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Authors: Andrew Hudson, Clara Chan, David Woolf, Alan McWilliam, Crispin Hiley, James O'Connor, Neil Bayman, Fiona Blackhall, Corinne Faivre-Finn

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Is heterogeneity in stage 3 non-small cell lung cancer obscuring the potential benefits of dose-escalated concurrent chemo-radiotherapy in clinical trials?

Andrew Hudson[a,b], Clara Chan[b], David Woolf[b], Alan McWilliam[a], Crispin Hiley[c], James O'Connor[a], Neil Bayman[b], Fiona Blackhall[a,d], Corinne Faivre-Finn[a,b]

[a] Division of Molecular and Clinical Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

[b] Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

[c] Translational Cancer Therapeutics Laboratory, The Francis Crick Institute, London, UK; Division of Cancer Studies, King's College London, London, UK

[d] Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Highlights

- A review of concurrent chemoradiotherapy in stage 3 non-small cell lung cancer
- Recent trial data suggests a detriment to dose-escalated radiotherapy in this setting
- Large degree of heterogeneity in patient, tumour and clinical factors between cases
- Heterogeneity may be limiting the ability to detect benefits of doseescalation
- Technology advances may better stratify cases and allow safer doseescalation

Abstract

The current standard of care for the management of inoperable stage 3 non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (cCRT) using radiotherapy dose-fractionation and chemotherapy regimens that were established 3 decades ago. In an

attempt to improve the chances of long-term control from cCRT, dose-escalation of the radiotherapy dose was assessed in the RTOG 0617 randomised control study comparing the standard 60Gy in 30 fractions with a high-dose arm receiving 74Gy in 37 fractions. Following the publication of this trial the thoracic oncology community were surprised to learn that there was worse survival in the dose-escalated arm and that for now the standard of care must remain with the lower dose. In this article we review the RTOG 0617 paper with subsequent analyses and studies to explore why the use of dose-escalated cCRT in stage 3 NSCLC has not shown the benefits that were expected. The overarching theme of this opinion piece is how heterogeneity between stage 3 NSCLC cases in terms of patient, tumour, and clinical factors may obscure the potential benefits of dose-escalation by causing imbalances in the arms of studies such as RTOG 0617. We also examine recent advances in the staging, management, and technological delivery of radiotherapy in NSCLC and how these may be employed to optimise cCRT trials in the future and ensure that any potential benefits of dose-escalation can be detected.

The standard of care in inoperable stage 3 non-small cell lung cancer (NSCLC) is concurrent chemo-radiotherapy (cCRT) [1]. Despite recent technological advancements, the currently used radiotherapy dose fractionation and chemotherapy were devised over 30 years ago [2]. The majority of patients with stage 3 disease treated with cCRT will eventually progress, translating into survival rates at 5 years of 20-30% at best [1,3]. A strategy to potentially improve local control is to escalate the dose of radiation delivered to the tumour. Martel et al demonstrated a clear dose response relationship in NSCLC, with 84Gy using conventional fractionation being required to get 50% probability of tumour control at 3 years [4]. Following this a number of early phase studies have investigated the concept of dose-escalation and concluded that radiation doses of 74Gy in 37 fractions can be delivered concurrently with chemotherapy using strict dose volume constraints for the organs at risk [5–8]. However the concept of dose-escalation as a strategy to improve outcome in stage 3 NSCLC is challenged by the surprisingly negative finding of the RTOG 0617 trial in which dose-escalation with cCRT to 74Gy in 37 fractions led to worse survival compared to standard of care (60Gy in 30 fractions) [9].

The following article is not a systematic review. It is intended to stimulate discussion regarding the disappointing results of RTOG 0617 and to offer solutions on how to improve future radiotherapy trials in locally advanced NSCLC. We aim to appraise the recent literature on cCRT since the publication of our previous review on this topic in 2014 and to identify research direction to optimise and intensify cCRT [3]. A recurring theme throughout this piece is the problem with heterogeneity in stage 3 NSCLC and its consequences for the results of randomised controlled trials in this field. Heterogeneity is defined as diversity between cases of a certain characteristic and in the case of stage 3 NSCLC may refer to patient and tumour related differences in burden of disease, anatomical location, histological subtype, and tumour and host genomics. In terms of tumour genomics, heterogeneity exists at an inter-patient, intra-patient, or intra-tumoural level, however we shall focus on the

former. Additional 'external' sources of heterogeneity refer to differences in radiotherapy technique, quality assurance (QA), diagnostic radiology, and technology. Table 1 summarises sources of heterogeneity and how they can impact on trial results. We propose that in recent trials heterogeneity of stage 3 NSCLC has been a major and overlooked confounder in the analysis and clinical interpretation of the findings. We highlight solutions that are currently being employed to exploit technological advances in diagnostics, radiotherapy planning, and treatment delivery that may enable improved outcomes through allowing for heterogeneity and individualisation of treatment.

