



EORTC recommendations

European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer



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ABSTRACT

Purpose: To update literature-based recommendations for techniques used in high-precision thoracic radiotherapy for lung cancer, in both routine practice and clinical trials.

Methods: A literature search was performed to identify published articles that were considered clinically relevant and practical to use. Recommendations were categorised under the following headings: patient positioning and immobilisation, *Tumour and nodal changes*, CT and FDG-PET imaging, target volumes definition, radiotherapy treatment planning and treatment delivery. An adapted grading of evidence from the Infectious Disease Society of America, and for models the TRIPOD criteria, were used.

Results: Recommendations were identified for each of the above categories.

Conclusion: Recommendations for the clinical implementation of high-precision conformal radiotherapy and stereotactic body radiotherapy for lung tumours were identified from the literature. Techniques that were considered investigational at present are highlighted.

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Considerable advances in thoracic radiotherapy have been made since the last recommendations of the European Organisation for Research and Treatment of Cancer (EORTC) were published in 2010 [1]. These include the routine integration of 4D-CT and Positron Emission Tomography (PET) imaging in treatment planning, accurate dose calculation algorithms, and improved imaging for treatment verification on the treatment machine. A large body of evidence supports the use of stereotactic body radiotherapy (SBRT) in early stage non-small cell lung cancer (NSCLC), where local tumour control rates of around 90% have been reported, with survival rates that match those of surgery in similar patient groups [2,3]. SBRT is currently under investigation for the treatment of

oligometastatic disease [4], and its use to activate the immune system is a promising area of research [5]. In locally advanced NSCLC and small cell lung cancer (SCLC), concurrent chemo-radiation remains the standard treatment for most patients, but more insight has been gained with regards to patient selection, such as the elderly [6].

The rapid pace of advances in technology and clinical practice led the EORTC Radiation Oncology and Lung Cancer Groups to update previous recommendations, in order to assist departments in implementing high-precision radiotherapy for thoracic tumours. Our working party focused on procedures and techniques that are relevant to the daily practice of clinicians, physicists and radiotherapy technologists. By their very nature, such recommendations have an element of subjectivity. As they are based upon current knowledge, they are neither static, nor necessarily applicable to every single individual patient.

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Methods

MEDLINE and EMBASE were searched with different key words and their permutations including radiotherapy, radiation, 3-D, 4-D, conformal, lung, bronchus, bronchogenic, cancer, carcinoma, tumour, treatment planning, imaging, functional imaging, PET scans, FDG, positioning, mobility, delivery, control, quality assurance, intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), adaptive radiotherapy, SBRT, SABR, stereotactic, side effects, toxicity, organs at risk, image-guided radiotherapy, dose-guided radiotherapy, gross tumour volume, clinical target volume, planning target volume, from January 2001 to March 2017. Studies that were included in the 2010 version [1] were reinterpreted again to re-evaluate their usefulness. The references identified in individual articles were manually searched. Articles referring to outdated techniques for example from the pre-CT scan and pre-3D era and investigational studies were excluded. Several multi-disciplinary task groups identified and analysed appropriate studies according to their topic: Patient positioning (JB, CWH), tumour and nodal motion (UN, MG, CWH, DM), definition of target volumes (UN, JB, UN, CLP, DDR), generating target volumes (CWH, SS, UN, DM), treatment planning (CWH, SS, DM), dose specification and reporting (CWH, CLP), radiotherapy techniques (CWH, SS, MG, DM), dose-volume constraints (JB, CF, MG, DDR) and treatment delivery (JB, CWH, DM). Thereafter, all evidence was discussed with the whole group.

The adapted scheme for grading recommendations from the Infectious Disease Society of America [7] (Table 1) was used.

Results

Patient positioning and immobilisation

We did not identify new studies that would change the 2010 recommendations [1]. Stable and reproducible patient positioning is essential. If possible, patients should be positioned with both arms above the head as this position permits a greater choice of beam positions. However, this position may be unsuitable for individual patients. Reproducible setup can be achieved using a stable arm support, in combination with knee support to improve patient comfort. Several studies have shown that SBRT can be safely delivered without the use of immobilization casts [8].

Table 1
Adapted grading recommendations from the Infectious Disease Society of America [7].

Levels of evidence	
I	Evidence of at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analysis of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies of case-control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk of the disadvantages (adverse events, costs, ...) optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Tumour and nodal changes

Inter-fractional tumour shifts

Inter-fractional changes in anatomy of the target region are frequent, and can be of clinical relevance for both early-stage [9-11] and locally advanced disease [12,13]. Inter-fractional shifts between primary tumour and vertebra positions range from 5 to 7 mm on average (3D vector), but may be as high as 3 cm [9,14]. The use of only an external reference system, such as a stereotactic body frame (SBF), cannot account for such deviations, and consequently, image guidance and patient setup corrections are essential [9,10].

