Current Strategies for Radiation Therapy in Non-small Cell Lung Cancer*

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Thoracic radiotherapy is widely used in patients with non-small cell lung cancer. Its role as adjuvant treatment before or after surgery has not been established clearly. In patients with locally advanced disease, the main cause of failure is the absence of local control. Recently, three treatment approaches have shown a beneficial effect on overall survival in randomized trials conducted in this group of patients: sequential combination of thoracic radiotherapy and cisplatin-based chemotherapy, concomitant use of radiation and daily low-dose cisplatin therapy, and hyperfractionated accelerated radiotherapy. Another area that merits further investigation is the role of adjuvant surgery.

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Thoracic radiotherapy has been widely used in patients with non-small cell lung cancer (NSCLC), both as adjuvant treatment after complete or incomplete resection and as main treatment in locally advanced disease. This article focuses on the latter category to discuss results of randomized trials and new developments in multidisciplinary management.

Adjuvant Radiotherapy

Despite promising results of pilot studies using preoperative radiotherapy, two large randomized trials did not show an advantage for this treatment in terms of surgical resectability or overall survival rates.1,2 The Veterans Administration trial3 included 339 patients, the total radiation dose varied from 40 to 45 Gy, the resectability rates were 51% for the preoperative group and 53% for the group treated by surgery alone, and 4-year overall survival rates were 13% and 21%, respectively. The National Cancer Institute trial4 included 566 patients, the total radiation dose varied from 40 to 50 Gy, the resectability rates were 61% for the preoperative group and 64% for the group treated by surgery alone, and 5-year overall survival rates were 14% and 16%, respectively. However, both studies have been criticized due to inclusion of all stages of disease and use of orthovoltage equipment.

Postoperative radiotherapy is indicated in patients having incomplete surgical resection because of the high risk of thoracic recurrence. However, its role in patients undergoing complete tumor resection remains controversial despite the results of seven randomized trials including 1,272 patients. A summary of the results of these trials is shown in Table 1.3-9 The heterogeneity of results (p=0.00012) precludes the addition of effects.10 Van Houette et al9 suggested a deleterious effect of postoperative radiotherapy in N0 disease, and the Lung Cancer Study Group and Medical Research Council (MRC) trials7,8 suggested a beneficial effect in N2 disease. The results of a large European trial including more than 700 patients are awaited.10

Thoracic Radiotherapy and Combined Sequential Radiotherapy and Chemotherapy

For many years, conventional thoracic radiotherapy alone has been the treatment of choice for patients with stage IIIB NSCLC. The results obtained, however, have been generally disappointing. The 1- and 5-year overall survival rates have ranged from 29 to 58% and from 4 to 10%, respectively.11 The high rate of distant metastases in stage IIIB disease was at one time considered the main cause of failure of this treatment modality. For this reason, the combination of thoracic radiotherapy and chemotherapy seems a logical step to treat local and distant disease simultaneously. Pilot studies showed promising results, but phase III trials showed a mixture of positive and negative results. One of the possible explanations for this was a lack of statistical power. To evaluate this hypothesis, a meta-analysis performed jointly by the Institut Gustave-Roussy and the British MRC analyzed the role of chemotherapy in lung cancer.12 The study used updated individual patient data from 52 randomized trials performed between 1965 and 1991. Among these trials, 22 compared radiotherapy alone with chemoradiotherapy. Trials using radiosensitizing drugs were not included in this meta-analysis. There were 3,033 patients evaluable, and 2,814 deaths occurred. In 11 trials, the chemotherapy regimen was cisplatin-based and 1,780 patients were included. The main results, summarized in Table 2,12 show a statistically significant overall benefit of chemotherapy. The overall hazard ratio was 0.90 (p=0.006), and the absolute survival benefit was 3% at 2 years. In the studies of cisplatin-based chemotherapy, the hazard ratio was 0.87 (p=0.005), and the absolute survival benefit was 4% at 2 years. A detailed analysis of the French trial13 showed that this effect may be explained by a reduction of distant metastases (from 60 to 40% at 2 years), but there was no detectable effect of chemotherapy on local control.

The Concept of Local Control in Locally Advanced NSCLC

Absence of local control is a major obstacle to long-term cure in patients with locally advanced NSCLC, as the 2-year local failure rate is 90% in locally advanced NSCLC following curative radiotherapy.13 This is in contrast to locally advanced small cell lung cancer, in which the 2-year local failure rate is 40%,14 demonstrating the major radiosensitivity and chemosensitivity of this type of tumor.

The definition of local control as an evaluation criterion varies widely from one center to another, and this complicates the evaluation of treatments aimed at improving

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local control in phase II studies, in which treatment response is the major end point. To clarify the treatment effect on local control using a “hard” end point, we recommend the following: (1) defining complete remission by chest CT scan, fiberoptic bronchoscopy, and routine biopsies; (2) including only patients in complete remission in the numerator; (3) including all patients in the denominator; (4) including local recurrence after complete remission as the only event in determining local control curves; and (5) using a competing risk approach, which provides the advantage of simultaneous consideration of other events like distant metastatic recurrence. When applied in the 353 patients included in the French trial, the very high rate of local failure (>90%) appears to completely overshadow the effect of chemotherapy on distant metastases, and this reasonably explains the small effect of chemotherapy on survival detected by the worldwide meta-analysis. It seems that a significant improvement in local control is needed to obtain an impact on overall survival.

