Radiotherapy for Small Cell Lung Cancer*

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The role of radiation therapy in the primary management of small cell lung cancer is very much a matter of current debate. Its value in palliative treatment is unquestioned. Disappointment in the apparent inability to demonstrate improvement in survival in some randomized studies as a result of locoregional radiotherapy and prophylactic cranial irradiation may be due to the use of inappropriate study analysis. Recent studies using the end points of 2-year survival and local thoracic control do demonstrate improvements associated with locoregional thoracic radiotherapy. Factors such as total dose and radiation fraction size may be important. Large-field irradiation is also currently attracting interest, but its use should remain a research investigation.

Radiotherapy has always had an important place in the treatment of small cell lung cancer (SCLC). However, the considerable advances made in studies on the biology, staging, and chemotherapy have overshadowed its role in recent years. This has led to debate as to whether it still has any value in treatment aimed at cure. The potential roles for radiotherapy include control of locoregional intrathoracic disease; adjuvant treatment of sites of election for metastasis such as brain; wide-field irradiation as a systemic treatment not cross-resistant with chemotherapy; preoperative treatment; and its very useful effect in the palliation of symptoms.

We shall briefly summarize the current position, particularly based on data from randomized studies, attempt to define a reasonable strategy for the use of radiotherapy and to highlight areas of uncertainty requiring further investigation.

There have been numerous recent reviews of the management of SCLC and the role of radiotherapy. In particular, recent consensus views have been published as a result of group discussion at 2 workshops held by the International Association for the Study of Lung Cancer (IASLC) in Ireland and in Cambridge, England. The reader is referred to these for more detailed references.

**Radiotherapy for Local Disease**

*Response*

The advantage of locoregional radiotherapy over surgery for operable SCLC was demonstrated in the first Medical Research Council (MRC) SCLC studies. More recently there has been a revival of interest in surgery for operable early SCLC, usually combined with chemotherapy. There has also been some advocacy for preoperative radiotherapy based on the results of one series in which 15% of 73 patients were surviving at 4 years. However, most studies now advocate chemotherapy with or without radiotherapy.

A significant improvement in survival achieved by the addition of single or combination chemotherapy to locoregional radiotherapy has been demonstrated in 5 studies. In the largest of these, the second MRC SCLC study on 236 patients, median survival time (MST) was improved from 6 months for radiotherapy alone to 9 months when chemotherapy (cyclophosphamide, methotrexate, and CCNU) was added (p = 0.009). However, at 3 years only 3% of the radiotherapy group and 4% of the combined-modalities group were still alive. In 2 other studies with cyclophosphamide alone, nonsignificant advantages were also seen for the radiochemotherapy. More recently, improved MSTs reported for a variety of chemotherapeutic regimens have led some workers to advocate a policy of abandoning locoregional radiotherapy. This section describes the evidence for the role of local thoracic radiotherapy added to chemotherapy.

Two retrospective analyses of several nonrandomized series suggest that combined-modality treatment does confer therapeutic advantages. In 1 series of 1,260 patients, combined treatment reduced the local relapse rate in the thorax to 28% compared with 82% among those receiving chemotherapy alone. In the second retrospective analysis no advantage for the addition of locoregional radiotherapy (n = 1,232) as opposed to chemotherapy alone (n = 797) was seen for extensive disease patients as assessed by either complete response (CR) or 2-year disease-free survival. However, for limited disease patients, the corresponding survivals at 2 years were 17% (n = 377) vs 7% (n = 246), in spite of no difference in the CR rate.

Such retrospective analyses are open to many criticisms. There are now 8 prospectively randomized studies investigating the value of the addition of locoregional radiotherapy. A variety of combination chemotherapy regimens and various radiation dose schedules and drug-radiation sequences have been employed. Radiation has sometimes been used only in limited disease patients, while in other trials only for those responding to chemotherapy. Prophylactic cranial irradiation (PCI) is variously employed. A detailed summary of these studies is given in Table I. The results range from no advantage for the addition of local radiotherapy to a definite advantage. The situation appears to be confusing, but it is possible to determine some patterns.
Table 1—Randomized Studies of Chemotherapy with or without Locoregional Thoracic Radiotherapy

