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An overview on personalisation of radiotherapy prescriptions in locally advanced non-small cell lung cancer: Are we there yet?

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Title Page

Title: An Overview on Personalisation of Radiotherapy Prescriptions in Locally Advanced Non-Small Cell Lung Cancer: are we there yet?

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Highlights

- Personalised radiotherapy prescriptions for locally advanced NSCLC may improve patient outcomes and are clinically feasible to implement
- Optimal method of prescribing radiotherapy for LA-NSCLC has not yet been determined
- A number of promising strategies are in pre-clinical development

Abstract

Standard of care radiotherapy in LA-NSCLC is 60-66 Gy in 30-33 fractions. However outcomes for these patients is poor with 5-year survival in the range of 10-20%. Randomised controlled trials have shown that dose escalation in a linear fashion does not improve outcomes for all patients, thus there is a need to tailor the prescription to the individual patient. This review assesses the strategies published to personalise the radiation therapy dose prescription in LA-NSCLC. A systematic and scoping search of the literature was performed to identify studies that met the inclusion criteria. 17 relevant studies were identified ranging from prospective clinical trials to mathematically modelled concept studies. Heterogeneity existed between all clinical studies. Nine heterogeneous publications proposed methodology to adapt the dose prescription to the individual patient. A number of encouraging strategies have been identified but fall short of the evidence level required to influence clinical practice.

Keywords

Non-Small-Cell Lung Cancer; Personalised Prescriptions; Radiotherapy; Personalised Medicine; Dose Fractionation;

Introduction

Non-Small Cell Lung Cancer (NSCLC) is the most common form of lung cancer and with poor treatment outcomes and an age-standardised 5-year survival reported to be 10-20% world-wide [1]. Early stage disease treatment for medically inoperable patients has been revolutionised with the advent of stereotactic ablative body radiotherapy (SABR), which has become a standard of care for patients with medically inoperable NSCLC and which has comparable outcomes to surgery for Stage I disease [2, 3]. Outcomes in the locally advanced (LA) setting remain poor with little improvement in overall survival (OS) over the past 40 years [4]. Radiotherapy (RT) is mainstay of treatment for LA-NSCLC and is delivered either as radiotherapy alone or in conjunction with chemotherapy either concurrently or sequentially. An established dose fractionation of 60-66 Gy in 30-33 fractions remains the RT standard of care [5] for patients with LA – NSCLC.

The benefit of RT dose escalation has been explored and a dose response relationship has been reported in the setting of curative intent RT for NSCLC [6]. Theoretically, dose escalation is key to improving local control (LC), progression free survival (PFS) and OS. The randomised control trial (RTOG 0617) sought to compare outcomes following standard dose RT of 60 Gy versus a higher dose of 74Gy in LA-NSCLC [7]. Dose escalation was found to be associated with worse outcomes and poorer overall survival. A more recent meta-analysis investigating RT dose response relationships in NSCLC reported survival benefits for escalation in the RT alone setting and no survival benefit in the concurrent chemoradiotherapy (CRT) setting [8].

It has been hypothesised that any potential benefit of dose escalation has not translated clinically in the findings of the RTOG 0617 due, at least in part, to the increased toxicity induced from both the RT and chemotherapy regimens as well as potential variation in RT delivery and quality assurance [9, 10]. The overall extension of treatment duration in a conventional 2 Gy per day fractionation schedule, may be contributing factor to the poorer outcomes given that longer treatment times may facilitate tumour repopulation. As a result adapting the dose fractionation schedule, without extending overall treatment duration, has been suggested as an alternative approach [11].

While the evidence is somewhat conflicting, it seems clear that universal dose escalation in a linear fashion is not the solution for this patient cohort. It thus follows that adopting a personalised, patient specific approach to modifying the radiotherapy prescription may permit safe RT dose escalation [11].

While recent advances in RT technology have been vast, the evolution is now moving away from increasing the geometric capabilities of the equipment and towards personalising and individualising treatment parameters to a patient's specific needs and requirements [12]. The poor OS associated with the treatment of LA-NSCLC with RT call for an urgent need to transform outcomes for patients. Personalisation of radiotherapy dose prescription and safe dose escalation may be one strategy to address this.

Isotoxic treatment planning has been suggested as a method of personalising radiotherapy for each patient based on their individual treatment plan [13]. In isotoxic RT planning, the prescribed dose is increased incrementally until an organ at risk (OAR) maximum tolerated dose is reached. As a result, each patient will have a personalised prescription. However, this approach of dose escalation is not based on any patient or disease specific features.

Several methodologies have been reported in the literature to modify LA-NSCLC prescriptions, which may prove more successful than RTOG 0617 in improving outcomes for these patients. This review aims to assess both the on-going clinical work being carried out in developing modified dose fractionation schedules, as well as evaluate emerging novel proposals to personalise LA-NSCLC radiotherapy prescriptions.

Search Strategy Methodology

A systematic search of the literature was carried out in PubMed and Embase databases using the key words 'Non-small cell lung cancer' 'Personalised Radiotherapy' 'Dose Optimization' and associated Mesh Terms. See Supplementary Material for complete search strategy. A scoping search of the literature was also performed.

