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Hypofraction in lung cancer

# Accelerated hypo-fractionated radiotherapy for non small cell lung cancer: Results from 4 UK centres

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ABSTRACT

*Background and purpose:* A variety of radiotherapy fractionations are used as potentially curative treatments for non-small cell lung cancer. In the UK, 55 Gy in 20 fractions over 4 weeks (55/20) is the most commonly used fractionation schedule, though it has not been validated in randomized phase III trials. This audit pooled together existing data from 4 UK centres to produce the largest published series for this schedule.

*Materials and methods:* 4 UK centres contributed data (Cambridge, Cardiff, Glasgow and Sheffield). Case notes and radiotherapy records of radically treated patients between 1999 and 2007 were retrospectively reviewed. Basic patient demographics, tumour characteristics, radiotherapy and survival data were collected and analysed.

*Results:* 609 patients were identified of whom 98% received the prescribed dose of 55/20. The median age was 71.3 years, 62% were male. 90% had histologically confirmed NSCLC, 49% had stage I disease. 27% had received chemotherapy (concurrent or sequential) with their radiotherapy. The median overall survival from time of diagnosis was 24.0 months and 2 year overall survival was 50%.

*Conclusion:* These data show respectable results for patients treated with accelerated hypo-fractionated radiotherapy for NSCLC with outcomes comparable to those reported for similar schedules and represent the largest published series to date for 55/20 regime.



Lung cancer is the leading cause of cancer mortality throughout the world and in 2008, was the cause of 1.4 million deaths [1]. Non-Small Cell Lung Cancer (NSCLC) accounts for 80% of all cases of lung cancer. In the UK, only about 5% of patients survive 5 years [2]. Potentially curative external beam radiotherapy is usually considered in patients presenting with localized NSCLC unsuitable for surgery though there is a disappointingly low long-term survival of about 15% at 5 years. The international standard radical radiotherapy schedule is 60–66 Gy delivered with once daily 2 Gy fractions over 6–6.5 weeks evolving from the study by the Radiation Therapy Oncology Group (RTOG) [3].

In the UK, several dose-fractionation radiotherapy schedules are used in the radical treatment of NSCLC. Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) to 54 Gy using 1.5 Gy fractions 3 times per day for 12 consecutive days (including weekends), when compared with conventional radiotherapy, (60 Gy in 6 weeks) showed a 9% absolute improvement in 2 year survival (29% v 20%, $p = 0.004$) with no evidence of a difference in acute or long-term toxicity [4]. Within the UK, NICE (National Institute for Health and Clinical Excellence) recommends that CHART or a radiobiological equivalent should be used in the potentially curative treatment of NSCLC. Accelerated hypo-fractionated regimen of 55 Gy in 20 daily fractions over 4 weeks (55/20) is in keeping with this NICE guidance and is one of the most commonly prescribed in the UK. However, this regimen has not been validated through randomized phase III trials that compare it to other fractionation schedules. This regimen shortens the overall treatment time which is believed to be beneficial in terms of tumour repopulation [5]. Studies in squamous cell carcinomas of the head and neck demonstrated that on average clonogen repopulation occurred after a lag period of approximately 4 weeks with a dose increment of 0.6 Gy per day required just to compensate for this repopulation [5].

Recently, data from 5 UK centres have been pooled confirming CHART in clinical practice is deliverable and effective [6]. The purpose of this audit was to perform a similar analysis for the 55/20 fractionation and thereby produce the largest published series to date for this schedule.

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## Materials and methods

### Design and eligibility

Four centres were identified that had been using 55/20 as a standard fractionation – Cambridge, Cardiff, Glasgow and Sheffield. In these centres all patients for radical radiotherapy were considered initially unresectable or medical inoperable following discussion in a multi-disiplinary meeting that had input from thoracic surgeons. One centre, the largest contributor to the series, only offered this schedule; the remaining three centres also offered the CHART fractionation schedule. In these centres the selection between the two regimes was largely on the basis of patient preference for in- versus out-patient treatment and the timing and availability of the next CHART treatment. It should be noted that in the 1990s CHART routinely included prophylactic nodal irradiation which may have lead to a higher percentage of peripheral lesions receiving the 55/20 fractionation in three of the contributing centres when CHART slots were filled in the first few years of our cohort.

A database was designed to collect anonymized retrospective demographic, treatment and outcome data on all patients treated with 55/20 between 1999 and 2007 inclusive. Patients were routinely staged with bronchoscopy and CT scan; FDG PET imaging became a routine investigation in the UK in 2005. Staging used the 6th edition of the TNM classification. Eligibility for treatment was based on individual centre protocols. Broadly, all patients had a histological or radiological diagnosis of non-metastatic NSCLC, which was unresectable or the patients were deemed unfit for or declined surgery. Patients were considered suitable if their WHO performance status was 0–2 and there was a reasonable respiratory reserve; the minimum $FEV_1$ accepted by any centre was $FEV_1 > 0.8$ litres.

