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GOECP/SEOR radiotherapy guidelines for non-small-cell lung cancer

Rodríguez De Dios N *et al.* Guidelines for non-small-cell lung cancer

Abstract

Non-small cell lung cancer (NSCLC) is a heterogeneous disease accounting for approximately 85% of all lung cancers. Only 17% of patients are diagnosed at an early stage. Treatment is multidisciplinary and radiotherapy plays a key role in all stages of the disease. More than 50% of patients with NSCLC are treated with radiotherapy (curative-intent or palliative). Technological advances-including highly conformal radiotherapy techniques, new immobilization and respiratory control systems, and precision image verification systems-allow clinicians to individualize treatment to maximize tumor control while minimizing treatment-related toxicity. Novel therapeutic regimens such as moderate hypofractionation and advanced techniques such as stereotactic body radiotherapy (SBRT) have reduced the number of radiotherapy sessions. The integration of SBRT into routine clinical practice has radically altered treatment of early-stage disease. SBRT also plays an increasingly important role in oligometastatic disease. The aim of the present guidelines is to review the role of radiotherapy in the treatment of localized, locally-advanced, and metastatic NSCLC. We review the main radiotherapy techniques and clarify the role of radiotherapy in routine clinical practice. These guidelines are based on the best available evidence. The level and grade of evidence supporting each recommendation is provided.

Key Words: Radiotherapy; Non-small cell lung cancer; Guidelines; Stereotactic radiation therapy; Hypofractionated radiation; Oligometastasis

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Core Tip: Radiotherapy is a critical component of multi-modality treatment of ¹²non-small-cell lung cancer (NSCLC). This guideline provides recommendations on the use

of radiation therapy to treat patients with different stages of NSCLC. Our goal is to promote medical knowledge among physicians and improve health-care quality on these patients. These guidelines are based on the best available evidence. The level and grade of evidence supporting each recommendation is provided.

5 INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in both men and women. In 2018, there were more than 1.7 million cancer-related deaths worldwide. In that same year, more than 2 million people were newly-diagnosed with lung cancer. At diagnosis, approximately 57% of lung cancers are metastatic, 22% present lymph node involvement, and only 17% of cases are diagnosed at early stages^[1]. Various environmental and lifestyle factors have been associated with the development of lung cancer. The main risk factor is tobacco use, accounting for 85%-90% of cases^[2]. Non-small cell cancer (NSCLC) comprises more than 85% of all lung cancer diagnoses. Despite important treatment advances in recent years, 5-year overall survival (OS) rates remain low, ranging from 0%-10% in stage IVA-IVB disease to as high as 68% in early stage^[3,4].

Advances in treatment and diagnosis include minimally-invasive diagnostic/therapeutic techniques such as endobronchial ultrasound (EBUS) and video-assisted thoracic surgery^[5]. In addition, determination of the histological subtypes has become standard practice to assess eligibility-based on tumor histology and molecular status-for systemic therapy^[6,7].

Radiotherapy (RT) is one of the three pillars of the multidisciplinary treatment of lung cancer. In recent years, technological advances have greatly improved this treatment modality. It is estimated that more than half of all cancer patients will require curative or palliative-intent RT at some point in the course of the disease^[8]. A series of important advances-including simulation with four-dimensional computed tomography (4D-CT), three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), volumetric modulated arc therapy (VMAT), cone beam CT (CBCT) image

verification systems, and control of respiratory movement-have made it possible to maximize tumor control while minimizing toxicity to adjacent healthy organs and tissues^[9]. As a result, the radiation dose can be precisely delivered to the target and adapted to the patient's individual characteristics [anatomy and tumor location, TNM stage, comorbidities, and general performance status (PS)].

In the present guidelines, we review the clinical indications for RT in NSCLC according to disease stage, with a discussion of fractionation schedules, treatment volumes, and organs at risk (OAR). We also discuss the management of the main clinical scenarios seen in routine practice, establishing the grades of recommendation for each treatment according to the strength of evidence.

METHODS

These guidelines are based on the most relevant studies published in peer reviewed journals. A comprehensive review of the clinical literature in the following databases was performed: MEDLINE (Pubmed), EMBASE (Ovid), Web of science (Web of Knowledge). Article selection was undertaken by the expert authors. The Infectious Diseases Society of America grading system^[10] was used to assign levels of evidence and grades of recommendation (Table 1). Statements without grading were considered justified standard clinical practice by the authors.

Diagnosis

The clinical manifestations of lung cancer are frequently nonspecific. If NSCLC is suspected, the patient should be referred to the pulmonologist and/or the rapid diagnosis unit and be evaluated by a multidisciplinary team (II, C)^[11,12]. The evaluation begins with CT^[13,14] and positron emission tomography (PET), which are essential for diagnosis, staging, and treatment planning (I, A). Brain magnetic resonance imaging (MRI) is also essential^[15]. All nodes > 1.5 cm on the CT scan should be biopsied, even if the PET scan is negative (I, C). A positive PET scan should be further evaluated, regardless of lesion size^[16,17], through EBUS or digestive endoscopic ultrasonography^{[18-}

^{20]} (I, A). In uncertain cases, conventional mediastinoscopy or video-assisted mediastinoscopy and video-assisted thoracoscopy are surgical alternatives to obtain samples for subsequent analysis^[21,22]. Peripheral lesions can be evaluated by CT-guided transthoracic fine-needle aspiration biopsy^[14,23]. Pathologic confirmation is required in patients with a single metastatic lesion and uptake on PET^[24].

Pathologic diagnosis of NSCLC should be based on the criteria established in the World Health Organization classification system^[6]. It is important to differentiate between the histological subtype: Squamous cell carcinoma, adenocarcinoma (the most common), large cell carcinoma, and neuroendocrine tumors (I, B). The International Association for the Study of Lung Cancer (IASLC) has developed a classification system for adenocarcinoma with prognostic implications^[25]. Immunohistochemical studies and determination of molecular alterations ² such as epidermal growth factor receptor (EGFR), Kirsten rat sarcoma, and anaplastic lymphoma kinase (ALK) mutations should be performed, as these alterations can predict sensitivity to certain drugs and/or targeted therapies^[26] (I, B). Classification of NSCLC or not otherwise specified histology should be avoided. Staging is based on the IASLC TNM classification system (8th edition), which is used to classify patients according to disease stage to determine the prognosis and appropriate treatment^[27].