Inclusion criteria were defined as personalised radiotherapy studies relating to NSCLC (including a pre-treatment change in dose per fraction, escalation, de-escalation based on Tumour Control Probability (TCP) or Normal Tissue Complication Probability (NTCP)), modelled personalised radiotherapy studies and studies published between January 2000 and June 2017. Exclusion criteria were defined as any other site (including small cell lung cancer), adaptive studies based on mid-treatment response rather than pre-treatment personalisation, change to chemotherapy prescription, no change to RT prescription, stereotactic radiotherapy studies, protons/carbon ion studies, genetic or biomarker based studies and non-EBRT escalation studies. Studies that reported prescription modification for stratified groups of patients were excluded and only those that individually adjusted the prescription on a per patient basis were included.

Due to heterogeneity between the study types and a limited sample size secondary analysis of the data was not feasible. As a result, the findings were evaluated in a qualitative manner. 19 relevant publications were identified (Figure1) [14-32].

Results

Feasibility of dose modification in LA-NSCLC – in-silico studies

Five retrospective treatment planning studies [14-18] were identified which evaluated the feasibility of adapting the NSCLC RT prescription dose, based essentially on isotoxic planning and established OAR dose volume constraints. Findings from these four studies are summarised in Table 1.

Two studies [14, 15] compared the effectiveness of RT techniques for the purpose of dose modification by evaluating 3DCRT, IMRT, simultaneous integrated boost (SIB) and adaptive RT (ART) techniques. The remaining three [16-18] focused solely on the dose adaptation using their current institutional planning techniques. All five studies concluded that a form of prescription personalisation via uniform dose escalation or SIB is achievable while adhering to accepted dose volume constraints on surrounding normal tissue. Mean Lung Dose (MLD) was the most frequently reported dose limiting parameter.

While all five planning studies [14-18] reported that dose modification was feasible in most patients with NSCLC Stage Ib-III, this was a small cohort of patients, n=101 in total. Additionally, a variety of technologies (3DCRT, IMRT, VMAT and helical IMRT), techniques (ART, SIB), and dose modification approaches (1.8Gy twice daily, 2.5Gy-5.4Gy Daily) were reported making these findings difficult to interpret in a clinically meaningful way. While the treatment prescription was personalised to the patient based on their normal anatomy and target volumes, the overarching aim was to escalate the dose for all patients rather than ascertain differences between those that may or may not benefit from a modified dose prescription. RTOG 0617 has demonstrated that this may not be beneficial to all patients [7].

Clinical evidence for personalised radiotherapy prescriptions

Following the establishment of feasibility, prospective clinical trials were implemented to evaluate the use of personalised prescriptions in a patient population. Five prospective clinical trials [19-23] were identified that utilised isotoxic treatment planning techniques to individually prescribe RT for LA-NSCLC. Findings from these five trials are summarised in Table 2.

There was sizeable heterogeneity between these trials. The study by van Baardwijk et al. (2010) and Wanet et al. were prospective single arm studies [19, 23] whilst the remaining three studies were Phase I and Phase II clinical trials [20-22]. The patient population inclusion criteria varied. Two studies [19, 21] included only patients receiving RT, whereas patients receiving concurrent CRT were included in the remaining three studies [20, 22, 23]. Disease stages I-IV were included over the five studies. There was heterogeneity reported in the RT techniques utilised. Three studies [19, 20, 22] report the use of 3DCRT techniques

and EPID imaging in contrast with the more advanced techniques of IMRT and tomotherapy reported in two trials [21, 23]. RT prescription was modified for each patient based on their individual plan features, mainly normal tissue dose volume constraints or FDG PET uptake values (see Table 2 for details). The resultant prescriptions ranged between 1.5 Gy-1.8 Gy twice daily and 2.28 Gy-4.8 Gy daily, with treatment duration ranging from 25 to 40 days.

Interpreting these trials in a clinically meaningful way is difficult due to the vast heterogeneity observed between patient and disease characteristics as well as the technical approaches taken. One of the main sources of clinical variation between these studies is the parameters used to determine the personalised dose. Standard normal tissue dose volume constraints were used as dose limiting parameters in two studies [19, 20] which had adopted a twice-daily accelerated fractionation schedule. One study [21] reported the mean fraction-normalized lung dose divided by the normalized prescription dose as the dose limiting constraint. One study reported DVCs in EQD2 doses[23]. The remaining trial [22] consisted of 2 trial arms, one with an escalating oesophageal dose limiting constraint. In the other treatment arm dose limiting parameters were modified based on the oesophageal toxicity outcomes from the first cohort. As a result, any direct comparative analysis between these studies is difficult and potentially unreliable.

The clinical outcomes reported in these trials were generally positive, with three of the five trials reporting an increased rate of OS with increased dose, which resulted from personalising the prescription. One study [21] found no significant difference in OS between the 57 Gy and 63.25 Gy cohorts. One study did not report OS in relation to dose modification[23]. Varying levels of toxicity were reported, ranging from mild and transient to Grade 5 fatal toxicities, depending on target location and dose delivered.