Current standard of care in inoperable stage 3 NSCLC

Following the failure to demonstrate the superiority of 74Gy in 37 fractions in RTOG 0617, the standard of care for inoperable stage 3 NSCLC patients with good performance status remains 60Gy in 30 fractions of 2Gy concurrently with chemotherapy. This dose is based on a study from 1980 that found 60Gy (2Gy/fraction) to be more efficacious than lower doses in terms of local control and survival [10]. Over the following 3 decades trials have persistently demonstrated the additional benefit of chemotherapy both sequentially and ultimately concurrently for patients with stage 3 disease [11]. The optimal chemotherapy regimen is unknown with a number of different platinum doublets being used based on studies from the 1990's [3]. Recent gains in the management of stage 4 NSCLC have not translated to benefits in the management of stage 3 disease. For example, despite the superiority of pemetrexed with cisplatin in the management of metastatic non-squamous NSCLC [12], a study of non-metastatic disease failed to show superiority of the same regimen over etopside / cisplatin when given concurrently in stage 3 non-squamous disease [13]. Furthermore, tyrosine kinase inhibitors successfully used in stage 4 disease against genetic targets, such as epidermal growth factor receptor (EGFR) [14], are not used in the stage 3 setting regardless of the driver mutation (although work is on-going to detect any potential

benefits) [15][16](ClinicalTrials.gov:NCT01822496). Therefore most centres are using regimens that have barely changed over the last 30 years. Advances in radiotherapy delivery, quality assurance (QA), staging and supportive healthcare have enabled improvements in survival for this cohort of patients [17]. However it remains that cCRT for stage 3 NSCLC is currently given in a 'one size fits all' basis despite great variability in the clinical and pathological features of this broad group of patients.

Staging and anatomical heterogeneity

The American Joint Committee on Cancer (AJCC) staging for stage 3 NSCLC is presented in Figure 1A [18]. Stage 3 encompasses a diverse spectrum of clinical presentations. It can refer to a small peripheral primary with chest wall involvement and solitary hilar node or a large 10cm tumour centrally located invading the mediastinum with diffuse mediastinal and supraclavicular lymph node involvement (Figure 1B). Such diverse presentations are because the TNM classification was primarily created to stratify the operability of lung tumours based on organ involvement and size. Technological advances in non-surgical therapies are not adequately accounted for. A number of studies of non-surgical radical patients show superior prognostic factors to the TNM system. For example, a single institution study of 270 NSCLC patients treated with radical radiotherapy found that overall gross tumour volume (GTV) and number of positive lymph nodes on PET was a better predictor of prognosis than TNM staging [19]. The importance of GTV as a prognostic factor has been demonstrated since [20–22], yet patients in the RTOG 0617 study were not stratified for GTV volume. Limitations of TNM staging are demonstrated for surgical patients, and most marked for the N-stage [23]. In N2 disease the number of nodal stations involved is a poor prognostic factor for survival in a multivariate analysis of patients undergoing surgery [23]. In a study of 702 patients the 5-year overall survival (OS) for patients with radiologically undetectable nodes subsequently confirmed after surgery, was 35% versus

