Original Article
The Quality of Curative-intent Radiotherapy for Non-small Cell Lung Cancer in the UK

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Abstract

Aims: Lung cancer is the leading cause of cancer-related death in the UK. The quality of curative-intent radiotherapy is associated with better outcomes. National quality standards from the National Institute for Health and Care Excellence (NICE) on patient work-up and treatment selection were used, with guidance from the Royal College of Radiologists on the technical delivery of radiotherapy, to assess the quality of curative-intent non-small cell lung cancer radiotherapy and to describe current UK practice.

Materials and methods: Radiotherapy departments completed one questionnaire for each patient started on curative-intent radiotherapy for 8 weeks in 2013.

Results: Eighty-two per cent of centres returned a total of 317 proformas. Patient selection with positron emission tomography/computed tomography, performance status and Forced Expiratory Volume in 1 second (FEV1) was usually undertaken. Fifty-six per cent had pathological confirmation of mediastinal lymph nodes and 22% staging brain scans; 20% were treated with concurrent chemoradiation, 12% with Stereotactic Ablative Radiotherapy (SABR) and 8% with Continuous Hyperfractionated Accelerated Radiotherapy (CHART). Sixty-three per cent of patients received 55 Gy/20 fractions. Although respiratory compensation was routinely undertaken, only 33% used four-dimensional computed tomography. Seventy per cent of patients were verified with cone beam computed tomography. There was consistency of practice in dosimetric constraints for organs at risk and follow-up.

Conclusions: This audit has described current UK practice. The latest recommendations for patient selection with pathological confirmation of mediastinal lymph nodes, brain staging and respiratory function testing are not universally followed. Although there is evidence of increasing use of newer techniques such as four-dimensional computed tomography and cone beam image-guided radiotherapy, there is still variability in access. Efforts should be made to improve access to modern technologies and quality assurance of radiotherapy plans.

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Key words: NSCLC; quality; radiotherapy

Introduction

Lung cancer is the leading cause of cancer-related death in the UK [1]. Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, with 28 525 cases in England and Wales in 2013 [2]. After surgery, radiotherapy is the second most frequently used curative treatment for NSCLC.

Research over the past two decades has improved cure rates by the combination of chemotherapy for advanced disease, and altered fractionation for localised disease.

Technological developments have allowed better targeting of tumour and avoidance of organs at risk.

UK outcomes for lung cancer are worse than many other European countries, linked to both late presentation and lower rates of treatment [3]. There is recognition that a better quality of radiotherapy is associated with improved cure rates [4]. A recent survey has shown variable access to advanced radiotherapy techniques and technologies throughout the UK [5]. National standards for patient selection and treatment are designed to optimise outcomes [6–8].

This study was designed to assess the quality of patient selection, radiotherapy treatment planning and delivery. Access to the newer technologies of four-dimensional computed tomography and cone beam verification were recorded. Current UK radiotherapy practice was assessed.
Materials and Methods

A questionnaire was sent to all radiotherapy departments in the UK. Centres were asked to complete one questionnaire for each patient starting radical radiotherapy for NSCLC between Monday 14 October 2013 and Friday 6 December 2013. The results on treatment decisions for patients eligible to receive Stereotactic Ablative Radiotherapy (SABR), Continuous Hyperfractionated Accelerated Radiotherapy (CHART) and concurrent chemoradiation (CRT) are reported elsewhere. The standards of the audit and overall performance are listed in Table 1.

Results

Forty-five of 55 (82%) centres returned a total of 317 questionnaires. A median of four questionnaires were returned (range 0–25). Six centres did not have any suitable patients. One centre collected for only 2 weeks because of its high workload. We estimate that 2649 patients are treated with radical radiotherapy per year in the UK. The quality of information was good, with stage recorded in 99%, performance status in 97% and Medical Research Council dyspnoea score in 71%.

