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Response to Reviewers

Dear Dr. Wang

Thank you for giving us the opportunity to submit a revised draft of the manuscript "GOECP/SEOR CLINICAL GUIDELINES FOR NON SMALL CELL LUNG CANCER." We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper. We have incorporated the suggestions made by the reviewers. Those changes are highlighted within the manuscript.

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 to 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 (VATS)[5]. In addition, determination of the histological subtypes has become standard practice to assess eligibility—based on tumour 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 maximise tumour control while minimising 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 tumour location, TNM stage, comorbidities, and general performance status).

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.

2. METHODS

These guidelines are based on the most relevant studies published in peer reviewed journals. A comprehensive review of the clinical literature of 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.

Level of evidence

I	Evidence from at least one large randomised controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control groups; case reports; expert 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 or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcomes, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

3. 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 computed tomography (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 endobronchial ultrasound (EBUS) or digestive endoscopic ultrasonography (EUS)[18][19][20] (I, A). In uncertain cases, conventional mediastinoscopy or video-assisted mediastinoscopy (VAM) and video-assisted thoracoscopy (VAT) are surgical alternatives to obtain samples for subsequent analysis[21][22]. Peripheral lesions can be evaluated by CT-guided transthoracic fine-needle aspiration biopsy (FNA)[23][14]. 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 (WHO) classification system[25]. It is important to differentiate between the histological subtype: squamous cell carcinoma, adenocarcinoma (the most common), large cell carcinoma, and neuroendocrine tumours. (I, B) The International Association for the Study of Lung Cancer (IASLC) has developed a classification system for adenocarcinoma with prognostic implications[26]. Immunohistochemical studies and determination of molecular alterations such as EGFR, KRAS, and ALK mutations should be performed, as these alterations can predict sensitivity to certain drugs and/or targeted therapies[27]. (I, B) Classification of NSCLC or NOS (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[28].

4. CLINICAL INDICATIONS BY TNM STAGE

4.A. Early stages: Stereotactic body radiation therapy (SBRT): indications, radiation dose, and fractionation schedules

Indications

SBRT, also known as stereotactic ablative body radiation (SABR), consists of delivery of high dose radiation to a very specific target volume, with a high dose gradient in all directions[29]. The indication for this technique is based on the patient's surgical risk category: inoperable, high-risk, or standard-risk[30].

A) Inoperable

Approximately 25% of patients with early-stage NSCLC (ES-NSCLC) are inoperable due to age or comorbidities[31]. In this population, prospective studies of SBRT have reported local control (LC) rates of 90% at 5 years[32] and 91.9% at 7 years[33] and, with a ≥ grade (G)3 toxicity rate under 10%. The well-designed phase II TROG 09.02 CHISEL trial[34] compared SBRT to conventional 3D-RT. SBRT was superior to conventional 3D-RT in terms of local control (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.13–0.77, p=0.0077) with no increase in treatment-related adverse events (AE). SBRT is therefore the treatment of choice in inoperable patients (III, A).

B) 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[36][35]. The findings of that study, published in 2015, were criticised for the underpowered statistical analyses and the poor surgical quality in the two trials[36].

Several non-comparative prospective studies of SBRT have been conducted, most notably the phase II RTOG 0618 trial[37]. In that trial, 33 operable patients received SBRT, with a 4-year LC rate of 96% and ≥ G3 toxicity of only 8%. The findings of retrospective series comparing SBRT to surgery through matched pair analysis are inconclusive[38][39]. However, a recent meta-analysis[40] suggested that surgery may provide better outcomes on various survival parameters, including OS, cancer-specific survival (CSS), 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 versus surgery in operable patients, unless the patient refuses surgery. (III, C)

C) High-risk patients or patients > 75 years of age

The American Society of Clinical Oncology (ASCO) and the American Society of Radiation Oncology (ASTRO) recommend offering SBRT as an alternative treatment in high-risk patients[41][42]. (III, A)

FRACTIONATION

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

equivalent dose (BED) is < 100 Gy[43]. Consequently, the dose should be determined according to the location of the target lesion and, therefore, to the tolerance of adjacent organs.

Tumour are classified as central, peripheral, or "safe" (> 2 cm from mediastinal structures and > 1 cm from the chest wall) depending on their location within the thoracic cavity.