13% for one compared with more than one lymph-node station involved. A further study has demonstrated that in N1/2 disease the number of lymph nodes positive at surgery is a better predictor for survival than AJCC nodal classification [24]. In non-surgical cases a study of 148 inoperable IIIA-N2 patients showed that outcome from cCRT correlated better with the Japanese Nodal Classification [25] [26]. This classification uses the primary tumour location to stratify N2 nodal positivity into limited and extensive groups based on the specific lymph node stations involved. In this study both progression free survival (PFS) and OS were significantly better in IIIA-N2 patients with limited nodal disease [26]. In RTOG 0617 patients were stratified to achieve a similar proportion of IIIA to IIIB in both treatment dose arms but the aforementioned data suggests that this is not sufficiently robust to ensure balance for prognostic stage and the risk of occult metastatic disease. The rationale for dose-escalation studies is that a higher radiotherapy dose will improve local control and thereby improve survival. The question then is whether the failure of dose-escalation strategies to date is due to a potential imbalance of inclusion of patients that are at high risk for occult metastasis at presentation? In both arms of RTOG 0617 one third of patients relapsed with clinically or radiologically detectable metastatic disease within 12 months of treatment. Given that local relapse is difficult to confirm radiologically (due to post radiotherapy fibrosis) the most reliable endpoint to detect treatment failure is OS and an imbalance of risk of metastatic disease based on nodal stage could skew results.

The large volume of the lungs within the thorax creates a wide variation in the location of tumours with regard to proximity to critical organs such as the heart. In RTOG 0617 the heart dose was higher in the high dose arm and a multivariate analysis of the survival data for all patients in the study revealed that higher heart V5 and V30 were associated with poorer survival [9]. In another study of 333 radical radiotherapy plans the heart was re-contoured according to RTOG 0617 guidelines and on multivariate analysis heart V50 was one of the variables associated with poorer survival [27]. When stratified by V50 heart dose

less than 25% versus 25% or greater the 2-year OS rates were 45.9% versus 26.7%. A data mining approach at our institute used the collation of approximately 1000 NSCLC radical radiotherapy plans to identify irradiated anatomical regions associated with poorer survival [28]. The plans were deformed to a reference and dose distributions compared to map dose differences between survivors and non-survivors at different time points. This identified a dose differential centred over the aorta and the origin of the left coronary artery with a 6Gy differential between survivors and non-survivors at 12 months and a 6 month survival difference between patients receiving above or below 20.2Gy to this critical region. Most recently an analysis was performed on all dose-escalated NSCLC patients (receiving between 70 and 90Gy) treated in trials of the Eastern Cooperative Oncology Group between 1996-2007 [29]. In the 112 patients reviewed, 26 (23%) had one or more cardiac events following dose-escalated radiotherapy with a median of 26 months to first event. On multivariate analysis, cardiac radiotherapy dose was significantly associated with the occurrence of cardiac events with 2-year risk-adjusted event rates of 4%, 7%, and 21% for mean heart dose <10Gy, 10 to 20Gy, and >20Gy respectively. Interestingly in this study heart doses were not associated with overall survival. RTOG 0617 did not stratify patients for tumour location so imbalances in this variable between the two dose arms may have contributed to the poorer outcomes seen with dose-escalation. In addition to the heart, proximity to other critical structures such as the spinal cord and brachial plexus, as well as overall dose to the lungs themselves, may limit the dose deliverable to the tumour and prevent dose-escalation. It is also important to consider the degree of respiratory motion present as there is variability depending on the location of the tumour in the lung with a higher degree of motion affecting lower lobe tumours [30][31]. A higher proportion of lower lobe tumours in one arm of a study may increase the incidence of geographic misses to worsen the outcome.

Diagnostic heterogeneity

Heterogeneity in diagnostic radiology between centres can affect trial outcome interpretation in two categories, pre-treatment staging determination and post-treatment recurrence detection. The last decade has seen the introduction of FDG PET-CT into routine clinical practice for the staging of potentially radically treatable NSCLC. PET-CT increases the detection of nodal and metastatic disease to reduce the incidence of occult metastatic disease in staging groups [32]. Using PET data in radiotherapy planning improves target volume delineation and reduces inter-clinician delineation variability [33]. Pre-treatment PET scanning was similar for both groups in RTOG 0617 (89% for high-dose arm vs 91% for low-dose arm). Recognising the high rate of false-positive PET reports, endobronchial ultrasound (EBUS) is now used in routine clinical practice for the staging of stage 3 NSCLC. Given the high risk of brain metastases in stage 3 NSCLC, brain imaging is the standard of care for patients considered for cCRT in many centres. Heterogeneity exists between centres in the modality of brain imaging used with CT, MR, and thin-slice MR available. Neither EBUS nor brain imaging usage was standardised in studies such as RTOG 0617 causing a potential imbalance of stage of disease in different dose arms.

