Advanced radiotherapy techniques in stage IIIB non-small cell lung cancer

Allan Price*, Andrew Reilly, Sara C. Erridge

Edinburgh Cancer Centre and University of Edinburgh, Western General Hospital, Edinburgh, UK

With certain rare exceptions, radical chemoradiotherapy remains the treatment of choice for patients with stage IIIB non-small cell lung cancer [1,2]. However, treatment outcomes are poor, with both local and distant relapse. Failures in radiotherapy may reflect inadequate radiation dose, tumour localisation and volume definition, or accuracy of treatment delivery. Major advances in imaging and radiotherapy technology have taken place over the last 10 years which offer the chance of greatly improving these failings and the potential for dose escalation reducing the number of surviving clonogens left after radiotherapy. These changes will be described here, and the feasibility of moving on to large scale clinical trials to validate their clinical benefit discussed.

Radiotherapy dose

It is generally accepted that increases in radiotherapy dose produce improvements in local control, although the evidence for this in NSCLC is limited. A number of groups carried out radiotherapy dose escalation studies in the 1990s and early this century [3–7]. Generally, these studies escalated dose according to normal tissue complication probabilities based on irradiated lung volumes rather than specific tumour stages. Most found it easy to achieve very high doses (even above 100 Gy) for small peripheral tumours, but for larger volumes, maximum tolerated doses ranged from 60.8–80 Gy. These increased doses have never been tested in a phase III study, but multivariate analyses of one of these trials suggested that radiation dose was the only significant variable predicting improved local control and survival [8]. An RTOG trial, 0617, will compare 64 and 74 Gy involved field radiation (IFRT) and concomitant chemotherapy in patients with stage IIIA or B NSCLC.

Dose limiting toxicities at these higher doses have included late pulmonary fibrosis, bronchial stenosis [9], pericardial constriction and oesophageal strictures [4]. These toxicities have led to the development of techniques to improve the conformality of treatment, and hence reduce normal tissue volumes and morbidity, but it should be noted that some of these structures may be unavoidably included in the high dose volume.

Radiotherapy volume

After much debate on the value of elective nodal irradiation (ENI), it is generally agreed that it is unnecessary at present while local control of known sites of disease is poor, but may become more important if technical developments produce improved levels of local control [10]. Several studies have attempted to look at isolated nodal failure retrospectively [11–13], but few have prospectively omitted elective nodal fields. This was accepted as a necessary part of effective dose escalation by the Ann Arbor group [3], although this group have suggested that conformal techniques may irradiate N1 nodes to a dose which may be effective in eradicating micrometastatic disease [14]. Similarly, the dose escalation study at the Netherlands Cancer Institute omitted uninvolved nodes, and reported isolated nodal relapse in only one of 88 patients [7]. The omission of ENI was investigated formally in Maastricht [15]. They delivered radiotherapy only to the sites of disease defined by CT-PET. Three of 44 patients failed in lymph nodes outside the target volume, but two of these failed simultaneously at local or distant sites and there was only one (2.5%) isolated nodal failure. Moreover, with the omission of ENI it was possible to deliver 64.8 Gy in 36 fractions over $3\frac{1}{2}$ weeks without significant toxicity. One trial of 200 participants comparing 64 Gy ENI and 74 Gy IFRT has been reported in abstract, the latter producing improved 3 year survival (27% *versus* 19%) and reduced radiation pneumonitis (17% *versus* 29%) [16]. This is now the basis for RTOG 0617. More recently, an algorithm has been

proposed for determining the risk of mediastinal nodal involvement based on tumour site and histology, and TNM stage [17].

