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ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: REVIEW ARTICLE

LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective

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ABSTRACT

Evidence supports stereotactic body radiotherapy (SBRT) as a curative treatment option for inoperable early stage non-small-cell lung cancer (NSCLC) resulting in high rates of tumour control and low risk of toxicity. However, promising results are mainly derived from SBRT of peripheral pulmonary lesions, whereas SBRT for the central tumours can lead to severe radiation sequelae owing to the spatial proximity to the serial organs at risk. Robust data on the tolerance of mediastinal structures to high-dose hypofractionated radiation are limited; furthermore, there are many open questions regarding the efficiency, safety and response assessment of SBRT in inoperable, centrally located early stage NSCLC, which are addressed in a prospective multicentre study [sponsored by the European Organization for Research and Treatment of Cancer (EORTC 22113-08113—LungTech)]. In this review, we summarize the current status regarding SBRT for centrally located early stage NSCLC that leads to the rationale of the LungTech trial. Outline and some essential features of the study with focus on a summary of current experiences in dose/fraction-toxicity coherences after SBRT to the mediastinal structures that lead to LungTech normal tissue constraints are provided.

Stereotactic body radiotherapy (SBRT) is a technique in which high doses of radiotherapy are very precisely delivered with steep dose gradients and a short overall treatment time (OTT). This achieves a very high biological dose.[1] Evidence supports SBRT as a curative treatment option for inoperable early stage non-small-cell-lung cancer (NSCLC).[2–5] High-precision, hypofractionated dose delivery enables a significant reduction in both target volume size and exposure of normal tissue (NT) to high doses, resulting in a decreased toxicity risk and high rates of local control.[6–8] However, promising results are mainly derived from the SBRT of small peripheral pulmonary lesions with low risk of treatment-related toxicity, as these tumours are surrounded by parallel organs at risk (OARs), specifically lung tissue. In contrast, the SBRT for central tumours can lead to severe, potentially life-threatening radiation sequelae owing to the spatial proximity to serial OARs. As robust, prospective and multicentre data on the tolerance of mediastinal structures to high-dose hypofractionated radiation is limited, there is generally caution in implementing SBRT for central lung tumours. Current published data are rather inconsistent regarding the definition of "central tumour", SBRT techniques, dose prescription and reporting, calculation algorithms, image guidance and evaluation of outcome. A recent systematic review has summarized the current limited evidence on this topic, mainly from single-centre experiences,[9] but there are still many open questions

regarding patient selection, efficiency, safety and response assessment, which hamper the use of SBRT for central lung tumours in routine practice.[10] A prospective study sponsored by the European Organization for Research and Treatment of Cancer (EORTC 22113-08113–LungTech) was launched in late 2014 and is expected to answer the question of the efficacy and toxicity of SBRT in inoperable and centrally located early stage NSCLC in a multicentre setting.

NSCLC: TREATMENT OPTIONS FOR EARLY STAGE NSCLC

The incidence and mortality of lung cancer in the European Union are 52/100.000 and 47/100.000 per year, respectively.[11] The NSCLC accounts for approximately 80%[11] of all cases with a poor 5-year survival rate of 16%, mainly owing to patients being diagnosed at advanced stages. If diagnosed at an earlier stage, 5-year survival for NSCLC can be as high as up to 80%.[12,13] The current standard of care for early stage tumours is anatomic surgical resection in medically fit patients, consisting of lobectomy or pneumonectomy accompanied by a systematic mediastinal lymph node sampling or lymphadenectomy.[13–15] Associated 5-year survival rates are commonly accepted to be 60–80% for Stage I and 40–50% for Stage II NSCLC.[13] The efficacy of routine sublobar resections for tumours <2 cm is currently being investigated worldwide. This technique spares lung tissue and preserves pulmonary function when compared with lobectomy. However, the results of a randomized controlled trial indicate that this is associated with inferior oncological outcome.[16] In contrast to peripheral tumours, those located centrally often show compression and/or invasion in vessels, major bronchi or other critical mediastinal structures and, therefore, require more extensive surgical procedures associated with higher mortality and morbidity.[17–19] Approximately 20% of all patients with NSCLC Stage I are medically inoperable because of poor general condition or coexisting morbidities such as chronic obstructive pulmonary disease and/or heart disease,[20] and $<50\%$ of all patients with early stage NSCLC older than 75 years undergo surgery.[21] It is expected that as the global population ages and lung cancer screening of high-risk populations is implemented,[22] the proportion of inoperable patients with lung cancer with comorbidities will increase.[23–25] In Stage I patients with NSCLC who refuse surgery and do not receive other treatments such as radiotherapy, 5-year overall survival (OS) and cancer-specific survival (CSS) are low, 6% and 16%, respectively.[26] The standard of care treatment option for medically inoperable patients with early stage NSCLC has been conventionally fractionated radiotherapy (CFRT), superior to best supportive care with CSS rates of about 30% after 5 years[27,28] and 5-year OS of 29–37% for T1 tumours.[29] Evidence supports a clear dose effect for local control and survival in NSCLC,[30,31] however, traditional CFRT-planning and delivery techniques are associated with low accuracy and broad safety margins resulting in increased toxicity rates,[32] therefore, limiting the delivery of higher doses in inoperable patients with early stage NSCLC. Although advanced techniques and positron emission tomography (PET) staging allow modern three dimensional (3D)-CFRT the application of high biological doses, resulting in local control rates $>85\%$ in Stage I patients with NSCLC,[33,34] the implementation of such 3D-CFRT regimes leads to longer OTT of approximately 3–6 weeks,[33,34] whereas SBRT usually can be performed in OTT of days rather than weeks.

SBRT AS AN EFFICIENT TREATMENT MODALITY FOR PERIPHERALLY LOCATED NSCLC

In the past two decades, SBRT has been accepted as a curative treatment alternative for inoperable patients with small (<5 cm) peripheral early stage NSCLC.[2–5] Several prospective studies reported excellent local tumour control rates of up to approximately 90%,[5,6,8,35,36] in the same range as those obtained with surgery.[37,38] Low rates of toxicity have been observed, including elderly, medically, inoperable patients with severe comorbidities.[6,8,35,36,39,40] Survival after SBRT is modest (approximately 50% at 3 years) but has to be interpreted in the context of patients with multiple comorbidities. As expected, survival after SBRT is higher in fitter, operable patients who refused surgery.[41] Furthermore, population-based studies indicated improved OS in medically inoperable patients following the introduction of SBRT.[42] Based on these data, SBRT for patients with early stage NSCLC has been recommended as the standard of care for medically inoperable cases by the European Society For Medical Oncology, Lugano, Switzerland,[43] the National Comprehensive Cancer Network, Fort Washington, PA[14] and by the Deutsche Gesellschaft für Radioonkologie e.V., Berlin, Germany.[20]