Central tumours

Central tumour fractionations as defined by the IASLC [43]: The most important prospective phase I/II trial for central tumours was the RTOG 0813 trial[44], 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 maximum tolerated dose (MTD) was 12.0 Gy/fx, with a ≥ 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[45] trial (Dose Level 1:60Gy/7fr-Dose Level 3 60Gy/5fr) and the Hilus[46] trial (56Gy/8fr to 65-70% isodose line) were both performed to assess high-dose SBRT in central/ultracentral tumours. The recently published, Hilus trial showed that this fraccionation regimen administered in tumours located at 1 cm or less from the main bronchus and trachea had a high risk of G3 to G5 toxicity (33.8%) including 10 patients with G5. These regimens contrast with the more conservative Dutch regimen (60 Gy/8 fx)[47], which obtained a 3-year LC rate of 92.6% and ≥ G3 toxicity of 7.9%.

Based on the available evidence, the optimal fractionation in central tumours 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.

Lesions adjacent to the chest wall

In patients with tumours located adjacent to or in contact with the chest wall, European guidelines[48] recommend a total dose of 48 Gy in four fractions. Prospective studies[49] have shown that this fractionation schedule yields 3-year LC rates ranging from 85.4% to 87.3%, with a ≥ G3 toxicity rate (rib fracture) of 3%. Other fractionation schedules have been proposed in this location. For example, Haasbeek and colleagues proposed 60 Gy in five fractions, with a 3-year LC rate of 89.3% and a late ≥ G3 toxicity rate (chest wall pain) of 2.1%[50]. Nyman et al.[51] proposed 45 Gy in three fractions, which achieved a LC rate of 80% with late toxicity (rib fracture) in 4%.

Tumours located in the "safe" zone

Lesions located in the "safe" zone can be considered non-central tumours located > 2 cm from the chest wall. Evidence from two prospective phase II trials—Singh et al.[52] and RTOG 0915[53]—support extreme hypofractionation (single 30-34 Gy fraction). Singh and colleagues found that a single 30 Gy fraction yielded a 2-year LC rate of 94.9%, with G3 toxicity in 17%, and no ≥ G4 toxicity. In RTOG 0915, which evaluated a single 34 Gy dose, the one-year LC rate was 97.0%, with ≥ G3 toxicity rate of 10.3%.

Timmerman et al. conducted a prospective phase II trial to evaluate SBRT in inoperable early-stage NSCLC[54]. The findings of that trial supported the classical Timmerman fractionation scheme, with a 3-year LC rate in peripheral tumours ranging from 90.6%- 94% and ≥ G3 AEs ranging from 10% to 16.3%.

TABLE 2: Recommended SBRT dose in early stage disease

Localization	Dose	Source	Evidence level
Central tumour	50/5 fx - 60/5 fx	RTOG0813	II, B
	60 Gy/8 fx	Haasbeek 2011	
Chest wall	48Gy/4 fx	ESTRO Guideline 2017	II, B
	60 Gy/5 fx	Nagata 2015	
	45Gy/3 fx	Nyman 2011	
Safe zone	30 Gy/1 fx	Singh 2018	II, B
	34Gy/1 fx	RTOG 0915	
	54Gy/3 fx	RTOG0618	

4.B. Locally-advanced, inoperable disease

Radical chemoradiotherapy (CRT): 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 ChT does not improve outcomes but does increase toxicity rates [55].

In patients with good performance status, the recommended treatment is concomitant CRT, which has been shown to improve OS vs. sequential CRT by 5.7% at 3 years and 4.5% at 5 years, with a mean survival time of 22-25 months and 5-year OS of 20%[56], probably due to better locoregional control (2.9% at 3 years and 2.2% at 5 years). (I, A) However, concomitant CRT also has a higher incidence of acute non-hematological toxicity[57], mainly G3-G4 esophagitis (range, 4%-18%), but no effect on acute pulmonary toxicity[58]. To date, no differences in treatment outcomes have been observed for the following variables: type or ChT scheme, age, sex, performance status (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 PD-L1 > 1% who do not progress after concomitant CRT [59].