The treatment volume in locally advanced lung cancer often consists of several spatially separated targets (tumour(s), nodes) which will exhibit differential motion and shifts [12]. These non-rigid uncertainties cannot completely be compensated by image-guidance based on couch corrections. Adaptive radiotherapy has been shown to reduce this source of error [13].

Intra-fractional tumour shifts

The intra-fractional target shifts are usually of small magnitude, ranging from 0.15 to 0.21 cm [12]. Small, but systematic, intra-fractional drifts in the cranial and posterior direction were reported [12]. Intra-fractional drifts increase when treatment times exceed 34 min [15].

Intra-fractional respiratory and cardiac motion

Respiratory tumour motion is frequently observed in primary lung tumours and lymph nodes, with the magnitude varying substantially between patients [16,17]. Increased motion has been observed in lower-lobe tumours [16], for smaller primary tumours [18] and for infra-carinal lymph nodes [19]. However, due to large inter-patient variability, patient-specific motion assessment should be performed [20]. The respiratory motion of a lymph node typically differs from respiratory tumour motion, both in terms of amplitude and phase [12,17,19]. For tumours close to heart or aorta, cardiac-induced motion can exceed respiratory motion [16].

Anatomical changes during fractionated radiotherapy

Changes in normal anatomy can be observed during a course of radiotherapy, due to pleural effusion, onset or resolution of atelectasis, tumour progression or shrinkage, and changes in body weight [21]. Transient anatomical changes were reported in 72% of patients during conventionally fractionated RT for lung cancer [22]. Persistent changes such as atelectasis, pleural effusion or pneumonia were reported in 23% of patients [21], and significant disease shrinkage observed in 30% of patients [22,23]. Changes observed indicated an average 1-2% volume reduction per treatment day [24]. Tumour progression has been reported in up to 10% of patients [22]. As these changes in anatomy may lead to either over- or under-dosage of the PTV and/or OARs, adaptation of the radiation plan may be required, making imaging during treatment mandatory.

Definition of target volumes

CT scanning

We did not identify new studies that would change the 2010 recommendations [1]. Planning CT scans should be acquired in treatment position, and incorporate techniques for evaluating motion compensation.

A planning CT scan should include the entire lung volume, and typically extends from the level of the cricoid cartilage to the second lumbar vertebra. Acquiring CT scans with a slice thickness of 2-3 mm is recommended [25]. Use of intravenous (IV) contrast for CT scanning enables improved delineation of centrally located

primary tumours and lymph nodes. In order to be able to account for motion, a 3D-CT is insufficient and a 4D-CT is recommended.

PET scanning

Multiple studies have evaluated the potential role for Positron Emission Tomography (PET) with ^{18}F -deoxyglucose (FDG) for radiotherapy treatment planning. FDG-PET has a higher diagnostic accuracy in detecting lymph node metastases, when compared to CT alone [26]. However, standardisation of the acquisition protocol is necessary, with PET data co-registered with anatomical imaging for radiotherapy planning process [27]. The equipment used for patient immobilisation during PET scans should be identical to that used for CT scanning and treatment, the quality of image co-registration should be verified prior to contouring, as patient movements may lead to incorrect hardware fusion, even when using a PET-CT machine. Caution is advised in using non-rigid registration algorithms, as they have not been evaluated in the context of RT-planning [27]. As chemotherapy can lead to a decrease in FDG-uptake [28], post-chemotherapy FDG-accumulations should not be used for the delineation of the gross tumour volume.

MRI scanning

MRI may give additional information to CT or PET-imaging, particularly for tumours invading the thoracic wall [29]. However, the choice of 4D MRI sequences remains investigational, and careful consideration of movement artefacts is needed.

Role of EBUS and mediastinoscopy

Although FDG-PET-CT scanning has the highest accuracy of all imaging modalities for the mediastinum, both false positive and false negative lymph nodes are observed [26]. Endobronchial ultrasound (EBUS) and/or oesophageal ultrasound (EUS) with needle aspiration (E(B)US-NA) have become standard practice for mediastinal staging in patients with positive nodes on FDG-PET or CT staging [30]. With a sensitivity of over 90%, and a specificity of 100%, mediastinoscopy is only added, in case of a negative EBUS/EUS findings when the FDG-PET-CT scan is positive, or in cN1, or in a central tumour with a diameter exceeding 3 cm [30,31]. The addition of EBUS/EUS to FDG-PET-CT can decrease geographical miss by 4–5% [32]. In general, lymph nodes that are FDG-PET-positive and EBUS/EUS-negative should be included in the GTV, as the false negative rates of EBUS/EUS are high [32].