<table>
<thead>
<tr>
<th>No. Ref</th>
<th>No. of Patients</th>
<th>Chemotherapy</th>
<th>Chest RT, Gy/Fractions</th>
<th>MST Mos</th>
<th>Alive at 2 yr</th>
<th>% local Response</th>
<th>% local Recurrence</th>
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<tbody>
<tr>
<td>19</td>
<td>25</td>
<td>CYC; VCR†</td>
<td>30/10</td>
<td>CT: 11.0</td>
<td>1/11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCNU; PCB</td>
<td></td>
<td>+ RT: 9.0</td>
<td>0/13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>32</td>
<td>CYC; VCR†</td>
<td>35</td>
<td>CT: 12.0</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCNU; MTX</td>
<td>Split</td>
<td>+ RT: 11.5</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>154</td>
<td>40/10</td>
<td>CYC; VCR</td>
<td></td>
<td>CT: 12.0</td>
<td>13%</td>
<td>—</td>
<td>78</td>
</tr>
<tr>
<td>22</td>
<td>371</td>
<td>VCR; ADR</td>
<td>40/20</td>
<td>+ RT: 10.5</td>
<td>8%</td>
<td>—</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CCNU; MTX</td>
<td>Split</td>
<td>CT: 7.5</td>
<td>8%</td>
<td>—</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>alt CYC; MTX</td>
<td></td>
<td>+ RT: 8.0</td>
<td>8%</td>
<td>—</td>
<td>28</td>
</tr>
<tr>
<td>24</td>
<td>291</td>
<td>CYC; ADR; VCR§</td>
<td>40/14</td>
<td>CT: 11.5</td>
<td>19%</td>
<td>48%</td>
<td>52%</td>
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<tr>
<td>23</td>
<td>124</td>
<td>CYC; ADR; MTX</td>
<td>40/20</td>
<td>Split</td>
<td>CT: 11†</td>
<td>1.6</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ RT: 12.5</td>
<td>10</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>25</td>
<td>74</td>
<td>CYC; MTX; CCNU†</td>
<td>40/15</td>
<td>CT: 12</td>
<td>11%</td>
<td>49%</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>alt ADR, PCB</td>
<td></td>
<td>+ RT: 16</td>
<td>32</td>
<td>78</td>
<td>41</td>
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<tr>
<td>26</td>
<td>368</td>
<td>CYC; VCR; VP16†</td>
<td>40/20</td>
<td>CT: 12</td>
<td>34**</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ 10 Boost</td>
<td>+ RT: 13.5</td>
<td></td>
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</tr>
</tbody>
</table>

*CYC = cyclophosphamide; VCR = vincristine; PCB = procarbazine; MTX = methotrexate; ADR = adriamycin; alt = alternating.
†Prophylactic cranial irradiation given.
‡p = 0.03. §p = 0.05. †p < 0.07. ‡p = 0.02. **p = 0.01.

The 2 earliest studies show no survival advantage for the addition of thoracic radiotherapy, although long-term survival data are available for only 1 of them.28,29 Two larger studies also show no survival advantage either as MST or at 2 years.28,29 However, in both of these there is a distinct trend toward reduced local recurrence. Thus, in the Danish study local recurrence at 2.5 years was 48% for the radiochemotherapy group and 78% for those only receiving chemotherapy.30 One possible criticism of this study is the dose schedule of the radiotherapy, which was given as a split course of 20 Gy in 5 days, followed later by a second, similar course. Some have argued that this relatively high dose may have reduced potential survival in the radiotherapy group. Also, PCI was not given. In the large British study on 371 patients,31 there was a slowing of the rate of local relapse in patients treated with radiochemotherapy that was more definite, but still not significant in chemotherapy responders (Souhami, personal communication, 1985). The significance of the results in this multicenter study is uncertain because of the inclusion of poor performance status patients, absence of PCI, and relatively low overall MST (about 8 months) and 2-year survivals (8%).

Three other studies have demonstrated a significant survival advantage conferred by thoracic irradiation. In the Australian study reported in 1980,26 MST did not appear to be improved by thoracic irradiation, although local relapse was reduced. More recently, after a longer follow-up time and after corrections for prognostic and treatment variables by multivariate analysis (Cox model), radiotherapy has been shown to be of significant value (Fox, personal communication, 1985). In this study of 124 patients, the MST for all receiving chemotherapy alone was 11 months vs 12.5 months for those receiving combined modality treatment (corrected p = 0.026). For limited disease (n = 84) the corresponding MSTs are 12.5 and 17 months (corrected p = 0.003). At 2 years there were only 1 (1.6%) vs 6 patients (10%) surviving, respectively. Of interest in this study is the absence of use of PCI but employment of intrathecal or high-dose methotrexate in addition to the fairly conventional chemotherapy with cyclophosphamide, doxorubicin (Adriamycin), and vincristine.