CLINICAL INDICATIONS BY TNM STAGE

Early stages: Stereotactic body radiation therapy

¹⁶ **Indications:** Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative body radiation, consists of delivery of high dose radiation to a very specific target volume, with a high dose gradient in all directions^[28]. The indication for this technique is based on the patient's surgical risk category: Inoperable, high-risk, or standard-risk^[29]. As follows: (1) Inoperable: Approximately 25% of patients with early-stage NSCLC (ES-NSCLC) are inoperable due to age or comorbidities^[30]. In this population, prospective studies of SBRT have reported local control (LC) rates of 90% at 5 years^[31] and 91.9% at 7 years^[32] and, with a \geq grade (G)3 toxicity rate under 10%. The

well-designed phase II TROG 09.02 CHISEL trial^[33] compared SBRT to conventional 3D-RT. SBRT was superior to conventional 3D-RT in terms of LC [hazard ratio (HR) = 0.32, 95% confidence interval (CI): 0.13-0.77, $P = 0.0077$] with no increase in treatment-related adverse events (AEs). SBRT is therefore the treatment of choice in inoperable patients (III, A); (2) Operable NSCLC: Only one prospective study (a pooled analysis of the ROSEL and STARS trials) has (indirectly) compared SBRT to 3D-CRT in operable patients^[34,36]. The findings of that study, published in 2015, were criticised for the underpowered statistical analyses and the poor surgical quality in the two trials^[35]. Several non-comparative prospective studies of SBRT have been conducted, most notably the phase II RTOG 0618 trial^[36]. In that trial, 33 operable patients received SBRT, with a 4-year LC rate of 96% and \geq G3 toxicity of only 8%. The findings of retrospective series comparing SBRT to surgery through matched pair analysis are inconclusive^[37,38]. However, a recent meta-analysis^[39] suggested that surgery may provide better outcomes on various survival parameters, including OS, cancer-specific survival, and disease-free survival (DFS). Prospective phase III trials are needed to confirm these findings. Currently, four prospective trials are underway to compare surgery to SBRT. Of these trials, the only non-randomised study is the Canadian RAXSIA trial (NCT03431415). The POSTILV trial (NCT01753414) is comparing SBRT to surgery in operable patients while the STABLE-MATES trial (NCT02468024) is comparing sublobar resection to SBRT. Although the VALUE trial (NCT02984761) was activated in 2016, they are still recruiting patients as of the last update (December 2020). Therefore, at present, there is no evidence to support SBRT *vs* surgery in operable patients, unless the patient refuses surgery (III, C); and (3) High-risk patients or patients > 75 years of age. The American Society of Clinical Oncology and the American Society of Radiation Oncology (ASTRO) recommend offering SBRT as an alternative treatment in high-risk patients^[40,41] (III, A).

Fractionation: In order to select the appropriate fractionation schedule in SBRT, it is essential to carefully weigh the risks and benefits. LC is poor when the biological

equivalent dose (BED) is $< 100 \text{ Gy}^{[42]}$. Consequently, the dose should be determined according to the location of the target lesion and, therefore, to the tolerance of adjacent organs. Tumors are classified as central, peripheral, or “safe” ($> 2 \text{ cm}$ from mediastinal structures and $> 1 \text{ cm}$ from the chest wall) depending on their location within the thoracic cavity.

Central tumors: Central tumor fractionations as defined by the IASLC^[42]: The most important prospective phase I/II trial for central tumors was the RTOG 0813 trial^[43], a dose escalation study comparing 50 Gy to 60 Gy, both administered in 5 daily fractions (fx), with an escalation schedule of 0.5 Gy per fraction/arm. The ¹¹ maximum tolerated dose was 12.0 Gy/fx, with a $\geq \text{G3}$ toxicity rate of 7.2%. Two-year LC rates in patients who received the lowest dose fraction (10 Gy/fx) was 87.5% *vs* 87.9% in the 12 Gy/fx regimen, with 2-year progression free survival (PFS) rates of 50% *vs* 54.5%, respectively.

The dose-escalated SUNSET^[44] trial (Dose Level 1:60Gy/7fr-Dose Level 3 60Gy/5fr) and the Hilus^[45] trial (56Gy/8fr to 65%-70% isodose line) were both performed to assess high-dose SBRT in central/ultracentral tumors. The recently published, Hilus trial showed that this fractionation regimen in tumors located $\leq 1 \text{ cm}$ from the main bronchus and trachea had a high risk of G3 to G5 toxicity (33.8%) with 10 patients experiencing G5 toxicity. These regimens contrast with the more conservative Dutch regimen (60 Gy/8 fx)^[46], which obtained a 3-year LC rate of ¹ 92.6% and $\geq \text{G3}$ toxicity of 7.9%.

Based on the available evidence, the optimal fractionation in central tumors appears to be 50 to 60 Gy delivered in five fractions. The dose per fraction should be adjusted to OAR tolerances, and can range from 10-12 Gy/fraction with a total dose of 50-60 Gy administered in 5 daily fractions or 8 fractions of 7.5 Gy each to a total of 60 Gy.

¹ **Lesions adjacent to the chest wall:** In patients with tumors located adjacent to or in contact with the chest wall, European guidelines^[47] recommend a total dose of 48 Gy in four fractions. Prospective studies^[48] have shown that this fractionation schedule yields

3-year LC rates ranging from 85.4% to 87.3%, with a \geq G3 toxicity rate (rib fracture) of 3%. Other fractionation schedules have been proposed in this location. For example, Haasbeek *et al*^[46] proposed 60 Gy in five fractions, with a 3-year LC rate of 89.3% and a late \geq G3 toxicity rate (chest wall pain) of 2.1%^[46]. Nyman *et al*^[49] proposed 45 Gy in three fractions, which achieved a LC rate of 80% with late toxicity (rib fracture) in 4%.

Tumors located in the “safe” zone: Lesions located in the “safe” zone can be considered non-central tumors located > 2 cm from the chest wall. Evidence from two prospective phase II trials - Singh *et al*^[50] and RTOG 0915^[31]-support extreme hypofractionation (single 30-34 Gy fraction). Singh *et al*^[50] found that a single 30 Gy fraction yielded a 2-year LC rate of 94.9%, with G3 toxicity in 17%, and no \geq G4 toxicity. In RTOG 0915, which evaluated a single 34 Gy dose, the one-year LC rate was 97.0%, with \geq G3 toxicity rate of 10.3%. Timmerman *et al*^[51] conducted a prospective phase II trial to evaluate SBRT in inoperable ES-NSCLC, the findings of that trial supported the classical Timmerman fractionation scheme, with a 3-year LC rate in peripheral tumors ranging from 90.6%-94% and \geq G3 AEs ranging from 10% to 16.3%.

Locally-advanced, inoperable disease

Radical chemoradiotherapy: Concomitant vs sequential: At diagnosis, approximately 35% of patients with NSCLC present locally-advanced disease, for which the standard treatment is CRT. The recommended RT dose is 60-66 Gy (I, A). Increasing the radiation dose in combination with chemotherapy (ChT) does not improve outcomes but does increase toxicity rates^[52].