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Genetic and histopathological heterogeneity

Due to the carcinogenic effect of cigarette smoke, lung cancers have one the highest mutational burdens of any cancer [34]. Therefore mutational drivers of lung cancer are heterogeneous and known therapeutically targetable drivers such as EGFR, EML4-ALK and ROS1 affect only a small proportion of cases, particularly in smokers. In one study patients with tumours harbouring activating mutations in EGFR who receive cCRT have longer local control and fewer local relapses than those without activating EGFR mutations [35]. Conversely another study found that patients with hotspot KRAS mutations had shorter median relapse-free survival and poorer response rates following cCRT [36]. Another interesting but unexplained observation is that maintenance gefitinib (EGFR tyrosine kinase

inhibitor) in molecularly unselected post cCRT patients gave worse survival [15]. Therefore there is much to learn about the molecular determinants and mechanisms of radiosensitivity and normal tissue toxicity. While randomisation may dilute varying radiosensitivity and tumour molecular characteristics, more precise molecular classification to stratify patients needs to be a major focus of future trials. In RTOG 0617 the addition of the EGFR inhibitor (cetuximab) to cCRT did not confer any survival benefit [9]. No prospective genetic stratification occurred although a planned retrospective analysis suggested that patients with high EGFR expressing tumours might receive a survival benefit with cetuximab (42.0 vs. 21.2 months median OS, p=0.032) as opposed to patients with low EGFR expressing tumours that might do worse with cetuximab (19.5 vs. 29.6 months median OS, p=0.056). In RTOG 0617 patients were stratified for histological subtype and no subtype was associated with a better survival on multivariate analysis. However, stage 4 chemotherapy NSCLC trials have demonstrated that there is a difference in response to chemotherapy regimens based on histological subtype [12]. Data from cone-beam CT imaging that verifies the accuracy of radiotherapy delivery during treatment suggests a correlation between rapid shrinkage and poorer outcome for non-adenocarcinoma but not rapidly shrinking adenocarcinoma histology in patients receiving cCRT [37]. Furthermore, histopathological evaluation of surgical specimens indicates that a larger clinical target volume (CTV) may be required for adenocarcinoma compared to squamous to ensure adequate coverage of microscopic disease [38]. Therefore, whilst there is currently no robust data to claim that different histological subtypes have different outcomes to cCRT, future trials should be designed to ensure adequate power for known molecular and histological subtypes.

Radiotherapy heterogeneity

Within the same dose-fractionation, the delivery of radiotherapy varies greatly between centres regarding technology used, target volumes, organs at risk (OAR) tolerances, set-up

protocols and care throughout treatment. Within departments, where the above variables are expected to be constant, there is often great variability between clinicians in terms of target delineation [39]. Therefore radiotherapy for stage 3 NSCLC is delivered in a very heterogeneous manner that could confound trial results. The simplest intervention is to introduce radiotherapy QA into the trial protocol so that the same planning methods, OAR tolerances and target volumes are used between participating centres. This was done to some extent for RTOG 0617 (OAR constraints were recommended but not mandated) and in NCT00686959 (evaluating different chemotherapy regimens in cCRT) but radiotherapy QA has been lacking for other major studies. In RTOG 0617 patients were recruited from 185 centres with a median of only 2 cases per centre. Despite a QA protocol for RT planning and delivery there was significant disparity between the two dose arms with a significantly higher rate of protocol non-compliance (26% vs. 17% p=0.02) in the high dose arm [9]. Also treatment delays were longer and contouring was poorer in the high dose arm. These disparities could be explained in part by inexperience with the higher dose in centres with a low volume of patients. The authors of RTOG 0617 highlighted the potential effects of using a large number of participating centres by publishing subsequent analysis of the RTOG 0617 data along with data from the phase I/II dose-escalation study [40][41]. Separating outcomes into those treated at low volume centres (LVC – 3 or less patients enrolled) and high volume centres (HVC – more than 3 patients) revealed that patients from the HVCs had statistically superior OS, PFS and mean heart dose [40]. In data from the early phase dose-escalation study there was a very high median survival for stage 3 patients (39.8 months) suggesting benefit to dose-escalation [41]. The discrepancy of this result compared to the larger subsequent phase III trial was attributed to lower heart doses and also plans being double checked by experienced staff to ensure protocol compliance in the smaller phase I/II study [41].