Target volumes definition

Gross tumour volume (GTV)

We did not identify new studies that would change the 2010 recommendations [1]. The measured diameter of tumours in lung parenchyma or mediastinum is dependent on the window width and level chosen to analyse CT slices [33]. CT-based delineation with standardized window settings is recommended. The best concordance between measured and actual diameters and volumes for CT was obtained with the settings: $W = 1600$ and $L = -600$ for parenchyma, and $W = 400$ and $L = 20$ for mediastinum. However, for larger tumours, the tumour volume on CT can be overestimated [34]. Accurate delineation of the lymph nodes regions, and identification of blood vessels, requires the use of a CT scan with intravenous contrast. Respiratory movements have also to be addressed (see Section “Target volumes definition”).

The identification of pathological lymph nodes has been discussed in Section “Target volumes definition”.

The easiest, and most widely used approach for FDG based target volume definition, is visual GTV-contouring, which uses a clinical protocol that integrates all relevant clinical information, the reports of the nuclear medicine physician and radiologist at standardized window setting [27]. Even when PET is co-registered with

CT, approaches other than those using visual contouring tools should be used with caution, and only in experienced centres that have calibrated and validated such methods appropriately. The use of FDG-PET scans to differentiate tumour from atelectasis has never been subjected to pathological or clinical studies. Elective nodal irradiation is not indicated in any patient group that receives curative or radical doses of radiotherapy for inoperable NSCLC [35,36], as well as for “limited disease” (i.e., stage I–III) SCLC [37], the latter when based on FDG-PET-CT scans for the supra- and infra-clavicular region.

Following prior induction chemotherapy, it is unclear if the volume of the primary tumour to receive full-dose radiotherapy can be limited to only the post-chemotherapy volume. For hilar or the mediastinal lymph nodes, pre-chemotherapy nodal CTV should be treated, even when a partial or a complete remission was achieved with chemotherapy [35,37]. The use of co-registered pre-treatment and planning CT and/or PET-CT scans can enable a more accurate reconstruction of pre-chemotherapy target volumes [38].

Clinical target volume (CTV)

Most studies in locally advanced lung cancer have used a GTV to CTV extension of approximately 5 mm, both for the primary tumour and for the lymph nodes. A CTV margin around the primary tumour and lymph nodes is recommended [39–41], which may be tailored according to the histology of the primary tumour [42], size of lymph node [43] and possibly, imaging characteristics of the tumour [44]. In the absence of prospective trials that have compared disease recurrence patterns with CTV margins adjusted for histology or size, the clinical relevance of the abovementioned factors remains uncertain. The CTV should be manually adjusted, for example when there is no evidence for invasion into a vertebral body or other neighbouring organs. In SBRT treatments, no CTV margins are generally used [45].

When post-operative radiotherapy is indicated in locally-advanced NSCLC, the CTV consists of the resected involved mediastinal lymph node regions, the bronchial stump, the ipsilateral hilar and station 4 node region, station 7 and the contra-lateral lymph nodes at risk [46,47].

Planning target volume (PTV)

The margins used from CTV to PTV depend on all uncertainties related to planning and delivery of radiotherapy (International Commission on Radiation Units and Measurements (ICRU) 83): mechanical, dosimetric, tumour deformation or growth, inter- and intra-fractional setup errors and baseline shifts, respiratory and cardiac motion [13,41,48,49].

While other factors determining the choice of planning margins are derived from specific clinical settings and populations, respiratory motion is a patient-specific factor which should be determined before treatment, typically using a pre-treatment 4D-CT or 4D PET/CT scan. Applying the same respiratory margin for all patients is discouraged since variations in respiratory motion amplitude are large [50].

In general, one can differentiate between passive motion compensation strategies (abdominal compression, internal target volume (ITV) concept, mid-ventilation concept, jet-ventilation) and active motion compensation strategies (gating, breath hold, tracking). Abdominal compression can modestly decrease the respiratory amplitude [51], but the dosimetric gain is limited [52]. Different gating strategies, where radiation is only delivered during specific phases of the respiratory cycle can be employed to reduce the margin accounting for respiratory motion [53]. Deep inspiration breath hold (DIBH) reduces tumour motion while increasing the lung volume, resulting in decreased doses to lung, and often also to the heart [54,55]. Real time tumour tracking is commer-

cially available using robotic radiotherapy [56] for SBRT treatment, but requires generally implanted markers. Application of one (either active or passive) 4D motion compensation strategy is highly recommended; however, current physical and especially clinical data do not support the superiority of one particular strategy. If respiratory motion management strategies are used, the inter- and intra-fractional shifts may differ from those observed in free breathing (FB). For DIBH, larger inter- and intra-fractional shifts are seen compared to FB [57] and the margins applied must account for this.

