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CLINICAL INVESTIGATION **Lung**

ROUTINE USE OF CONTINUOUS, HYPERFRACTIONATED, ACCELERATED RADIOTHERAPY FOR NON–SMALL-CELL LUNG CANCER: A FIVE-CENTER EXPERIENCE

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Purpose: To report the results from continuous, hyperfractionated, accelerated radiotherapy (CHART) used as the standard fractionation for radical RT in the management of non–small cell lung cancer (NSCLC) in five United Kingdom centers.

Methods and Materials: In 2005, the CHART consortium identified six U.K. centers that had continued to use CHART after the publication of the CHART study in 1997. All centers had been using CHART for >5 years and agreed to use a common database to audit their results. Patients treated with CHART between 1998 and December 2003 were identified to allow a minimum of 2 years of follow-up. Patient demographics, tumor characteristics, treatment details, and survival were recorded retrospectively. Five centers completed the data collection.

Results: A total of 583 patients who had received CHART were identified. Of these patients, 69% were male, with a median age of 68 years (range, 31–89); 83% had performance status 0 or 1; and 43% had Stage I or II disease. Of the 583 patients, 99% received the prescribed dose. In only 4 patients was any Grade 4-5 toxicity documented. The median survival from the start of RT was 16.2 months, and the 2-year survival rate of 34% was comparable to that reported in the original study.

Conclusion: The results of this unselected series have confirmed that CHART is deliverable in routine clinical practice, with low levels of toxicity. Importantly, this series has demonstrated that the results of CHART reported from the randomized trial can be reproduced in routine clinical practice. © **2008 Elsevier Inc.**

Continuous hyperfractionated accelerated radiotherapy, CHART, Radiotherapy, Non–small cell lung cancer, Hyperfractionation, Acceleration.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide, with >1.2 million new cases and 1.1 million deaths in 2000 (1). Current treatments for non–small cell lung cancer (NSCLC), which accounts for 80% of all cases of lung cancer, remain unsatisfactory. In the United Kingdom, only about 7% of patients survive 5 years (2). The morbidity of the disease and limited success of treatment represent a very serious public health problem.

Patients presenting with localized NSCLC who are considered unsuitable for surgery are usually treated with thoracic RT but have had a disappointingly low long-term survival rate of about 15% at 5 years (3). The international standard radical RT schedule is 60 Gy delivered with once-daily 2-Gy fractions over 6 weeks according to a study by the Radiation Therapy Oncology Group (RTOG) (4). In the United Kingdom, continuous hyperfractionated accelerated radiotherapy (CHART) to 54 Gy using 1.5-Gy fractions three times daily for 12 consecutive days (including weekends) was compared with conventional RT (60 Gy over 6 weeks). This resulted in a 9% absolute improvement in 2-year survival (29% vs. 20%, $p = 0.004$) for CHART with no evidence of a difference in acute or long-term toxicity (5).

In the United Kingdom, CHART is the currently recommended standard for patients undergoing radical RT for NSCLC (6). However, this regimen has not been accepted into practice in the United States and other countries because of the need for inpatient hospitalization, weekend treatment, and concern about acute mucosal side effects. Even within the United Kingdom, where CHART is recommended instead

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of conventional thoracic RT in the National Health Service's National Institute of Clinical Excellence guidelines for lung cancer management, it has proved difficult to implement, mainly because of a shortage of radiographic technicians able to deliver weekend treatment.

At the inaugural meeting of the CHART consortium in 2005 (involving the 14 U.K. centers currently using CHART), it was agreed that the centers who had been able to offer CHART promptly after publication of the trial results should use a common database to audit the treatment outcomes (5, 7). Five centers have been able to complete this retrospective audit, and the results are presented in this report.

METHODS AND MATERIALS

Design and eligibility

In the first CHART Consortium meeting in June 2005, six centers were identified that had been using CHART as a standard fractionation regimen since 1997—Bristol, Cardiff, Cheltenham, Edinburgh, Nottingham, and Sheffield. Only five centers were able to collect the data within the agreed time, and it is the data from these five centers that we present. A database was designed to collect anonymized retrospective demographic, treatment, and outcome data on all patients treated with CHART between January 1998 and December 2003 inclusive. In one center (Nottingham), the data were collected prospectively; in the other four centers, the data collected were retrospective.

