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A Meta-Analysis of the Timing of Chest Irradiation in the Combined Modality Treatment of Limited-Stage Small Cell Lung Cancer

MICHAEL HUNCHAREK, a RONALD McGARRY b

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Key Words. Lung cancer · Thoracic radiation · Combined modality therapy

ABSTRACT

The objective of this study was to determine whether initial combined chemoradiation results in superior 1-, 2-, and 3-year survivals in the treatment of limited-stage small cell lung cancer versus sequential or split-course therapy. Using a prospective meta-analysis protocol outlining study inclusion criteria, literature search strategy, and statistical procedures, data from all available randomized controlled trials addressing the above-noted objective were pooled using a fixed effects model (Peto). Results were expressed as summary odds ratios (ORp), and statistical tests for data heterogeneity were performed prior to calculation of ORps. Odds ratios greater than 1.0 favored the experimental arm versus control (i.e., early chest irradiation). If statistical heterogeneity was demonstrated, sensitivity analyses were performed by previously described methods to evaluate possible sources of heterogeneity across the included studies. Pooling data from eight randomized controlled trials enrolling over 1,500 patients showed that early integration of chest radiotherapy with systemic chemotherapy increases overall survival by 34%-216%, depending on the end point of interest. Etoposide (E) plus cisplatin (P) in conjunction with chest irradiation appears to offer the greatest increase in survival versus delayed or split-course radiation therapy and non-EP-containing drug schedules. The available randomized trial data support early concurrent chest radiotherapy and systemic chemotherapy in the form of E and P in the management of limited-stage small cell lung cancer. The Oncologist 2004;9:665-672

INTRODUCTION

Small cell lung cancer is a highly aggressive neoplasm characterized by high growth fraction, short doubling time, and early dissemination. The majority of patients present with tumor outside the chest, although upwards of one-third are diagnosed with limited-stage disease (as defined by the Veterans Administration Lung Cancer Group) [1]. This latter group is the subject of continued clinical research in an attempt to improve the dismal long-term survival experience of the majority of such patients despite the presence of disease confined to the thorax.

Small cell lung cancer exhibits substantial sensitivity to available chemotherapeutics [2]. Nonetheless, chemotherapy as single modality therapy leads to an unacceptably high failure rate, with local failure occurring in 50%-90% of cases [3]. Available data confirm the need for the addition of thoracic irradiation to the treatment regimen for improved local control and increased survival [4]. These findings have been confirmed by two published meta-analyses [5, 6].

Although it appears that combined modality therapy is superior to chemotherapy alone, the optimal method of integrating thoracic radiation and drug therapy remains
unresolved. Current dogma favors concurrent use of radiation therapy and chemotherapy [5]. Unfortunately the exact timing of radiation in the treatment scheme remains an unresolved issue [7]. The present meta-analysis is designed to examine the impact of early versus late thoracic radiation therapy in the multimodality treatment of limited-stage small cell lung cancer.

**MATERIALS AND METHODS**

The methods employed in the design and execution of this study were previously described by Cooper and Hedges [8]. Briefly, a prospective study protocol was developed outlining a meta-analysis to evaluate how the timing of thoracic radiation among patients with limited-stage small cell lung cancer treated with both chemotherapy and chest irradiation impacts survival at 1 and 2 years post treatment. More specifically, the analysis was designed to examine early integration of thoracic radiation with chemotherapy versus delayed radiation therapy on the outcome of interest. Eligibility criteria for study inclusion were determined prospectively, as were the data points to be extracted from each published report. A plan for statistical analysis was also outlined in the study protocol.

A data extraction form was developed for recording relevant information from each included study. Data extraction was performed by two researchers (one oncologist: M.H.) with differences in extraction forms resolved by consensus. Additional data collected, but not specified as inclusion criteria, included: type of chemotherapy used, chemotherapy schedule and dosing, radiation dose and schedule, patient demographic information, use of prophylactic cranial irradiation, and occurrence of pneumonitis and esophagitis.