The demographic characteristics were as expected for a UK population (Table 2). The average age was 72 years and 41% were at least 75 years of age. A significant proportion of patients had poor performance status (26% World Health Organization performance status 2+) or significant breathlessness (14% limited to less than 100 yards). Thirty-three per cent were current smokers, 55% were ex-smokers, 4% never smokers and 8% unknown. Smoking cessation advice was offered to 57% of smokers. The rate of pathological confirmation was high (85%). The reasons for not being able to get tissue seemed reasonable; 23% had attempted confirmation but failed, in 73% the biopsy was either too difficult or the patient was not fit enough and 2% refused. Forty-eight per cent had stage I/II disease and 52% had locally advanced disease.

Most patients (96%) were positron emission tomography/computed tomography (PET/CT) staged. The remainder either refused PET/CT scanning or the scan could not be undertaken in a timely manner. Only 56% of patients with PET/CT-positive mediastinal lymph nodes had these pathologically sampled. Endobronchial Ultrasound (EBUS) was used to sample lymph nodes in 60% of cases. Only 26% had brain staging (78% of these were with computed tomography, 22% with magnetic resonance imaging). Whereas 22% had a staging brain scan for stage I disease, 38% had a scan for stage III disease ($P = 0.08$). Forced Expiratory Volume in 1 second (FEV1) was available in 82% of patients and transfer factor (corrected transfer factor, KCO) in 60%. The median FEV1 was 1.71 (range 0.6–3.6); 8% of cases had an FEV1 of 40% or less; 6% of cases had a KCO of 40% or less.

Fifty cases (16%) were surgical candidates. Fifty-two per cent of these refused an operation, preferring radiotherapy, 24% were not able to have planned surgery and 12% had a futile thoracotomy. In total, 267 cases (84%) were not surgical candidates. Forty-eight per cent were technically inoperable, 47% medically inoperable and 5% were unknown.

Patients were included in the study if they were referred to, or from, another centre. Very few fell into this category, with 1% referred to another centre (all three for SABR) and 2% referred from another centre (three were treated with SABR, one with CHART, one with CRT, one with sequential chemoradiotherapy and one with radiotherapy alone). There was a low rate of accrual to clinical trials (4%).

Treatment Paradigm

There was treatment data on 314 of the patients, because there was no further data on the three patients referred to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Audit standards and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>317</td>
</tr>
<tr>
<td>Patient selection</td>
<td></td>
</tr>
<tr>
<td>Pathological confirmation [2]</td>
<td>75%</td>
</tr>
<tr>
<td>PET/CT staged [6]</td>
<td>95%</td>
</tr>
<tr>
<td>Pathological confirmation of PET/CT N2/3 nodes [6]</td>
<td>95%</td>
</tr>
<tr>
<td>CT brain staging (all) [6]</td>
<td>95%</td>
</tr>
<tr>
<td>(stage III)</td>
<td>33%</td>
</tr>
<tr>
<td>RFTs; FEV1 [6]</td>
<td>95%</td>
</tr>
<tr>
<td>KCO</td>
<td>60%</td>
</tr>
<tr>
<td>Smoking cessation advised [6]</td>
<td>95%</td>
</tr>
</tbody>
</table>

### Treatment paradigm

#### Stage I/II

- **Offer CHART [6]**
  - 95% 26%
- **If not available: 55 Gy/20 fractions or 64–66 Gy/32–33 fractions**
  - 87%
- **Consider SABR as per UK consortium guidelines [9]**
  - 100% 68%
- **Stage III**
  - **Consider CRT [6]**
    - 100% 64%
  - **If not suitable for CRT consider CHART [6]**
    - 100% 31%

#### Treatment delivery

- **Immobilisation device**
  - 100% 100%
- **Respiratory motion compensation**
  - 100% 99%
- **Organs outlined**
  - Lung
    - 100% 100%
  - Oesophagus
    - 100% 68%
  - Spinal cord
    - 100% 98%
  - **Recorded as category I**
    - 100% 94%
  - **Treatment verification with orthogonal images**
    - 100% 100%
  - **Follow up <6 weeks**
    - 100% 99%

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PET/CT, Positron Emission Tomography/Computed Tomography scan; RFTs, respiratory function tests.
FEV1, Forced Expiratory Volume.
KCO, corrected Transfer Factor.
CHART, Continuous Hyperfractionated Accelerated Radiotherapy.
SABR, Stereotactic Ablative Radiotherapy.
CRT, Concurrent chemoradiation.