PET and volume definition

In addition to its use in staging, PET has been extensively explored as a means of improving target volume delineation in the planning of radiotherapy for NSCLC. Various studies have shown both an increase and decrease in target volumes, but neither correlation of PET appearances with the pathological extent of the primary tumour, nor sites of treatment failure where PET has been used to avoid areas of atelectasis [18] has been reported. A further planning study from Maastricht suggested that the use of PET-CT would reduce the target volume, the doses to organs at risk (OAR), and potentially allow an increase in target dose [19,20]. However, other studies have suggested that target volumes may also increase in some cases [21–24]. Grills [25] advocated using CT-PET fusion for contouring, which increased target volumes compared to either modality separately in 13/21 plans, reduced them in 5/21 and had no effect on size in 3/21, but also produced qualitative differences which would have resulted in significant under dosing of parts of the target volume in 8/21 plans. Other studies have also raised questions about which SUV is most appropriately used for delineating the tumour [26–29]. Significant reduction in target volume was apparent if areas of atelectasis [30] or uninvolved nodes were omitted. A further problem is the different image acquisition times of PET and CT, with significant differences in SUV between end inspiration and end expiration, and the effects of respiratory phase on SUV [31,32]. One study reported misalignments of PET and CT up to 4.5 cm without allowance for respiratory phase [33], but this was reduced by the use of 4D PET [33,34]. There is some evidence that CT-PET may reduce inter-observer variation in target delineation [24,35].

4D radiotherapy, gating and breathing control

One of the major problems of treating lung cancers is the movement of the target (and organs at risk) during and between treatment fractions. For example, Mageras [36] reported movements with respiration of >1 cm in superoinferior and anteroposterior directions, with hysteresis, and inter-fraction variation of >1 cm, while Shih [37] estimated a need for internal margins of up to 18 mm beyond the GTV. Movement of the target during respiration has led to the development of 4D radiotherapy and gating to accommodate these movements, of breathing control to reduce them, and of image-guided radiotherapy with cone-beam CT to monitor and adapt to them.

At its simplest, 4D radiotherapy, incorporating the range of movement of the tumour and normal structures throughout the respiratory cycle into the planning process to produce a fused CT image comprising the full range of the respiratory cycle, allows a new target volume which incorporates all phases of the respiratory cycle. These images may either be obtained by 'slow CT' in which the acquisition of images is obtained on one CT scan lasting the entire respiratory cycle as a single dataset, or by a series of images obtained in a variety of phases of the respiratory cycle which are then fused into a composite dataset. Alternatively, the data from these multiple phases can be used to gate treatments excluding the extremes of the respiratory cycle, by turning the beam off and hence not delivering any radiation when the target is outside the treatment volume. This gating of the target may be done with either internal fiducial markers, external markers or by predicting respiratory movements. Phantom studies have suggested the superiority of dynamic (i.e. gated) 4D treatments [38] over static (i.e. simply expanding the volume to incorporate movements) 4D treatments, but developments in patients have been more difficult. Initial studies with internal markers were successful with peripheral but not central tumours [39]. EPID-based gold-seed marker tracking has been shown possible in phantom studies [40] and commercial systems have more recently been tested in patients, albeit with a 30% pneumothorax rate for seed insertion [41]. Uncomplicated treatment times were about 20 min and patient repositioning possible. Monitoring of respiratory movement using external markers may be feasible [42–45], but introduces yet another variable, the accuracy and reproducibility of placement of the external monitor, which may not be an ideal surrogate for internal tumour movement and may still be limited if target movement is rapid (e.g. during cough) or highly irregular. Finally, simply predicting the position of the tumour based on assumptions of the regularity of the breathing cycle may also introduce errors because breathing is inherently irregular, especially in the many patients with lung cancer who also have chronic obstructive pulmonary disease. Incorporating movement of tumour and OAR into planning also creates problems because the electronic dose disequilibria which occur at air-soft tissue interfaces will also move. Monte Carlo dose calculations are superior to collapsed cone or pencil beam

algorithms for these added levels of complexity [46], but may not be universally available in all centres using 4D or gated techniques. Despite these limitations, gating may be superior to free techniques in most situations [47]. Underberg [48] reported that gating reduced the volume of lung receiving 20 Gy (V_{20}) and hence the risk of pulmonary toxicity, particularly for middle and lower lobe tumours.

Breath holding protocols have also been investigated [49]. These usually involve coaching of and feedback to the patient by radiation technologists before and during treatment. The phase chosen for breath holding does not seem to affect the risk of toxicity greatly, although favouring end inspiration [50]. Deep inspiration breath holding (DIBH) with feedback techniques appears reliable and reproducible [49] although some protocols have favoured patient control without feedback [51,52]. However, not all patients are able to cooperate with these techniques. Some dosimetric studies have suggested breath holding reduces irradiated normal lung volumes. They may be particularly useful for lower lobe tumours, where diaphragmatic excursion up to 5 cm has been reported [53]. Gagel [54] used active breathing control to reduce breath volume, and managed to limit inter-fraction displacements of the diaphragm, the structure which appeared most mobile in their study, to 3–5 mm. Again, Monte Carlo dose calculations appear useful with DIBH [55].