The findings presented suggests that dose escalation is not only clinically feasible, but also potentially desirable in terms of improved outcomes (Table 2). An increase in OS was associated with an increase in dose in three of the five studies. However, significant toxicity was reported in all studies with Grade 5 adverse events also reported in four of the five studies. Cannon et al [21] reported that long term follow-up revealed unacceptable late toxicity and recommended a maximum tolerated hypofractionated dose of 63.25Gy in 25 fractions. This toxicity may well be due to the lack of established evidence-based dose volume constraints (DVCs) in the moderately hypofractionated setting. QUANTEC guidelines caution the user on the limitations of applying standard DVCs to modified fractionation schedules and highlighted the need for further work in this area [33]. A review of DVCs utilised in moderately hypofractionated RT for NSCLC highlights the lack of consensus in the clinical setting [34]. Additionally, it has recently been shown that heart dose is a key factor in predicting OS, however, the optimal DVC is yet to be determined[35].

One potential method of reducing this toxicity could be improving the dose conformity to the target using more modulated techniques. In these trials, a number of 3DCRT planning approaches were reported. It is possible that the use of isotoxic planning techniques which require the increased conformity that

comes with IMRT or VMAT, could translate to reduced clinical toxicity and the published outcomes of the Isotoxic IMRT are eagerly awaited[13]. However, two studies that reported Grade 5 haemoptysis utilised modulated techniques but studies observed this toxicity in patients with centrally located tumours[21, 23].

All trials summarised here modified the RT prescription to increase the dose delivered per fraction or per day, rather than extending the prescription in a linear 2 Gy per fraction manner. In spite of the negative outcome of RTOG 0617 [9, 10], these results are encouraging and warrant further investigation. However, these studies do not consider RT dose personalisation based on the molecular or genomic characteristics of the tumour thus there is potential for a further personalised medicine approach to the treatment of NSCLC with RT.

Future directions of personalised radiotherapy prescriptions

Nine studies [24-32] were identified that outlined novel concepts which may prove to be a future basis for personalised RT prescriptions, findings are summarised in Table 3. These studies can be broadly categorised depending on the patient specific feature they are utilising as a basis for personalisation.

Spatial relationship between target and OARs

Exploiting the patient specific spatial relationship or distance between target volumes and OARs in order to individually modify the dose prescription was the focus of two publications [24, 25]. Petit et al. [24] utilised retrospective planning data to model a patient specific maximum achievable dose, based on PTV to OAR distance. The model performed well in predicting the max dose in 79% of patients (n=89).

A similar concept utilised a spatio-temporal model [25]. This study considered the distance between target and OARs but also integrated factors, such as tissue α/β ratios and the linear quadratic model of response, to select an optimal prescription for an individual. This incorporated both the physical features of the patient's anatomy but also tumour doubling and lag times to predict the optimal fractionation schedule. It concluded that the biologically effective dose (BED) could be increased. However, in some patients, there was no significant difference in the tumour BED achieved with the model-determined optimal fractionation and the standard of care approach. The use of this model may result in a more personalised approach for patients, as it was successful in distinguishing between those who may or may not benefit from a dose prescription modification, albeit only in relation to BED. This may lead to improved stratification of patients and potentially reduce the toxicity observed in the clinical trials.

Targeting Sub-volumes of Disease

These studies focused on identifying a sub volume within the tumour that may represent a radio-resistant portion of disease. Once identified, a boost was prescribed to this volume only. One approach attempted to generate a mathematical model that would predict visible tumour response to radiation therapy during treatment and consequently also predicted a residual disease volume that would remain at the end of RT delivery. This was generated from a database of treated patients was the focus of both a feasibility study [26] and a follow up analysis [27]. Disease response to treatment was predicted prior to treatment delivery and an individualised simultaneous integrated boost (SIB) to this 'residual' volume would then be prescribed at the outset. Dose escalation to the residual volume was determined to be feasible [26] but the cohort of patients was small (n=5). The follow up study n=10 [27] found that use of this predictive approach facilitated mean dose escalation of 10.4Gy, to the actual residual tumour volume. One limitation of these studies, similar to the planning studies and clinical trials, is that they assume that dose escalation is the most desirable strategy. Modification of the prescription is optimised to the patient's anatomy and the highest achievable dose, rather than predictive disease features.

Hypoxia targeting

Tumour hypoxic regions are known to be an area of radioresistance and as such they make an attractive target for dose modification studies. A radiobiology focused personalised model was proposed [28] which recommended a dose fractionation schedule that was based on a reoxygenation model, revised to also account for repopulation and repair. Changes in tumour hypoxia over the duration of treatment delivery was considered in this model, which lead to a heterogeneous fractionation approach, with the dose per fraction increasing after short breaks, such as weekends. This mathematically modelled study identified that a theoretical benefit in tumour control probability (TCP) was only observed in well-oxygenated tumours. In a hypoxic setting, the heterogeneous dose schedule was not comparable to the extreme hypofractionation as is commonly seen in the SABR protocols. At present, extreme hypofractionation does not seem a feasible approach for patients with LA-NSCLC, but this method of hypoxia targeting may still be clinically applicable in this cohort of patients. This methodology of modelling tumour hypoxia would require routine hypoxic imaging, perhaps in a longitudinal setting, in order to accurately determine tumour oxygenation status, which is not widely clinically available.