In patients with good PS, the recommended treatment is concomitant chemoradiotherapy, which has been shown to improve OS vs sequential chemoradiotherapy by 5.7% at 3 years and 4.5% at 5 years, with a mean survival time of 22-25 mo and 5-year OS of 20%^[53], probably due to better locoregional control (2.9% at 3 years and 2.2% at 5 years) (I, A). However, concomitant chemoradiotherapy also has a higher incidence of acute non-hematological toxicity^[54], mainly G3-G4 esophagitis

(range: 4%-18%), but no effect on acute pulmonary toxicity^[55]. To date, no differences in treatment outcomes have been observed for the following variables: Type or ChT scheme, age, sex, PS, histology, or disease stage. Neither induction nor consolidation ChT are indicated, although data from the phase III PACIFIC trial showed that consolidation therapy with durvalumab improves both PFS and OS in patients with programmed death ligand 1 > 1% who do not progress after concomitant chemoradiotherapy^[56].

Neoadjuvant chemoradiotherapy: Several studies, including the SAKK Lung Cancer Project Group trial^[57] and the Lung Intergroup Trial 0139^[58], have evaluated the role of neoadjuvant chemoradiotherapy, finding this approach improves PFS in patients who receive trimodal treatment, but without any benefit for OS. This lack of benefit in the surgical arm may be due to higher early mortality rates, especially in patients undergoing right pneumonectomy. A subanalysis found a significant improvement in survival in patients treated with induction chemoradiotherapy followed by lobectomy *vs* those who received concomitant chemoradiotherapy ^[58].

Induction chemoradiotherapy has been shown to achieve a greater reduction in nodal downstaging than ChT alone, but with no benefit in OS^[53] except for potentially resectable superior sulcus tumors, for which the treatment of choice is concomitant chemoradiotherapy (45-54 Gy, 1.8-2 Gy/d) (III, A). However, it is important to plan radical dose RT in case surgery is ultimately not performed^[59].

Adjuvant RT: Adjuvant RT is indicated when complete resection (R0) has not been achieved and salvage surgery is not feasible (I, A). In these cases, sequential chemoradiotherapy (ChT followed by RT) should be offered, although with a less aggressive ChT scheme. Concomitant chemoradiotherapy should be limited to patients with macroscopic residual disease (V, C).

The role of adjuvant RT has long been controversial, especially after a meta-analysis published in 1998 showed higher mortality rates after postoperative RT (PORT) in

patients with N0-N1 disease^[60]. However, the increased mortality was probably due to the excessive toxicity associated with older radiation therapy techniques. By contrast, no deleterious effects of adjuvant RT have been observed in N2 disease. A recent meta-analysis concluded that adjuvant RT is associated with better OS and PFS rates in these patients^[61].

The role of PORT was evaluated in two recent phase III trials. In the phase III Lung-ART trial (definitive results still pending publication) patients with N2 involvement were randomized to receive PORT (54 Gy) or observation after complete tumor resection. The initial results showed that PORT did not improve DFS or OS, although fewer thoracic relapses were observed in the group treated with PORT (25% *vs* 46.1%). The lack of improvement in survival outcomes (DFS and OS) could be due to higher rates of cardiopulmonary toxicity \geq G3 (10.8% *vs* 4.9%). In this regard, it should be noted that 89% of the patients were treated with 3D-CRT and only 11% with IMRT^[62].

The second recently-published phase III trial was a single-center study involving 394 patients with stage IIIA-pN2 disease randomized to receive PORT (50 Gy) or observation after complete resection and four cycles of adjuvant chemotherapy. Most of the patients (89.3%) were treated with IMRT (10.7% received 3D-CRT). In the intention-to-treat analysis, PORT did not improve DFS, although it did improve DFS in the per-protocol analysis. The results of a pre-planned exploratory analysis in which patients were stratified according to the number of resected nodes (≤ 20 *vs* > 20) and involved nodes [(1-3) *vs* ≥ 4] revealed ¹⁰ a significant improvement in DFS (HR = 0.75; 95%CI: 0.58-0.98; $P = 0.04$). PORT had no impact on OS. Toxicity rates were lower than observed in the Lung-ART trial, probably due to the high proportion of patients treated with IMRT, stricter dose limits to the OARs, and the exclusion of the contralateral mediastinal nodes from the treatment volume^[63].

Despite the significant improvement in LC achieved in both trials, this did not lead to better survival outcomes. For this reason, PORT is not currently recommended as part of standard treatment in patients with N2 involvement and R0 resection. However, stage IIIA-N2 patients are a heterogeneous group and some of these patients could

benefit from PORT, as suggested by data from previous studies as well as the recently published findings of the Lung-ART trial (ESMO 2021), which show that a mediastinal nodal involvement ratio (nodes involved/nodes evaluated) $\geq 25\%$ is a prognostic factor for DFS, suggesting that the extent of nodal involvement could help to select patients who may benefit from PORT. Nonetheless, more studies are needed to better determine, through a comprehensive analysis of clinical and molecular characteristics, the patients most likely to benefit from PORT. Based on the postoperative pathologic findings, the recommended PORT doses are as follows: (1) R0: 50-54 Gy, 1.8-2 Gy/fx; (2) Involved margins or microscopic disease: 54-60 Gy; and (3) Macroscopic residual disease: ≥ 60 Gy^[59,64].

Altered fractionation schemes: Various dose-intensification strategies have been explored, including accelerated hyperfractionation and other hypofractionated schemes.

Accelerated fractionation and hyperfractionation: Three phase III trials compared different hyperfractionated schemes to conventional RT, demonstrating that hyperfractionated RT yields positive results when administered alone or after induction ChT (I, A). Those trials include the Continuous Hyperfractionated Accelerated Radiotherapy Trial (CHART)^[65,66], HART^[67], and Continuous Hyperfractionated Accelerated Radiotherapy weekend less (CHARTWEL)^[68]. The findings of these trials were recently confirmed in a large retrospective series^[69].

A meta-analysis evaluated the results of nine trials (2000 patients) - including the CHART, HART, and CHARTWEL trials - comparing conventional RT to various hyperfractionated and accelerated RT schemes. All of the altered fractionation schemes improved OS, although without any significant between-group differences in PFS. The administration or not of ChT did not impact OS. The modified fractionation schemes, particularly very accelerated RT, increased the risk of acute severe esophagitis in Table 3^[70].

Moderate hypofractionation: Some patients - due to advanced age, the presence of comorbidities, and/or travel-related difficulties - are poor candidates for conventional (60-66 Gy, 30-36 daily fractions) or hyperfractionated RT. In recent months, due to the coronavirus disease 2019 (COVID-19) pandemic and the consequent need to reduce the number of hospital visits, the use of moderately hypofractionated RT has become more common in patients eligible for radical RT.

The available evidence suggests that dose escalation with standard fractionation techniques (achieved by extending treatment duration) does not improve outcomes^[52]. However, radiobiological models show that each 1% increase in the radiation dose improves LC by 1% to 2%^[71]. A systematic review of clinical data from dose escalation studies^[72] found a BED₁₀ dose-response relationship for NSCLC. That review evaluated studies that applied various fractionation schemes, including standard fractionation, hyperfractionation, and hypofractionation. Although the best results were obtained with hypofractionated RT, the differences were not significant.