The two most common passive methods used to take the respiratory motion into account in a patient specific way are:

1. *Internal target volume concept (ITV)*: Delineating all phases of the 4D-CT scan and combining them [58] or delineation guided by a Maximum Intensity projection (MIP) [59]. The ITV method takes into account all respiratory motion, including tumour deformations during breathing.
2. *Mid-ventilation/mid-position concept*: Delineating on a 4DCT image reconstruction technique such as the Mid-ventilation scan [50] which displays the frame whereby the tumour is closest to its mean time weighted tumour position, or the Mid Position scan which displays every voxel in its average position. The respiratory uncertainty is then taken into account as a random error in the CTV to PTV margin calculation [11,50,60,61].

No clinical studies have directly compared the above two methods, but both approaches have shown high local control rates over 90% in patients treated with SBRT [61,62] thereby indicating their safety.

Respiratory motion can also be managed by irradiating the tumour at a fixed part of the trajectory (gating) or irradiating the tumour by following the tumour (tracking) [56,63-65]. However, one has to take into consideration the increased complexity of these techniques.

Changes arising during the course of irradiation, that cannot be corrected for by on-line image guidance, may require adaptive radiotherapy, where a new treatment plan is made based on the new anatomy [66,67].

Planning organ at risk volume (PRV)

The planning organ at risk volume (PRV) concept [68] can be relevant when treating lung cancer, especially in case where a maximum dose constraint is used. For serial organs, including the spinal cord, the main bronchi, the brachial plexus, the oesophagus and large blood vessels, the use of a PRV might be helpful, since it reduces the probability of over dosage [69]. The PRV concept is not relevant for the lung because it is a parallel structured organ [69]. It should nevertheless be stressed that all published OAR constraints are *not* based on the PRV concept.

Treatment planning

Dose calculations

Dose calculation algorithms currently used for lung radiotherapy generally take into account changes in electron transport due to density variations, and are referred to as so-called type B or Monte Carlo based algorithms [70-75]. Use of older algorithms are not recommended as they have been associated with more local recurrences [71]. Differences between more advanced algorithms still exist [76-79], with Monte Carlo algorithms possibly more accurate for estimating dose at the tumour periphery [80]. There is no consensus yet about the clinical acceptability and relevance of reported differences [76,81,82]. Comparisons between 3D dose calculations using the 'average CT' dataset and full 4D calculations show small differences of a few per cent [83,84].

Dose specification and reporting

Dose prescriptions and reporting should comply with international standards [39-41]. Additionally, the type of dose calculation algorithm and CT dataset on which the calculations are based, should also be reported [41].

Beam arrangements

In principle, all radiotherapy delivery techniques can be used, as long as established dose distribution criteria are met. As intra-fraction motion increases with time, it is advisable to limit treatment times. This can be achieved using co-planar techniques or volumetric arc therapy and flattening filter-free beams [85-87].

Dose-volume constraints (Tables 2 and 3)

To predict the probability of radiation-induced damage, many studies have analysed the relationship with dose-volume histogram (DVH) parameters, either with or without patient characteristics. However, many DVH parameters, strongly correlated with each other, have not been validated in independent data sets [88]. Furthermore, studies correlating DVH parameters to clinical outcomes have generally included few patients. As normal tissues may be displaced during radiotherapy, a single imaging study performed before therapy may not accurately reflect the actual delivered dose [89]. There is a need for improved biomarkers or imaging features in radiotherapy prediction models, but these are considered experimental now.

Any application of DVH parameters or Normal Tissue Complication Probability (NTCP) models in clinical practice should consider only those based on published data, and with a clear knowledge of their limitations [88,89]. The LQ model accurately describes the biological effects of different fraction doses for both modelling of tumour control probability and normal tissue complication probability [90-93]. In the following paragraphs, physical doses are described in the context of conventionally fractionated radiotherapy.