Although histological or cytological confirmation of NSCLC is recommended before performing SBRT, biopsy is sometimes not feasible or associated with an unacceptably high risk because of the severe comorbidities of the patient. Thus, an inevitable percentage of patients are treated based on clinical suspicion and imaging criteria of malignancy only. However, in Western Europe, the likelihood of having NSCLC has been demonstrated to be well over 90% using a calculation based on clinical parameters, CT characteristics of malignancy and significant uptake of fluorine-18 fludeoxyglucose (^{18}F-FDG) on PET scan.[43] Moreover, when malignancy is highly likely based on these imaging criteria, SBRT without pathological confirmation was shown to lead to the same outcome as in pathology-proven NSCLC.[44]

With regard to dose/fractionation, there is vast heterogeneity in the SBRT regimes used routinely. Internationally, 3×18 Gy is one of the most frequently used regimes, whereas in Germany for small peripheral lesions, lower doses of 3×13.5–15.0 Gy are recommended[20] and have been demonstrated to result in local control rates of $>90\%$.[45] Local tumour control has repeatedly been reported to show a dose-dependent increase with a minimum biologically effective dose (BED; α/β ratio, 10 Gy) of 100 Gy to the planning target volume (PTV) surrounding isodose resulting in local tumour control rates $>90\%$,[46,47] that even translates into improved OS.[46,48] Interestingly, in a recent meta-analysis, Zhang et al[49] demonstrated a plateau effect with regard to OS with doses of 83.2–146.0 Gy BED and a detrimental effect on OS with doses >146 Gy.

SBRT FOR CENTRALLY LOCATED NSCLC

The major difference between peripherally and centrally located NSCLC is the spatial proximity to centrally located serial OARs, such as, main airways, large blood vessels, the heart, the oesophagus, the phrenic nerves or the brachial plexus, where hypofractionated high doses might lead to severe, potentially life-threatening consequences. Several articles have reported high rates of toxicity after SBRT of centrally located NSCLC. A prospective study by Timmerman et al[50] from the Indiana

University reported a 2-year freedom from severe toxicity of only 54% for central tumours compared with 83% for peripheral tumours, in 70 patients treated with 60–66 Gy total in three fractions. Furthermore, SBRT may have contributed to the events leading to the death of six patients (four patients from bacterial pneumoniae; one patient from pericardial effusion; and one patient owing to massive haemoptysis), of which four of the six patients had central tumours.[50] These deaths occurred after a median of 10.4 months following SBRT (range, 1–20 months). The 2-year incidence of toxicity grade ≥3 was 17% and 46% for peripherally and centrally tumours, respectively. The observation of severe toxicity after SBRT of centrally located NSCLC was subsequently confirmed by two studies: grade 5 toxicity was observed in 1 out of 17 patients after treatment with 60 Gy in 4 fractions[36] and in 1 out of 9 patients after irradiation with 48 Gy in 4 fractions[51] delivered on consecutive days. Moreover, a case report was published by the University of Pennsylvania, Philadelphia, PA, reporting on a fatal central airway necrosis more than 8 months after 50 Gy in five fractions was delivered to a central lung tumour.[52] Conversely, investigators from the Free University in Amsterdam demonstrated that the use of "risk-adapted SBRT" using a more fractionated regime (60 Gy in eight fractions) did not result in excess toxicity for centrally located early stage lung tumours ($n = 63$), and clinical outcomes were comparable with those seen for peripheral tumours.[53] However, none of the retrospective data included detailed dose–volume histogram/toxicity analyses. A PRISMA structured literature review published in 2013 identified 20 publications reporting outcomes for 563 central lung tumours treated with SBRT, including 315 patients with early stage NSCLC.[9] The majority of these studies were retrospective and conducted at single institutions. Only four studies were prospective and reported on 68 patients with central tumours. Local control was 85% when the prescribed BED_{10} was >100 Gy. Tumour location (central *vs* peripheral) did not impact on OS, and treatment-related mortality was 2.7% overall. Grade 3/4 toxicities following SBRT for central tumours were more common than for peripheral tumours, and occurred in <9% of patients. It should however be noted that there was heterogeneity in the common toxicity criteria used to define toxicities and treatment–response criteria. Furthermore, the follow-up of these studies was relatively short (median, 18 months), and long-term toxicity data are needed given the high dose and hypofractionated nature of the treatments delivered. The BED_{10} delivered ranged between 60 and 180 Gy. It is important to note that published studies vary widely in their reporting of dose/fractionation as well as dose specifications and calculations. Only 11 of the 20 reviewed studies used tissue heterogeneity correction, and the prescription isodoses ranged between 50% and 100%.

In summary, there is a clear need for a prospective, multicentre study using standardized RT techniques, treatment–response criteria and toxicity assessment. As the maximum tolerated doses and optimal fractionation schemes for SBRT near mediastinal structures are currently unknown, collective knowledge of the complex relationship between the radiation dose and the volume of irradiated tissue for each mediastinal structure is a pre-requisite to the safe future routine use of SBRT for central tumours. The lack of high-quality evidence to support SBRT in centrally located tumours is reflected in international guidelines that only recommend SBRT for peripheral and medically inoperable early stage NSCLC.[43,54] We therefore advocate that treatment of central lesions should preferably be performed within the context of a well-conducted prospective trial.

EORTC 22113-08113 LungTech: CONCEPT OF THE TRIAL

The LungTech trial aims to evaluate the efficiency and toxicity of SBRT for patients with histologically or cytologically proven early stage, centrally located, inoperable NSCLC in a multicentre setting. The primary end point will be freedom from local progression at 3 years as assessed by serial CT scans and confirmed by ^{18}F-FDG-PET/CT. If still unclear, biopsies or 3 monthly repeated imaging will be performed. Using one-sided 5% Type I error and 80% power, 150 patients (included so far from 23 planned centres in Belgium, France, Germany, Poland, Switzerland and UK) should be sufficient to reject the hypothesis of freedom from the local progression rate at 3 years of ≤80% under the assumption that SBRT is expected to achieve a freedom from local progression rate of 90%. The trial will also investigate acute and late toxicities as well as patterns of local and distant recurrence, including mediastinal failure, assessed by serial CT scans and confirmed by ^{18}F-FDG-PET/CT and subsequent repeat imaging or biopsy, if necessary. Moreover, this study offers a unique opportunity to evaluate the role of ^{18}F-FDG-PET/CT to monitor disease progression and toxicity, as translational research end points, including staging comparison between 3D- and four-dimensional (4D) ^{18}F-FDG-PET/CT assessment, possible impact of 4D ^{18}F-FDG-PET/CT on target volume contouring and external validation of Huang et al[55] response criteria.