A recent study [29] modelled individualised dose escalation based on either hypoxic sub-volume targeting or whole tumour dose escalation. This study evaluated the uniform vs. non-uniform dose escalation in mathematically modelled population exhibiting varying ranges of hypoxia. It was reported that uniform dose escalation was more beneficial at the early stages of treatment, followed by a hypoxia-targeted dose escalation at a later stage. It was postulated that this is due to the hypoxic regions changing rapidly in the early stages of RT delivery. Again, routine hypoxia imaging would be required to implement such a technique.

TCP/NTCP models

Two studies [30, 31] incorporated radiobiological modelling into the treatment planning process in order to select the most appropriate dose fractionation schedule for the individual case. The basis for the selection was TCP and NTCP models [30] and a novel 'Bifurcation Number' [31]. Both studies reported the proposed methodologies to be beneficial in selecting an optimal prescription.

BioSuite, a novel software program, was developed and was the subject of a feasibility study [30], which incorporates a number of TCP and NTCP models into the RT prescription process. The method proposed dictates that an optimal treatment plan is created and exported to BioSuite. Based on the patient specific anatomy and the individual's treatment plan BioSuite identifies the optimal dose fractionation considering TCP and NTCP models to maximise the therapeutic window for the patient. The concept was used in the treatment of two patients with NSCLC and utilised lung TD₅₀ and oesophageal max dose as the dose limiting constraints. The software calculates a desirable dose fractionation schedule suited to the individual. The individualised approach is clear here, however it is reliant

on an optimal dosimetric plan being produced to determine what can be achieved. As such is potentially limited by the skill of the individual dosimetrist. This uncertainty may be mitigated by the introduction of automatic planning techniques, which have been shown to produce high quality treatment plans in patients with late stage NSCLC [36].

The novel concept of a Bifurcation Number has been developed by Keller et al. [31], and is defined as a dose ratio between the tumour and one OAR. The Bifurcation Number was then compared to the α/β ratios between normal tissue and tumour, to determine the optimal fractionation schedule for an individual. This methodology begins to take into account patient specific features as well as known radiobiological principles. Furthermore, this option indicates the optimal dose modification strategy, which is in keeping with the desire to tailor treatment to the patient. However, as only one OAR is considered in these calculations, this may be a limiting factor in the clinical application of this concept.

Modelled proliferation rate

A patient specific Proliferation Saturation Index (PSI) was the focus of one study [32], which is generated from tumour volume changes over time and the host organ's tumour carrying capacity. The carrying capacity is an ecological concept that defines the maximum ecosystem (tumour) that a host environment can sustain (patient) and is often used in mathematical modelling of cancer dynamics. It was hypothesised that a high PSI indicates a tumour volume is close to the host's maximum carrying capacity and hence it would have a low proportion of cells rapidly proliferating. This in turn would indicate a poor sensitivity to RT and therefore a need for a modified prescription. The concept was tested on a mathematically modelled population (n=500) and four clinical cases. It was reported that the PSI correlated with tumour volume reduction during RT when using standard fractionation schedules. While promising, this study was limited by the lack of patient data. Further work on this concept has been encouraging in predicting treatment early response in patients with oropharyngeal carcinoma [37] however, clinical evaluation is necessary to ascertain the potential benefit of this concept in alternative fractionation schedules. The most recent work published on this concept highlights the dependence of the model of tumour growth law utilised for the calculations [38]. One advantage of the PSI is that it is calculated from routinely acquired CT datasets that are used for diagnostic and planning purposes. As a result, this may have little impact on departmental resources or the patient pathway through treatment.

Discussion

In the literature reviewed, a variety of methodologies have been proposed and investigated to personalise RT prescriptions in patients with LA-NSCLC, however, most are not yet being tested in the clinical setting. One clear reason for this lack in clinical progression is the lack of robust in-silico evidence. Many of the proposed models have been tested on mathematically generated populations in an academic setting. Further work is required to translate these potential models into clinical RT treatments.

The retrospective planning studies reviewed have shown that dose modification is feasible and hence implementation of this concept is clinically possible. Some clinical evidence has been gained from a small number of trials looking at the alternative dose fractionation schedules, though these are largely focused on dose escalation, mainly exploiting the spatial relationship between targets and OARs. To an extent, this approach is personalised to the individual's gross anatomy. However, to truly personalise the treatment we should also target disease features that are identifiable at a cellular level.

Furthermore, a true person-centred approach is lacking in this research, with the majority of studies and proposals aiming to simply escalate dose without a focus on the patient characteristics. A recent publication [39] highlights the vast heterogeneity within this population and the myriad of factors that are not yet considered in our treatment approach. This may well provide a starting point for improved patient stratification and thus personalisation. Whilst our efforts should not move entirely away from personalising the RT plan, we cannot continue to do this without also giving equal consideration to patient related factors.