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another centre. The most commonly used fractionation was 55 Gy/20 fractions (63%), 14% received 64–66 Gy/32–33 fractions, 8% received CHART (54 Gy/36 fractions) and 12% received SABR. Most SABR treatments used a five fraction regimen (65%), 16% three fractions, 16% eight fractions and 3% 10 fractions. Three per cent of dose schedules were outside the recommended ranges [6,8]. The reason for this was unknown in 50%, clinical trial doses (20%), dose reduced due to critical structures (20%) and one patient starting with emergency palliative hypofractionated treatment subsequently changed to a radical dose. Forty-two per cent were treated with radiotherapy alone, 20% with CRT and 18% with sequential chemotherapy. CRT was predominately delivered with either vinorelbine/cisplatin (76%) or vinorelbine/carboplatin (13%), a further 10% had etoposide/cisplatin and one patient received pemetrexed/cisplatin. Twenty per cent had had induction chemotherapy and 34% had planned chemotherapy after radiation was completed. Half the patients started radiotherapy at cycle 1, 29% at cycle 2, 14% at cycle 3 and 7% at cycle 4. Forty-eight per cent of patients received 64–66 Gy/32–33 fractions, whereas 47% received 55 Gy/20 fractions. Vinorelbine/platinum was the most commonly used regimen in the sequential setting (52%), with 35% receiving gemcitabine/platinum, 10% pemetrexed/platinum and 3% taxane/platinum. Seventy per cent received carboplatin. 55 Gy/20 fractions was used in most (82%) sequential treatments. Four per cent of patients received chemotherapy before CHART and 8% after CHART.

Treatment Planning

Although PET/CT information was used in most cases to contour the gross tumour volume, only 3% fused scans with the planning computed tomography. Lymph nodes were contoured separately from the primary in 45% of node-positive cases. Sixty-five per cent of cases had intravenous contrast during their planning scan. Contrast was more likely to be used for node-positive than node-negative cases (76% versus 54%, P < 0.005). Radiologist involvement at the time of planning was uncommon (4% of cases). The margins applied to the gross tumour volume were examined as per ICRU 50 [10]. Internal margin and tumour motion were formally accounted for in 99% of cases. Sixty-one per cent were compensated with standard margins applied to the gross tumour volume, 33% with four-dimensional computed tomography and 2% with fluoroscopy. Most (99%) four-dimensional computed tomography scans were used to create an irradiated target volume (ITT), whereas only 1% were used for gating. More complex treatments, such as SABR, were more likely to use four-dimensional computed tomography (Figure 1).

Microscopic spread was usually accounted for by a standard fixed margin (74%). Forty per cent had a margin that varied dependent on squamous or non-squamous histology. Although 6% had no margin for microscopic spread, 95% of these were SABR cases, in line with UK consortium guidelines. The remaining 7% used either anatomical boundaries for clinical target volume delineation or were uncertain as to the method used. Most cases (51%) benefitted from an audit of their individual centre’s set-up error. Forty-five per cent of treatments used standard margins taken from the literature and 4% were unknown.

In 50% of cases, outlining organs at risk was carried out by physics staff and in 33% by radiographers. Table 3 shows the frequency of outlining organs at risk and the preferred dosimetric parameter used to assess tolerance. The lungs and spinal cord were outlined in most cases (100% and 98%, respectively). V20 was usually (84%) used to assess lung tolerance; 54% of cases used combined lung minus gross tumour volume, 37% used combined lung minus planning target volume. The maximum dose to the spinal cord was usually (86%) used to define the limit of cord tolerance.