Both the lung V_{20} (which is in the original definition the percentage volume of both lungs minus the PTV receiving 20 Gy, although in some studies the GTV has been used) and the mean lung dose (MLD, being the volumes of both lungs minus the GTV), correlate with the risk for radiation pneumonitis [94]. Although a V_{20} of 35-37% or an MLD value of 20 Gy (both calculated with a more advanced RT planning algorithm) have been considered "safe", 10-15% of the patients who meet these constraints may still develop significant (grade 2 or more) radiation-induced toxicity after receiving much lower doses. Conversely, higher V_{20} or MLD levels may be delivered safely. Lower dose parameters such as lung V_5 have in some studies been correlated with higher risk of lung toxicity with either conventional RT or SBRT [95,96]. A systematic review showed that cisplatin or carboplatin-based chemotherapy can be used safely with concurrent chest radiotherapy [6,97]. Predictors of grade 5 pneumonitis were daily dose >2 Gy, V_{20} and lower-lobe tumour location. Patient features such as lung function, age and gender fail to identify patients at high risk of radiation pneumonitis. However, interstitial lung disease and more particularly idiopathic pulmonary fibrosis, should be highlighted as risk factors for severe pneumonitis [98-105]. Such patients should be assessed by an expert pulmonary physician, and patients counselled and informed about high risk of radiation-related side-effects.

Although a meta-analysis comparing concurrent to sequential chemo-radiotherapy did not observe use of concurrent chemotherapy to be associated with increased lung toxicity [106], drugs such as gemcitabine are not recommended for routine use with concurrent radiotherapy in standard practice [6,107,108]. At present, no

Table 2

EORTC recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer.