Data from an unplanned subset analysis of the RTOG 0617 patients whose RT treatment plans were compliant to the planning and contouring protocol showed the detriment of dose-escalation on survival remained. Examining the protocol reveals permitted variations in radiotherapy planning between centres. There is flexibility in the GTV to CTV expansion, allowing 0.5-1.0cm. Secondly, to allow for challenging critical structure geometry, the prescribed dose was allowed to cover as little as 90% of the PTV. Finally the heart was ranked lowest (behind spinal cord, lungs, oesophagus, and brachial plexus) in terms of priority for meeting normal tissue dose constrains and the limits to the heart (60Gy to <1/3, 45Gy to <2/3, and 40Gy to <100% of the heart) are relatively high and not mandatory. In addition it has been shown elsewhere that despite detailed contouring protocols there is still significant inter-clinician variability in contouring target volumes in NSCLC [42].

Clinical trials across multiple institutions over long time periods must account for changes in the technology used to plan or deliver the radiotherapy. The last decade has seen a shift from a 3D conformal approach (3DCRT) to the use of Intensity Modulated Radiotherapy (IMRT). Stratification occurred in RTOG 0617 to give equal numbers of 3DCRT and IMRT in the treatment arms. A subsequent analysis showed no difference in OS or local control between the two techniques although patients treated with IMRT had larger PTVs, more stage 3B disease, and worse socioeconomic demographics [43]. It was proposed that as IMRT and 3DCRT had similar outcomes the use of IMRT might have mitigated against these potential negative impacts on survival. It was also found that IMRT patients had lower heart and lung doses, fewer grade 3 pneumonitis episodes, and better quality of life post treatment [43][44]. No prospective randomised datasets demonstrate a survival benefit of IMRT over 3DCRT although some retrospective series support the finding that IMRT offers equivalent survival for poorer prognosis tumours and reduces normal tissue irradiation. A recent retrospective analysis of 7492 stage 3 NSCLC patients treated between 2003 – 2011, of which 10% received IMRT, showed a small but significant advantage in OS versus non-

IMRT treatments [45]. The availability of IMRT may influence the clinical decision of whether or not a curative dose of cCRT can be safely delivered. The stratification of IMRT and 3DCRT in RTOG 0617 prevented bias in this regard. An emerging technology is four-dimensional CT (4DCT) radiotherapy planning that takes account of the motion of the tumour in the respiratory cycle to prevent geographical misses. Like the advanced technologies that preceded it, there is currently variation in the use of 4DCT between centres. There is also heterogeneity between 4DCT centres regarding methods used for reconstruction of the imaging data and the protocols used for image acquisition.

Clinical response heterogeneity

There is conflicting data on the prognostic value of tumour shrinkage during and immediately post-cCRT for stage 3 NSCLC. In one retrospective study the GTVs pre-treatment and 1-month post-treatment, as assessed by CT, were analysed for 157 patients [21]. This showed, in concordance with previous studies, that patients with smaller pre-treatment GTVs had better survival. However they also found a trend to worse OS with a larger volume reduction ratio (indicating better short-term response to treatment) in a multivariate model ($p=0.075$) [21]. Another study of 99 patients undergoing RT and cCRT supported this finding using an automated analysis of tumour regression on cone-beam CT scans during treatment to show that pronounced tumour regression was associated with worse loco-regional control and OS [37]. Conflicting data from another study shows better survival in patients with greater tumour regression on cone-beam imaging during cCRT [46]. Differences between all 3 studies may account for the conflicting results such as assessment time points, patient demographics, and method of tumour measurement. However it is clear that the era of cone-beam treatment imaging has revealed heterogeneity between tumours regarding early response to cCRT and further work may identify those patients more likely to benefit from treatment intensification such as dose-escalation. Weight loss throughout treatment may

also indicate those patients with a poor prognosis. This was initially described in stage 3 patients receiving cCRT who lost weight between the first and last day of treatment with inferior OS and PFS in patients whose body mass index reduced by 0.5kg/m2 over this time [47]. Early weight loss (5% loss between the start and third week of radiotherapy) is also associated with a significantly poorer OS [48]. In this study all patients were weight-stable prior to the commencement of cCRT and received weekly dietetic support. The weight loss group had similar toxicities, chemotherapy doses, and GTVs so the mechanism for poorer outcome is not known. However it appears the detriment associated with early weight loss is not merely a surrogate for locally advanced disease or de-escalation of treatment. Further work is required before early weight change can be used as clinical biomarker but in the future this observation may guide decisions regarding dose-escalated treatment.