Recently, the Radiation Therapy Oncology Group (RTOG) has performed a dose-escalation Phase I/II study (RTOG 0813) in centrally located NSCLC.[56] Derived from the North American standard, the study is based on a five-fraction regime, the results are awaited. Although the RTOG study includes only T1/T2 tumours, the LungTech study will also include a limited population of T3 tumours and therefore supplement the available data pool. In Europe, owing to the risk of toxicity with three- to five-fraction regimes as described above, it was decided to investigate a less hypofractionated "risk-adapted" approach (60 Gy in eight fractions) as reported by the Free University in Amsterdam.[53] To ensure the feasibility and safety of the planned treatment, only those centres that have used SBRT for a period of at least 12 months and have treated a minimum of 20 patients will be eligible. The study will be conducted only within EORTC centres and will benefit from the EORTC and Radiation Oncology Group Quality Assurance infrastructure. A pooled data analysis of both studies maybe an interesting future option.

Some essential features of the protocol are outlined below.

Definition of central tumour

In current literature, the definition of what constitutes a "central" tumour varies widely and further hampers the comparison between trials. Only 11 out of the 20 studies reviewed by Senthi et al[9] used the same definition as RTOG 0813;[56] Modh et al[57]

even included two different definitions of "central tumours" within the same publication of their study.

Haasbeek et al[53] defined central tumours as located within a 1-cm zone from the mediastinal envelope. In RTOG 0236,[58] the following definition is used: a tumour within 2 cm of the proximal bronchial tree (carina, right and left main bronchi, and bronchial tree to the second bifurcation), whereas RTOG 0813 sticks to the definition of Timmerman et al:[50] a tumour located within 2 cm in all directions around the proximal bronchial tree and immediately adjacent to mediastinal or pericardial pleura with a PTV expected to touch or include the pleura. This definition has also been slightly modified in the LungTech trial: "Centrally located tumour defined as tumour within 2 cm or touching the zone of the proximal bronchial tree or tumour that is immediately adjacent to the mediastinal or pericardial pleura, with a PTV expected to touch or include the pleura."

Some tumours might be "too central" to be safely treated with SBRT when applying BED >100 Gy. Even using the "risk-adapted" LungTech regime, there will be central tumours, for example, invading the proximal bronchial tree and/or hilar structures, which will not be treatable within the trial owing to a very high risk of severe toxicity (Figure 1). In current literature, a selection bias with regard to the inclusion of certain anatomical subgroups within the SBRT "danger zone" cannot be excluded. Indeed, the examples and description of patient cohorts, for example, in the Haasbeek's study[53] show that "very central" tumours have not been included in the larger published series. However, a clear definition of what constitutes "too central tumours" is lacking. In the LungTech protocol, T3 tumours >7 cm, all T4 tumours and tumours abutting the oesophagus or presenting with separate tumour nodule(s) in the same lobe are excluded to increase the safety of this treatment. Furthermore, all potential LungTech cases will undergo a central expert review of eligibility relating to tumour anatomical location and treatment planning before enrolment in the study treatment, thus confirming central tumour localization and excluding tumours that are "too central" according to the eligibility criteria and dose constraints (*e.g.* proximity to the central bronchi, Figure 1).

Prescribed dose, normal tissue constraints

In order to define dose/fractionation and NT constraints for the LungTech trial, current literature and experiences in other trials were reviewed (Tables 1 and 2).[9,36,50–53,56,57,59–75]

In terms of tumour dose, the LungTech protocol will investigate a medium hypofractionated approach, applying 8.0 × 7.5 Gy to a total dose of 60 Gy; this is equal to a BED of 105 Gy ($\alpha/\beta = 10$). Referring to report 83 of the International Commission on Radiation Units and Measurements (ICRU), 95% of the PTV has to receive at least the nominal fraction dose, and 99% of the PTV receives a minimum of 90% of the nominal dose. The maximum dose within the PTV should not be <110%, nor should it exceed 130% of the prescribed dose. Gross tumour volume (GTV) delineation is based on 4D-CT in treatment position, mandatory 3D-PET/CT scan and supplementary clinical information, for example, results of bronchoscopy. To account for tumour motion during the breathing cycle, the protocol allows the individual internal target volume (ITV) and the average mean position approach. The PTV margin based on the ITV concept is primarily meant to take into account patient set-up uncertainties, thus requiring an isotropic ITV expansion of 3–5 mm. For PTV generation, based on the average mean position of the tumour, the margin should take into account both the set-up error and breathing-induced motion and should not be <3 mm. All patients treated in this trial will receive image-guided SBRT. Further details on the technical aspects of the radiotherapy planning including dose specification and radiation therapy quality assurance (RTQA) procedures will be reported elsewhere.

Defining NT constraints for thoracic OARs, in the context of SBRT, is a major challenge, as the maximum-tolerated doses and optimum fractionation for mediastinal structures are currently unknown. Another challenge is the assessment of treatment-related toxicity in patients with multiple comorbidities, which

Figure 1. (a) An 81-year-old patient with centrally located non-small-cell lung cancer (NSCLC), T1N0M0, meeting the eligibility criteria for inclusion in the LungTech trial. Delineation of tumour: gross tumour volume (GTV) (purple), internal target volume (ITV) (red), planning target volume (PTV) (pink) and organs at risk. (b) The proximity to the right central bronchus (cyan) does not allow planning according to the LungTech protocol without exceeding the dose constraint for the proximal bronchus tree (prox BT) 44 Gy [equivalent dose in 2 Gy fractions (EqD2), 74.8 Gy]—maximum dose for prox BT here 66.76 Gy (EqD2, 151.3 Gy)—leading to secondary exclusion from the trial.