The South Eastern Oncology Group (SECOG) in the United States presented a preliminary report of the study on 291 patients, of whom 218 were evaluable and 208 assessable for response at the time of publication.28 The protocol was somewhat complex, with the thoracic radiotherapy given in 3 courses between cycles of chemotherapy, and all patients receiving PCI. The MST for the radiochemistry group was 14 months vs 11.5 months for drugs alone (p = 0.03). Two-year survivals were 28% and 19%, respectively. There was also a significantly higher CR rate in the combined treatment group of 63% vs 48% for drugs alone (p = 0.05) and primary failure in the chest of 36% vs 52%, respectively (p = 0.03).

The National Cancer Institute (NC1) group presented preliminary results of an alternating combination chemotherapy regimen given simultaneously with PCI and chest irradiation.26 There was a nonsignificant improvement in MST for the combined treatment (16 vs 12 months), and the 2-year survival of 32% vs 11% for chemotherapy alone approaches significance (p = 0.07). The CR rate is 78% vs 49%, respectively (p < 0.02).

The CALGB group have reported preliminary findings of a study that included chemotherapy with or without radiotherapy.26 Survival data are not yet available, but local control was significantly improved by the local treatment. Some of the differences in these various studies may be due to the selection of different end points, and in particular the relative insensitivity of MST to determine advantage as opposed to the better parameters, long-term survival (>2 years) and pattern-of-failure analysis. It is important to define whether the site of thoracic failure is included within the treatment volume. Peripheral failure is the result of inadequate chemotherapy rather than radiotherapy. Likewise, the evaluation of the role of thoracic radiation...
therapy in patients who are chemotherapy complete responders is important.

The quality of the delivery of treatment is also important. Thus, in an analysis of South West Oncology Group (SWOG) patients receiving radiotherapy, the most important prognostic factor was the quality of the radiation treatment. Patients who were considered major protocol deviations had a worse survival (40 weeks vs 60 weeks) than those receiving the designated radiotherapy \( p = 0.002 \), together with a higher failure rate in the chest \( 22 \% \) vs \( 55 \% \). Differences in quality control may therefore also explain apparently conflicting results.

Radiochemotherapy Sequence

There are no obviously clear differences between the treatment parameters for those studies in which significant improvements in survival or control have or have not been demonstrated. One possible exception is the manner in which chest radiotherapy is sequenced. In the NCI study, it was given simultaneously, with the first cycle of chemotherapy following the high survivals reported in earlier NCI studies. The 3-arm CALGB study is comparing the role of immediate radiochemotherapy vs delayed thoracic treatment vs no thoracic radiotherapy. No definite results are yet available for the optimum sequence, but a preliminary report shows a significant difference in response and time to progression in favor of radiochemotherapy patients. This study interdigitates 3 phases of a split-course regimen between cycles of chemotherapy. A nonrandomized study from Paris also reported relapse-free survival at 2 years of 32% in 35 patients treated with alternating courses of chemotherapy and three courses of radiotherapy to a total dose of 55 Gy in 22 fractions together with PCI.

The optimal sequence of radiation and chemotherapy is an open question. The best published results appear to have been obtained when radiotherapy is given simultaneously with drugs or alternated for 3 cycles as discussed above. Two randomized studies investigated whether it is better to start with chemotherapy or radiotherapy alone followed by the other modality. In the Swiss group for Clinical Cancer Research (P. Alberto, personal communication, 1982) no survival advantage was seen. The MRC also reported a study on 190 patients with limited disease in which no advantages were seen either in MST or 3-year survival when immediate radiotherapy followed by 6 cycles of chemotherapy was compared with 2 of the cycles of drugs being given before the thoracic radiation. In any case, most workers intuitively now prefer to begin with chemotherapy, with or without radiation, to treat potential metastatic disease from the start.