Determination of local relapse post-radiotherapy for lung tumours is notoriously difficult even for experienced radiologists due to fibrotic changes caused by radiation. In one study of 50 patients who received hypofractionated lung radiotherapy, 20 patients had abnormalities deemed suspicious for recurrence (at a median of 20.7 months) yet only 3 of those were proven to have recurred on further follow-up [49]. Most data on the challenges associated with radiotherapy response assessment come from hypofractionated studies where increased dose per fraction appears to enhance the fibrotic and inflammatory response [50]. The effect of dose-escalation on severity of fibrosis is not quantified and it is possible that the high incidence of local recurrence reported in some studies could be a consequence, at least in part, of misinterpretation. This effect could be compounded by the aforementioned heterogeneity in participating institutions of RTOG 0617 in which radiologists may have misinterpreted CT scans as showing local recurrence. Data suggests that differing radiotherapy techniques can influence the appearance of fibrosis, adding further potential heterogeneity between centres [51]. The use of PET scanning may be beneficial to

distinguish fibrosis from recurrence [52], but again heterogeneity in its use between centres is problematic for the interpretation of trial results.

Currently available solutions and future directions

Despite the disappointing results of RTOG 0617, a number of studies are currently evaluating treatment intensification in stage 3 NSCLC. As things stand currently there are 2 key questions. Firstly is there enough evidence of a potential benefit to dose-escalation in stage 3 NSCLC cCRT to justify further trials? Secondly how could these new trials be optimised to ensure a benefit (or conclusive negative result) is detected? Regarding evidence of potential benefit from dose-escalation, the justification for RTOG 0617 was based upon radiobiological calculations that dose-escalation should improve outcome in stage 3 NSCLC [4]. Following RTOG 0617, the publication of initial early phase data showing a benefit of dose-escalation and the identified shortcomings of the original phase III trial justify further exploration of dose-escalation, but employing individualised regimens rather than a single fixed dose based on 2Gy per fraction [41]. The question of how to optimise further trials is more complex as the sections above have illustrated the factors that make stage 3 NSCLC such a heterogeneous group. Unless these factors are controlled for in phase III trials then there is a risk they could compromise trial results as suggested by subsequent analyses of RTOG 0617. Table 1 summarises potential solutions available to limit the effects of heterogeneity in NSCLC. Some of these solutions are based upon current evidence and could be implemented immediately whereas some are based upon promising technologies in development that are yet to be proven beneficial. Strategies such as isotoxic radiotherapy, functional boosting, and adaptive techniques all aim to improve survival through superior local control via dose escalation whilst limiting normal tissue dose. Others are solutions that may be employed to better balance trial arms for risk of metastatic disease and prognosis and enhance the ability to demonstrate benefit.

Regarding measures that could be made immediately an important starting point is to determine what stages of disease should be included in future trials and whether stratification by AJCC staging should be replaced by other variables such as total GTV. Similar considerations may be made regarding the anatomical location of tumours such as tumour centrality. Other immediately available measures are enhancing QA and protocols, regulated use of different technologies, and centralising aspects of the trial such as diagnosis of relapse or plan review.

Current technology allows approaches that permit the heterogeneity of NSCLC to be embraced in treatment planning to produce individualised escalated doses with the aim of improving local control. Isotoxic radiotherapy aims to increase the tumour dose by allowing an individualised dose prescription of radiotherapy that can be escalated up to a maximum as long as OAR dose tolerances are not exceeded. An in silico exercise found that a twice-daily accelerated radiotherapy regimen with total dose determined by an individualised maximal tolerated dose led to superior tumour control probability to standard dose fractionations [53]. An early phase feasibility study showed accelerated individualised dose prescriptions allowed escalated doses to be safely delivered to the tumour (no excess toxicity and comparable survival) [54][55]. The original study used 3DCRT so 2 further studies have been conducted in the UK (ClinicalTrials.gov:NCT01836692) and the Netherlands (ClinicalTrials.gov:NCT01166204) using IMRT alongside 4DCT planning and image guided radiotherapy techniques with the hypothesis that these technologies will allow safe dose-escalation to the tumour without breaching OAR tolerances [56].