Predictive models of tumour position may be valid when based on daily inter-fraction imaging, although there were patients in whom predicting the tumour position was not possible in these studies [56,57]. Sharp [58] found that prediction was useful in the early stages of a fraction when an initial respiratory history could be extrapolated to succeeding breathing cycles, but they did not test whether this would be feasible for the whole duration of a gated IMRT treatment. Again, while problems remain with these systems, they appear better than currently used techniques. However, none take into account the effect of cardiac movement on the tumour.

Jiang [59] has extensively reviewed this area. The major problems remain the reliability of external tracking given that seed insertion for internal tracking has not been possible with central tumours, and the excessive treatment times (>30 min) with gated IMRT.

IMRT

IMRT uses the multi-leaf collimator to modulate the radiation fluences across the target volume, allowing a gradient of doses to be given to the target volume. This can be used either to accommodate sites where a different dose is required (for example potential microscopic nodal disease rather than known tumour) or with multiple beams to improve conformality and reduce normal tissue doses. This may both reduce doses to OAR and offer the opportunity for dose escalation. Grills [60] reported IMRT reduced doses to OAR by 15–40% and increased target doses by 25–30% compared to 3D-CT planned RT. Murshed [61] found a 7–10% reduction in lung V_{10} and V_{20} but slight increase in V_5 and the spinal cord maximum with IMRT compared to 3D CTRT. Christian [62] reported that IMRT plans using 5, 7 or 9, but not 3, coplanar beams or 6 non-coplanar beams, improved the percentage of the planning target volume (PTV) receiving 90% of the prescribed dose and reduced the volume of lung receiving 20 Gy compared to 3D-conformal plans. Planning studies by Chapet [63,64] reported reductions in doses to oesophagus and heart with IMRT without compromising lung doses. However its use in the thorax is complicated by respiratory movement. Yom [65] reviewed the MD Anderson experience of conformal and intensity modulated concomitant chemoradiotherapy in patients with locally advanced NSCLC. In 68 patients treated with IMRT the GTV (194 mls) was bigger than in the 222 treated with conformal radiotherapy (142 mls), but the risk of CTCAE v3.0 grade 3 or greater pneumonitis was substantially lower (8 [95% CI 4–19]% *versus* 32 [95% CI 4–19]%). They were unable to identify dosimetric parameters which indicated an increased risk of lung injury, although they suggested that a V_5 >70% might be important. This contrasts with the experience in patients with mesothelioma treated post-operatively, where increased toxicity has been reported with IMRT compared to conventional techniques [66]. The dosimetric comparisons are very difficult because of the high doses to the ipsilateral lung in patients with lung cancer, and the possibility of underlying interstitial lung disease related to asbestos exposure in the mesothelioma group has not been explored. However, it is noteworthy that the median V_5 in the Boston series was greater than 90%, but only 63% in the patients receiving IMRT at the MD Anderson.

Hugo [67] showed IMRT delivery with target motion significantly altered the delivered dose distribution in relation to the planned distribution. The use of gating for imaging, planning, and delivery significantly reduced the errors introduced by object motion. Duan [68] reported that variations in doses to points in individual treatments induced by respiratory movement might even out over fractionated

treatments. Schwarz [69,70] suggested that dose could be significantly increased by IMRT, particularly if inhomogeneity in the plan was accepted, but that this would necessitate simulating the effect of geometrical uncertainties as part of the planning process. However, Vedam [71] found that even for response times as short as 0.6 s between the acquisition of tumour position and multileaf collimator response, dosimetric errors due to respiratory prediction could approach delivery errors when respiratory motion was not considered, and that better predictive models and/or shorter response times were required. As with 4D RT, breath holding might be an alternative to gating, with potential for dose escalation [72].