Paragraph on ongoing clinical trials to be inserted here.

One potential barrier of implementing personalised radiotherapy prescriptions is the resource burden of such approaches. Clinical departments do not have unlimited resources available to deliver an entirely personalised approach to every patient at present. Those concepts and theories which have a minimal impact on workflow and resources, are most likely to be the first introduced to clinical practice, if shown to be beneficial.

Conclusions

Personalised medicine is fast becoming a basic requisite in the modern era of cancer treatment. The treatment of LA-NSCLC with RT is an area of on-going investigation in the pursuit of a personalised approach. Much of the data identified in this review was retrospective planning studies and this limits the strength of

any conclusions. The current clinical evidence, although promising in terms of improving outcomes, is lacking sufficient patient numbers or focus on personalisation to lead to a change in clinical practice and results from ongoing trials are eagerly awaited. Several encouraging strategies have been identified but do not yet provide the level of evidence required to inform clinical practice and a renewed effort to personalise RT dose prescription in the treatment of NSCLC is needed.

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Supplementary Material

Medline/ PubMed Search Strategy

Non-Small Cell Lung Cancer[Title/Abstract]
AND dose fractionation schedule[Title/Abstract])
OR optimised dose[Title/Abstract])
OR (personalized[All Fields]

AND radiotherapy dose[Title/Abstract]))
OR hypofractionated radiotherapy[Title/Abstract])
OR Hyperfractionated radiotherapy[Title/Abstract])
OR Accelerated fractionation[Title/Abstract])
OR (Isotoxic[All Fields]
AND planning[Title/Abstract]))
OR Dose escalation[Title/Abstract])
NOT Breast[Title/Abstract])
NOT Prostate[Title])

AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR
"radiotherapy"[MeSH Terms])) AND ("carcinoma, non-small-cell lung"[MeSH
Terms] OR ("carcinoma"[All Fields] AND "non-small-cell"[All Fields] AND
"lung"[All Fields]) OR "non-small-cell lung carcinoma"[All Fields] OR ("non"[All
Fields] AND "small"[All Fields] AND "cell"[All Fields] AND "lung"[All Fields] AND
"cancer"[All Fields]) OR "non small cell lung cancer"[All Fields]) AND
("2000/01/01"[PDAT] : "2017/12/31"[PDAT]))

Embase Search Strategy

Population

Non Small cell Lung cancer

Intervention

Personalized Medicine

Radiotherapy

Outcome

Local control

Tumour control probability

Normal tissue complication probability

3'non small cell lung cancer'/exp OR 'bronchial non small cell cancer' OR
'bronchial non small cell carcinoma' OR 'carcinoma, non-small-cell lung' OR
'lung cancer, non small cell' OR 'lung non small cell cancer' OR 'lung non small
cell carcinoma' OR 'non small cell bronchial cancer' OR 'non small cell cancer,
lung' OR 'non small cell lung cancer' OR 'non small cell lung carcinoma' OR 'non

small cell pulmonary cancer' OR 'non small cell pulmonary carcinoma' OR
 'pulmonary non small cell cancer' OR 'pulmonary non small cell carcinoma'
 AND ('personalized medicine'/exp OR 'individualised medicine' OR
 'individualised therapy' OR 'individualized medicine' OR 'individualized
 therapy' OR 'personalised medicine' OR 'personalised therapy' OR
 'personalized medicine' OR 'personalized therapy' OR 'precision medicine' OR
 'radiotherapy'/exp OR 'bioradiant therapy' OR 'bucky irradiation' OR 'bucky
 radiation' OR 'bucky radiotherapy' OR 'bucky ray' OR 'bucky ray radiation' OR
 'bucky therapy' OR 'fractionated radiotherapy' OR 'hemibody irradiation' OR
 'hypophysectomy, radiation' OR 'hypophysis irradiation' OR 'hypophysis
 radiation' OR 'irradiation therapy' OR 'irradiation treatment' OR 'irradiation,
 hypophysis' OR 'lymphatic irradiation' OR 'pituitary irradiation' OR 'radiation
 beam centration' OR 'radiation repair' OR 'radiation therapy' OR 'radiation
 treatment' OR 'radio therapy' OR 'radio treatment' OR 'radiohypophysectomy'
 OR 'radiology, therapeutic' OR 'radiotherapy' OR 'radiotherapy setup errors'
 OR 'radiotreatment' OR 'roentgen irradiation, therapeutic' OR 'roentgen
 therapy' OR 'roentgen treatment' OR 'rontgen therapy' OR 'therapeutic
 radiology' OR 'therapy, irradiation' OR 'therapy, radiation' OR 'therapy,
 roentgen' OR 'treatment, irradiation' OR 'treatment, radiation' OR 'treatment,
 roentgen' OR 'x radiotherapy' OR 'x ray therapy' OR 'x ray treatment' OR 'x-ray
 therapy') AND ('local control'/exp OR 'tumour control probability' OR 'normal
 tissue complication probability'/exp)