Planning Technique

The most common technique was three-dimensional conformal (86%). Arc therapy, tomotherapy or intensity-modulated radiotherapy were used in 14%. These therapies were used by 33% of centres.

Quality assurance of the planning process may be helped by colleague-led peer review; 51% of centres used colleague review in at least one case entered into the audit (41% of all cases).

Table 2

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>317</td>
</tr>
<tr>
<td>Average age (±standard deviation)</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>% aged ≥ 75 years</td>
<td>41%</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>56%</td>
</tr>
<tr>
<td>World Health Organization performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17%</td>
</tr>
<tr>
<td>1</td>
<td>54%</td>
</tr>
<tr>
<td>≥2</td>
<td>26%</td>
</tr>
<tr>
<td>X</td>
<td>3%</td>
</tr>
<tr>
<td>Median %FEV1 (range)</td>
<td>72% (26–164%)</td>
</tr>
<tr>
<td>Median % transfer factor (range)</td>
<td>64% (24–133%)</td>
</tr>
<tr>
<td>Medical Research Council dyspnoea score</td>
<td></td>
</tr>
<tr>
<td>0 (climbs stairs without dyspnoea)</td>
<td>14%</td>
</tr>
<tr>
<td>1 (walks any distance on the flat)</td>
<td>24%</td>
</tr>
<tr>
<td>2 (walks over 100 yd without dyspnoea)</td>
<td>18%</td>
</tr>
<tr>
<td>3 (dyspnoea on walking 100 yd or less)</td>
<td>13%</td>
</tr>
<tr>
<td>4 (dyspnoea on mild exertion)</td>
<td>1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>29%</td>
</tr>
<tr>
<td>Stage I</td>
<td>33%</td>
</tr>
<tr>
<td>II</td>
<td>15%</td>
</tr>
<tr>
<td>IIIA</td>
<td>28%</td>
</tr>
<tr>
<td>IIIB</td>
<td>24%</td>
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<tr>
<td>IV</td>
<td>0%</td>
</tr>
<tr>
<td>Missing</td>
<td>1%</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>30%</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>46%</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
</tr>
<tr>
<td>Clinical lung cancer/unknown</td>
<td>15%</td>
</tr>
<tr>
<td>Gross tumour volume size (cm³): average ± standard deviation</td>
<td>64 cm³ (±84 cm³)</td>
</tr>
</tbody>
</table>
Most planning pathways (77%) were completed within 31 days of the decision to treat. SABR treatments took longer than others to organise (51% treated within 31 days compared with 81%, \( P < 0.0001 \)).

Treatment Delivery

All treatments used some form of image-guided radiotherapy. Most patients (67%) had access to cone beam; 33% of centres did not use cone beam verification. Kilovoltage orthogonal films were used in 21% and megavoltage in 11%.

Radical NSCLC courses should not be unduly prolonged and are identified as ‘category I’ [11]. Most (94%) were categorised in this way, although four centres did not use this for any of their patients; 41% of ‘category I’ cases had their treatment prolonged longer than the recommended time. Only one patient was not seen at all during treatment. Most were seen at least once per week (91%). There was a record of toxicity in 96%. Where there was information available on anaemia assessment (73%), 71% had their haemoglobin kept above 10 g/dl.

Follow-up

Only two centres did not plan to follow up any patients; 91% of patients were followed up by the treating radiotherapist. Ninety-nine per cent of patients had their first planned follow-up within 6 weeks. Eighty-nine per cent were seen 3–4 monthly in the first year and 93% 4–6 monthly in the second year. Ninety-three per cent were offered a post-radiotherapy computed tomography scan, with 43% offered further routine follow-up computed tomography scans. Four per cent were offered follow-up respiratory function tests.