IGRT

IGRT is the use of on-line imaging, usually with kilovoltage cone-beam CT on the treatment machine, to monitor target position. The aims of IGRT were summarised by Lefkopoulos [73]: 4D imaging for modelling the intra-fraction organ motion; integrated imaging systems or devices registered to the treatment machines for inter-fraction patient localization; and treatment planning and delivery schemes incorporating the information derived from the new imaging techniques. The scan is usually taken before the fraction rather than during, and again may rely on prediction of target position in relation to radiation portal rather than real-time tracking of the target and correction of set-up. Most work in the thorax has focused on peripheral stage I lesions rather than central stage III disease (e.g., ref. [74]), because of poor localisation of mediastinal structures. A megavoltage cone-beam CT (MVCBCT) system has been described [75]. It has not been compared with kilovoltage systems, but one group felt image quality was inadequate for mediastinal structures [76]. Ramsey [77] reported the use of an MVCBCT to allow the PTV to be shrunk weekly, although they did not describe the rate or sites of relapse. The doses to OAR were reduced in consequence. Bortfield [78] analysed whether the use of different fraction sizes at specific points from day to day in adaptive radiotherapy had any harmful effect, but concluded this was probably negligible if the standard deviation of dose was less than 10%. Sonke [79] described a method of overcoming the lack of gating of CBCT images and produced a 4D CBCT data set in both phantoms and three patients. The image quality was still degraded by irregular breathing, but much less so than with 3D scans.

Protons

Protons differ in their interactions with tissues from photons, depositing energy over a narrow range in Bragg peaks which allow for much more precision (sculpting) of dose delivery in planning, but also potentially more variation when set-up errors and target movement come into play. Shioyama [80] reported 70% 2 year but 0% 5 year overall and cause-specific survival for nine patients with stage III or IV NSCLC treated with protons. Sites of failure were not reported. Muruyama [81] reported 100% local control using proton therapy for the 15 people with NSCLC included in their series of 125 patients. Only reversible grade 2–3 toxicities were seen. Chang [82] compared dose volume histograms for 3D-CRT and proton plans. The lung volumes receiving doses of 5, 10 or 20 Gy (V_5, V_{10}, and V_{20}) were lower with protons, even with a 17% increase in prescribed dose, and spinal cord, heart, oesophagus, and integral dose were all lower. Paganetti [83] reported that dose gradients were more rapid with 4D proton planning, but Monte Carlo calculations were useful. Having previously shown the substantial under dosing caused by respiratory movement in proton treatments, with equivalent uniform doses (<60% of the prescribed dose in some situations [84]), Engelsman [85] examined 4D planning for proton treatments, and, as with photons, reported a significant improvement in target coverage, and reduction in dose to normal lung.

Planning systems

Mention has been made above of the superiority of Monte Carlo calculations for photons and protons when 4D treatment and IMRT are used, particularly at sites of electronic disequilibrium such as soft tissue air interfaces [46,55,83]. Vanderstraeten [86] reinforced this. Jang [87] compared two commonly used commercial planning systems (Pinnacle and Corvus) and found good agreement with Monte Carlo calculations in high dose regions, but less good in low dose regions (i.e. OAR) where dose was underestimated. A commercial Monte Carlo based planning system for lung stereotactic radiotherapy is likely to be introduced soon.

Trials and the future

Much of the development described here has been technology driven, and aimed at proving feasibility rather than defining which methods and systems are best, and whether they produce real clinical benefit

rather than simply improved radiotherapy treatment plans. The current evidence strongly suggests that they do represent an improvement, albeit incomplete, over 3D techniques.

Comparing the new technology with existing 3D protocols will be much harder than comparing different drugs, simply because radiotherapy departments tend to develop along fixed paths related to their preferred equipment supplier, which may be very difficult to change. Each system tends to entail large financial outlays, both in initial capital for equipments and buildings and in the subsequent set-up procedures, which make moving from one system to another difficult, particularly for experimental purposes in clinical trials rather than established service uses. Consequently, different departments may have very different technologies for achieving broadly the same ends. Accordingly, the appropriate clinical trial may be to compare maximum use of new technology, including PET for planning, 4D and gated systems, IMRT and IGRT at conventional and escalated dose levels *versus* old technology without any of these systems, at the highest dose possible. While some investigators will doubtless argue it would be unethical not to use the new technology, the very large additional costs, both of time and money, for health care systems, and the considerable increase in potential for treatment errors mandate obtaining evidence that these changes are worthwhile. If the differences in doses delivered to normal tissues, and possible increases in target doses, are as large as the available evidence appears to indicate, these may not need to be large studies.

Conflict of interest statement

None declared.

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