Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial

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Summary

Background Human tumour cells can proliferate rapidly, and giving radiotherapy in many small fractions may reduce long-term normal-tissue morbidity. In response to these observations, we developed the CHART (continuous hyperfractionated accelerated radiotherapy) regimen, which uses thirty-six small fractions of 1·5 Gy given three times per day, to give 54 Gy in only 12 consecutive days. We report the long-term follow-up of a trial of CHART versus conventional radiotherapy in patients with locally advanced non-small-cell lung cancer (NSCLC).

Methods 563 patients were entered by thirteen centres between April, 1990, and March, 1995. We included patients with NSCLC localised to the chest with a performance status of 0 or 1 in whom radical radiotherapy was chosen as the definitive management. Patients were randomly allocated in a 3:2 ratio to CHART or conventional radiotherapy. The latter was thirty fractions of 2 Gy to a total dose of 60 Gy in 6 weeks.

Results The groups were well matched for possible prognostic factors. Overall there was a 24% reduction in the relative risk of death, which is equivalent to an absolute improvement in 2-year survival of 9% from 20% to 29% (p<0·004, 95% CI 0·63–0·92). Subgroup analyses (predefined) suggest that the largest benefit occurred in patients with squamous cell carcinomas (82% of the cases), in whom there was a 34% reduction in the relative risk of death (an absolute improvement at 2 years of 34% from 19% to 33%). During the first 3 months, severe dysphagia occurred more often in the CHART group than in the group on conventional radiotherapy (19 vs 3%). Otherwise, there were no important differences in short-term or long-term morbidity.

Interpretation CHART compared with conventional radiotherapy gave a significant improvement in survival of patients with NSCLC. Further improvement may be achieved with dose escalation in conformal radiotherapy, by the addition of cytotoxic chemotherapy, and by hypoxic cell radiosensitisation.

Lancet 1997; 350: 161–65
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Introduction Lung cancer is the most common cause of cancer death in the developed world and the incidence is rising steeply in the developing world.1 Non-small-cell lung cancer (NSCLC) accounts for about three-quarters of all cases.2 Surgery is the most successful treatment but is only beneficial in the minority of patients with early disease.3 Radiotherapy can benefit the patient with early disease.4 Patients with advanced tumours, which are apparently localised to the chest, may be treated by radiotherapy with curative intent but the results remain unsatisfactory (survival of 40% and 15% at 1 and 2 years).4,5 Attempts have been made to improve results by combining radiation with cytotoxic chemotherapy given before, during, or after radiotherapy to enhance the local response and to eradicate occult metastases. Small benefits have been shown in some trials: a meta-analysis showed an absolute improvement in survival of 4% at 2 years.6 Despite the high frequency of distant metastases, most patients die of uncontrolled disease within the chest.7,8 Therefore, efforts to improve primary tumour control, if successful, could prolong survival. Further, distant metastasis may follow failure to eradicate the primary tumour and so the overall frequency of metastasis might be reduced by more effective treatment to the primary site.9 Conventional radiotherapy with curative intent commonly involves a daily dose increment of 2 Gy Monday to Friday for 6 weeks to achieve a total of 60 Gy. However, human cancer cells can rapidly proliferate.10 Giving radiotherapy in many small fractions may reduce long-term normal-tissue morbidity.11 These observations led to the introduction of continuous hyperfractionated accelerated radiotherapy (CHART) at Mount Vernon Hospital in January, 1985. The overall duration was reduced from 40 to 12 days to minimise the opportunity for cell proliferation. A small dose per fraction of 1·5 Gy was used to improve tolerance and was given three times per day every day including the weekend. In a pilot study of 76 patients with NSCLC, there was improved primary tumour control and survival compared with historical controls.12 A multicentre randomised trial in NSCLC was designed in 1989 to run in parallel with a similar study in head and neck cancer. In both, the CHART regimen was...
compared with conventional radiotherapy. A 3:2 randomisation in favour of CHART facilitated the giving of CHART to groups of patients. Endpoints were survival, disease-free interval, local tumour control, and morbidity. An interim report on both trials was prepared immediately after closure of entry in April, 1995. Here we report the definitive results of the trial in NSCLC.

