotherapy regimens.

Of great interest is the second series reported by Engelhardt and colleagues.\textsuperscript{18} They randomized 37 patients with extensive SCLC to receive chemotherapy with or without WBH. The preliminary results show a nonsignificant advantage in terms of response rate and of duration of response (153.7 vs 105.1 d, respectively). Although hematologic toxicity was greater in the WBH group, it was acceptable.

However, the methodology involved in WBH is so intensive for both patients and physicians that few groups are using this technique. Toxicity of WBH has also been reported to include a few major complications of coagulopathies.

**Table 2—Studies on Whole Body Hyperthermia for Lung Cancer**

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>No. Pts</th>
<th>Method*</th>
<th>Heat Dose °C × h × No. Treatments</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Tumor Response</th>
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<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>Blanket</td>
<td>$42 \times 2 \times 1$</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>Siemans</td>
<td>$41.8 \times 2 \times 1$-$3$</td>
<td>0</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>Siemans</td>
<td>$41 \times 1 \times 5$</td>
<td>+</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>EC</td>
<td>$42 \times 6 \times 4$</td>
<td>+</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>25</td>
<td>EC</td>
<td>$42 \times 3 \times 7$-$4$</td>
<td>+</td>
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<td>5</td>
</tr>
<tr>
<td>15</td>
<td>4</td>
<td>EC</td>
<td>$41.8 \times 4 \times 8$-$3$</td>
<td>+</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>12$^+$</td>
<td>19</td>
<td>Siemans</td>
<td>$41 \times 1 \times 6$</td>
<td>+</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>16$^+$</td>
<td>18</td>
<td>Nil</td>
<td>Nil</td>
<td>+</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*EC = extracorporeal perfusion; Siemans = Siemens-Pomp heated cabinet.
†Randomized study: patients received chemotherapy (adriamycin 50 mg/m², cyclophosphamide 250 mg/m² po d2-5; vincristine 2 mg d1 × 6 q 21d) with or without hyperthermia (41°C × 1h for the first 3 cycles).

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cardiac arrhythmia, and renal and pulmonary damage. Further reports of a simpler method of inducing WBH, which has been briefly reported, are awaited.\(^{14}\)

**CONCLUSIONS**

It is technically difficult to heat tumors in the thorax. Whole body heating gives the best tumor temperature distribution but is limited to 42°C, while external RF heating is uncertain. Implant techniques may be worth developing to overcome some of these problems. Hyperthermia alone is ineffective and needs to be combined with radiotherapy or chemotherapy.

Does hyperthermia have a place in the management of lung cancer? As clinical results remain largely anecdotal, it can only be recommended as an experimental technique to be studied within the framework of well-designed clinical trials.

**REFERENCES**