Combining functional imaging data may identify regions of tumours that will benefit from a dose-escalation boost to improve local control. Using imaging pre and post-radiotherapy it

was shown that residual PET avid areas post-treatment correspond to poorer prognosis and these areas correspond to regions on the pre-treatment scan with the highest avidity [57][58]. A phase II randomised trial investigated the feasibility of delivering dose-escalation to PET avid regions and demonstrated it is possible to boost dose to PET avid lesions to 86.9 +/- 14.9Gy without excess OAR dose [59]. Another phase II trial has demonstrated favourable local control and survival using a mid-treatment PET-CT scan to give escalated doses to residual tumour [60]. This approach is now being evaluated in a phase 3 trial using PET scanning midway though the radiotherapy course and either continuation to conventional 60Gy in 30# or adaptive planning with dose-escalation to PET avid regions up to a total of 80.4Gy in 30# (RTOG 1106). [18F]-Fluoromisonidazole (F-MISO) is a tracer used in functional imaging to identify areas of hypoxia [61]. A phase II study has been performed using F-MISO imaging to identify areas to deliver dose-escalated boost resulting in doses of up to 86Gy [62]. In this study there was no reported extra toxicity with dose-escalation and, whilst it concluded that dose-escalation could not reverse the poor prognosis of F-MISO positive patients, further work is required to see if dose-escalation to hypoxic regions is beneficial. Using other advances trials are assessing the benefits of dose-escalation to peripheral primaries using hypofractionated SBRT whilst delivering conventional fractionated radiotherapy to mediastinal lymph nodes (ClinicalTrials.gov:NCT01933568).

Adaptive radiotherapy may improve the accuracy of radiotherapy delivery, ensuring that geographical misses and OAR doses do not dilute the benefits of dose-escalation. In the LARTIA trial patients undergoing cCRT for stage 3 NSCLC received weekly CT scans and were re-planned if there was tumour shrinkage [63]. Re-planning was performed in 50 of 217 patients with 42% average reduction of CTV between initial planning and re-planning CTs. Compared to historical data the re-planned patients had lower pulmonary toxicity. The infield (within re-planned CTV) and marginal (within initial but not re-planned CTV) relapses were

20% and 6% respectively suggesting that routine re-planning of shrunken CTVs is safe to reduce toxicity and allow the dose-escalation to tumours in proximity to critical regions that shrink significantly during treatment. It is hoped the use of linear accelerators with integrated MR imaging will allow enhanced adaptive radiotherapy and the superior conformality of protons may allow dose-escalation to central regions whilst keeping OAR doses within tolerance [64].

Looking to future technological advancements it may be possible to use radiomics characteristics to stratify patients. Radiomics describes the use of imaging modalities to extract quantitative data (such as size, shape and texture of a tumour) that can be used to characterise the phenotypes of different tumours and predict clinical outcomes [65]. In addition radiomics can be performed non-invasively at multiple time-points allowing temporal assessment of a tumour [66]. Whilst this is a relatively new field, work has already demonstrated how radiomics signatures can be prognostic in NSCLC patients receiving radiotherapy [67]. Therefore determining inclusion criteria using radiomics features associated with lower risk of occult metastases may be an effective strategy to identify a trial population with a greater potential benefit from dose-escalation. Further ahead it is envisioned that artificial intelligence will be applied to radiomics data to aid and automate tumour and OAR delineation [68].

Large sequencing studies have demonstrated that, despite their high mutational burden, actionable genetic drivers are unknown for a majority of NSCLC [69]. Functional biological studies are required to identify more drivers so that targeted agents can be trialled concurrently with cCRT. Genomic signatures have been validated in other tumour subtypes to identify specific tumours with poorer responses to radiotherapy [70][71]. Hopefully similar signatures could be developed for NSCLC so that patients with radioresistant tumours could

be identified as potential beneficiaries of dose-escalation. In a similar vein, genomic profiles may be used to detect patients more likely to benefit from the addition of immune checkpoint inhibitors to their treatment. The difficulties of determining relapse may also be aided by new biological technologies, for example circulating tumour DNA (ctDNA) profiling has been demonstrated to detect disease relapse earlier than conventional radiology in patients undergoing resection of stage 1-3 NSCLC in the TRACER-X study [72]. It is conceivable that the incorporation of circulating biomarkers could aid in the delivery and intensification of RT in patients with stage 3 unresectable NSCLC. Biological methods of relapse detection may also augment radiological methods to improve and standardise assessment of response as well as identify patients with a high risk of relapse who should be spared the toxicity of cCRT.