Markers of Quality

Peer review and centre activity were associated with some markers of quality, such as additional staging investigations and increased access to SABR, four-dimensional computed tomography and cone beam (Table 4).

Discussion

This prospective study aimed at providing a comprehensive picture of NSCLC radical radiotherapy in the UK. The return from centres was high, similar to that from previous Royal College of Radiologists audits [12]. Although we were reliant on recording by individual clinicians, the data fields had a high degree of completion with, for example, performance status being recorded in 97% and stage in 99%. The study ran for 2 months, to reduce the burden of data collection on centres. The demographics of the study population are similar to other reported case series from the UK [13,14], and in particular many patients are elderly and of poor performance status or functional reserve. We conclude that the current study is representative of UK practice.

We have confirmed that PET/CT staging is now routinely used in clinical practice, in line with its ability to upstage 8–24% [15]. The accuracy of PET/CT staging of the mediastinum [16] has been improved with EBUS pathological sampling [17,18]. Pathological confirmation of mediastinal lymphadenopathy is advised in addition to PET/CT staging [6], particularly if this will change the target volume. Mediastinal sampling was attempted in only 56%, predominantly with EBUS (67% of cases). As EBUS becomes more widely available, pathological confirmation of nodes may become more frequent. Cerebral metastases have been shown in 4–9% of patients considered for radical treatment [19], with a higher rate in those of more advanced disease. Twenty-two per cent of our patients had brain staging, although 38% with stage III disease were scanned. Respiratory function tests are used as a marker of the ability to tolerate radiotherapy lung damage [6]. FEV1 is a measure of gas movement, whereas KCO is a measure of diffusing capacity. Reduced KCO independently increases the risk of developing radiation pneumonitis [20]. Although FEV1 was routinely tested, KCO was recorded in 60%.

Fractionated regimens using a traditional 2 Gy fraction size are commonly used in Europe and North America. UK
departments have tended to offer hypofractionated schedules, partly due to capacity constraints and patient convenience. Hypofractionation offers the potential for delivering a radical dose within a shorter time, overcoming potential difficulties with accelerated repopulation [21]. A meta-analysis of accelerated or hyperfractionated radiotherapy showed a 2.5% improvement in 5 year overall survival [22]. Both CHART and 55 Gy/20 fractions benefit from acceleration. Although CHART was used infrequently (8% of patients), 55 Gy/20 fractions was the most commonly used regimen. As in previous studies [5,23] we conclude that 55 Gy/20 fractions has been widely adopted across the UK. This regimen has not been formally tested against 2 Gy per fraction alternatives. It has been reported in a cohort study [14], comparing favourably with CHART and in a phase II trial [24] of sequential versus concurrent chemoradiation, in which it was shown to be tolerable and with promising disease control. Further studies should formally test the relative effectiveness and toxicity of this regimen.

There was evidence of consistency of practice in outlining and setting tolerance levels for the spinal cord and lungs. There is less consistency with the heart and oesophagus, perhaps reflecting the lack of internationally agreed standards for these organs.

The quality standards for radiotherapy delivery were met, with all patients having some form of immobilisation and on-set verification, and 99% of patients having respiratory compensation. Over the past decade, technology has developed, with improved respiratory compensation techniques such as four-dimensional [25] and better set-up accuracy with cone beam image-guided radiotherapy [26]. We have shown improved access to advanced radiotherapy practices in the UK. In 2011 [5], 46% of centres described access to image-guided radiotherapy, with 50% using cone beam. In our study, 100% of patients had image-guided verification, with 66% of centres using cone beam. Twenty-eight per cent of centres in 2011 had access to intensity-modulated radiotherapy, arc therapy or tomotherapy in this study. In addition, 82% of cases were planned with a type B algorithm, which more accurately accounts for electron transport and 51% had audited their individual departmental set-up errors in line with national guidance [7]. However, access to four-dimensional CT for respiratory compensation was low (33%).