Figure 1

Table1: Feasibility of dose modification in LA-NSCLC – in-silico studies

Author, Year (ref)	Study Type	Participants n=	Participant stage	Target Definition	Target Volumes	Dose Escalation Limiting Parameter	Maximum Allowed Dose	RT Technique	IGRT Technique	Dose Achieved	Dose Achieved in biologically equivalent 2Gy fractions (EQD2,T)	Study Conclusions
Warren, 2014 (14)	Retropective planning study (3DCRT vs. IMRT for isotoxic planning)	n=20	II-III	union of GTV delineated on all phases of a 4DCT	GT V and involved nodes	Spinal cord $PRV_{SEP}^{[1]}$ <50 Gy to 1 cm3, Lungs (excluding GTV) MLD <20 Gy, Brachial plexus $PRV_{SEP}^{[1]}$ <66 Gy to 1 cm3, Proximal bronchial tree and great vessels $PRV <75.1$ Gy to 1 cm3	79.2 Gy/1.8Gy per fraction twice daily	3DCRT vs. Inverse-planned CRT vs. IMRT (step and shoot)	n/a	70.2Gy/39 fractions, twice daily RT.	69.0 Gy EQD2	Use of IMRT allows for higher isotoxic dose escalation than 3DCRT
Guckebarger, 2012 (15)	Retropective planning study (Only Isotoxic dose escalation section included)	n=13 n=1 Radiology, n=12 Concurrent chemotherapy	III	Planning CT and FDG PET	GT V and involved nodes (no elective nodal irradiation)	MLD level achieved with a prior 3DCRT plan	not stated	IMRT ±SIB ±ART	n/a	average for n=7 planned with IMRT + SIB+ ART 78.8Gy ±2.7Gy SD	not reported	Isotoxic SIB adaptive replanning is a promising strategy to safely escalate dose
Evens, 2015 (16)	feasibility study comparing various boost	n=10	Ib-IIIb	Mid ventilation phase of 4D FDG PET (Boost volume	GT V and involved nodes	Lungs $D_{mean} < 20$ Gy (corrected to EQD2); spinal cord $D_{0.1} < 51$ Gy (EQD2 < 52 Gy);	129.6 Gy/24 fractions to PTV boost	VMA T SIB to F D	n/a	The average prescribed doses to the boost volume were 87.1 ±	not reported	Statistically higher prescriptions achieved for boost volume plans than primary alone. No significant

	volu mes			es SUV5 0% max and HX4 TBR > 1.4 or whole tumou r)		oesophagus V36 < 80%; brachial plexus D0.1 < 66 Gy (EQD2 < 66 Gy); whole heart Dmean < 46 Gy (EQD2 Dmean < 46 Gy); planning organ-at- risk volume mediastinal structures (OAR + 5- mm margin) D0.1 < 76 Gy (EQD2 < 94 Gy), (D0.1 the dose delivered to 0.1% of the OAR)	volu me	G an d H X 4 vo lu m es		10.1 Gy (PTV Prim), 107.3 ± 20.6 Gy (PTV FDG) and 117.6 ± 15.2 Gy (PTV HX4).		difference in OAR DVHs
Hof fma nn, 201 2 (17)	retro spect ive plann ing study (incr easin g dose per fracti on ± the num ber of fracti ons, up to 33, base d on norm alise d total doses)	n= 38	III	FDG PET CT	not rep orte d	NTDmean ≤19 Gy, NTDmax, (Dmax in 2-Gy fractions using EQD2) oesophagus NTDmax 80 Gy, NTDmean 34 Gy,; spinal cord NTDmax 50 Gy; brachial plexus NTDmax 66 Gy; heart NTDmean 26 Gy	82.5 Gy in 33 fracti ons	St ep an d Sh oo t I M R T	n/a	median total tumour dose of 74.2Gy (Range: 67.5- 79.9Gy) in 33 fraction s	64.9Gy (Range 57.0- 71.9Gy) TED in 2- Gy fractions corrected for overall treatment time. *note greater TED was achieved using 15 fraction schedule (67.0Gy (57.0-75.4 Gy)	Individualise d prescription enabled dose escalation and theoretical therapeutic gain in 79% of cases

Table Legend:

IGRT: Image Guided Radiotherapy

3D CRT: 3-Dimensional Conformal Radiation Therapy

IMRT: Intensity Modulated Radiation Therapy

GTV: Gross Tumour Volume

4DCT: 4 Dimensional Computed Tomography

PRV: Planning Organ at Risk Volume

MLD: Mean Lung Dose

Gy: Gray

RT: Radiation Therapy
 EQD2: Equivalent Dose in 2 Gy per fraction
 FDG PET
 SIB: Simultaneous Integrated Boost
 ART: Adaptive Radiation Therapy
 HX4: 3-[18F]fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1 H-1,2,3-triazol-1-yl)propan-1-ol (Hypoxia tracer)
 TBR: Tumour-to-Background Ratio
 Dmean: Mean dose
 OAR: Organ at Risk
 PTV: Planning Target Volume
 VMAT: Volumetric Modulated Arc Therapy
 DVH: Dose Volume Histogram
 NTDmean: mean normalized total lung dose: MLD, adjusted for the dose per fraction
 NTDmax: maximum normalized total dose
 TED: Tumour Effective Dose
 D_V: The absorbed dose in Gray that covers a specified percent volume V
 V_D: The percentage volume that receives a dose of at least D in Gray.