Phase I dose escalation trials of hypofractionated RT have evaluated various regimens^[73-75]. Prospective and retrospective series^[76-80] have found that accelerated RT is both feasible and well-tolerated when administered alone or concurrently/sequentially with ChT, a finding that was also confirmed in the interim analysis of a phase III trial (Iyengar *et al*^[81]) comparing accelerated hypofractionated RT to conventional RT.

The phase III EORTC 08972-22973 trial^[82] and the randomised phase II SOCCAR trial^[83] compared concurrent to sequential CRT in patients receiving hypofractionated RT. Based on the excellent results obtained with concomitant CRT in the SOCCAR trial^[83], this scheme is now widely used in routine practice in the United Kingdom. Iqbal *et al*^[84] showed that modifying the ChT dose, incorporating advanced imaging techniques such as PET-CT for staging, and the use of IMRT and VMAT improved survival outcomes at 2-years (58%), with acceptable rates of acute toxicity (Table 4).

A systematic review evaluated 33 studies (1902 patients) involving radical-intent hypofractionated RT for the treatment of stage III NSCLC. The number of fractions in

those studies³ ranged from 15 to 35, with dose fractions ranging from 2.3 Gy to 3.5 Gy, and total doses from 45.0 to 85.5 Gy. Nearly half of those studies (15/33) included concurrent ChT with radiation schemes ranging from 52.5 to 75 Gy at 2.24-3.5 Gy/dose in 15-30 fractions. The other studies included neoadjuvant, adjuvant, or no ChT, at RT doses ranging from 45-85.5 Gy (2.25-3.42 Gy/fx, 15-35 fractions). There was a linear relationship between BED₁₀ and OS:³ Every 1 Gy increase in BED₁₀ yielded an absolute survival benefit of 0.36% to 0.70%. Compared to non-concurrent schemes, concurrent CRT was associated with better OS, albeit with higher - but still acceptable - rates of esophageal toxicity^[85].

A single-centre study evaluated 563 patients; 43% received CHART and 57% hypofractionated RT (55 Gy in 20 fractions of 2.75 Gy). Both treatment regimens yielded comparable results in terms of survival and treatment-related AEs^[86]. Based on their findings, the authors concluded that moderately hypofractionated RT with concurrent ChT is safe when delivered with modern RT techniques and may improve treatment outcomes. However, these findings need to be confirmed in phase III trials.

The ongoing COVID-19 pandemic has led to an increase in the use of hypofractionated RT. To address the challenges presented by the pandemic, a group in the United Kingdom^[87] and the ESTRO-ASTRO^[88] have both published recommendations for hypofractionated schemes during this period. The United Kingdom group recommends 55 Gy in 20 fractions of 2.75 Gy with concurrent ChT in patients with good PS. In patients unable to tolerate concurrent CRT, those guidelines recommend either sequential CRT or RT alone. If ChT is not administered, then hypofractionated RT schemes (*e.g.*, 50-58 Gy in 15 fractions) can be considered^[87]. The ESTRO-ASTRO practice guidelines, developed through a modified Delphi consensus process, proposed recommendations for two different scenarios: (1) Early pandemic phase, focused on risk mitigation; and (2) A later phase (severe pandemic scenario) in which RT resources may be limited. In the first scenario, there was strong support (97% of the expert panel)⁹ for hypofractionated RT (60 Gy in 15 fractions, 60 Gy in 20 fractions, 60-66 Gy in 24-30 fractions, or 55 Gy in 20 fractions) if treatment was limited to RT

alone. For sequential CRT, there was also strong support (97%) for the same fractionation and dose schemes, although with a clear preference for the 55 Gy (20 fractions) or 60-66 Gy (24-30 fx at 2.2-2.75 Gy/d) schemes (II, A). There was no consensus to support concomitant hypofractionated CRT. An alternative would be 55-60 Gy in 20 fractions^[88] (II, B).

RT in advanced NSCLC

RT in oligometastatic patients: Approximately two-thirds (60%-70%) of patients with NSCLC are diagnosed with stage IV disease. Of these, 20% - or more if PET-CT imaging is used for staging - are oligometastatic at diagnosis^[89]. Oligometastasis may present in one of two ways: (1) “*De novo*” oligometastasis: Patient with ≤ 3 -5 lesions at diagnosis (synchronous) or after 3-6 mo of treatment of the primary tumor (metachronous); and (2) Induced oligometastatic: Polymetastatic patient with metastatic disease in ≤ 3 -5 locations after systemic therapy.

This recently described concept of oligometastatic disease^[90,91] can be further subdivided as follows: (1) Oligopersistence: Persistent disease that is stable on imaging studies, with < 5 lesions after systemic treatment; (2) Oligoprogression: Progression (new lesions or growth of known lesions) in 3 to 5 sites after systemic treatment; and (3) Oligorecurrence: Recurrent disease in 3-5 sites in patients not receiving active systemic therapy.

In these patients, a prior with disseminated disease, the use of local treatments has been shown to improve OS^[92] (II, B). In this regard, three prospective^[93-95] studies involving patients with oligometastasis at diagnosis have been published (Table 5). Those trials demonstrated that the patients most likely to benefit from local treatments are those whose disease remains stable or responds to systemic therapy, which is why the National Comprehensive Cancer Network guidelines for oligoprogression recommend mutation-directed therapies (EGFR, ALK). However, it is important to keep in mind that patients in the experimental arms of those trials did not receive immunotherapy, an approach that has altered the treatment paradigm in metastatic

disease. In this regard, several studies are currently evaluating radioimmunotherapy, which combines local RT with immunotherapy^[96].

Multiple studies have sought to identify the characteristics of the “true” oligometastatic patient and those with the best prognosis based on predictors identified in retrospective series (Table 6), as well as other predictive variables currently under investigation^[97,98]. These patients are candidates for radical RT, with the dose adjusted for the lesion location and size. ¹ The most common metastatic sites in patients with stage IV NSCLC are the brain, lungs, liver, bone, and adrenal glands.

RT in metastatic patients: In metastatic disease, the main objective of RT is symptom relief and better quality of life (QoL). Prior to RT, it is important to assess the patient’s functional status, social and family situation, and systemic treatment. Thanks for the important advances in targeted therapies and immunotherapy in recent years, survival in this subgroup has substantially improved^[99]. The specific symptoms will depend on the tumor location; symptom relief is the main indication for RT in this setting. The recommended doses and fractions for each indication are shown in Table 7.

Based on currently available data^[100], symptom control appears to be similar regardless of the specific palliative RT scheme (I, A). Short course RT is associated with a higher risk of reirradiation, which is why it is recommended only in patients with poor PS or short life expectancy^[101,102] (II, A). Higher doses (20-30 Gy in 5-10 fractions) have been shown to improve OS by 5% in selected patients^[103], which is why this RT scheme is recommended for thoracic lesions (II, B). Another option is endobronchial brachytherapy, which until recently was reserved for the treatment of airway obstruction in previously-irradiated patients. However, a systematic review published in 2012 comparing endobronchial brachytherapy + external beam RT (EBRT) to EBRT alone reported better symptom control in the EBRT group^[104] (II, B).