**LITERATURE SEARCH**

Information retrieval was performed by previously described methods [8]. An English language search covering the years 1966 through March 2003 was performed using MEDLINE, Current Contents (up to March 2003), and the Cochrane Database. Terms used were lung neoplasms, carcinoma, small cell, and antineoplastic combined chemotherapy protocols as well as an algorithm for randomized controlled trials. Since computer searches fail to yield all relevant literature, the electronic database searches were supplemented by manual searching of bibliographies of all retrieved papers as well as textbooks and relevant review articles. If a series of papers was published, all data were retrieved from the most recent report. Abstracts were obtained from any reference that appeared relevant to the search. The initial citations (in the form of abstracts) were screened by an oncologist (M.H.) to exclude those that did not meet protocol inclusion criteria. Studies employing photodynamic therapy, biologic therapies, or other nontoxic therapies were excluded, as were studies published as letters to the editor. Copies of full articles for the remaining citations were obtained and screened using the following eligibility criteria: A) published randomized trials enrolling adult patients (18 years old or older) comparing initial (with first or second course of systemic therapy) versus delayed chest irradiation (i.e., sequential, split course) combined with chemotherapy in the management of newly diagnosed limited-stage small cell carcinoma of the lung; B) minimum 1-year follow-up after treatment; C) minimum of 20 patients per study arm; D) availability of information on radiation treatment schedule; and E) no prior radiation or chemotherapy.

**STATISTICAL METHODS**

The statistical procedures used were those described by Yusuf et al. [9]. This method is a modification of the Mantel-Haenszel method and is based on a fixed effects model. Study data are arranged in a 2×2 matrix and a summary odds ratio (ORp) and its 95% confidence interval (CI) is calculated. The outcome (event) of interest is survival at 1 and 2 years post treatment. The expected number of events in the experimental arm (early radiation therapy) of each study is calculated and an estimate of the variance of the observed minus expected number of events in each study was then determined as well as the variance (v) across all studies. For k studies, the pooled estimate of the odds ratio is given by,

$$T_{PETO\_OR} = \exp[\sum_{i=1}^{k}(O_i - E_i)\sum_{i=1}^{k}v_i].$$

Prior to estimation of a summary odds ratio, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all the studies. If Q exceeds the upper tail critical value of $\chi^2 (p < 0.10)$ with k-1 degrees of freedom (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect size is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogeneous is rejected, the studies are not measuring an effect of the same magnitude. In this instance, calculation of a pooled estimate of effect (i.e., ORp) may be of questionable validity. Study effect sizes may be disaggregated by grouping studies in appropriate categories until Q is not rejected within those categories or regression techniques can be employed. That is, reasons for the observed heterogeneity must be sought. In essence, Q is a diagnostic tool for determining whether all the variance in the observed effect sizes is accounted for.

In addition to an analysis for heterogeneity, sensitivity analyses were employed when necessary. These tests assess
the robustness of the results to specific methods employed in the conduct of the meta-analysis [8]. The potential for publication bias was not statistically examined. Publication bias may occur because published studies are not representative of all studies that have ever been done. The funnel plot method and other statistical adjustments have been developed in an attempt to address this issue. Unfortunately, these methods lack firm statistical theoretical support and are not generally recommended for medical applications [10].

**RESULTS**

The literature search yielded 36 citations for initial review. Of these, 12 appeared to meet protocol-specified inclusion criteria [11-22] and copies of full papers were obtained for review. Bonner et al. [19] examined split-course radiation versus once-daily chest irradiation in limited-stage patients rather than the impact of early versus delayed radiation therapy and was therefore excluded from the analysis. The study by Perry et al. [20] was excluded since an update of this study was published in 1998 [15]. Therefore, all data were extracted from the more recent study. The Schultz et al. study [21] was published only as an abstract with no updated information available; the authors did not provide adequate survival data in the abstract precluding its use. A study by Gregor and colleagues [22] examined sequential versus alternating radio/chemotherapy and was therefore excluded. The remaining eight studies [11-18] form the database for the present meta-analysis.

Table 1 provides details of patient demographics and radiation therapy treatment schemes for the included reports. Overall, 1,574 patients were included with a median age of 60 years. Radiation schedules were evenly split between once-daily and twice-daily treatment, with seven of the studies reporting using prophylactic cranial irradiation (PCI). Goto et al. [11] did not provide information on the use of PCI. There was some variability in PCI schedule ranging from 20 Gy in 5 fractions [16] to 33 Gy in 11 fractions [18].