<i>Fractionation for stereotactic body radiotherapy (SBRT)</i>
<ul style="list-style-type: none"> • SBRT using high doses per fraction should <i>not</i> be given to “ultra-centrally” located tumours (<i>Recommendation grade II, E</i>) • SBRT with lower doses per fraction that are adapted to critical organs (“risk adapted”) should be used carefully for centrally located tumours (<i>Recommendation grade IV, C</i>)
<p><i>Reproducibility of patient positioning and tumour position</i></p> <ul style="list-style-type: none"> • A stable and reproducible patient position during all imaging procedures and treatment is essential (<i>Recommendation grade IV, A</i>) • SBRT can be safely delivered without rigid immobilization devices (<i>Recommendation grade IV, A</i>) • Interventions to reduce tumour motion may be useful in selected patients (<i>Recommendation grade IV, C</i>) • Gating and tracking may be of value in a small subgroup of patients with large tumour motion (<i>Recommendation grade IV, B</i>)
<p><i>CT scanning</i></p> <ul style="list-style-type: none"> • A planning CT scan should include the entire lung volume, and typically extends from the level of the cricoid cartilage to the second lumbar vertebra (<i>Recommendation grade IV, A</i>) • A 4D-CT scan is recommended as it allows to take into account tumour movements and reduced systematic errors and geographical miss (<i>Recommendation grade IV, A</i>) • The use of CT slice thickness of 2–3 mm is recommended as it permits generation of high-resolution digitally reconstructed radiographs (DRR) and facilitates accurate tumour delineation (<i>Recommendation grade IV, A</i>) • The use of intravenous contrast can improve the delineation of centrally located primary tumours and lymph nodes (<i>Recommendation grade III, A</i>)
<p><i>PET scanning</i></p> <ul style="list-style-type: none"> • FDG-PET is recommended in the process of target volume definition (<i>Recommendation grade III, A</i>) • Strictly standardised protocols, preferentially in cooperation with a department of nuclear medicine, are preferred when FDG-PET scans are used for radiotherapy treatment planning (<i>Recommendation grade IV, A</i>) • FDG-PET scans for radiotherapy treatment planning should be acquired in radiotherapy position, and co-registered with a planning CT using rigid methods if the acquisitions are not simultaneously (<i>Recommendation grade IV, A</i>)
<p><i>Generating target volumes</i></p> <p><i>Gross Tumour Volume (GTV)</i></p> <ul style="list-style-type: none"> • Recommended CT settings for tumour delineation are: for lung: $W = 1600$ and $L = -600$, and $W = 400$ and $L = 20$ for mediastinum (<i>Recommendation grade III, A</i>) • Elective irradiation of mediastinal lymph nodes is not recommended for NSCLC and for limited disease SCLC (<i>Recommendation grade III, A</i>) • For NSCLC, selective nodal irradiation based on information from CT, FDG-PET and bronchoscopy, ultrasound-guided fine needle aspiration, mediastinoscopy (if available) is the recommended standard. (<i>Recommendation grade III, A</i>) <p><i>Clinical Target Volume (CTV)</i></p> <ul style="list-style-type: none"> • A fixed 5 mm CTV margin may be used (<i>Recommendation grade III, B</i>) • Manual adjustment of the CTV according to normal tissues (e.g. the bones) may be appropriate (<i>Recommendation grade III, B</i>) <p><i>Planning Target Volume (PTV)</i></p> <ul style="list-style-type: none"> • Generation of CTV to PTV margin should be calculated from uncertainties based on the patient population, patient positioning, treatment technique, treatment unit used and imaging and setup strategies applied. If any of the above are changed the margins should be changed accordingly. The uncertainties should preferably be determined in each institution. (<i>Recommendation grade III, A</i>) • The respiratory induced tumor motion is non-uniform and patient dependent. The applied margins should reflect this (<i>Recommendation grade III, A</i>) <p><i>Planning organ at risk volume (PRV)</i></p> <ul style="list-style-type: none"> • The use of a PRV margin around critical serial organs should be encouraged to avoid overdosing organs at risk (<i>Recommendation grade IV, C</i>)
<p><i>Treatment planning</i></p> <p><i>Dose calculation</i></p> <ul style="list-style-type: none"> • Advanced dose calculation algorithms (type B or Monte Carlo based) are strongly recommended for thoracic radiotherapy as they allow for more accurate computation of dose distributions (<i>Recommendation grade III, A</i>) • Absolute doses and dose distributions calculated with type A vs. type B or Monte Carlo based algorithms cannot be compared (<i>Recommendation grade III, A</i>) • Full 4D dose calculations do not appear to be essential when type B or Monte Carlo based algorithms are used (<i>Recommendation grade III, C</i>) <p><i>Dose specification and reporting</i></p> <ul style="list-style-type: none"> • Dose prescriptions and reporting should follow the appropriate international ICRU standards (<i>Recommendation grade III, B</i>) <p><i>Beam arrangements</i></p> <ul style="list-style-type: none"> • Beams directions should be chosen to minimise dose to OARs while maintaining target coverage. If co-planar techniques can be applied with no compromise in terms of dose to OARs compared to non-co-planar techniques they should be used to limit treatment time (<i>Recommendation grade III, A</i>) <p><i>Dose-volume constraints</i></p> <ul style="list-style-type: none"> • If possible, the V20 or the mean lung dose should be kept than 35–37% and 20 Gy, respectively (<i>Recommendation grade III, A</i>) • Patients with idiopathic pulmonary fibrosis (IPF) are at high risk for developing severe and even lethal radiation pneumonitis; radiotherapy should therefore be avoided if possible (<i>Recommendation grade III, A</i>) • With conventional concurrent chemo-radiotherapy, doses to the central bronchi in excess of 80 Gy increase the risk of bronchial stenosis and fistula (<i>Recommendation grade III, A</i>) • Grade 3 acute esophagitis is associated with higher mean oesophageal dose, V60 and neutropenia, but usually heals within 6 weeks. Dose reductions are in general not recommended (<i>Recommendation grade III, A</i>) • Late oesophageal toxicity (stenosis) is only associated with the maximal dose; doses over 76 Gy are not recommended (<i>Recommendation grade III, A</i>) • In conventionally fractionated radiotherapy, the dose to 2 cm³ of the brachial plexus should not exceed 76 Gy (<i>Recommendation grade IV, A</i>) • In stereotactic radiotherapy, the dose to the brachial plexus should not exceed 26 Gy in 3–4 fractions, the maximal dose should not be over 35 Gy in 3–4 fractions and the V30 not more than 0.2 cm³ (<i>Recommendation grade IV, A</i>) • In stereotactic radiotherapy, to keep the incidence of chest wall pain below 5%, the D70cc of the chest wall should not exceed 16 Gy in 4 fractions and the D2cc should not be over 43 Gy in 4 fractions (<i>Recommendation grade III, A</i>) • In stereotactic radiotherapy, to keep the incidence of symptomatic rib fractures below 5%, the Dmax should not exceed 225 Gy BED ($\alpha/\beta = 3$ Gy) (<i>Recommendation grade III, A</i>) • Vertebral fractures occur at doses over 20–30 Gy and are associated with the V30. Avoidance of the vertebra should be attempted (<i>Recommendation grade IV, A</i>) • The mean heart dose should be kept as low as possible; no clear safe threshold can be defined (<i>Recommendation grade III, A</i>) • Concurrent administration of established carboplatin or cisplatin-based regimen with chest radiotherapy is safe (<i>Recommendation grade I, A</i>)

(continued on next page)

Table 2 (continued)

Fractionation for stereotactic body radiotherapy (SBRT)	
<ul style="list-style-type: none"> As for most targeted agents no safety data are available for their combination with thoracic radiotherapy, their concomitant administration should be avoided (Recommendation grade III, A) Angiogenesis inhibitors combined with radiotherapy to the mediastinum may lead to lethal haemorrhages and should therefore be avoided (Recommendation grade III, A) 	
Treatment delivery	
<ul style="list-style-type: none"> Daily online imaging and soft tissue setup is recommended for all patients and should be mandatory for SBRT treatments (Recommendation grade III, A) Adaptive radiotherapy is recommended for patients with large anatomical changes (Recommendation grade IV, A) 	

Table 3
Summary of Organs at Risk constraints.