### Radiotherapy treatment planning

A single phase technique was generally used, without elective nodal irradiation. During the early part of this time period, there was a change in planning technique from 2-D to 3-D conformal radiotherapy planned using pencil beam algorithms. For 3-D planning, gross tumour volume (GTV) included the primary tumour and any involved lymph nodes defined by a short axis greater than 10 mm on CT imaging. Clinical target volume (CTV) was achieved by a 5 mm expansion of GTV in all directions. Planning target volume (PTV) was derived by CTV expansion of 10 mm in the horizontal plane and 15 mm cranio-caudally. Dose was prescribed to the ICRU 50 reference point with correction for lung inhomogeneity. Dose volume histograms were calculated on all those having CT based treatment plans with the recommendation that the PTV receives 100 ± 7% of the prescribed dose. Lung and spinal cord were identified as the organs at risk and the percentage volume of total lung receiving greater than 20Gy (V20) was calculated and this value was used to limit the risk of post radiation pneumonitis [7] and the policy at the time of this study was to ensure a V20 (including the PTV) of less than 40%.

### Statistical analysis

Statistical analysis was performed using SPSS version 16.0 statistical software. Survival analysis was undertaken using Kaplan Meier methodology and log rank test for significance. Overall survival (OS) was calculated from date of diagnosis (or date first seen in a few patients where date of diagnosis was unavailable) to date of death or censored at date of last follow-up, if alive. Progression-free survival (PFS) was calculated from date of diagnosis to date of relapse (any site). In those patients without relapse, date of death was used as an event or they were censored at last follow-up. Multivariate analysis was performed using Cox Regression.

### Follow up

Patients were reviewed regularly following treatment with initial reviews in the 6 weeks after completion for toxicity assessment which was graded according to the Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE). Treatment response was assessed by CT imaging between 6 weeks and 3 months which were reported by local radiologists and not independently verified. Subsequently patients were reviewed at 3 monthly intervals when examination, toxicity assessment and chest plain film radiography were performed. Other investigations were performed as clinically indicated with CT imaging (±bronchoscopy) done on suspicion of recurrence.

## Results

Six hundred and fifteen patients were identified as having been intended to receive 55/20. The clinical records could not be traced for 6 patients leaving 609 suitable for analysis. Five hundred and ninety-three received the actual dose of 55/20 over four weeks; the remaining patients received doses between 49.5 and 54 Gy given in 18–20 fractions. A summary of patient and tumour characteristics are shown in Table 1.

At the time of analysis, 406 of the 609 patients had died. The 1, 2, 3 and 5 year overall survival rates measured from diagnosis were 81%, 50%, 36% and 20%, respectively, as illustrated in Fig. 1. Stage IA disease conveyed the best prognosis with a 2 year survival of 72% (median survival of 38 months) which falls to 51% for stage IB disease. As expected the worst outcomes were seen in stage III patients with a 2 yr survival of 40% (median survival 20 months). Adenocarcinomas had a better median survival (31 months) than squamous cell carcinoma (20.4 months) (Fig. 2).

Both univariate and multivariate analyses were performed to explore the different prognostic factors. Univariate analysis, as demonstrated in Table 2 revealed response, stage, gender and histology, to be significant prognostic factors but not performance status or prior chemotherapy. None of the prognostic factors remained significant on multivariate analysis.

378 patients from three of the centres had response, site of relapse data and toxicity data collected. These were categorized as follows: complete response (24.3%), partial response (46.3%), stable disease (13.8%), progressive disease (2.6%) and unknown (13.0%). In 37% of patients local recurrence was documented; patients treated for stage II disease accounted for the majority and recorded local recurrence rates for stage 1 disease was low at 10%. In 31% overall metastatic relapse was documented. The commonest sites of metastases were the lung, bone, brain and liver. There were no grade III – V toxicities identified using the CTCAEv3 and the incidence of recorded grade I and II toxicities was also low. For example grade I/II radiation pneumonitis was documented clinically in 15.1% of patients and radiologically detected pneumonitis diagnosed in 18%.

In this series 168 (28%) of 609 received combined treatment with sequential chemo-radiotherapy. Of this group of patients, 115 (69%) were male, with a median age of 66 years (range 33–86 years) with a histological distribution very similar to that described for the whole trial population. The distribution according to stages I, II and III was 8%, 8% and 83%, respectively. Eighty-three percent received platinum based doublet chemotherapy. Other regimens used included MIC, MVP, and concurrent gemcitabine (patients on the GRIN study). The median number of cycles given was 4 (range 1–5). The overall survival of the chemotherapy group