Patients and methods

Design and eligibility

This was a multicentre randomised comparison of CHART versus conventional radiotherapy in patients with NSCLC (figure 1). Eligible patients were those with pathologically proven, inoperable NSCLC with a WHO performance status of 0 or 1 who were suitable for radical radiotherapy.

Radiotherapy

The planning process was identical for all patients regardless of the treatment allocated. The course of treatment was divided into two phases. During the first, "a large volume" was irradiated which included the mediastinum and the primary tumour with a 1 cm margin. The ipsilateral hilar nodes and paratracheal nodes which included the mediastinum and the primary tumour with a 1 cm margin was irradiated: the maximum area of this field was not to exceed 140 cm². Correction for dose distribution was made for transmission through the lung. Radiation doses were prescribed to the intersection point of the beams of treatment.

Those randomised to conventional radiotherapy received a daily dose of 2 Gy 5 days a week. The large volume received 44 Gy in twenty-two fractions and the small volume 16 Gy in eight fractions, to give a total of 60 Gy in thirty fractions. For those receiving CHART, an individual dose of 1·5 Gy was given three fractions, to give a total of 60 Gy in thirty fractions. For those 16 Gy in eight fractions and the small volume 16 Gy in eight

Assessments

All patients were seen weekly for the first 6 weeks from the start of treatment. Follow-up was then at 8 weeks and 3 months after the first day of treatment and then 3 monthly until 2 years, 6 monthly to 3 years, and annually thereafter. At each visit, the chest was radiographed and at 6 months, computed tomography (CT) was done. During treatment or until all acute reactions had settled, the severity of dysphagia was recorded weekly. At all subsequent follow-ups, the presence or absence of dysphagia was noted. Radiation pneumonitis and fibrosis was assessed clinically and by radiography or CT.

Design, endpoints, and analysis

A 2-year survival of 15–20% in the conventional radiotherapy arm was expected. To detect an absolute improvement in this 2-year survival of 10%, that is to 25–30% in the CHART group, a trial of about 600 patients (observing a total of 475 deaths) was required (power approaching 90%, type I error 5%). At the outset of the trial this was considered by the participants to be the improvement in survival required with CHART to justify a change in clinical practice. An independent data-monitoring committee was established to confidentially review the progress of the trial. No prospectively defined stopping rules were seen.
and the trial was monitored with Bayesian methods. Full details of the design and monitoring of this trial have been given by Parmar et al. Randomisation was by telephone call to the MRC Cancer Trials Office. Minimisation was used and patients were stratified by centre, nodal status, and WHO performance status. Kaplan-Meier curves of overall survival, local tumour progression, and disease-free interval were compared with the Mantel-Cox version of the logrank test.

Local tumour control was defined as being achieved when there was either complete disappearance of all abnormalities in a chest radiograph or CT, or when any residual abnormality observed at 6 months remained stable for a further 6 months or more. Patients who did not achieve local control were defined as never being free of disease and thus were considered as an event at time zero.

Disease-free interval was defined as the time from randomisation to progression of local disease or appearance of distant metastatic disease. Patients dying without progression of local disease or appearance of metastatic disease were censored at the time of death. All other patients were censored at the time of their last follow-up. Overall survival was defined as the time from randomisation to death; patients still alive were censored at the time last seen alive. All analyses were by intention-to-treat. To calculate the absolute improvements with CHART, the hazard ratio was applied to the 1-year and 2-year rates for the conventional radiotherapy group for all endpoints.