Toxicity

Should thoracic radiotherapy improve survival, its main disadvantage is the possibility of increased local and systemic toxicity. In general this has not been a major problem except in the early series reported from the NCI. In that NCI study in which high-dose thoracic radiotherapy was given concurrently with chemotherapy to 36 patients, an MST of 18.5 months and 2-year disease-free survival of 10% was reported. However, there were 30 esophageal strictures and a 24% treatment-related mortality, largely because of the pulmonary and esophageal reactions. In the more recent NCI study using a similar but less aggressive strategy with careful lung and esophageal shielding, toxicity still remains high. Thus, in 40 patients receiving thoracic RT there were 4 esophageal strictures before esophageal blocking was introduced and 6 deaths related to pulmonary toxicity. There were only 2 deaths in the 40 patients treated by chemotherapy alone. These authors reported a significantly lower initial pulmonary function status in patients developing pulmonary toxicity.

The recent IASLC workshop recommended that further work should include studies on the appropriateness of shielding methods. Thus, the question of whether to treat the original tumor volume before shrinkage by chemotherapy or to commence with the reduced postchemotherapy volume was not yet settled.

The toxicities reported for the other randomized studies discussed above were similar in the chemotherapy and radiotherapy arms. Thus, although life-threatening toxicity was reported in 37% and 42% of patients receiving chemotherapy or radiotherapy in the SECOG study, there was only one treatment related death in each group.

The role of locoregional radiotherapy for limited SCLC remains uncertain. However, it has been shown that, using the correct end points of long-term survival and absence of relapse within the treatment volume, an advantage may be conferred.

Radiobiology

The possibility that patients with SCLC may also have other histologic types of cancer raises the question of the comparative radiosensitivities of the various types. Recent studies on the biology of SCLC have included investigations of its response to x-rays as assessed by a variety of clonogenic assays.

Reports from the NCI have demonstrated a marked radiosensitivity for 7 classic SCLC lines irradiated and assayed in vitro with a slope \( (Do) = 0.51-1.74 \) and extrapolation number \( (n) = 1.0-3.3 \). In contrast, 3 variant SCLC lines showed similar values of \( (Do) = 0.8-0.9 \) but large values of \( (n) = 5.6-11.1 \) and one large cell line \( (Do) = 0.9, n = 14 \). In our own \( in vitro \) data with 9 SCLC lines \( (Kwok, unpublished) \), we also found similar values \( (Do) = 0.68-2.40, n = 0.70-2.06 \). Two of the 8 lines that were biologically variant (on the basis of morphology but not biochemistry) did not differ notably from the others in their radiation response. No recovery from potentially lethal damage was seen at 24 h after irradiation (Kwok, unpublished data).

There are few reported studies of the \( in vivo \) response of SCLC to radiation with subsequent survival assay. Values for \( Do \) of 1.31 and \( n \) of 1.4 were reported for one xenograft experiment, and in our laboratory the surviving fraction after 2-Gy doses for xenografts of four different lines were in the range of 23-37% values compatible with the in vitro parameters (N. Fox, unpublished data). Of more interest are our recent studies in which accessible tumors in patients have been irradiated in vivo with various doses of x-rays (up to 9 Gy), then biopsied and cell survival measured by clonogenic assay. In 2 such patients values for both \( Do \) and \( n \) did not differ significantly from 1.0.

While one cannot rule out selection of radiosensitive lines
Table 2—In Vitro Radiation Response of Several Lung Cancer Lines

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Source</th>
<th>No.</th>
<th>2 Gy</th>
<th>3 Gy</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>SCLC</td>
<td>Cambridge (untreated)</td>
<td>5</td>
<td>5 (0.7-17)</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>SCLC</td>
<td>Cambridge (treated)</td>
<td>2</td>
<td>24 (7-35)</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>SCLC</td>
<td>NCI, M. Ellison</td>
<td>4</td>
<td>22 (14-39)</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>SCLC</td>
<td>NCI, (classic)</td>
<td>7</td>
<td>7-32</td>
<td></td>
<td>32, 33</td>
</tr>
<tr>
<td>SCLC</td>
<td>NCI (variant)</td>
<td>3</td>
<td>56-58</td>
<td></td>
<td>32, 33</td>
</tr>
<tr>
<td>Adeno</td>
<td>NCI</td>
<td>5</td>
<td>28-60</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Adeno</td>
<td>M. Ellison</td>
<td>1</td>
<td>40</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Large</td>
<td>Cambridge</td>
<td>1</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>NCI</td>
<td>2</td>
<td>56-58</td>
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<td></td>
</tr>
</tbody>
</table>

*Kwok T-T. Cambridge, unpublished data.

by reason of the cultural techniques, all of these data do suggest that SCLC is very radioresponsive and does not exhibit much, if any, capacity to accumulate reparable radiation damage. In contrast, data from the NCI and our own (Kwok, unpublished) suggest a significant shoulder in the survival curves of non-small cell lung cancer (NSCLC) lines, indicating accumulation of reparable radiation damage.

