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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.

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