The optimal management of brain metastases is increasingly controversial. In patients ineligible for stereotactic radiosurgery (SRS) and patients with multiple diffuse brain metastases, the treatment of choice is whole-brain RT (WBRT). However, the findings of

the QUARTZ trial, a randomised phase III trial comparing WBRT to supportive treatment in patients unsuitable for SRS, which found no benefit for WBRT in terms of OS or QoL, called this indication into question^[105] (I, A).

In patients with asymptomatic brain metastases who have not yet started systemic therapy - and could potentially benefit from targeted therapy due to the presence of oncogenic driver mutations (*e.g.*, ALK mutation) - the start of RT can be considered given the intra- and extra-cranial effects of RT^[106] (III, B).

At present, there are no clear recommendations on how to best combine RT and immunotherapy. However, two phase II studies (one randomised)^[107,108] found that combined treatment was safe and provided adequate symptom control without negatively affecting QoL (III, B).

DEFINITION OF VOLUMES AND RISK ORGANS, CONSTRAINTS

Definition of tumour volumes

Systematic errors (inaccurate contouring of the target volume, OARs, and/or margins) reduce the likelihood of LC while increasing treatment-related toxicity. In 2018, the ESTRO published consensus guidelines for target volume definition in the treatment (radical and PORT) of locally-advanced NSCLC, with four grades of recommendation^[109].

According to those guidelines, contrast-enhanced CT should be used for treatment planning. If possible, a recent PET-CT scan in the treatment position is recommended^[110]. Respiratory motion should be quantified by 4D-CT, particularly in lower lobe tumours or treatments involving SBRT (IV, A). Treatment volumes^[111]: (1) Gross tumour volume (GTV): The primary tumor GTV (GTV-P) and lymph nodes (GTV-N) should be delineated separately. It is important to select the correct window on CT (lung window: $W = 1600$, $l = 600$ for lesions surrounded by the lung; mediastinum window: $W = 400$, $l = 20$, for lymph nodes and tumors invading the mediastinum/chest wall) (III, A); (2) GTV-P: Areas of atelectasis should be excluded^[112], which is why PET-CT imaging is particularly valuable. If neoadjuvant ChT is

administered, the initial volume based on the current CT scan should be used for contouring (III, B); and (3) GTV-N^[113-115]: Lymph nodes that are positive on biopsy or pathologic by PET-CT or CT (≥ 1 cm) should be included. Nodes that are highly suspicious on PET-CT imaging but with negative findings on EBUS should be included due to the risk of false negatives (III, A).

If neoadjuvant ChT has been performed, include the lymph nodes or nodal stations involved prior to ChT, regardless of the response. Contouring atlases should be used for nodal station delineation^[116-118]. Clinical target volume (CTV): The CTV includes the GTV plus adjacent subclinical disease. It is generally not contoured in SBRT (III, B). CTV-P^[119]: For the CTV-P, the GTV should be expanded by 5-8 mm and manually edited to account for surrounding anatomy. CTV-N: The CTV-N can be created in two ways: Either by including the involved nodal station with a margin ≥ 5 mm around the GTV-N^[109] or through geometric expansion of the GTV-N (5-8 mm), adapted to anatomical barriers. Elective or prophylactic nodal radiation is not recommended since it does not improve locoregional control but does increase toxicity. PORT^[120]: The following areas should be irradiated: Involved lymph nodes, bronchial stump, ipsilateral hilum, and lymph node stations 4 and 7. In left lung cancers, levels 5 and 6 should also be irradiated.

Internal target volume: The internal target volume (ITV) takes into account the internal motion of the tumor. Various systems are available to estimate this motion, which can be limited to reduce the ITV, or monitored with 4D-CT or target lesion tracking^[121,122]. One of the most widely used and recommended systems is 4D-CT. The CTV-GTV is contoured in each respiratory phase, or directly in the maximum intensity projection reconstruction. If this is not possible, a slow acquisition CT, or CT on inspiration, expiration and free breathing can be acquired, contouring the CTV-GTV at each point (III, B).

Planning target volume: This is generated by expanding the ITV to account for geometric uncertainties. The planning target volume (PTV) will vary according to the RT centre since differences between centres (*e.g.*, the immobilization system, the method used to compensate for respiratory motion, the specific image-guided technique, *etc.*) can affect the PTV (III, A).

OARs in SBRT and 3D/4D-RT

In many cases, the radiation dose is limited by OARs in the chest cavity. Accurate contouring of these organs is essential, especially for extreme hypofractionated schemes. In 2003, Collier *et al*^[123] described the intra- and inter-observer uncertainty in manual contouring of thoracic OARs, thus making it possible to determine the dosimetric impact of these uncertainties. In the last decade, several different contouring atlases have been published to assist in contouring tissues in this anatomic region^[124,125].

Lung (lung window settings): Although each lung should be contoured separately, the dosimetric evaluation should be based on the sum of doses to both lungs, excluding the main bronchial tree, the trachea, areas of atelectasis, and the primary GTV (IV, A).

Esophagus (mediastinal window): All layers (mucosa, submucosa and muscular) from the cricoid cartilage to the gastroesophageal junction should be included (IV, A). Oral contrast can be used to ensure correct visualization. For SBRT, contouring of the esophagus should start ≥ 10 cm above the upper limit of the PTV to ≥ 10 cm below the lower limit.

Heart (mediastinal window): There are various approaches to contouring this organ, although the most common approach is to contour the entire heart, including the pericardium and cardiac base, from the lower limit of the pulmonary artery below the aortic arch to the cardiac apex at the level of the diaphragm (IV, A). The pulmonary artery, aorta, and superior vena cava should be excluded. In some cases, other subvolumes, such as the coronary arteries (IV, C), can be included^[125].

Spinal cord (mediastinal window): Generally, for EBRT, the spinal canal is delineated on the planning CT, corresponding to the planning risk volume (PRV) for the spinal

cord (IV, B). For SBRT, the GTV should be contoured if it is located close to the spinal cord; MRI images are useful in these cases. Next, a PRV of the area of interest should be created.

Brachial plexus^[126]: Tumors located at the lung apex should be contoured to avoid neurotoxicity (IV, B). A contrast-enhanced CT (or fusion MRI/CT) should be performed to ensure contouring accuracy. The brachial plexus is located between the anterior and middle scalene muscles. There are 5 roots (C5-T1), as follows: (1) Upper limit: The exit point between C4-C5; (2) Lower limit: Subclavian artery and vein; (3) Internal limit: The neural foramina extending from the lateral aspect of the spinal canal to the small space between the two scalene muscles; and (4) Outer limit: The space between the two scalene muscles. For tumors located in the right lung base, the liver should also be contoured (IV, C).