**Thoracic Radiotherapy Parameters in Locally Advanced NSCLC**

Multiple parameters such as total radiation dose, fraction size, volume and type of normal tissues to be irradiated, definition of target volume, and quality control of radiotherapy techniques should be taken into account. These factors are of paramount importance in assessing the effects of combined-modality approaches. Modern megavoltage radiotherapy standards include a clear definition of the volumes to be treated and unequivocal definition of the tumor dose, including fractionation considerations, an optimal beam arrangement to cover the previously defined volume and protect critical organs, computer dosimetry to describe dose distribution, and check of film in the treatment machine to ensure reproducibility and CT scan-based planning.

**Table 1—Randomized Trials of the Role of Postoperative Radiotherapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Stage</th>
<th>RT Dose, Gy/wk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchester¹</td>
<td>202</td>
<td>I-II</td>
<td>45/3</td>
<td>NS</td>
</tr>
<tr>
<td>Bangma²</td>
<td>73</td>
<td>I-II</td>
<td>45/5</td>
<td>NS</td>
</tr>
<tr>
<td>EORTC⁵</td>
<td>230</td>
<td>I-II</td>
<td>45-53/4.5-5.5</td>
<td>Prevents local recurrence</td>
</tr>
<tr>
<td>Van Houtte et al⁶</td>
<td>175</td>
<td>I</td>
<td>60/6</td>
<td>Deleterious effect</td>
</tr>
<tr>
<td>LCSG⁷</td>
<td>210</td>
<td>II-III</td>
<td>50-5-6</td>
<td>May favor patients with N2 disease</td>
</tr>
<tr>
<td>MRC⁸</td>
<td>308</td>
<td>II-III</td>
<td>40/3</td>
<td>May favor patients with N2 disease</td>
</tr>
<tr>
<td>Slovenia⁹</td>
<td>74</td>
<td>III</td>
<td>30/2</td>
<td>NS</td>
</tr>
<tr>
<td>EORTC II</td>
<td>150</td>
<td>II-III</td>
<td>60/6</td>
<td>Closed</td>
</tr>
<tr>
<td>04CB90²</td>
<td>189</td>
<td>II-III</td>
<td>60/6</td>
<td>Being analyzed</td>
</tr>
<tr>
<td>05CBSS¹</td>
<td>539</td>
<td>I-II</td>
<td>60/6</td>
<td>Being analyzed</td>
</tr>
</tbody>
</table>

*RT=radiotherapy; NS=no significant differences between randomized groups; EORTC=European Organization for Research and Treatment of Cancer; LCSG=Lung Cancer Study Group.

¹ Coordinated by the Groupe d'étude et de traitement des cancers bronchiques in France and Europe, respectively.

**Table 2—Meta-analysis of Chemotherapy in Locally Advanced NSCLC: Radical Radiotherapy Alone vs Chemotherapy and Radical Radiotherapy**

<table>
<thead>
<tr>
<th>Drugs Used</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>Absolute Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>At 2 yr, %</td>
</tr>
<tr>
<td>Long-term alkylating agents</td>
<td>0.98 (0.83-1.16)</td>
<td>0.81</td>
<td>0.5</td>
</tr>
<tr>
<td>Vinca alkaloid or etoposide</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
<td>4</td>
</tr>
<tr>
<td>Other drugs</td>
<td>0.98 (0.74-1.29)</td>
<td>0.88</td>
<td>0.5</td>
</tr>
<tr>
<td>Cisplatin-based regimens</td>
<td>0.87 (0.79-0.96)</td>
<td>0.005</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>0.90 (0.84-0.97)</td>
<td>0.006</td>
<td>3</td>
</tr>
</tbody>
</table>

*Adapted from Non-small Cell Lung Cancer Collaborative Group. HR=hazard ratio (the reference category is radiotherapy alone); CI=confidence interval.

**Total Dose**

The traditional approach has been to deliver 60 Gy to the tumor in 6 weeks. However, it has become clear that this dose is not sufficient to achieve significant tumor control in a large tumor volume. Many prospective trials conducted by the Radiation Therapy Oncology Group have investigated the question of dose and dose intensity. An initial randomized study suggested that patients treated with a continuous course of 50 to 60 Gy over 5 to 6 weeks have better tumor control than those treated with the lower doses. Since the 1980s, different regimens of hyperfractionated radiotherapy have enabled the total radiation dose to be raised with no increase in morbidity. Cox et al performed studies in which patients were given 1.2 Gy per fraction twice a day to total doses of 60 to 79.2
Gy. These nonrandomized studies showed a trend toward better survival in the higher-dose group.