Table 2: Clinical evidence for personalised radiotherapy prescriptions

Author, Year (ref)	Trial Type	Participants n(=)	Participants stage	Target Definition	Target Volumes	Dose Escalation Limiting Parameter	Maximum Allowed Dose	RT Technique	IGRT technique	Dose Act
van Baardwijk, 2010 (18)	Prospective, single arm study	n=116, no concurrent chemo RT	I, & II if inoperable, III	Fused PET-CT with planning CT	GTV and involved nodes (no elective nodal irradiation)	MLD dependant on lung function between 10 and 19 Gy, Cord Dmax 54Gy $\pm$ 0.5Gy, Great Vessels or Bronchi Dmax 70.02Gy, brachial plexus Dmax 66Gy	79.2Gy. 1.8Gy per fraction, bidaily treatment, 8 hours apart	3D CRT	EPID	Median prescription = 64.8 $\pm$ 1.5 Gy with OT 5.8 days 2 to 50 c
van Baardwijk, 2012 (19)	Phase II Trial	137, Concurrent chemo RT	Stage III (Stage II n=1)	Fused PET-CT with Mid ventilation planning CT dataset	GTV and involved nodes (no elective nodal irradiation)	MLD 19.0 $\pm$ 1.0 Gy, Spinal cord Dmax 54.0 $\pm$ 0.5 Gy, and Brachial Plexus Dmax 66 Gy, Oesophagus Dmax 75Gy	69Gy (due to proximity to central structures) 1.5 Gy fractions twice daily up to 45 Gy with an interfraction interval of at least 8-hours, followed by once daily fractions of 2 Gy based on the ESPATU phase III trial scheme	3D CRT	EPID	Median prescription = 65.0 $\pm$ 6 (51–69 Gy) OT of 5 days (18 days).
Cannon, 2013 (20)	Phase I	n=79, n=75 evaluable per protocol patients (no concurrent chemo)	All stages eligible Stage I/II =9%, Stage IIIA=27%, stage IIIB =44%, Stage IV=13%, Recurrent patients = 8%	CT $\pm$ PET	GTV and involved nodes (no elective nodal irradiation)	rNTDmean. At a given dose level, patients with higher rNTDmean (and therefore higher bin number) were predicted to be at higher risk for radiation pneumonitis	Dose per fraction escalation to 57 Gy at 2.28 Gy/fraction, 63.25 Gy at 2.53 Gy/fraction, 69.25 Gy at 2.77 Gy/fraction, 75 Gy at 3.0 Gy/fraction, 80.5 Gy at 3.22 Gy/fraction, and 85.5 Gy at 3.42 Gy/fraction (all delivered in 25 Fractions, once per day, 5 days per week)	IMRT/ Helical tomotherapy	not reported	median delivered was 57 Gy (range, 28–85.5 Gy) fractions
Landau, 2016 (21)	Phase I/II	n= 84 with concurrent chemo (n= 82 evaluable patients)	Stage II & II	3DCT or 4DCT	reported as 'gross tumour volume' no distinction made as to nodal volumes	Split into 2 groups 1: an escalating oesophageal dose constraint (progressively raised from 65 Gy to 68 Gy and then 71 Gy to 1cm3 of oesophagus). Group 2: lung and	73Gy/30 fractions, once daily over 40 days	3DCRT (n= 81) and VMAT (n=3)	not reported	overall n= 67.7 Gy means of 67.7 Gy and 67.7 Gy for group 2, respec

						other normal tissue dose constraints (MLD EQD2mean 18.2 Gy, Heart D100% <45 Gy, D67% <53 Gy, D33% <60 Gy, Cord D0.1cc ≤47 Gy, Brachial Plexus D30% ≤ 60 Gy, D0.1cc ≤ 65 Gy, Oesophagus initially 63Gy but increasing to 65Gy then 68 Gy as trial progressed				
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Table 2 Legend

RT: Radiation Therapy

PET-CT: Positron emission tomography

GTV: Gross Tumour Volume

MLD: Mean Lung Dose

Dmax: Maximum point dose

Gy: Gray

3DCRT: 3-Dimensional Conformal Radiation Therapy

EPID: Electronic Portal Imaging Device

TTD: Total Tumour Dose

OTT: Overall Treatment Time

OS: Overall Survival

EQD2: Equivalent Dose in 2 Gy per fraction

WHO PS: World Health Organisation Performance Status

rNTDmean: mean fraction-normalized lung dose divided by the normalized prescription dose