Table 2 outlines chemotherapy regimens employed and treatment schedules in both the early radiation therapy and late radiation therapy arms. Etoposide and cisplatin (considered the ad hoc standard regimen in limited-stage disease) [23] was used exclusively in three trials [11, 12, 17], while Skarlos et al. [16] employed etoposide and carboplatin. Perry et al. [15] were the only investigators that did not use cisplatin or carboplatin. The remaining trials used a variety of alternating drug regimens. The sequencing of radiation and chemotherapy is also outlined in Table 2. All randomized trials, with the exception of Lebeau et al. [13], started chest irradiation with the first cycle of chemotherapy in the early treatment arm. These investigators began chest irradiation in the early radiation arm following the second cycle of chemotherapy and used a split-course schedule in the delayed radiation arm.

Initially, all trials except Goto et al. [11] were combined in a meta-analysis using 1-year survival as the end point of interest, with odds ratios greater than one favoring increased

<table>
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<tr>
<th>Author</th>
<th>$n$ Pts on initial XRT arm</th>
<th>$n$ Pts on delayed XRT arm</th>
<th>% Male</th>
<th>Median/mean age (years)</th>
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<td>Jeremic et al. [12]</td>
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<td>82</td>
<td>74</td>
<td>54</td>
<td>initial arm: 50 Gy</td>
<td>2.5 Gy q.d.</td>
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<td>Work et al. [18]</td>
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<td>100</td>
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<td>2.05 Gy q.d.</td>
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*Given simultaneously with chest irradiation

**Initially, chest irradiation was 40 Gy then changed to 45 Gy after October 1984. PCI was initially given as 33 Gy in 11 fractions then changed in late 1984 to 25 Gy in 11 fractions.

Abbreviation: NG = not given.
survival among those treated with early versus late chest irradiation. (Goto et al. did not provide 1-year survival data). Statistical pooling of these data from 1,345 patients showed a summary odds ratio of 1.11 with a 95% CI of 0.88-1.40. Although the ORp favors the early radiotherapy arm, the CI is not statistically significant. An analysis for heterogeneity gave a value of $Q$ equal to 24.4. With 6 degrees of freedom, this demonstrated substantial statistical heterogeneity ($p < 0.001$), i.e., the studies are not measuring an effect of similar magnitude across all trials. This brings into question the validity of pooling the studies to derive a summary estimate of effect. Therefore, reasons for the demonstrated heterogeneity were sought via sensitivity analyses.

Examining the data in Table 2 along with treatment schemes outlined in Table 1 indicated that the two reports employed split-course radiation therapy [13, 18]. The theoretical advantage of such a scheme has been suggested to be decreased additive toxicity and improved drug dose intensity [24]. These studies also used alternating chemotherapy regimens (Table 2). Additional problems with Work et al. [18] include changes in chest irradiation and PCI schedules during the course of the study as well as the delivery of PCI “up front” and independent of chest radiation therapy timing. All of the above could contribute to statistical heterogeneity. This is supported by the data outlined in Table 3, since it appears that these study characteristics resulted in decreased patient survivals as compared with the other trials included in the meta-analysis.

To test this hypothesis, a sensitivity analysis was performed by dropping the Lebeau et al. and Work et al. studies and recalculating an ORp. This yielded a summary odds ratio of 1.34 with a statistically significant 95% CI of 1.01-1.78. The observed statistical heterogeneity was substantially reduced ($Q = 18.7$), although heterogeneity still

<table>
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<th>Table 2. Overview of chemotherapy regimens used in pooled studies</th>
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<td><strong>Chemotherapy</strong></td>
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<td><strong>Murray et al. [14]</strong></td>
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The observed heterogeneity was even more substantially reduced when the three randomized trials using etoposide and cisplatin were pooled [12, 14, 17]. This combination is considered by many to represent the standard drug combination in this disease setting [25]. This combination is favored due to the toxicity associated with use of anthracyclines, nitrosoureas, or cyclophosphamide and concurrent radiotherapy seen in earlier trials [25]. The resultant ORp was 1.95 (CI: 1.35-2.8), a statistically significant result showing an almost doubling of 1-year survival when these drugs are employed as part of the treatment scheme with early versus delayed chest irradiation. The residual heterogeneity was due to the fact that 1-year survival in the report by Takada et al. [17] was identical in both the early radiotherapy arm and the delayed arm (76%). It was anticipated that this heterogeneity would disappear when 2- and 3-year survival data were analyzed given the data displayed in Table 3.