The implications of these observations are demonstrated by reviewing the likely surviving fractions of SCLC and NSCLC after conventional radiation fraction sizes of 2-3 Gy (Table 2). For SCLC these will be much lower (5-32%) than for variant SCLC or NSCLC (28-60%).

One may postulate that if one major problem in local relapse is the change to or persistence of NSCLC or variant type SCLC, the use of fractions of radiation larger that are conventionally used might be advantageous. This thesis is supported in 1 nonrandomized series in which there was a significant reduction in initial and total intrathoracic relapse when 30 Gy was delivered in 10 rather than 15 fractions. Also, in the 6 most recent randomized studies of chemotherapy with or without thoracic radiotherapy (40 Gy total ± boost dose), in general a reduction in local recurrence was seen with the most intensive fractionation (see Table 1). Of course, this may just be another way of saying that one is giving a higher effective radiation dose, but the question of fraction size may well be important and needs further investigation.

The apparent absence of ability to accumulate sublethal or potentially lethal radiation damage by SCLC in contrast to what is normally expected in most normal tissues and tumor cell lines is also of therapeutic interest. Thus, the use of multiple daily radiation fractions at time intervals to permit recovery in normal tissues will permit shortening of overall treatment times and reduce the recovery in surviving fraction as a result of cell proliferation. This may be of value in both locoregional and wide-field radiotherapy.

Resistance

The discussion on the radiosensitivity of SCLC and NSCLC is also relevant when one considers patterns of failure. It is not clear whether locoregional relapse after thoracic radiotherapy is due to recurrence of SCLC, to the development of a radioresistant variant component, or to an initial mixed SCLC-NSCLC histology. The general patterns of failure after treatment have been documented in terms of gross pathology, but few studies report details of the histologic types at relapse as opposed to the initial pretreatment diagnosis. Should the initial radiochemotherapy eliminate the sensitive majority population of classic SCLC, a small residual population of variant SCLC, or NSCLC, which is more resistant to therapy, may take over and result in local relapse, even after an apparently complete initial response. The same, of course, may apply to the response of metastatic disease to either TBI or chemotherapy. The most detailed autopsy reports now available are from the studies from the NCI25,26 and the Baltimore group.27

The initial response to treatment according to various histologic subtypes of SCLC has been discussed by several groups. Reports vary from no differences between types to survival advantages for particular histologic subtypes. One report compared of results for patients with mixed SCLC and large cell and those with pure SCLC.28 The mixed-histology type represented about 12% of all of the cases of SCLC presenting to the NCI group that were eligible for aggressive protocols. When matched with a comparable pure SCLC group, results of treatment were worse, with CR + PR of 58% vs 91% and CR rate of 16% vs 46%, respectively. Overall median survival was also lower (6 vs 10.5 months). Of the mixed-pathology patients, all 6 who came to autopsy still had SCLC elements present. Indeed, 1 of the 6 was described as having no identifiable NSCLC present.

The same group reported an extensive autopsy study on 91 patients with SCLC.25,26 Only 5 patients showed no identifiable SCLC. The most frequent morphologic changes observed were intermediate or mixed cell variants, anaplastic large cells, squamous cell nests, or glandular tubules. No differences were seen between patients receiving chemotherapy alone or chemotherapy plus radiotherapy or between classic small cell (type 21) and variant (type 22), either by survival or recurrence pattern. But there were differences between these patients and a small group of 6 variant type patients (type 22/40).

However, the NCI group have reported that in their current study of 6 patients with a first failure at the locoregional site following combined-modality treatment from a total of 29 patients so treated, 5 had failure due to NSCLC.3 This included 1 outside the radiation portal. None of the 5 local failures in the 18 patients in whom first relapse was after chemotherapy alone were reported as showing NSCLC. Whether the addition of locoregional radiotherapy increases the incidence of change to NSCLC must therefore remain
open.