IMRT: Intensity Modulated Radiation Therapy

3DCT: 3 Dimensional Computed Tomography

4DCT: 4 Dimensional Computed Tomography

VMAT: Volumetric Modulated Arc Therapy

HR: Hazard Ratio

RTPN: Radiation Therapy Pneumonitis

Table 3: Future directions of personalised radiotherapy prescriptions

Author, Year (ref)	Proposed parameter for individualisation (model based on?)	Brief overview of Concept	Participants n=()	Participants stage	Target Definition	Target Volumes	Dose Escalation Limiting Parameter
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Petit, 2015 (22)	Patient anatomy and prior plans (OAR to PTV distance)	Optimal achievable DVHs were predicted based on OAR distance to PTV, based on this max achievable dose escalation is predicted	Training cohort n= 50, Validation Cohort n=39	II-III	not reported	GTV and involved nodes	OAR dose: MLD excluding GTV <20 Gy; plexus brachialis Dmax <70 Gy; heart Dmean<46 Gy; Dmax to the heart, mediastinal envelop and oesophagus <76 Gy; D0.1cc spinal cord <54 Gy.
Kim, 2015 (23)	Spatiotemporal optimization	Model to predict optimal dose based on spatial relationship of target to OARs and incorporating Td and Tk	16	n/a	n/a	n/a	Heart Dmean ≤ 45 Gy, lungs D mean ≤20 Gy, cord Dmax ≤45 Gy, oesophagus Dmax ≤63 Gy, and unspecified tissues D05 ≤60 Gy,
Zhang, 2014 (24)	Predicted residual tumour based on prior patients treatment response (feasibility Study)	The predictive atlas should identify the location of residual disease following treatment, this volume is then prescribed an escalated personalised SIB	n=5	locally advanced	CBCT and planning CT	Tumour only	in house dosimetric OAR constraints
Zhang, 2017 (25)	Predicted residual tumour based on prior patients treatment response	The predictive atlas should identify the location of residual disease following treatment, this volume is then prescribed an escalated personalised SIB	n=10	locally advanced	RO and Medical physicist delineated on Planning CT and last fraction CBCT	GTV Tumour	local standard DVCs (Lung - GTV Mean dose <20Gy, Cord Dmax < 50Gy
Lindblom, 2015 (26)	Radiobiology modelling on <i>in silico</i> population	inclusion of repopulation and repair into a model that considers reoxygenation. A heterogeneous fractionation schedule was considered (increasing dose per fraction after short breaks)	n/a	n/a	n/a	n/a	n/a
Chvetsov, 2017 (27)	hypoxic areas as seen on functional imaging (uniform vs. non-uniform dose distributions) <i>in silico</i> trial	modelling of uniform vs. non uniform dose escalation using mathematical formulae accounting for hypoxia and re-oxygenation	n/a	n/a	n/a	n/a	n/a
Uzan, 2012 (28)	BioSuite software (utilizing a number of TCP/NTCP models)	creating a standard plan, exporting to BioSuite and modelling TCP/NTCP based on the patient specific anatomy	n=2 (NSCLC)	I & III	not reported	GTV or GTV and involved nodes	NTCP parameters Lung TD50 = 29.2 Gy, Oesophagus Dmax = 72 Gy

Keller, 2013 (29)	Bifurcation Number(B) 'a generalized dose ratio between the normal tissue and the tumour'	Calculate the bifurcation number to determine optimal fractionation 'If B is smaller than the ratio of alpha/beta ratios between normal tissue and tumour, then a single fraction is optimal; otherwise the optimal treatment is an infinite number of doses. These fractionation schedules correspond clinically to hypo- and standard/hyperfractionation.'	n=46	not stated (Conventional, hypofractionated and SBRT all included)	not reported	GTV and involved nodes	n/a
Prokopiou, 2015 (30)	Proliferation Saturation Index (PSI)	A PSI is generated based on tumour volume changes between diagnosis and CT simulation, predicting the rate of growth and proliferation, therefore the radiosensitivity of the tumour. This may indicate the need for alternative fractionation schedules	n=500 in a modelled population(matlab), n=4 (patient data from the literature)	n/a	n/a	GTV tumour (modelled and reported)	n/a

Table 3 legend

OAR: Organ at Risk

PTV: Planning Target Volume

DVH: Dose Volume Histogram

GTV: Gross Tumour Volume

MLD: Mean Lung Dose

VMAT: Volumetric Modulated Arc Therapy

Gy: Gray

Td: Tumour doubling time

Tk: Tumour lag time

Dmean: Mean Dose

EUD: Equivalent Uniform Dose

IMRT: Intensity Modulated Radiation Therapy

BED: Biologically Equivalent Dose

DVC: Dose Volume Constraint

SIB: Simultaneous Integrated Boost

CBCT: Cone Beam Computed Tomography

CT: Computed Tomography

PTP: Predictive treatment planning

RT: Radiation Therapy

Dmax: Maximum point dose

SBRT: Stereotactic Body Radiation Therapy

TCP: Tumour Control Probability
NTCP: Normal Tissue Complication Probability
NSCLC: Non-Small Cell Lung Cancer
TD50: dose that would result in 50% probability of developing complications
3DCRT: 3-Dimensional Conformal Radiation Therapy
2D: 2 Dimensional
PSI: Proliferation Saturation Index