Organ	Organ at risk	Endpoint	Dosimetric parameter	Maximum value
<i>Conventionally fractionated radiotherapy</i>				
Lung	Lungs minus GTV	Symptomatic radiation induced pneumonitis	V20	35–37%
Lung	Lungs minus GTV	Symptomatic radiation induced pneumonitis	MLD	20 Gy
Central bronchi	Proximal bronchial tree	Stenosis and fistula	Maximum dose	80 Gy
Oesophagus	Oesophagus	Acute grade 3 oesophagitis	Mean oesophageal dose, V60	ALARA
Oesophagus	Oesophagus	Stenosis	Maximum dose	76 Gy
Brachial plexus	Brachial plexus	Plexopathy	D2cm ³	76 Gy
Heart	Heart	Cardiac toxicity	Mean heart dose	ALARA
<i>Stereotactic Body Radiotherapy</i>				
Brachial plexus	Brachial plexus	Plexopathy	Maximum dose	35 Gy in 3–4 fractions
Brachial plexus	Brachial plexus	Plexopathy	V30	0.2cm ³
Chest wall	Chest wall	Chest wall pain	D70cm ³	16 Gy in 4 fractions
Chest wall	Chest wall	Chest wall pain	D2cm ³	43 Gy in 4 fractions
Ribs	Chest wall	Fracture	Maximum dose	225 Gy BED ($\alpha/\beta = 3$ Gy)

targeted agents have shown proven benefit when combined with radiotherapy, and experience with concurrent radiotherapy and EGFR tyrosine kinase inhibitors and bevacizumab has shown increased toxicity [109].

Severe bronchial stenosis and fistula may manifest 2 years or more after the main bronchi have received over 80 Gy, which emphasises the need to limit doses to central structures to 80 Gy, and also to follow patients for more than 2 years in order to observe late side effects [109]. Late proximal bronchial tree complications have been reported following both hypofractionated RT and SBRT, and safe dose constraints remain to be refined [110–115].

The incidence of transient grade 3–4 acute oesophagitis is low (<5%) when radiotherapy alone or sequential chemo-radiation is used, but may be as high as 30% with concurrent chemo-radiation [106]. Dosimetric factors predictive of grade 3 or higher toxicity, include the mean oesophageal dose (MED) and V60 [116,117]. As grade 3 oesophagitis generally heals within 3–6 weeks post-treatment, with late side effects such as strictures occurring in less than 1% of patients, the survival benefits of concurrent chemo-radiation generally outweighs the risk of high-grade acute oesophagitis in good performance status patients. For severe late oesophageal toxicity, the maximum oesophageal dose is predictive, and not the mean dose [118].

Retrospective studies suggest that as long as the maximal dose to the brachial plexus (2 cm³) is kept below 76 Gy, the risk of radiation plexopathy is low [119,120]. In patients treated with SABR, delivery of absolute brachial plexus doses over 26 Gy in three to four fractions, and brachial plexus maximal dose over 35 Gy, and V30 of more than 0.2 cm³, all increased the risk of brachial plexopathy [121].

In SBRT, the chest wall, ribs and vertebral bodies have become organs at risk, despite the fact that the majority of patients are asymptomatic or complain of mild toxicity. For chest wall pain, the risk increases when the D70cc is over 16 Gy in 4 fractions, and the D2cc above 43 Gy in 4 fractions [122,123]. The risk of symptomatic rib fractures after SBRT was significantly correlated to dose, and was <5% at 26 months when Dmax < 225 Gy (biologi-

cal equivalent dose (BED), $\alpha/\beta = 3$ Gy) [124,125]. However, target coverage should generally not be compromised for chest wall sparing, and more fractionated SBRT regimens should be considered in such cases [126].

In locally advanced NSCLC, thoracic vertebral fractures were reported in 8% of patients after a 12 month median follow up time [127,128]. Significant dosimetric factors associated with vertebral fractures were the V30 and mean vertebral dose, with doses of 20–30 Gy being associated with bone injury [128]. Although vertebral SBRT is associated with a risk of vertebral fracture, there is limited data available on the risk of such fracture after lung SBRT [126].