At the outset there was no clear prespecified hypothesis that CHART would be more or less effective in any subgroups of the population. Nevertheless it was planned to assess the relative benefit of CHART in an exploratory manner in subgroups: age, sex, performance status, stage, site, and histology. To test for differences in the size of the effect of CHART, a chi-squared test for interaction was performed, or when appropriate a chi-squared test for trend. A quality assurance team of a physicist, radiographer, and bioengineer, drawn from the staff of the Cancer Treatment Centre at Mount Vernon Hospital, visited all centres to assess the delivery of radiotherapy.

Results

From April 1, 1990, to March 31, 1995, 563 patients with NSCLC were entered by thirteen centres. Two of the patients randomised to CHART and two to conventional radiotherapy were found later to be ineligible: three showed unacceptable histologies and the fourth a performance status of 2. All four have been included in this analysis. The distribution of patients by age, sex, performance status, T, N, and clinical stage, and by histology or cytology was similar in both arms of the trial (table).

Primary endpoints

444 patients have now died. Comparison of the Kaplan-Meier curves (figure 2a) gave a hazard ratio of 0·76 (p=0·004, 95% CI 0·63–0·92), indicating a 24% reduction in the relative risk of death with CHART. This translates to an absolute improvement in 1-year survival of 8% (from 55% to 63%) and in 2-year survival of 9% (from 20% to 29%).

Local disease failed to completely regress or recurred in 454 patients (figure 2b). The hazard ratio was 0·77 (p=0·027, 95% 0·61–0·97), indicating a 23% reduction in the relative risk of progression with CHART. This translates to an estimated absolute improvement in the 2-year local progression rate of 8% (from 15% to 23%).

486 patients developed progressive local disease or metastatic disease (figure 2c). The hazard ratio was 0·82 (p=0·176, 95% CI 0·66–1·02). This translates to an
absolute improvement in the 2-year progression rate of 5% (from 13% to 18%).

In exploratory analyses, well-defined subgroups were investigated to assess whether CHART was any more or less effective than conventional radiotherapy. There was no influence of age, sex, performance status, stage, subsite, or differentiation of the squamous cell tumours. There was evidence that CHART was more effective than conventional radiotherapy in patients with squamous cell compared with other histologies (test for trend, p=0.007).

For the survival of 461 patients with squamous cell carcinoma (82% of all cases), comparison of the Kaplan-Meier curves gave a hazard ratio of 0.66 (p<0.001, 95% CI 0.53–0.82, figure 2d), indicating a 34% reduction in the relative risk of death with CHART. This translates to an absolute improvement in survival at 2 years of 14% (from 19% to 33%). Similarly, there were greater relative margins of improvement in local tumour progression for this group of patients (hazard ratio 0.70, p=0.01, 95% CI 0.54–0.90) and in disease-free interval (0.73, p=0.01, 0.57–0.93).

Morbidity due to treatment during the initial 3 months

Morbidity during treatment was confined to dysphagia which occurred sooner and was severer in the CHART patients, of whom 19% were reduced to fluids only or were classified as having severe difficulty compared with 3% of conventionally treated cases (figure 3). Dysphagia settled satisfactorily in patients in both arms of the study; at 3 months, 9% of the CHART patients and 7% of the conventional cases were reported to have some persistent dysphagia due to treatment compared with that reported in the meta-analysis of conventionally treated cases. Clinically, 19% of the conventional group had symptoms considered due to radiation pneumonitis and requiring treatment compared with 10% in the CHART group.

Intermediate morbidity

Paraesthesia in the lower limbs on neck flexion (Lhermittes sign21) was recorded at one follow-up in eight patients, all treated with CHART. In these patients, Lhermittes occurred 3–16 months after treatment with a mean time of occurrence of 9–1 months. In later follow-up which ranged from 3 to 19 months, no further neurological symptoms were recorded.