Conclusion

We have highlighted multiple levels of heterogeneity between cases of stage 3 NSCLC and for future studies a priority is to ensure better equality in trial arms for newly identified prognostic factors. It may be argued that using large numbers of patients in randomised arms protects against some of these factors. However these potentially confounding factors need to be considered at the trial planning stage so that the benefits of stratification can be realised and factors that may result from differences in the treatment schedules (such as heart dose or anatomical location) can be controlled using dose constraints or protocol definitions. There is a balance to be achieved, as if trial entry criteria are too prescriptive it reduces the pool of eligible trial participants and limits the application of results to large segments of the actual patient population. However lung cancer is one of the most common cancers therefore it is conceivable that trials could be more selective with regards to entry criteria for subtypes of stage 3 and still enrol adequate numbers. This may provide evidence needed to justify dose-escalation trials in higher-risk patients using emerging technologies to

limit dose to critical structures. Another priority is the use of new technology, QA, and diagnostics to be standardised across multicentre trials. Critical facets of this approach such as central review of diagnostics are expensive and radiotherapy trials, disadvantaged by lack of pharmaceutical industry funding, need a collaborative approach to solve this. In summary, despite radiobiological rational and logical assumption there is currently paucity of modern phase III data for any cancer subtype showing survival benefit for dose-escalation with external beam radiotherapy in stage 3 disease. However despite the negative finding in RTOG 0617, there is enough justification to support further investigation into dose-escalated cCRT. Recent technological advances and the knowledge acquired from subsequent analyses of RTOG 0617 offer novel opportunities to safely assess dose-escalation in NSCLC and hopefully redress previous limiting factors to improve patient outcomes.

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Table 1 – Sources of heterogeneity and solutions to balance trial arms

Source of heterogeneity	Solutions	
	Currently available	Potential future strategies
Tumour characteristics / Staging • Diverse clinical presentations account for same stage • Gross tumour volume (primary and nodes) • Number / location of involved nodes	• Stratify / exclude cases into smaller prognostic groups based on: - GTV - Number of lymph nodes	• Stratify / exclude cases into smaller prognostic groups based on: - Radiomic features
Anatomical • Proximity to critical structures e.g. heart • Tumour motion variability	• Isotoxic radiotherapy to individualise treatment based on proximity of OAR • Stratify / exclude cases into smaller prognostic groups based on anatomical location.	• Better dose sparing of OAR (e.g. heart) using - Improved 'beam-on' imaging of tumour and OAR with MR-guided radiotherapy - Proton beam radiotherapy
Genetic / Histopathological • Diverse genetic drivers – many unknown / some sensitising • EGFR expression • Squamous vs. non-squamous histology	• Stratify / exclude genetic or histopathological subtypes e.g. EGFR mutant / squamous histology	• Identify biomarkers of intrinsic radiosensitivity for stratification
Radiotherapy • Radiotherapy quality assurance • Centre Experience (high volume vs. low volume	• Stratify use of advanced technology (e.g. 4DCT planning) • Comprehensive radiotherapy QA / centralised radiotherapy	• Automation of radiotherapy planning tasks e.g. target and OAR delineation.

centres) • Technology – IMRT / PETCT/ 4D planning / IGRT and adaptive radiotherapy	plan review / site training	
Clinical Response • Tumour shrinkage during treatment • Weight loss	• Image-guidance and adaptive radiotherapy • Nutrition / dietician support	• Functional imaging acquired during radiotherapy to adapt treatment.
Diagnostic • Use of PET / EBUS / brain imaging to stage patient • Definition of local relapse	• Centralise relapse definition	• Enhanced imaging for relapse e.g. PET • Biological markers of relapse e.g. cfDNA

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Radiotherapy • Radiotherapy quality assurance • Centre Experience (high volume vs. low volume	• Stratify use of advanced technology (e.g. 4DCT planning) • Comprehensive radiotherapy QA / centralised radiotherapy	• Automation of radiotherapy planning tasks e.g. target and OAR delineation.

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