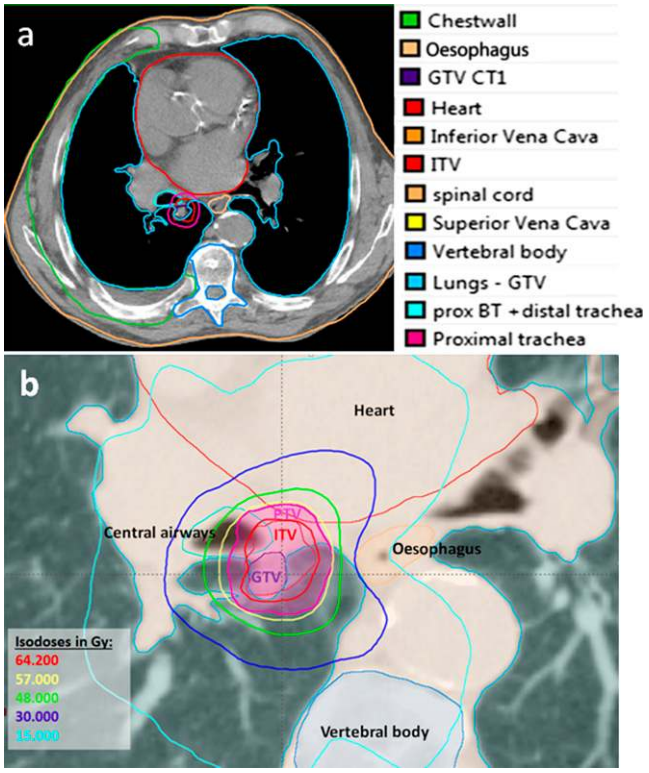


Table 1. Literature review of severe radiation induced toxicities for central lung tumors for definition of normal tissue (NT) constraints for the LungTech trial

Study	Number of reported patients (treated tumours)	Number of centres	p/r	Results[a]
Bronchial tree/trachea (α/ß, 3 Gy), potential side effects: fatal haemoptysis, fistula, stenosis, necrosis, atelectasis, pneumonia and abscess				
Timmerman et al[50]	70	1	p	Central lesions: 11× more likely to experience grade 3–5 lung toxicity than those with peripheral tumours, 1× local recurrence next to carina with subsequent fatal haemoptysis (19.5 months after SBRT) 3× 20–22 Gy = 60–66 Gy (EqD2: 276–330 Gy)[b]
Fakiris et al[59]	22	1	P	4-year results of above study: lung toxicity rates of 10.4% (peripheral) and 27.3% (central lesions); 1× fatal haemoptysis (same as above), three patients died of pneumonia
Li et al[60]	43	1	p	One case of fatal haemoptysis, 70 Gy, ten fractions, hilar D_{max} = 83 Gy (EqD2, 187.6 Gy)
Modh et al[57]	91	1	r	Two cases of fatal haemoptysis, 47 Gy (EqD2, 116 Gy) and 48 Gy (EqD2, 121 Gy), five fractions. Tumours were found involving the hilum and encasing the left superior segmental bronchus, respectively
Corradetti et al[52]	1	1	r	Central airway necrosis, 5 × 10 Gy = 50 Gy (EqD2, 130 Gy)[b]
Nishimura et al[61]	133	1	r	Fatal haemoptysis in two cases with D_{max} >50 Gy (EqD2, 130 Gy) to the pulmonary artery /bronchus (five fraction regime)
Song et al[51]	9	1	r	8× partial or complete bronchial strictures, 1× complete bronchial stricture with fatal consequences (bleeding, aspiration and pneumonia), 4 × 12 Gy = 48 Gy (EqD2, 144 Gy)[b]
Milano et al[62]	53	1	r	1× fatal haemoptysis (bronchus received a cumulative dose of 98 Gy; EqD2 not applicable)
Oshiro et al[63]	21	1	r	1× fatal haemoptysis (re-treatment: 1× 25 Gy; EqD2, 140 Gy)[b]
Bral et al[36]	17	1	p	1× bronchial stenosis and successively fatal haemoptysis after stent insert, 4 × 15 Gy = 60 Gy (EqD2, 216 Gy)[b]
Unger et al[64]	17	1	r	1× bronchial fistula, mainstem bronchus received a maximum point dose of 49 Gy (EqD2 not applicable)
Canon et al[65]	75[c]	1	p	CFRT: EqD2 of 75×3 Gy predicting a 5% complication rate, 3× fatal haemoptysis, 85 and 75 Gy, 25 fractions (EqD2, 118 and 90, respectively), tumours encasing or abutting a mainstem or proximal lobar bronchus and partially local invasion of adjacent normal structures
Heart (α/ß, 3 Gy), potential side effects: congestive heart failure, pericarditis, pericardial effusion and arrhythmia				
Bonomo et al[68]	16	1	r	Paracardiac and cardiac lesions treated with SBRT (36 Gy, three fractions, $D_{100\%}$: 51.4 Gy; EqD2, 108–204 Gy): no cardiological symptoms or electrocardiographic abnormalities, even months after SBRT

(Continued)

Table 1. (Continued)

Study	Number of reported patients (treated tumours)	Number of centres	p/r	Results[a]
Great vessels (aorta, vena cava superior and inferior brachiocephalic veins) (α/ß, 3 Gy), potential side effects: haemoptysis and fatal bleeding				
Timmerman et al[50]	70	1	p	Single cases of haemoptysis and fatal bleeding with varying SBRT regimens (see also Brochial tree/trachea)
Senthi et al[9]	(563)	20[d]	r/p (4)	Single cases of haemoptysis and fatal bleeding with varying SBRT regimens (Song et al[51], Milano et al[62], Oshiro et al[63], Braley et al[36])
Canon et al[65]	75[c]	1	p	(see also Brochial tree/trachea)
Oesophagus (α/ß, 3 Gy), potential side effects: fistula, stenosis, perforation, oesophagitis, ulcer, haemorrhage				
Onimaru et al[69]	45(57)[c]	1	p	One death owing to radiation-induced ulcer in the oesophagus 5 months after SBRT, 48 Gy, eight fractions (EqD2, 86.4 Gy)[b], maximum dose of 50.5 Gy at the oesphagus (EqD2, 93.7 Gy)
Stephans et al[70]	52	1	r	Two cases of oesophageal fistula, when the oesophageal point dose >51 Gy and 1-cm^3 doses >48 Gy, EqD2 not applicable
Modh et al[57]	91	1	r	One fistula with an oesophageal D_{max} of 46 Gy in five fractions (EqD2, 112Gy). Oesophageal toxicity ≥grade 2: 12.8% (median D_{max} of 29.5 Gy for those patients with oesophageal toxicity), EqD2 could not be derived from those data
Spinal cord (α/ß, 1-3 Gy), potential side effects: radiation-induced myelitis				
Kirkpatrick et al[71]	335[g] 1946[g] 1400[f]	5[d] 12[d] 9[d]	r r r	CFRT of 2 Gy per day including the full cord cross-section: total dose of 50 Gy, 60 Gy and approximately 69 Gy (= EqD2) are associated with a 0.2, 6 and 50% rate of myelopathy. For partial cord irradiation as part of spine radiosurgery, maximum cord dose of 13 Gy in one fraction (EqD2, 48.8 Gy) or 20 Gy in three fractions (EqD2, 110 Gy) appear associated with a <1% risk of injury
Brachial plexus (α/ß, 3 Gy), potential side effects: brachial plexopathy				
Forquer et al[72]	(37[e])	2	r	37 apical lesions treated to a median total dose of 57 Gy, median maximum brachial plexus dose of patients developing brachial plexopathy: 30 Gy (18–82 Gy) (EqD2 not applicable). 7/37 apical lesions developed grade 2–4 plexopathy. Brachial plexus maximum dose should be kept <26 Gy in three (EqD2, 59.9 Gy) or four (EqD2, 49.4 Gy) fractions
Lungs (α/ß, 3 Gy), potential side effects: radiation-induced pneumonitis, fibrosis and decrease in lung function, atelectasis, pneumonia (see also Bronchial Tree /Trachea) and abscess				
Borst et al[73]	128[c]	1	r	No difference between SBRT and CFRT for the relationship between the lung dose and the incidence of radiation-induced pneumonitis
Stanic et al/ RTOG0236[74]	55	43	p	No clinically significant changes in pulmonary function following SBRT for early stage peripheral NSCLC
Unger et al[64]	17	1	r	1× grade 3 radiation pneumonitis (EqD2 not applicable)