Late morbidity

A clinical assessment of symptoms considered due to pulmonary fibrosis after radiation was made at each follow-up. Of those alive at 2 years, 16% of those treated with CHART and 4% treated conventionally had pulmonary fibrosis that required outpatient treatment. Similarly, radiation changes were assessed radiographically; at 2 years 45% of the CHART cases and 48% of those conventionally treated showed moderate or severe changes in the treatment volume. A small number of patients also reported dysphagia and at 2 years, 7% and 5% were considered to have dysphagia related to radiotherapy in the CHART and conventional arms, respectively. In all the assessments no important difference has emerged in the frequency of morbidity according to treatment arm.

Cause of death

444 patients have now died and a similar distribution of cause was observed in both arms of the trial. The primary tumour was the principal cause of death in 61% of the CHART cases and in 60% of those treated conventionally. There were six cases in which the principal cause of death was considered to be radiation morbidity—three in each arm of the study—and all were related to changes in the lung secondary to treatment.

Discussion

We have shown that CHART improved survival compared with conventional radiotherapy for patients with locally advanced NSCLC. There was evidence that the largest benefit was gained by patients with squamous cell carcinoma. The survival improvement we saw can be compared with that reported in the meta-analysis of randomised controlled trials of chemotherapy in NSCLC. That meta-analysis of over 3000 cases entered into twenty-two trials of chemotherapy added to radiation showed a 13% reduction in the relative risk of death, which translates into an absolute improvement of survival at 2 years of 4% (16% to 20%). With CHART, we achieved in all cases a 24% reduction in relative risk and an absolute improvement at 2 years of 9% (20% to 29%).

The CHART regimen was well tolerated in patients with NSCLC in a randomised multicentre trial. The frequency of oesophagitis was increased but at 3 months was not greater than that in the conventionally treated patients. The greater severity in the CHART cases was partly compensated by a more rapid settling of symptoms. In the long term, no case of radiation stricture of the oesophagus requiring dilatation has so far been reported. As must be expected, most long-term survivors in both treatment arms show radiation fibrosis within those areas of lung included in the treatment volume. Late morbidity has been closely monitored in surviving patients but so far no evidence of difference has emerged.

The difference in the rates of failure to complete treatment as planned—18% for conventional patients and 9% for CHART—can be related to the different conditions which apply when a course is given in 42 as.
opposed to 12 days. Transient myelitis giving Lhermittes sign was noted in eight patients, all treated with CHART. Considering all 1481 included in this trial and the accompanying head and neck study, the frequency was 12 (1.3%) of the 890 patients given CHART and three (0.5%) of the 591 conventionally treated patients. Lhermittes sign is not associated with late spinal-cord damage and indeed no case of radiation myelitis was reported in either trial.

The presence of 158 stage I and 40 stage 2 carcinomas suggests that earlier cases were included in this European study compared with some chemotherapy with radiation trials carried out in North America. In the UK the general pattern of referral is from general practitioner to chest physician who, with colleagues in chest surgery, considers operability in all cases. Among the older age groups there is a high frequency of chronic lung disease and thus a tendency towards a more conservative approach to surgery compared with some North American institutions. Nevertheless, there was no good evidence to suggest that the benefit of CHART was confined to a single stage of the disease.

Our results in this trial of CHART in NSCLC together with the companion trial in head and neck cancer, which showed maintenance of tumour control with lowered late morbidity, gives strong confirmation of the hypothesis that cellular repopulation of a tumour may occur during conventional radiotherapy and be an important cause for treatment failure.

There has been slow progress in the management of patients with NSCLC who present with inoperable disease. Our trial gives evidence that the use of an accelerated regimen with a high standard of radiotherapy achieves an increase in tumour control and survival. Further improvements may occur with new techniques of delivery of radiotherapy which may allow higher doses to be achieved at the site of gross tumour without increasing morbidity with the use of cytotoxic chemotherapy and by combining with hypoxic cell radiosensitisers. Our findings suggest that repopulation is an important factor in the treatment of NSCLC and that the overall duration of treatment should be kept as short as possible to minimise cellular repopulation.

References