The high incidence of NSCLC elements in these postmortem studies is confirmed in a surgical series. Squamous carcinoma was demonstrated in a quarter of the patients with a preoperative diagnosis of SCLC. In another small postmortem series on four patients with SCLC, all had giant cell formation at the primary site and 3 at metastatic sites.

The Baltimore group described the autopsy findings in 40 patients with pretreatment diagnosis of SCLC. The recurrent or residual disease in 5 patients was NSCLC, while 6 had both SCLC and NSCLC. The remaining 29 cases only had SCLC identified. Thus, in the large series 85/131 (64.9%) relapsed with SCLC only identified as present. Of the remainder, 36 (27.5%) had mixed SCLC and NSCLC, and NSCLC only was present in 10 (7.6%).

Thus, overall approximately 1/3 patients at autopsy had NSCLC, but 2/3 have had only SCLC identified. The latter group must be regarded as failures of control by the measures directed against SCLC. However, of the patients with NSCLC and in particular those without any evidence of SCLC as well (7.6%), may have benefited by therapeutic strategies aimed at NSCLC as well as SCLC. In this regard the nature of the radiation fraction schedule should be considered. With regard to the mixed recurrences, a second drug regimen aimed both at SCLC and NSCLC should be selected.

Two major related problems exist in this analysis. The first relates to the sites of recurrence and the accuracy of postmortem histologic diagnosis. Thus, locoregional radiotherapy directed at NSCLC will be of value only in local disease control, although the same strategy might be extended to wide-field therapy. It is also likely that the estimates of pure NSCLC or pure SCLC recurrence are overestimates because of incomplete histologic examination.

Second, the reported growth rates, as measured by tumor volume doubling time (DT), for the various histologic types differ. In a general review reported times varied considerably but were generally low for SCLC, with a mean DT of 29 days in contrast to 88-161 days for NSCLC. It is generally accepted that SCLC does grow more rapidly, so identifiable initial histologic diagnosis and treatment failure may well be biased toward that histologic type.

Despite these uncertainties, more detailed reports on the effect of initial mixed pathology at time of diagnosis and histologic pattern of failure linked with sites of relapse will be important to help determine the role of radiation therapy.

**Prophylactic Cranial Irradiation**

The frequent development of brain metastases has led to the use of PCI. In a nonrandomized retrospective literature survey of 956 patients not receiving PCI, 22% developed central nervous system (CNS) relapse in contrast to 8% of 422 patients who received PCI. In a retrospective survey of 322 patients treated at the NCI, actuarial 2-year survival was significantly improved to 18%-20% by the addition of PCI vs 5% without it (p<0.005). This was particularly important for patients in CR when primary CNS relapse was seen in 8/48 patients not given PCI and 9/715 receiving it.

In spite of these nonrandomized observations, 7 randomized studies assessing the value of PCI failed to demonstrate its benefit on survival in spite of reducing the overall incidence of CNS relapse from 20% to 6%. Survival was usually assessed by such a short-term end point as MST in contrast to the 2-year survival employed in the NCI retrospective study.

It seems premature to dismiss PCI until long-term survival has been assessed in patients who have achieved CR. Also, at least 1 retrospective study has shown that the quality of life in patients given PCI is better than in those given elective treatment when they develop overt evidence of cranial disease, although the opposite conclusion is reached in a further review of a large number of reported cases in the literature.

The radiation dose used in PCI has varied in the range of 24 Gy in 10 fractions over two weeks to 30 Gy in 15 fractions over three weeks. PCI has been given in various ways. It has been delivered to all patients early in treatment during induction, or in the middle of treatment, or late before consolidation to those in either CR or PR. Recently, some concern has been expressed about possible morbidity, either short- or long-term, in terms of neuropsychologic function. Patients receiving CCNU and methotrexate in particular may be at risk.

Several current questions concerning PCI need answering. The most important is whether PCI can increase long-term survival in selected groups of patients, such as those achieving CR. Another is determining the lowest effective radiation dose and its timing with respect to other treatments. Finally, the effects of these treatments depend not only on the duration of survival but also morbidity needs documenting.

**Large-field Irradiation**

Several groups have investigated the use of total (TBI) vs hemibody irradiation (HBI) for the management of SCLC, either as a palliative measure for advanced disease or as a non-cross-resistant treatment in combined modality therapy, reviewed recently. There have been relatively few randomized studies; some pilot studies are still in progress; and late results have frequently not been reported. It is therefore difficult to assess the role of wide-field radiotherapy in the management of SCLC. Initial studies were with TBI or sequential upper (UHBI) followed by lower hemibody (LHBI) irradiation. Because of the relative infrequency of metastatic disease in the lower abdomen and legs, most treatments have recently used only UHBI that includes the upper abdomen.