(Continued)

Table 1. (Continued)

Study	Number of reported patients (treated tumours)	Number of centres	p/r	Results[a]
Chest wall (α/ß, 3 Gy), potential side effects: chest wall pain and rib fractures				
Taremi et al[75]	46 (49[c])	1	r	Description of risk factors for radiation induced bone injury after SBRT: increasing age, female gender and high RT dose to 0.5 cm^3 of nearby ribs

CFRT, conventional radiotherapy; D_{max}, maximum dose; EqD2, equivalent dose in 2 Gy fractions; NSCLC, non-small-cell lung cancer; p, prospective; r, retrospective; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiotherapy.
The number within parenthesis for column "p/r" are the number of treated tumours.
[a]Maximum point dose or dose/fractionation and EqD2 in Gray provided if possible.
[b]Doses applied to the tumour.
[c]Including peripheral and central tumours.
[d]Studies, [e]apical of 276, [f]treated with stereotactic fractionated radiotherapy (SBRT), [g]treated with CFRT.

may be a confounding factor. Whilst toxicity for SBRT delivered to peripheral tumours is well documented, this is not the case for central tumours, and long-term data are necessary given that late effects can become apparent more than 1 year post treatment.[65] For this reason, patients will be prospectively assessed for at least 3 years after treatment in the LungTech study.

Although the linear quadratic model (LQM) has been criticized for not being applicable to SBRT,[76] data from Guckenberger et al[77] suggested accurate modelling of local tumour control in fractionated SBRT for Stage I NSCLC with the traditional linear-quadratic formalism. Brown et al[78] reported that there is compelling *in vitro* and *in vivo* NT evidence that the LQM

Table 2. Normal tissue (NT) constraints for the LungTech trial derived from literature review of severe toxicities (Table 1) and used NT constraints

Study	Recommendations/NT constraints
Bronchial tree/trachea (α/ß, 3 Gy), potential side effects: fatal haemoptysis, fistula, stenosis, necrosis, atelectasis, pneumonia and abscess	
Timmerman et al[66]	Maximum point dose, 20.2 Gy (one fraction regime; EqD2, 93.7 Gy) 40 Gy (five fraction regime; EqD2, 88 Gy)
RTOG 0813[56]	>105% PTV, EqD2 not applicable
Haasbeek et al[53]	Maximum dose restriction (0.5 cm^3), 8 × 5.5 = 44 Gy (EqD2, 74.8 Gy)
Nuyttens et al[67]	Maximum dose restriction (0.5 cm^3), 6 × 8 = 48 Gy (EqD2, 105.6 Gy)
EORTC 22113-08113	Dose constraint, 8 × 5.5 Gy = 44 Gy (EqD2, 74.8 Gy)
Heart (α/ß, 3 Gy), potential side effects: congestive heart failure, pericarditis, pericardial effusion and arrhythmia	
Timmerman et al[66]	Maximum point dose, 22 Gy (one fraction regime; EqD2, 110 Gy) 38 Gy (five fraction regime; EqD2, 80.6 Gy)
RTOG 0813[56]	Maximum point dose: 63 Gy (five fraction regime; EqD2, 196 Gy) 60 Gy (ten fraction regime; EqD2, 108 Gy)
EORTC 22113-08113	No restrictions, but recording of DVH data for toxicity
Great vessels (aorta, vena cava superior and inferior, brachiocephalic veins) (α/ß, 3 Gy), potential side effects: haemoptysis and fatal bleeding	
Timmerman et al[66]	Maximum point dose, 37 Gy (one fraction regime; EqD2, 296 Gy) 53 Gy (five fraction regime; EqD2, 144.2 Gy)
RTOG 0813[56]	Maximum point dose, 63 Gy (five fraction regime; EqD2, 196.6 Gy) 75 Gy (ten fraction regime; EqD2, 157.5 Gy)
EORTC 22113-08113	No restrictions, but recording of DVH data for toxicity
Oesophagus (α/ß, 3 Gy), potential side effects: fistula, stenosis, perforation, oesophagitis, ulcer, haemorrhage	
Timmerman et al[66]	Maximum point dose, 15.4 Gy (one fraction regime; EqD2, 56.7 Gy) 35 Gy (five fraction regime; EqD2, 70 Gy)

(Continued)

Table 2. (Continued)