The above analyses were repeated using 2- and 3-year overall survival as the outcome of interest. All eight randomized trials documented 2-year overall survival. Pooling the 2-year survival data (1,575 patients) gave an ORp of 1.60 with a 95% CI of 1.29-1.99, a statistically significant result, indicating a 60% greater 2-year survival among those treated on the early chest radiation therapy arm versus delayed radiation. As anticipated, these data showed no heterogeneity with a Q of 8.60 (p = 0.24, with 7 degrees of freedom). Repeating the previously performed sensitivity analyses also showed results consistent with those shown for 1-year overall survival. Exclusion of the Lebeau and Work studies increased the ORp to 1.78 (CI: 1.40-2.26) for 2-year overall survival. Combining the randomized trials employing etoposide and cisplatin showed a further statistically significant increase in the summary odds ratio to 1.81 (CI: 1.38-2.37).

The 3-year survival data also demonstrated the superiority of initial combined modality therapy versus delayed chest irradiation. Analysis for heterogeneity showed Q equal to 3.79 (p = 0.81), a non-statistically-significant result consistent with an absence of heterogeneity. Pooling all trials using 3-year survival as the outcome of interest revealed a 49% greater survival experience among the early versus delayed radiation therapy arms, (ORp = 1.49, CI: 1.15-1.93). Exclusion of references 13 and 18 increased the ORp to 1.61 (CI: 1.22-2.14), a statistically significant result, while combining those trials utilizing etoposide and cisplatin gave similar results of an ORp of 1.59 with a 95% CI of 1.18-2.15. At 3 years post-treatment, therefore, early initiation of chest irradiation results in a roughly 50%-60% improvement in 3-year survival when compared with regimens using delayed chest irradiation schedules.

**DISCUSSION**

Small cell lung cancer represents a highly aggressive malignancy characterized by rapid progression and early dissemination to regional lymph nodes and distant, extrathoracic sites. More than 70% of patients have mediastinal lymph node involvement at diagnosis and at autopsy; less than 5% show disease confined to the thorax [26, 27]. These data highlight the fact that small cell lung cancer is a systemic disease and that reliance on local therapy alone leads to a high rate of distant failure. Early work demonstrates that this neoplasm is highly sensitive to cytotoxic therapy, with overall response rates of 80%-95% using optimum drug regimens [28]. Nonetheless, it was soon realized that local recurrence represented a major mode of failure and prompted further work integrating thoracic radiation therapy during or following chemotherapy, particularly among patients with limited-stage disease. Since the early 1980s, numerous clinical trials demon-

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NG = not given.
strated the superiority of systemic chemotherapy plus thoracic radiation versus chemotherapy alone [20], with two subsequent meta-analyses supporting the integration of chemotherapy with local radiation treatment [5, 10]. These studies showed that combined therapy improves both survival and locoregional control. Despite the data provided by the above-noted meta-analyses, these overviews did not provide insight into the optimum timing for integrating chemotherapy and local irradiation or delineate the most effective drug regimen.

The present analysis was designed to directly address whether early concurrent use of radiotherapy and chemotherapy produces significant increases in 1-, 2-, and 3-year survival versus sequential or delayed alternating chemoradiation. An additional limitation addressed by the present meta-analysis is the small sample size of most of the available trials. That is, most of the published randomized trials are statistically underpowered, possibly leading to spurious negative results. Pooling the available data allows for a more rigorous, systematic analysis of factors that may affect study outcomes based on a substantially larger study population.

Initially pooling data from over 1,500 patients showed that initiation of chest radiotherapy with the first cycle of chemotherapy clearly results in superior survivals than that seen with delayed or split-course radiation therapy. This increase ranges from 34% to more than 80%, depending on the end point of interest. Split-course radiation therapy appears inferior although data are available from only two randomized trials [13, 18]. Additional problems with the study by Work et al. [18] are that chemotherapy doses were reduced in the concurrent chemoradiation arm and the radiation therapy schedule was changed during the trial from 40 Gy in 20 fractions to 45 Gy in 22 fractions. The initial radiation doses of 40 Gy in 20 fractions would be considered inadequate by current practice standards and may have also contributed to inferior results. Failure to adequately control distant disease due to a suboptimal systemic therapy regimen may also have compromised study outcome.