Major problems with TBI and HBI are the systemic effects, which include hemopoetic, pulmonary, and gastrointestinal toxicities, together with hypotension and pyrexia. However, a considerable advantage is the relatively short duration of the treatment and toxicity compared with multifraction regimens. The pioneering work of Rider and colleagues determined the safe single doses possible. They showed that the actuarial risk of severe radiation pneumonitis increases from 17.5% for single lung doses of 6 Gy to the whole lung (uncorrected for air transmission) to 35.6% at 8 Gy and 83.5% at doses of 10 Gy. The danger of the higher doses is seen in the early series of HBI reported by Eichhorn and colleagues, in which 17/25 patients receiving UHBI...
followed by LHBI of 8.8 Gy single dose, together with 30-40 Gy (15-20 fractions) to the primary site, developed a fatal pneumonitis.

The treatment details and results of TBI studies for SCLC are summarized in Table 3. Of the 3 studies without chemotherapy only 1 reports in sufficient detail to demonstrate the potential promise of the method with a 13-month MST and 94% CR rate for 18 limited disease patients. Additional local treatment to thoracic disease and the liver was also given. One small study randomly compared chemotherapy with TBI. Both groups received local treatment to chest disease, and there was no significant difference between the average survival times of 11.4 and 13.3 months, respectively. Similarly, other workers also found a comparable MST and 1-year survival in 19 patients treated with TBI + PCI together with induction and consolidation chemotherapy.

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>No. of Patients</th>
<th>TBI Total Dose, Gy/No. Fractions</th>
<th>Other Radiotherapy</th>
<th>Chemotherapy</th>
<th>Survival</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MST, wk</td>
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<tr>
<td>56</td>
<td>6</td>
<td>1.5/10</td>
<td>Local</td>
<td>Nil</td>
<td>20</td>
</tr>
<tr>
<td>57</td>
<td>2</td>
<td>1.5/1</td>
<td>Local</td>
<td>Nil</td>
<td>*</td>
</tr>
<tr>
<td>58</td>
<td>30</td>
<td>1.0/10 (n = 15) Liver 10-20/10</td>
<td>Local 40/20</td>
<td>On relapse</td>
<td>56</td>
</tr>
<tr>
<td>59</td>
<td>8</td>
<td>Randomized 1/10</td>
<td>Local 30/10</td>
<td>CAV on relapse</td>
<td>11.4</td>
</tr>
<tr>
<td>60</td>
<td>7</td>
<td>or nil</td>
<td>Local 30/10</td>
<td>CAV at start</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>1/10</td>
<td>PCI 20/10</td>
<td>VP16, VCR, CYC, ADR CYC, MTX, HXM for consolidation</td>
<td>40-44</td>
</tr>
<tr>
<td></td>
<td>11†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* MST for all 22 patients receiving TBI/HBI = 20 weeks.
† Only 11 received TBI after induction chemotherapy.

It is difficult to reach any firm conclusions from these results for TBI with or without chemotherapy. The randomized study of Byhardt and colleagues suggested that TBI together with chemotherapy in relapses gives as good results as immediate chemotherapy for the regimens tested at that time.

The results of HBI are even more difficult to interpret because of differences in technique (Table 4). Apart from the early cases in the study reported by Eichhorn et al., toxicity was within acceptable limits. Most studies have employed the wide-field treatment as a non-cross-resistant modality to be added to responders from conventional regimens with chemotherapy and locoregional radiotherapy. A general conclusion with respect to survival is that single fraction HBI probably does not add to the results obtained by the more conventional treatment. In a randomized study of UHBI vs chemotherapy reported by Urtasun and colleagues the