**Split Course**

Split-course radiotherapy has been criticized because of the rebound effect of tumor cell proliferation when therapy is discontinued. Two randomized studies comparing continuous and split-course radiotherapy failed to show any survival difference.\(^{18,19}\) Although Pérez et al.\(^{16}\) suggested a slightly better survival rate in patients treated with high-dose continuous treatment vs split-course treatment in their preliminary report, this difference was no longer present after 3 years of follow-up. In the United States, standard radiotherapy consists of 60 Gy delivered over 6 weeks (five fractions of 2 Gy/wk), whereas in continental Europe, 65 or 66 Gy is delivered over 6.5 weeks (four fractions of 2.5 Gy/wk or five fractions of 2 Gy/wk, respectively).

**Fractionation**

Two approaches to increase radiation dose intensity are under evaluation: hyperfractionation, in which many small doses of radiation are delivered to increase the total dose while keeping the total time constant, and accelerated fractionation, in which the overall duration of treatment is shortened while keeping the total number of fractions constant.

Preliminary results from a Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study,\(^{20}\) in which two of the three arms compared conventional radiotherapy (2 Gy per fraction to a total dose of 60 Gy) with a hyperfractionated schedule (two fractions of 1.2 Gy/d to a total dose of 69.6 Gy), recently have been reported. The preliminary results did not show any significant difference between these two radiation modalities (1-year survival rates of 46% and 51%, respectively). The CHART (continuous hyperfractionated accelerated radiotherapy) regimen, in which 36 fractions of 1.5 Gy are given over 12 consecutive days, appeared to show promise in a pilot study by Saunders et al.\(^{21}\) More recently, the initial results of a randomized trial comparing CHART with conventional fractionation in 563 patients showed a significant advantage for CHART in terms of overall survival.\(^{22}\)

**Concomitant Radiotherapy and Chemotherapy**

The simultaneous combination of radiotherapy and chemotherapy is supposed to provide better local tumor control. The concomitant use of radiotherapy with mainly cisplatin or carboplatin has been explored in phase II and III trials, which are summarized in Table 3.\(^{23–26}\) The EORTC three-arm randomized trial\(^{23}\) showed an improvement in overall survival in patients treated with concomitant daily cisplatin (6 mg/m\(^2\)) and radiotherapy vs radiotherapy alone. The survival benefit was attributed to improved local control. The local progression-free rate was 31% in the daily cisplatin group compared with 19% in the radiation alone group. Other trials, however, did not show a significant difference in survival between treatment groups (Table 3).

**Adjuvant Surgery**

Patients with stage IIIB disease are usually considered “definitely inoperable.” In fact, a small number of these tumors are technically completely resectable. Most studies of surgery in locally advanced NSCLC included patients with both stage IIIA and IIIB disease, raising the question of whether surgery added more to the risk than to the benefit of concurrent chemoradiotherapy.\(^{29}\) Response rates in these studies have varied from 51 to 84% and resectability rates from 33 to 85%. Table 4 summarizes pilot studies including more than 50 patients.\(^{30–33}\) Small randomized trials of preoperative chemotherapy have been conducted in patients with stage IIIA disease, and

**Table 3—Randomized Trials of Concomitant Chemotherapy and Radiotherapy in Locally Advanced NSCLC**

<table>
<thead>
<tr>
<th>Source</th>
<th>Drug(s)</th>
<th>Total RT Dose, Gy</th>
<th>No. of Evaluable Patients</th>
<th>Median Survival</th>
<th>2-yr Survival, %</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC(^{25})</td>
<td>Cisplatin</td>
<td>Daily 55</td>
<td>107</td>
<td>NA</td>
<td>26</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekly 55</td>
<td>110</td>
<td>NA</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Ball et al.(^{26})</td>
<td>Carboplatin</td>
<td>60</td>
<td>Ongoing</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kiseleva et al.(^{27})</td>
<td>5-FU/Mtx</td>
<td>60</td>
<td>76</td>
<td>13.2 mo</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Ansari et al.(^{28})</td>
<td>Cisplatin</td>
<td>60</td>
<td>93</td>
<td>35 wk</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Soresi et al.(^{29})</td>
<td>Cisplatin</td>
<td>Weekly 50</td>
<td>45</td>
<td>16</td>
<td>NA</td>
<td>0.18</td>
</tr>
<tr>
<td>Trovo et al.(^{30})</td>
<td>Cisplatin</td>
<td>45</td>
<td>83</td>
<td>NA</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
</table>

*RT = radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; NA = not available; 5-FU = fluorouracil; Mtx = methotrexate; NS = not statistically significant.
promising results have been reported.34,35 The results of a large multicentric French trial are awaited.36 Adjunctive surgery in patients with stage III B NSCLC certainly merits further investigation in phase III trials.

**PERSPECTIVES**

The need to improve local and distant control in patients with locally advanced NSCLC warrants new combined-modality strategies. Such approaches may include novel regimens like accelerated radiotherapy, use of concurrent radiosensitizing drugs, adjunctive surgery, and improved chemotherapy. The moderate improvements reached until now by the use of each treatment may prove at least partially additive if mechanisms of action are different and toxicity levels maintain a positive therapeutic ratio.

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**REFERENCES**

1 Shields TW. Preoperative radiation therapy in the treatment of bronchial carcinoma. Cancer 1972; 5:1389-93