Study	Recommendations/NT constraints
RTOG 0813[56]	Maximum point dose, 63 Gy (five fraction regime; EqD2, 196 Gy) 50 Gy (ten fraction regime; EqD2, 80 Gy)
Haasbeek et al[53]	Maximum dose restriction (0.5 cm^3), $8 \times 5 = 40$ Gy (EqD2, 66 Gy)
Nuyttens et al[67]	Maximum dose restriction (0.5 cm^3), $6 \times 6 = 36$ Gy (EqD2, 64.8 Gy)
EORTC 22113-08113	Dose constraint, 8×5 Gy = 40 Gy (EqD2, 64 Gy)
Spinal cord (α/ß, 1-3 Gy), potential side effects: radiation induced myelitis	
Timmerman et al[66]	Maximum point dose, 14 Gy (one fraction regime, EqD2: 56 Gy) 30 Gy (five fraction regime; EqD2, 60 Gy)
RTOG 0813[56] (56)	Maximum point dose, 25 Gy (four fractions regime; EqD2, 51.66 Gy) 30/40 Gy (five/ten fraction regime; EqD2, 60 Gy)
Haasbeek et al[53]	Maximum dose restriction (0.5 cm^3), $8 \times 3.5 = 28$ Gy (EqD2, 36 Gy)
Nuyttens 7et al[67]	Maximum dose restriction (0.5 cm^3), $6 \times 4.5 = 27$ Gy (EqD2, 43.9 Gy)
EORTC 22113-08113	Dose constraint, 8×4 Gy = 32 Gy (EqD2, 48 Gy)
Brachial plexus (α/ß, 3 Gy), potential side effects: brachial plexopathy	
Timmerman et al[66]	Maximum point dose, 17.5 Gy (one fraction regime; EqD2, 71.8 Gy) 30.5 Gy (five fraction regime; EqD2, 55.5 Gy)
RTOG 0813[56]	Maximum point dose, 32 Gy (five fraction regime; EqD2, 60.2 Gy) 55 Gy (five/ten fraction regime; EqD2, 93.5 Gy)
Haasbeek et al[53]	Maximum dose restriction (0.5 cm^3), $8 \times 4.5 = 36$ Gy (EqD2, 54 Gy)
Nuyttens et al[67]	Maximum dose restriction (0.5 cm^3), $6 \times 8 = 48$ Gy (EqD2, 105.6 Gy)
EORTC 22113-08113	Dose constraint, 8×4.75 Gy = 38 Gy (EqD2, 58.9 Gy)
Lungs (α/ß, 3 Gy), potential side effects: radiation-induced pneumonitis, fibrosis and decrease in lung function, atelectasis, pneumonia (see also Brochial tree/trachea) and abscess	
RTOG 0813[56]	V12.5 > 1500 cm^3 and V13.5 Gy < 1000 cm^3; EqD2 not applicable
EORTC 22113-08113	No restrictions, but recording of DVH data for toxicity
Chest wall (α/ß, 3 Gy), potential side effects: chest wall pain and rib fractures	
Timmerman et al[66]	Maximum point dose, 30 Gy (one fraction regime; EqD2, 198 Gy) 43 Gy (five fraction regime; EqD2, 99.8 Gy)
RTOG 0813[56]	Maximum point dose 32 Gy (five fraction regime; EqD2, 60.2 Gy) 82 Gy (ten fraction regime; EqD2, 183 Gy)
EORTC 22113-08113	No restrictions, but recording of DVH data for toxicity

DVH, dose–volume histogram; EORTC, European Organization for Research and Treatment of Cancer; EqD2, equivalent dose in 2 Gy fractions; PTV, planning target volume.

provides a reasonable estimate of dose–response relationships including single high doses. Therefore, the NT constraints defined in LungTech have been derived from the available literature on SBRT coupled with LQM estimates related to CFRT experience (Tables 1 and 2).

While translating stated dose/fraction from the varying data to comparable equivalent dose in 2 Gy fractions (EqD2), wide ranges of allegedly comparable equivalent doses become apparent (Tables 1 and 2). This is most likely because different α/β ratios have been used and/or other factors than LQM estimates might have contributed to dose calculation or recommendation. This obvious heterogeneity underlines the need for systemically collected data for defining maximum-tolerated doses and optimum fractionation for mediastinal structures, and thus robust NT constraints for thoracic OARs. The dose constraints and possible deviations chosen for the LungTech trial are presented in the EORTC 22113-8113RTQA guidelines (Table 3).

Primary end point assessment

Clinical symptoms of acute radiation-induced lung injury develop within approximately 3–6 months after treatment. A proportion of patients will subsequently develop radiation fibrosis (from 6 months after SBRT). The assessment of tumour response after SBRT by CT-based criteria [response evaluation criteria in solid tumour (RECIST)] is therefore challenging, as such changes are typically seen within the high

Table 3. EORTC 221133 LungTech trial: dose constraints for organs at risk (OARs)

OAR	α/β (Gy)	D_{max} (Gy)	EqD2 (Gy)	Acceptable variation (Gy)	Acceptable variation EqD2 (Gy)	Unacceptable variation (Gy)	Unacceptable variation EqD2 (Gy)
Trachea/main bronchus	3	$8 \times 5.5 = 44$	74.8	$<8 \times 5.81 = 46.68$	<81.9	$\geq 8 \times 5.81 = 46.68$	>81.9
Heart[a]	3						
Great vessels[a]	3						
Oesophagus	3	$8 \times 5 = 40$	64	$<8 \times 5.44 = 43.52$	<73.6	$\geq 8 \times 5.44 = 43.52$	≥73.6
Spinal cord[b]	2	$8 \times 4 = 32$	48			$>8 \times 4 = 32$	>48
Brachial plexus[b]	3	$8 \times 4.75 = 38$	58.9	$<8 \times 5.17 = 41.36$	<67.7	$\geq 8 \times 5.17 = 41.36$	≥67.7
Body-PTV[b]	3	$8 \times 7.5 = 60$	126	$<8 \times 7.785 = 62.28$	<134.2	$\geq 8 \times 7.785 = 62.28$	≥134.2
Lung-CTV[a]	3						
Chest wall[a]	3						

CTV, clinical target volume; DVH, dose–volume histogram; EORTC, European Organization for Research and Treatment of Cancer; EqD2, equivalent dose in 2 Gy fractions; PTV, planning target volume.
Source: EORTC 22113-0813-LungTech radiation therapy quality assurance guidelines.
[a]No restrictions are provided but recording of DVH data for toxicity evaluation is required.
[b]For $<0.5\,cm^3$.

dose area. However, some changes, independently of the tumour size change, have been identified as more reliable indicators of local recurrence (*e.g.* opacity with a convex border, disappearance of air bronchograms[55]). In order to confirm a suspicion of local recurrence, it has been shown that ^{18}F-FDG-PET/CT may play an important role in increasing the sensitivity of the diagnosis. In a systematic review of the literature, Huang et al[55] proposed a set of criteria for the evaluation of local recurrence with CT and PET findings in patients with primary lung tumours or lung metastases treated with SBRT. A value of maximum standard value uptake (SUV_{max}) > 5 was suggested[79,80] for the differential diagnosis between local recurrence and post-treatment changes. However, the quantitative measurement criteria set by Huang et al,[55] are derived from various single-centre studies with heterogeneous PET imaging protocols. Therefore, Huang et al[55] recommend conducting all PET scans for a specific patient on the same machine and with a standardized scanner. This is obviously not possible in the context of a multicentre trial.

In the LungTech trial, ^{18}F-FDG-PET/CT will be requested in case of equivocal findings or progressive soft-tissue abnormalities. The integration of quantitative measurement criteria would require the standardization of all the ^{18}F-FDG-PET/CT scanners. Given that such standardization, *e.g.* the "European Association of Nuclear Medicine" (EANM) accreditation, is not used in all the participating centres, a modified Huang et al[55] criterion is being applied with local progression defined as "focal ^{18}F-FDG accumulation significantly above the mediastinal blood pool" (Figure 2). However, quantitative assessment (SUV_{max}) of the treated tumour and regional lymph nodes will also be measured and collected in order to prospectively evaluate the robustness of the criteria set by Huang et al[55] in a subset of centres that have EANM accreditation. In difficult cases, reimaging or biopsy will be requested to confirm progression if clinically indicated.