### Table 4—Summary of Studies Employing Hemibody Irradiation (HBI) as Single or Fractionated Doses*

<table>
<thead>
<tr>
<th>Ref. No.</th>
<th>No. of Patients</th>
<th>HBI Total Dose, Gy</th>
<th>Other Radiotherapy to Primary Site Gy/Fractions</th>
<th>Chemotherapy</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upper</td>
<td>Lower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>21/7</td>
<td>Nil</td>
</tr>
<tr>
<td>61</td>
<td>19</td>
<td>6</td>
<td>6</td>
<td>20/5</td>
<td>CYC, CCNU</td>
</tr>
<tr>
<td>62</td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>20/5</td>
<td>CYC, CCNU, MTX</td>
</tr>
<tr>
<td>54</td>
<td>25</td>
<td>8.8</td>
<td>8.8</td>
<td>30-40/15-20</td>
<td>Nil</td>
</tr>
<tr>
<td>54</td>
<td>17</td>
<td>6 + 2</td>
<td>6 + 2</td>
<td>40/20</td>
<td>Nil</td>
</tr>
<tr>
<td>63</td>
<td>41</td>
<td>3-5.7</td>
<td>25/10 Responders only</td>
<td>CYC, ADR, VCR</td>
<td>47</td>
</tr>
<tr>
<td>64</td>
<td>38</td>
<td>6</td>
<td>6</td>
<td>Nil</td>
<td>CYC, ADR, VCR</td>
</tr>
<tr>
<td>65</td>
<td>29</td>
<td>7</td>
<td>7</td>
<td>Nil</td>
<td>CYC, ADR, VCR</td>
</tr>
<tr>
<td>66</td>
<td>30</td>
<td>8/1†</td>
<td>35/15</td>
<td>Nil</td>
<td>CYC, MTX, CCNU</td>
</tr>
<tr>
<td>53</td>
<td>66</td>
<td>10/42</td>
<td>10/4</td>
<td>50/25 (lim)</td>
<td>CYC, ADR, VP16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35/17 (ext)</td>
<td></td>
</tr>
</tbody>
</table>

* Lim = limited; ext = extensive; NR = nonresponders.
† Randomized.
‡ Lungs shielded to give 6 Gy corrected. LHBI discontinued later.
results for limited disease were very similar, as assessed by both MST for limited disease (43 vs 42 weeks) and overall 2-year survival (4/30 vs 5/35). However, the results for extensive disease in terms of MST were distinctly worse for HBI (15 vs 44 weeks).

Fractionated HBI has been proposed as a method of avoiding some of its toxicity and potentially permitting an increase in the total dose to tumor. Eichhorn and colleagues reduced the incidence of fatal pneumonitis in their second series by giving both upper and lower HBI in doses of 6 Gy followed 3 hours later by 2 Gy. Only 1/11 patients developed fatal pneumonitis compared with the 17/25 in the earlier series previously discussed. Urtasun and colleagues gave 10 Gy UHBI divided into 4 daily fractions, partially shielding the lung to receive 6 Gy total dose (corrected for lung density). The treatment proved acceptable and is shorter than many regimens (18 weeks’ duration), but survival results so far show no improvement over conventional radiotherapy results. More recently they have been using upper HBI as part of an induction regimen alternating with chemotherapy (Urtasun, personal communication, 1985).

The present role of wide-field radiotherapy for SCLC must therefore remain a research tool. The areas for future work recommended at a recent IASLC workshop include studies on the perfection of dose/fractionation regimens. In view of the absence of an initial shoulder on the radiation survival curve, giving multiple daily doses seems a particularly promising approach. This may permit an increased role for HBI as a non-cross-resistant agent to be intercalated with combination chemotherapy. The workshop emphasized the importance of lung inhomogeneity corrections for absorbed dose. It also suggested the investigation of the role of radioprotectors for the lung and the possible value of HBI or TBI combined with autologous bone marrow to permit even higher radiation doses.

CONCLUSIONS

This brief review has concentrated on areas of topical interest, many of which remain unsolved. Radiotherapy still plays a significant part in the primary management of limited-disease SCLC. Its value in locoregional treatment may be seen when 2-year survival and local relapse rates are considered. The role of PCI may be more clearly demonstrated if reserved for chemotherapy responders. Large-field radiotherapy (TBI and HBI) may be a useful non-cross-resistant agent with chemotherapy, but its integration into therapeutic schedules must remain a research tool.

Future advances will almost certainly come from better understanding of the biology of the disease. Studies designed to select the appropriate subgroups of patients should define the role of radiotherapy in limited disease with more precision. Its role in extensive disease currently is largely palliative. However, it may convert some chemotherapy partial responders to CR with improved survival. This role should not be overlooked in future work. It is premature to discard radiotherapy from the definitive primary management of SCLC.

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