Complex processes such as radiotherapy benefit from rigorous quality assurance programmes [27]. Only 41% of treatments were assessed by a consultant-led review programme. Access to peer review was associated with other quality measures. Despite evidence that a radiologist would be helpful in the planning process [28] we found that only 4% cases had the benefit of radiologist input at the time of outlining.

A delay in treatment delivery increases the risk of disease progressing beyond the radiation field [29,30]. Most patients were treated within 31 days of decision to treat. Curative-intent courses for NSCLC delivered over a protracted time lose their effectiveness [21]. The Royal College of Radiologists recommends identifying these as Category I. Although most cases were recorded as category I, many had their treatment times prolonged longer than the recommended time.

There was a general consensus on the follow-up of patients. Most patients were planned to be seen on a 3–4 monthly basis in the first 2 years then reducing to a 6 monthly review pattern. Most patients had a post-treatment computed tomography scan and 42% had planned further routine computed tomography scanning. Respiratory function tests were not usually planned. These findings could inform a national follow-up policy.

Recruitment to clinical trials was low (3%). This may be a reflection of how few radical NSCLC studies were open in the period, given that a recent survey has shown that 74% of centres were recruiting to National Lung Cancer Radiotherapy trials [5].

High procedure volume has been linked to better outcomes for surgically treated NSCLC patients [31]. We found that a higher workload was associated with some, but not

### Table 4

**Analysis of quality by peer review and centre activity**

<table>
<thead>
<tr>
<th>Centre activity &gt; median</th>
<th>No peer review</th>
<th>172</th>
<th>25%</th>
<th>40%</th>
<th>35%</th>
<th>60%</th>
<th>17%</th>
<th>35%</th>
<th>64%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre activity &lt; median</td>
<td>130</td>
<td>33%</td>
<td>66%</td>
<td>74%</td>
<td>60%</td>
<td>19%</td>
<td>42%</td>
<td>83%</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square test 0.03 0.07 >0.0001 NS NS 0.09 0.03

Centre activity < median 58 14% 54% 15% 68% 19% 12% 40% 0.01 NS 0.001 <0.0001 <0.0001

Centre activity > median 243 30% 62% 65% 56% 17% 42% 73% 0.01 NS 0.001 <0.0001 <0.0001

KCO, corrected Transfer Factor.
SABR, Stereotactic Ablative Radiotherapy.
CRT, Concurrent chemoradiation.
CHART, Continuous Hyperfractionated Accelerated Radiotherapy.
4DCT, four-dimensional computed tomography.
ABC, Active Breathing Control.
* % of those eligible who received the treatment.
all, measures of quality. This is worthy of further study. We estimate that 8.4% of NSCLC patients are treated with radical radiotherapy in England and Wales. A previous study [32] of four Scottish centres determined that the radical radiotherapy rate varied from 1 to 9%, with an average of 4%. The rate of radical radiotherapy is less than the surgical resection rate in the UK (15% [2]), which has improved with annual monitoring and feedback to centres. Monitoring the radical radiotherapy rate would be of value.

We intend to report the reasons underpinning access to CHART, CRT and SABR in a separate paper and to assess the 2 year survival of this cohort. We would hope to examine the effect of different radiotherapy techniques on survival.

Conclusions

This audit has described current UK practice. Many patients are elderly with a significant proportion having a poor performance status and respiratory reserve. There is variability in access to the newer techniques of four-dimensional computed tomography and cone beam image-guided radiotherapy, but with evidence of increasing use. The latest recommendations for patient selection with pathological confirmation of mediastinal lymph nodes, brain staging, and respiratory function tests are not universally followed. The hypofractionated regimen 55 Gy/20 fractions is the most commonly used treatment, but is lacking in clinical trial evidence. There is consistency in practice for the assessment of organ at risk tolerance and follow-up. Efforts should be made to improve access to modern technologies and quality assurance of radiotherapy plans. Monitoring of the rate of radical radiotherapy would be welcomed.

Acknowledgements

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References