SBRT OARs^[127]: Chest wall^[128] (mediastinal window): The involved hemithorax should be contoured from the sternal border to the vertebral body, including the ribs and intercostal muscles, excluding other muscles and skin (IV, B). In peripheral tumors, the ribs closest to the tumor should be contoured separately in a bone window setting (IV, C). Trachea (mediastinal window): Include the mucosa, submucosa, and tracheal rings from the lower edge of the cricoid to the upper limit of the proximal bronchial tree (2 cm above the carina). This can also be delineated starting 10 cm above the PTV extension or 5 cm above the carina (whichever is more superior). The lower border is the upper limit of the proximal bronchial tree (IV, B). Proximal bronchial tree (mediastinal window for the trachea and carina and lung window for the bronchi). This includes the area 2 cm distal from the trachea, right and left (R/L) main bronchi, upper lobe (R/L), intermediate bronchus, middle lobe bronchus, lingula, and lower lobe (R/L). (IV, B). Aorta and great vessels^[129] (mediastinal window): The aorta and superior vena cava should be included. The vascular wall and all muscle layers must be included (IV, B), and contoured starting ≥ 10 cm above the upper limit of the PTV continuing to at least 10 cm below the lower limit. Skin (mediastinal window): This is a hollow organ. Automatically contour the body and subtract 5 mm (IV, B).

Constraints in normofractionated RT, hypofractionated RT, and SBRT

Normofractionated radiation therapy: The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study was published in 2010^[130]. The aim of this study was to review the available data on the effects of radiation on normal tissue. QUANTEC updated and further refined the tolerance doses for normal tissues described by Emami *et al* in 1991. QUANTEC provides normal tissue complication probability (NTCP) models, with summary tables of specific results for each organ. However, as the authors indicate, these limitations are not intended to replace comprehensive data provided by organ-specific reviews, and they apply primarily to adult patients. The NTCP according to organ and dose is summarised in Table 8.

The specific limits are as follows: (1) Lung: With conventional fractionation (2 Gy/fx), the recommended V20 Limit for both lungs is $\leq 30\%-35\%$ and MD $\leq 20-23$ Gy to minimize the risk of symptomatic pneumonitis to $< 20\%$ ^[131,132]. However, several different factors must be considered, included the patient's age and any concurrent systemic treatments. A meta-analysis of data from 836 patients treated with concurrent CRT (60 Gy; cisplatin-etoposide in 38%, carboplatin-paclitaxel in 26%, other schemes in 36%)^[133] found that two variables - the lung volume receiving ≥ 20 Gy (V20) and carboplatin/paclitaxel ChT - were predictors of pneumonitis. The highest risk was observed in patients > 65 years receiving carboplatin/paclitaxel-based chemotherapy. The probability of fatal pneumonitis was greater if the daily dose was > 2 Gy and the tumor was located in the lower lobe. Although the latest results presented at ESMO 2020 have called into question the role of PORT in the absence of a definitive analysis, in patients with involved margins PORT is still indicated. A recent study published by a group from the Memorial Sloan Kettering Cancer Center^[134] compared dosimetric parameters in 285 patients with NSCLC treated with PORT between 2004 and 2017. The incidence of pneumonitis $\geq G2$ was 12.6%. The following factors were associated with pneumonitis: Lung and heart dose, age, and carboplatin-based ChT. These data suggest that elderly patients may be more susceptible to lower lung doses. To limit the risk of

pneumonitis \geq G2 to less than 5% in patients receiving PORT, the authors recommended the following limits: (1) Lung V5 \leq 65% in patients $<$ 65 years of age and V5 \leq 36% in patients \geq age 65. After pneumonectomy, the recommended limits are lung V5 $<$ 60%, V20 $<$ 4%-10%, and median lung dose $<$ 8 Gy^[131]; (2) Esophagus: In a study published in 2015, Al-Halabi *et al*^[135] evaluated 20 patients who underwent CRT for tumours located $<$ 1 cm from the esophagus. The median radiation dose was 70.2 Gy (range: 63-72.15 Gy). Due to measures taken to protect the contralateral esophagus, there were no cases of esophagitis \geq G3. The proposed dose constraints to the contralateral esophagus were: V45 $<$ 2.5 cc and V55 $<$ 0.5 cc. IMRT and VMAT allow for dose reduction to the esophagus, thus reducing the incidence of esophagitis; (3) Heart: A subanalysis of the RTOG 0617 dose escalation trial^[136] evaluated the association between heart dosimetric parameters and OS. Heart V₅₀ $<$ 25% *vs* \geq 25% was associated with a significant improvement in OS at both one and two years: 70.2% *vs* 46.8% and 45.9% *vs* 26.7% ($P < 0.0001$), respectively. The median heart V₅₀ was significantly higher (20.8% *vs* 13.9%, $P < 0.0001$) in patients with \geq G1 cardiac toxicity; and (4) Plexus: An analysis of 90 patients with apical lung cancer treated with CRT found an association between brachial plexopathy and the mean dose to the brachial plexus $>$ 69 Gy (60% of doses $>$ 69 Gy *vs* 13% \leq 69 Gy) and maximum dose $>$ 75 Gy at 2 cc of the brachial plexus. (43% *vs* 13%)^[137].

Hypofractionated radiation therapy: Several different total and fractional dose schedules have been used for moderate hypofractionation, including concurrent CRT with various ChT schemes and sequential RT after ChT, or EBRT alone. The dose constraints were not reported in all studies. Table 9 summarises the recommended dose constraints for the most common moderately hypofractionated schemes^[76,81,83,84,87,138,139].

RT TECHNIQUES (3D-RT, IMRT, VMAT, RESPIRATORY CONTROL, PROTONS, ADAPTIVE RT)

Technological advances in recent years have led to significant changes in the radiotherapeutic treatment of NSCLC, which has progressed from 3D-CRT to IMRT and VMAT, together with advances in image-guided RT (IGRT) and the introduction of proton RT.

Based on data from non-randomised studies, these more sophisticated techniques reduce toxicity to OARs and improve tumor control, thereby leading to better survival outcomes when compared to 3D-CRT^[147,148]. The phase III RTOG 0617 trial comparing IMRT to 3D-CRT in advanced stage disease showed that IMRT reduced lung doses (V20), leading to lower rates of severe (\geq G3) pneumonitis and lower heart doses, which is a predictor of survival^[149,150]. VMAT offers many of the same advantages as IMRT, including a reduction in the number of treatment sessions, similar lung doses and PTV coverage, but with lower heart doses; as a result, VMAT is becoming more common in the treatment of NSCLC^[151].