The present meta-analysis also provides further support for the superiority of etoposide and cisplatin versus other drug combinations. Statistically pooling those studies either using this two-drug combination alone or, in the case of Murray et al. [14], alternating with cyclophosphamide/daunorubicin/vincristine (CAV), showed substantially improved 1-, 2-, and 3-year survival rates when combined with early chest irradiation. This improvement ranged from a 59% to 95%, depending on the end point of interest. Since the study by Murray et al. employed etoposide plus cisplatin alternating with CAV, a sensitivity analysis was performed by excluding this study and recalculating an ORp pooling those reports using only etoposide plus cisplatin. This analysis provides additional evidence that etoposide plus cisplatin should be considered the optimum regimen since exclusion of the Murray et al. [14] data further increased overall survival. For instance, the 2-year pooled ORp increased from 1.81 to 2.16, while the ORp for 3-year survival increased from 1.59 to 1.63. As stated earlier, the toxicity profile of the etoposide/cisplatin combination is more favorable than that seen with older regimens such as CAV [28]. In addition, etoposide plus cisplatin results in shorter treatment duration (i.e., four cycles of etoposide plus cisplatin versus six cycles of CAV). This two-drug combination has been widely adopted in the U.S. and the present meta-analysis confirms its clinical benefits. Since only one randomized trial employed etoposide in combination with carboplatin [16], it was not possible to compare the effects of substituting carboplatin for cisplatin. Although cisplatin has been adopted as the standard, there are no comparative data with long-term follow-up. The outcomes noted in the study by Skarlos et al. [16] suggest that carboplatin/etoposide may produce similar clinical results. Additional trials will be needed to address this issue.

The issue of twice-a-day versus once-a-day thoracic radiation is not easily addressed by the data presented in this meta-analysis. Only a limited number of trials are available with differing radiation schemes and chemotherapy schedules. All of the studies employing etoposide plus cisplatin alone utilized twice-a-day radiation, making it impossible to evaluate the relative response of once-a-day treatment. The Intergroup study published in 1999 [29] demonstrated that accelerated hyperfractionation resulted in an increase in the proportion of patients surviving 5 years over those treated with a once-a-day schedule to a similar total dose (45 Gy), i.e., an increase from 16% to 25%. A valid criticism of this trial is that 45 Gy delivered in a once-a-day fashion is not biologically equivalent to 45 Gy given in a twice-a-day fashion. Therefore, even this trial does not unequivocally demonstrate clinical superiority of twice-a-day treatment. Nonetheless, twice-a-day radiation is also supported by in vitro data indicating that small cell lung cancer cells lack the ability to repair sublethal damage. This allows for increased tumor kill with multiple small doses of radiation. In the absence of additional supporting data, twice-daily radiation therapy represents a reasonable approach in good performance status patients concurrent with etoposide/cisplatin chemotherapy.

Prophylactic cranial irradiation plays an important role in the management of patients with limited-stage small cell lung cancer [30]. Data from several pooled analyses confirm the ability of PCI to improve survival and decrease the risk of brain metastases [31, 32]. Its cost effectiveness and positive impact on patient quality of life has also been documented [33]. The database used for the present meta-analysis details PCI regimens used in seven of the eight available studies. Unfortunately, the data are too limited to make
definitive statements regarding optimum dosing, fractionation, etc. It is interesting though, that two randomized trials employed PCI concurrent with systemic chemotherapy [15, 18]. Both of these studies had relatively poor survival experiences although other factors also contributed to this, as discussed previously (e.g., reduced chemotherapy dosing in the Work et al. trial). Nonetheless, it is possible that concurrent PCI and systemic chemotherapy could contribute to increased toxicity, resulting in poorer outcome. Most authoritative sources advise instituting PCI in those patients shown to have a complete or near complete response in the thorax to chemotherapy [30] following the completion of systemic therapy. Unless or until data to the contrary are forthcoming, this appears to represent the most prudent approach to decreasing central nervous system (CNS) failure.

In summary, the available data support the integration of chest radiotherapy with systemic chemotherapy early in the treatment scheme, preferably concurrent with the first cycle of chemotherapy. Delayed treatment clearly compromises overall survival. Twice-a-day radiotherapy has been adopted by most investigators as providing a survival advantage with manageable toxicities in patients with good functional status [29] and is also supported by in vitro studies of the radiobiology of small cell tumors. Etoposide plus cisplatin represents the current systemic therapy gold standard in the United States and its continued use is supported by the present meta-analysis. PCI is an important feature of management of patients with this disease and is known to decrease CNS failure, increase survival, and improve quality of life. Further trials are needed to clearly define the most effective dosing schedule for PCI and the optimum timing for its integration with currently employed chemoradiation regimens.

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References


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