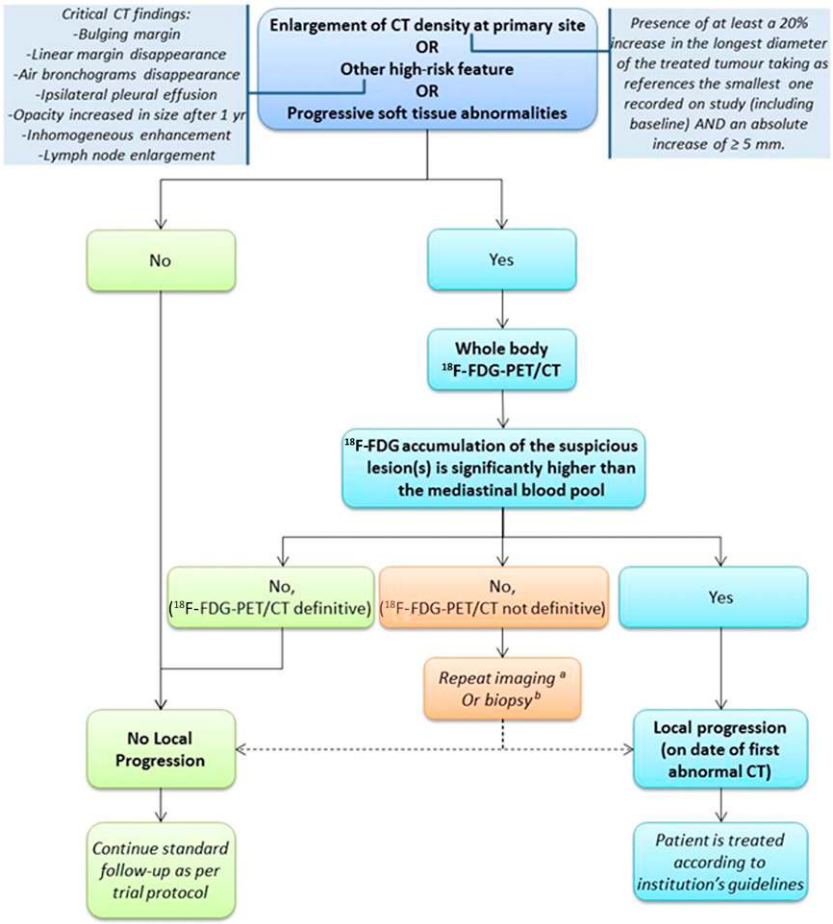
Toxicity assessment

An important secondary end point of the LungTech trial is the prospective evaluation of toxicity. As previously described, there is a paucity of prospective data regarding the relationship of dose fractionation, irradiated volume and toxicity of SBRT in centrally located tumours. One of the objectives of LungTech is to elaborate on such coherences and thus be able to provide robust recommendations on central NT constraints in patients treated with SBRT. In order to make recommendations that will be applicable to other SBRT dose/fractionation, pooling the data of LungTech and RTOG 0813[56] (five-fraction regime) is furthermore an interesting future option. Adverse events are assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v. 4 at baseline, at the end of treatment, 6 weeks after SBRT, 3 monthly for the first 3 years, 6 monthly for up to 5 years and yearly thereafter. Additionally, CT imaging is performed and pulmonary function tests recommended. *Serious Adverse Event* and *Suspected Unexpected Serious Adverse Reactions* reporting are conducted according to the Good Clinical Practice.[81]

Radiation therapy quality assurance and imaging quality control

Differences in delivery of care between institutions may induce variations affecting trial outcome. These variations may be multifactorial such as failure to adhere to protocol guidelines or differences in the equipment quality and/or its use. To prevent these biases, a high-technology quality assurance (QA) procedure has been developed. The RTQA

Figure 2. Local progression evaluation based on modified Huang et al[55] criteria. ^{18}F-FDG, fluorine-18 fludeoxyglucose; PET, positron emission tomography. yr, year. [a] Repeat imaging should be performed no later than 3 months after the first abnormal CT. [b] Biopsy should be considered to confirm outcome if patient is fit enough and in particular if radical treatment remains an option should isolated local progression be confirmed.



procedure aims to ensure for each treatment plan an acceptable level of conformity to the protocol guidelines.[82] The process includes the requirement to submit a benchmark case for review prior to entry of the first patient in the trial (Figure 3). During the recruitment phase, all treatment plans are sent for a prospective central review by a team of experts,

Figure 3. A 54-year-old patient with centrally located non-small-cell lung cancer, T1N0M0, meeting the eligibility criteria for inclusion in the LungTech trial (benchmark case). (a) Delineation of tumour: gross tumour volume (GTV) (purple), internal target volume (red), planning target volume (pink), brachiocephalic vein (orange), superior trachea (pink), chest wall (green), vertebral body (blue), oesophagus (orange) and lungs-GTV (cyan). (b) Stereotactic body radiotherapy planning with dose prescription and adherence of organ at risk dose constraints according to LungTech protocol, isodoses: 64.2 Gy (red), 57.0 Gy (yellow), 48.0 Gy (green), 30.0 Gy (blue) and 15.0 Gy (cyan).