Historically, heart toxicity was not considered to be of relevance for most lung cancer patients. However, it has become increasingly clear that radiotherapy-related cardiac events may occur within months after radiotherapy [129]. Both dose to the heart and patient's cardiac risk factors determine the incidence of cardiac events. The mean heart doses associated with cardiac events were <10 Gy, 10–20 Gy, or ≥ 20 Gy and 4%, 7%, and 21%, respectively. It is unclear which regions of the heart are most susceptible for radiation injury. The contribution of heart doses to mortality has not been consistently demonstrated [129–131], but it is preferred that heart doses be limited as much as possible.

The tolerance of the spinal cord, like other organs, is a sliding scale, with estimated risks of myelopathy to the full-thickness cord using conventional fractionation of 1.8–2 Gy/fraction of <1% and <10% at 54 Gy and 61 Gy, respectively, with a strong dependency on the dose per fraction ($\alpha/\beta = 0.87$ Gy) [132,133].

Treatment delivery including imaging and dose guidance during treatment

Image guidance

Daily online pre-treatment imaging, and setup corrections to reduce the inter-fractional systematic and random errors, allow for use of a smaller CTV to PTV margin [14,15]. The use of cone beam CT (CBCT) scans has been shown to allow a more accurate

setup than portal imaging [134]. For SBRT, 4D-CBCT is preferable over 3D-CBCT [135]. The highest accuracy is achieved with soft-tissue match on either anatomical landmarks or primary tumour, compared with bones and this accuracy is reported to translate into smaller margins, lower lung dose and less pneumonitis [68,69]. The differential motion of tumour and lymph nodes implies that a setup strategy prioritizing one target will result in greater uncertainty in the position of the others, and margin calculations should reflect this uncertainty. Primary tumours are often visible on a CBCT scan but mediastinal lymph-nodes are more difficult to visualise; their position however can be derived from anatomical landmarks [12,13]. The carina is frequently used as a surrogate for nodal position [12,57], which is most accurate for node stations 4, 5, 7, while other anatomical landmarks may be more suitable for stations 1, 2, 6, 10, 11 [13]. Daily image guidance with soft-tissue setup is recommended for all fractionation schemes because of frequent intra thoracic anatomical changes [29,30,66]. In SBRT delivery, image guidance based on tumour setup is mandatory, but tumour baseline shifts which could impact on doses to organs at risk should be evaluated [133].

Adaptive radiotherapy

Soft-tissue setup combined with corresponding margins ensures target coverage in the majority of patients, but this approach may be insufficient for selected patients with either large differential shifts of tumour and nodes, or anatomical changes occurring during treatment [29,30,66]. In deciding when to adapt treatment plans, it is important to keep in mind that only the inter-fractional changes are observed on the pre-treatment CBCT. Since the CTV to PTV margin includes all planning and delivery uncertainties, maintaining the planned dose is therefore not sufficient to keep the target within the PTV. The use of 3D portal dosimetry for detecting dosimetric consequences of anatomical changes has the potential to automate the evaluation, but this represents work in progress [136,137].

Developing technologies

New technologies are likely to change the way lung cancer patients will be treated with radiotherapy, with or without emerging targeted drugs and immune therapy.

Proton therapy has the potential to limit the radiation dose to organs at risk, especially the low dose volumes, or when maximal advantage can be taken from the Bragg peak and the virtual absence of radiation dose distal to it [138]. The sensitivity of proton beams for anatomical changes are larger than for photons, and the technical requirements are more challenging.

The MRI-linac combines regular linear accelerator technology with MRI guidance on the machine [139]. This could theoretically result in margin reduction and improved adaptation processes. The first machines are being installed, and no clinical data or randomized trials are yet available.

Discussion

As many departments are currently equipped with modern radiotherapy tools discussed in this review, it is increasingly feasible to implement high-precision thoracic radiotherapy and SBRT. However, centres must be familiar with the application of these tools for the treatment of lung cancer. The main aim of this review was to formulate practical recommendations for use in departments wishing to introduce such techniques, and these are summarised in Table 2.

It should be emphasised that nearly all data have been derived from patients treated for NSCLC.

As the precision in radiotherapy delivery is rapidly evolving, any conclusion or statement in these recommendations may need to be updated as required. This document will be used within the EORTC for the development of study protocols, and to evaluate the technical capabilities of participating centres.

Conflict of interest

None of the authors have a conflict of interest to declare.

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