Intrathoracic motion of lung tumor and healthy tissues is a major challenge that can significantly influence treatment delivery. Breathing control techniques can help reduce PTV margins and allow for more precise treatment delivery based on the unique motion of a given tumor, thus providing better tumor control and lower doses to OARs. During planning, several techniques can be used to quantify tumor motion, including “slow” CT, inspiration-expiration CT, or 4D-CT, as well as techniques to control movement, such as abdominal compression, deep-inspiration breath hold, and breath synchronization techniques such as “gating” in which CT acquisition and treatment are performed in specific phases of the respiratory cycle, and “real-time” tumor tracking—used mainly in SBRT^[152]. A useful resource for the implementation of respiratory control is the AAPM Task Group 76 report, which can be used to develop institutional guidelines based on the technical resources available at each centre^[153].

The incorporation of CBCT has improved IGRT. CBCT allows for more accurate positioning and reduces inter- and intrafraction errors, thus resulting in smaller PTV margins and lower OAR doses. In addition, CBCT can measure changes in location, morphology, and physiology, thus permitting changes in the initial treatment plan^[154].

^{156]}. This capacity to adjust the treatment plan, known as adaptive RT, permits administration of higher radiation doses to the tumor with lower doses to the OARs^[155,157,158]. Data from small studies suggest that adaptive RT improves LC^[159]. This technique is currently being evaluated in the phase II RTOG 1106 trial (NCT01507428) comparing standard concomitant CRT (60 Gy) to adaptive RT based on PET-CT imaging.

Data from both retrospective and prospective studies suggest that proton radiation therapy (PRT) may be superior to photon RT in the treatment of NSCLC^[160-162]. However, only one randomised study has compared SBRT to PRT in stage I disease and that trial was closed early^[163]. In patients with stage III disease, prospective and retrospective studies have shown acceptable locoregional control with PRT combined with ChT^[164]. PRT has the potential to reduce toxicity to OARs such as the lung, heart, and esophagus, especially in unresectable central tumors^[165-167]. However, to date, only one randomised phase II trial has compared IMRT to PRT, finding no significant advantages for PRT, nor any significant differences between these modalities in terms of pneumonitis or LC^[168]. Consequently, the theoretical advantages of PRT need to be validated in randomised trials, such as RTOG 1308, which is currently recruiting patients^[169].

REIRRADIATION

Approximately 20%-40% of patients with early stage or locally-advanced NSCLC develop locoregional progression or metachronous disease at 2 years^[170]. Most of these recurrences or second primaries are unresectable, which explains the growing interest in reirradiation. Due to technological advances in radiation therapy delivery - IMRT, SBRT, proton therapy, and IGRT - it is now possible to consider reirradiating certain tumors. However, there is no consensus on the optimal approach to RT for local recurrences in previously-irradiated patients^[171].

Reirradiation with photons

The two most common techniques in the radical dose reirradiation setting are IMRT and SBRT. To select the technique that provides the best local disease control with acceptable toxicity, it is important to consider the following parameters: Type of prior RT, anatomic location of the recurrence, and whether the lesion is located in or outside of the original RT field. Several factors - good PS, lung function, small PTV, and a BED dose > 100 Gy - are predictive of better LC and survival. Consequently, these factors should be considered when determining suitability for reirradiation.

SBRT is the technique of choice for peripheral recurrences located far from the mediastinum^[172] because SBRT-related toxicity can be severe when the tumor is located near the bronchial tree and/or esophagus. Vyfhuis *et al*^[173] reported a 92% LC rate in patients treated with 50 Gy in four fractions (SBRT) while Kilburn *et al*^[174] reported a 2-year LC rate of 67% for recurrences located within the prior treatment field, with an acceptable toxicity profile (G2 = 30%, only case of G3 toxicity). The findings of the MD Anderson studies^[175] show that IMRT is the most appropriate technique for reirradiation in central tumors, as high doses are required to achieve better LC. IMRT also reduces the dose to healthy tissues, thus limiting toxicity.

Reirradiation with particle therapy (protons and carbon ions)

Particle therapy (protons/carbon ions) is another option to consider for re-irradiation, mainly to reduce toxicity to OARs, as the physical characteristics of these particles reduces the integral dose (low-dose bath of photons at the beam exit point). However, these patients have a high rate of metastases. Some studies reported a significant decrease in OAR toxicity in patients reirradiated with PRT^[175,176].

Proton therapy is increasingly being used as a primary treatment for NSCLC and may also have an important role in the reirradiation setting, mainly due to the lack of exit doses. Although carbon ion radiation therapy (CIRT) appears to be superior to proton therapy, due to greater linear energy transfer and relative biological effectiveness, its use is currently very limited^[178].

The ROCOCO dosimetric comparison study^[179] showed that PRT reduced the integral dose and doses to OARs, even with dose escalation. Chao *et al*^[180] found that patients treated with PRT had a high rate of toxicity, with 39% of patients developing \geq G3 toxicity. In that study, the one-year OS and DFS rates were 59% and 58%, respectively. However, given the toxicity findings, the authors recommended careful selection of patients.

Several studies are currently evaluating reirradiation in NSCLC. Some of these trials have completed patient recruitment and results are pending. One trial (NCT01808677) is evaluating reirradiation with IMRT or PRT; the main endpoint is severe toxicity (\geq G3) and survival is a secondary endpoint.

Reirradiation with CIRT has shown moderate efficacy and acceptable toxicity, suggesting that this modality could be an effective treatment option in selected patients^[181]; however, large multicentre trials are required to confirm these findings.

To conclude this section, the best candidates for reirradiation have the following characteristics: Good PS, small volume recurrences, non-central locations, and the capacity to tolerate high dose radiation (SBRT, IMRT, or particle therapy)^[175,182].

MANAGEMENT OF TREATMENT INTERRUPTIONS

Management of the overall treatment time (OTT) is especially important in NSCLC. Depending on the fractionation scheme, the effects of prolonging the OTT may vary, and different strategies can be employed to minimize these deleterious effects. In normofractionated schemes, extending the OTT will negatively impact locoregional control and OS^[183-186]. One report suggested that OS rates may decrease by up to 1.8% for each day of treatment prolongation^[187]. In hyperfractionated regimens, interruptions that increased the OTT by ≥ 5 d in high dose schemes (≥ 69.6 Gy) negatively impact OS, especially in patients with good prognostic factors, such as Karnofsky Performance Status 90%-100%, weight loss $< 5\%$, and $\leq N2$ ^[185].

Compensation for treatment interruption

In the year 2000, the Royal College of Radiologists in the United Kingdom published recommendations for the management of unscheduled treatment interruptions, which were updated in 2019^[188]. These recommendations divide the treatment type into three categories: Radical (categories 1 and 2) and palliative (category 3) treatment, as follows: (1) Category 1: Patients whose tumors have a high repopulation rate (*e.g.*, squamous cell tumors) who are being treated with radical curative-intent RT. The United Kingdom recommendations include both NSCLC and SCLC in this group. Treatment prolongation in these patients should be no more than two days beyond the prescribed time in 95% of patients; (2) Category 2: Patients with slow growing cancers (mainly adenocarcinomas) receiving radical-intent RT. This group includes breast, transitional bladder carcinoma, and prostate cancer; and (3) Category 3: Patients undergoing palliative-intent RT. OTT prolongation is less critical in these cases. However, it is advisable to compensate for prolonged (> 7 d) interruptions.