Patients were routinely staged with bronchoscopy and computed tomography (CT); 14-fluorodeoxyglucose-positron emission tomography was not a routine investigation in the United Kingdom until 2005. Eligibility for CHART was determined by the individual center protocols. Broadly, all patients had a histologic or radiologic diagnosis of nonmetastatic NSCLC that was unresectable or the patients had been deemed unfit for, or had declined, surgery. Patients were considered suitable if their World Health Organization performance status was 0–1 and they had a reasonable respiratory reserve; the minimum forced expiratory volume in 1 s (FEV1) accepted by any center was a FEV1 of 0.8 L.

Radiotherapy

All centers used a dose of 1.5 Gy/fraction, given three times daily on each of 12 consecutive days, including weekends. An interval of ≥6 h was required between fractions. In the CHART trial, RT was given in two phases; the first phase included elective nodal RT, and the second phase reduced the volume to treat the primary tumor and involved nodes only. Treatment planning was largely two dimensional, with the dose prescribed to the beam intersection point and some correction made for air transmission. During the study period, treatment planning and delivery evolved. The centers involved adopted and applied three-dimensional conformal RT planning and treatment techniques to the CHART fractionation. A further modification has been the use of one phase for treatment delivery to the primary tumor and involved nodes, because elective nodal RT is no longer performed.

Radiotherapy techniques

Patients underwent CT and were treated in the supine position with their arms supported above their head holding arm poles. Using a three-dimensional planning system, the gross tumor volume and involved nodes were outlined using lung and mediastinal window settings. A 5-mm margin was added for microscopic disease and expanded to a planning target volume with the addition of another 1-cm margin (1.5 cm in the superoinferior direction).

Treatment planning was performed with lung correction. Generally, three field plans, prescribed to the isocenter using 6-MV photons, provided acceptable homogeneity for the planning target volume, which followed the dose constraint recommendations of the International Commission on Radiation Units and Measurements reports 50 and 62. Dose–volume histograms were used to confirm that the lung volume receiving ≥20 Gy did not exceed 35% and that the dose to the spinal cord did not exceed 44 Gy. Beam's eye views were produced and used in verification when respiratory movement was screened. Portal images were taken in the first 3 days of treatment, and correction was made for systematic errors >0.5 cm.

Follow-up

Patients were reviewed regularly after treatment with initial reviews in the 6 weeks after completion for toxicity assessment. The treatment response was assessed by CT 6 weeks to 3 months after treatment. Patients then were generally reviewed at 3-month intervals with regular chest plain film radiography. Other investigations were performed as clinically indicated, with CT (with or without bronchoscopy) done on suspicion of recurrence. Toxicity was graded according to the Common Terminology Criteria for Adverse Events.

Statistical analysis

Overall survival was calculated from the start of RT and the date of diagnosis, because a proportion of patients had undergone chemotherapy before CHART. Of the patients, 46 were lost to follow-up and were censored at the point of their last clinic attendance. The actuarial survival curves were estimated using the Kaplan-Meier method. Univariate analysis was performed using the log–rank test for significance. Cox regression analysis was used to look for prognostic factors.

RESULTS

Between January 1998 and December 2003 inclusive, 583 patients underwent radical RT with CHART fractionation, and 99% of these received the prescribed dose of 54 Gy in 36 fractions within 12 days. The five contributing centers were Bristol, Cardiff, Edinburgh, Nottingham, and Sheffield. A comparison of the patient and tumor characteristics with those from the original CHART trial is listed in Table 1.

Survival with CHART

At analysis, 428 of the 583 patients had died. The 2- and 3-year overall survival rate measured from the first day of RT was 33.6% and 20.0%, respectively. The median overall survival time was 16.2 months (Fig. 1). In patients who had undergone primary chemotherapy, the median time from diagnosis to the start of RT was 133 days, significantly longer than the 61-day period for patients undergoing CHART alone (this estimate was determined from the data from 276 patients). The randomized trial reported that those with the squamous cell subtype had a better overall survival rate, but this was not apparent in our series, which showed no statistically significant difference according to histologic type ($p = 0.121$).