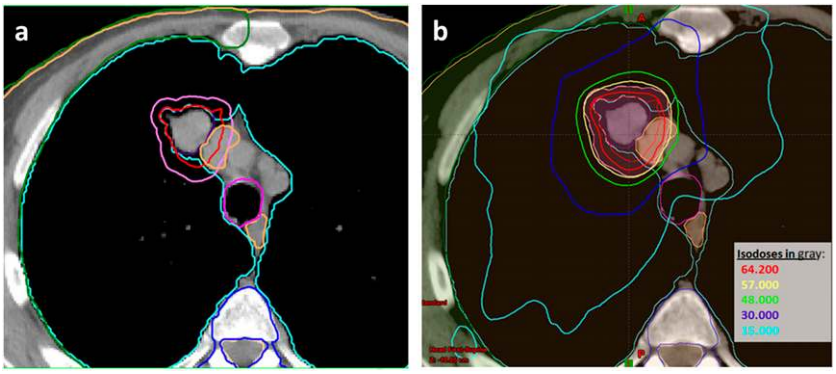
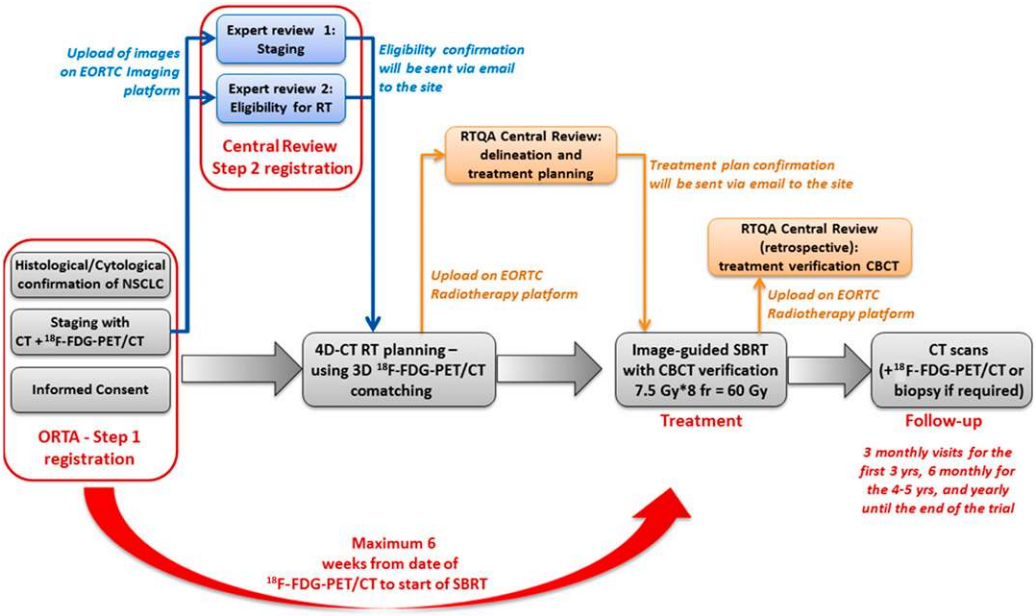
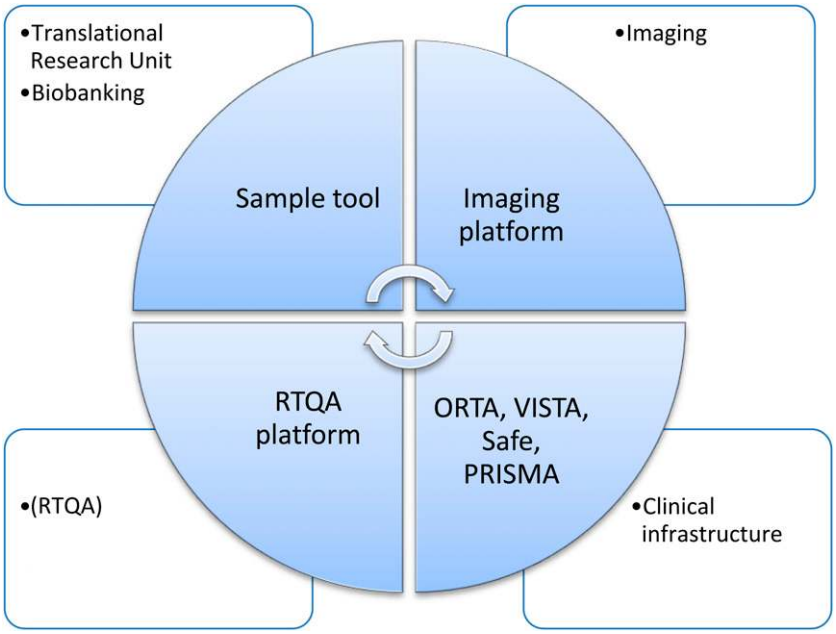


Figure 4. Design of the LungTech trial [European Organization for Research and Treatment of Cancer (EORTC) 22113-08113]. 3D, three dimensional; 4D-CT, four-dimensional CT; ^{18}F-FDG, Fluorine-18 Fludeoxyglucose; CBCT, cone beam CT; fr, fractions; NSCLC, non-small-cell lung cancer; ORTA, online randomized trials access; PET, position emission tomography; RT, radiotherapy; RTQA, radiation therapy quality assurance; SBRT, stereotactic body radiotherapy; yrs, years.



who will decide whether the patient is allowed to be treated based on the treatment plan provided (Figure 4).[83] Another aspect of RTQA is the verification of the correct use of RT techniques within the trial. End-to-end tests will be performed during site visits using a specific breathing phantom (carrying films and an ionization chamber). Owing to the moving nature of the target, the RTQA procedure also includes an evaluation of the PET/CT, CT and 4D-CT

Figure 5. European organization for research and treatment of cancer (EORTC) infrastructure to support new generation clinical trials. ORTA (online randomized trials access), web-based application designed to facilitate the registration and randomization of patients in EORTC clinical trials; RTQA, radiation therapy quality assurance; VISTA, web-based application designed for the completion of most case report forms; PRISMA (protocol repository and integrated project management application), the EORTC clinical trial management system provides a global overview of all projects and also very detailed information about specific protocols.



techniques to assess the impact of potential motion artefacts on target volume accuracy. Furthermore, the LungTech QA evaluation will also include the assessment of consistency of Hounsfield units and SUV values, which is of particular relevance given the use of PET/CT data in this study.

Integration of technology advancement techniques in prospective trials

With technology advancement, the conduct of modern clinical research requires a major upgrade of clinical research organizations and the infrastructure for performing such sophisticated trials. Indeed, implementing this high-technology research brings new challenges to international multicentre clinical trials in terms of QA and standardization. For instance, imaging technologies such as PET scans have existed for decades and are widely available, their full use in clinical research, however, remains challenging. The quality and comparability of images collected within international multicentre clinical trials are not always optimal. Reliable clinical research involving imaging or radiotherapy can only be achieved within quality-assured, multicentre trials supported by robust methodology and operational infrastructures, allowing the processing, storage and analysis of imaging or treatment plan data by experienced researchers to be fully integrated with clinical and biological data (Figure 5). Maintaining quality-assured clinical trials infrastructure is a cornerstone of independent clinical research, which will guarantee consistent, long-term and reliable research to patients. To have the necessary academic clinical research infrastructure available, skilled, experienced staff must be retained.

PERSPECTIVES/CONCLUSIONS

In summary, the LungTech trial is expected to provide high-quality, prospective, multicentre data on the efficacy and toxicity of moderately hypofractionated SBRT for central early stage NSCLC. The data generated by this trial will inform future recommendations on technique, prescription, risk estimation and response assessment for the routine use of this promising new radiotherapy technology. This is of particular importance given the likelihood of an increase in the proportion of patients with lung cancer diagnosed at an earlier stage through screening programs.

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