Compensation methods

Some authors have suggested that modern RT techniques such as IMRT reduce the incidence of treatment interruptions^[189]. Nevertheless, the general principle is to ensure that interruptions are kept as short as possible and to anticipate interruptions whenever possible.

In general, treatment delays can be classified into two main groups: Planned and unplanned interruptions. Two types of measures - universal and specific - can be applied to address these scenarios. Universal measures are useful in both groups, while specific measures will depend on whether the interruption is programmed or not.

There are two main types of universal compensation measures, as follows: (1) Compensation on weekends and holidays; and (2) The use of compatible linear accelerators, which allow for treatment delivery on either machine. Although this is a “planned” measure, it also allows for compensation in the event of unexpected equipment malfunction.

Specific measures can be classified according to whether the interruption was planned or unplanned, as follows: (1) Unplanned: Option 1: Administer two sessions on the same day, 6 h apart, to compensate for the delay. Option 2: Compensate for the dose in the remaining fraction based on the BED, taking into account the α/β for healthy tissue or tumor according to the following formula^[190]: $N \cdot d \left[1 + \frac{d}{\alpha/\beta} \right]$, where N is the number of fractions, d is the dose per fraction, and α/β is the repair coefficient between lethal and sub-lethal damage. If we take into account the accelerated repopulation time, assuming a tumor α/β ratio of 10, the formula would be as follows: $N \cdot d \left[1 + \frac{d}{\alpha/\beta} \right] - K (T - T_K) = 30.2 \left[1 + \frac{2}{10} \right] - 0.45 (39 - 28) = 67.05$ Gy, where: + K (estimated loss of biological efficacy in Gy per day of delay that would need to be added to compensate)^[183]; (1) Stages T1-3, N0-1: 0.27 Gy/d; stages T1-3 N2-3 or T4: 0.75 Gy/d; all stages: Mean 0.45 Gy/d. + T : Total treatment time. In the example, the T is 39 d and treatment is assumed to start on a Monday. + T_K (time from the start of RT at which accelerated repopulation begins) reported: 3-4 wk^[187]: 28 d. Therefore, to calculate the dose per remaining fraction, we need to consider the remaining BED needed to reach 67.05 Gy, and the remaining fractions not to exceed two days of treatment extension. Using this equation, we calculate the d (dose per fraction); and (2) Planned: Option 1: Compensate on a holiday. Option 2: Perform the dose calculation per fraction to compensate for the missed treatment days using the formulas described above, provided that the dose is ≤ 3.5 Gy/fx and the OAR dose tolerance is within the stipulated limits, after adjusting for the relevant biological calculation

Recommendations: Prioritise patients with squamous cell tumors. Use IMRT whenever possible, especially in locoregionally-advanced cases. Conventional fractionation: Keep delays to a minimum. Compensate if the OTT is > 45 -50 d and/or the interruption is ≥ 4 -5 d. Adjuvant RT: Although there are no published data in this scenario, as a precautionary measure, avoid delays ≥ 5 -10 d, especially in patients without signs of poor prognosis or squamous cell tumors. In hyperfractionated schemes, compensation

strategies are more complex, which is why treatment on holidays is preferred. However, if the treatment delay is ≥ 10 d, full compensation is not recommended due to the risk of excess toxicity^[188]. The number of indications for moderately hypofractionated RT and SBRT has increased substantially during the COVID-19 pandemic. Specific guidelines for these cases have been published^[191].

FOLLOW-UP (AFTER SBRT, EARLY STAGE AND LOCALLY ADVANCED)

Approximately 40% of patients with lung cancer will develop a distant recurrence from 3 to 5 years after treatment completion. At 3-years, approximately 30% of patients will develop a locoregional recurrence (potentially-curable)^[55]. After SBRT, approximately 12% of patients develop locoregional recurrence at 4 years^[36].

The risk for development of a second primary lung cancer after treatment ranges from 1% to 6% per patient per year and this risk does not decrease over time. The mean interval from the first to the second primary tumor ranges from 59 to 62 mo^[192]. Early management of these relapses, whether curative or palliative intent, is associated with better survival and QoL, which underscores the importance of close follow-up^[193,194]. For the assessment of treatment-related toxicity and recurrence, we recommend the following follow-up measures.

Patients treated with SBRT

Most recurrences occur more than 6 mo after treatment. Based on recommendations from the ESTRO^[47], the United Kingdom SBRT consensus statement^[195], and updates on high-risk CT features^[196], the following follow-up procedures are recommended.

First year post-treatment: The first clinical follow-up visit (complete medical history and physical examination) should take place within 4-6 wk of treatment completion. The first CT scan should be performed at least 3 mo after treatment. Clinical evaluation, including contrast-enhanced CT, should be performed every 3 mo for at least one year.

Second to third year after treatment: After the first year, follow-up should be performed every 3-6 mo for three years. CT images performed every 3 mo should be compared to previous CTs.

Third to fifth year after treatment: CT imaging should be performed every 6 mo from year three to year five. Low-dose CT should be performed annually from that time if risk factors are present. If the CT scan reveals risk factors^[197,198], then a PET scan (III, B) should be ordered. If salvage therapy is feasible, then a biopsy should be performed to confirm the PET findings (III, B). Lung function testing should be performed annually.

CONVENTIONAL FRACTIONATION AND LOCALLY-ADVANCED DISEASE

Based on recommendations from ESMO^[59], the Italian Association of Medical Oncology^[199], and SEPAR^[15], we recommend the following: (1) Unsalvageable patients. Perform clinical evaluations (complete medical history, physical examination, and blood tests) every 6 mo for two years. A chest CT should be performed at months 12 and 24, with annual follow-up thereafter (III, B); and (2) Salvageable patients. First three years: CT IV contrast every 3-6 mo (III, B). Years four and five: Follow-up every 6 mo; thereafter, annual low-dose CT without contrast. If pathologic findings are detected on CT, perform PET-CT and brain MRI. Obtain histopathologic confirmation of PET findings in accordance with the therapeutic option (III, B). Maintain follow-up for at least 5 years.

General recommendations: The treating physician should actively participate in follow-up (I, C). In patients unlikely to benefit from salvage therapy, the frequency of follow-up should be adapted to the patient's individual needs (V, B). Follow-up with PET-CT or abdominal ultrasound is not recommended (I, C). Smoking cessation^[200] (III, A). Behavioral therapy combined with pharmacological intervention (I, A). Influenza and pneumococcal vaccination should be offered if not contraindicated.

RECOMMENDATIONS

Summary of recommendations is provided in Table 11.

CONCLUSION

Summary of recommendations is provided in Table 11.

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