Neoadjuvant chemoradiotherapy

Several studies, including the SAKK Lung Cancer Project Group trial[60] and the Lung Intergroup Trial 0139[61], have evaluated the role of neoadjuvant CRT, 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 CRT followed by lobectomy versus those who received concomitant CRT[61].

Induction CRT has been shown to achieve a greater reduction in nodal downstaging than ChT alone, but with no benefit in OS[56] except for potentially resectable superior sulcus tumours, for which the treatment of choice is concomitant CRT (45-54 Gy, 1.8-2 Gy/day). (III, A) However, it is important to plan radical dose RT in case surgery is ultimately not performed[62].

Adjuvant radiotherapy

Adjuvant RT is indicated when complete resection (R0) has not been achieved and salvage surgery is not feasible. (I, A) In these cases, sequential CRT (ChT followed by RT) should be offered, although with a less aggressive ChT scheme. Concomitant CRT 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 radiotherapy (PORT) in patients with N0-N1 disease[63]. 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. Recently published findings from the phase III LungArt trial[64] showed that PORT does not appear to improve DFS or OS in patients with N2 disease and R0. Although the PORT group presented fewer thoracic recurrences (25% vs. 46.1%), PORT was associated with higher rates of ≥ G3 cardiopulmonary toxicity, potentially attributable to the low percentage (11%) of patients treated with IMRT. Nevertheless, a recent meta-analysis concluded that adjuvant RT is associated with better OS and PFS rates in these patients [65].

Based on the postoperative pathologic findings, the recommended PORT doses are as follows: R0: 50-54 Gy, 1.8-2 Gy/fx; involved margins or microscopic disease: 54-60 Gy; and macroscopic residual disease: ≥ 60 Gy[62][66] .

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 CHART

(Continuous Hyperfractionated Accelerated Radiotherapy) trial[67][68], HART (Hyperfractionated Accelerated Radiotherapy)[69], and CHARTWEL (Continuous Hyperfractionated Accelerated Radiotherapy weekend less)[70]. The findings of these trials were recently confirmed in a large retrospective series[71].

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(supplementary Table 3)[72].

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 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[55]. However, radiobiological models show that each 1% increase in the radiation dose improves LC by 1% to 2%[73]. A systematic review of clinical data from dose escalation studies[74] found a BED_{10} 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 radiotherapy have evaluated various regimens[75][76][77]. Prospective and retrospective series[78][79][80][81][82] 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.)[83] comparing accelerated hypofractionated RT to conventional RT.

The phase III EORTC 08972-22973 trial[84] and the randomised phase II SOCCAR trial[85] compared concurrent to sequential CRT in patients receiving hypofractionated RT. Based on the excellent results obtained with concomitant CRT in the SOCCAR trial[85], this scheme is now widely used in routine practice in the United Kingdom (UK). Iqbal et al.[86] 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 (supplementary Table 4).

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

fractions in those studies 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 BED_{10} and OS: every 1 Gy increase in BED_{10} 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[87].

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[88]. 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 radiotherapy. To address the challenges presented by the pandemic, a group in the UK[89] and the ESTRO-ASTRO[90] have both published recommendations for hypofractionated schemes during this period. The UK group recommends 55 Gy in 20 fractions of 2.75 Gy with concurrent ChT in patients with good performance status. 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[89]. 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) 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/day) schemes. (II, A) There was no consensus to support concomitant hypofractionated CRT. An alterative would be 55-60 Gy in 20 fractions[90] . (II, B)

4.c. Radiotherapy in advanced NSCLC

4.C.1 Radiotherapy (SBRT) 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[91]. Oligometastasis may present in one of two ways:

- **"De novo**" oligometastasis: patient with ≤ 3-5 lesions at diagnosis (synchronous) or after 3-6 months of treatment of the primary tumour (metachronous).

- **Induced oligometastatic**: polymetastatic patient with metastatic disease in ≤ 3-5 locations after systemic therapy.

This recently described concept of oligometastatic disease[92][93] can be further subdivided as follows:

- **Oligopersistence:** persistent disease that is stable on imaging studies, with < 5 lesions after systemic treatment
- **Oligoprogression**: progression (new lesions or growth of known lesions) in 3 to 5 sites after systemic treatment
- **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[94]. (II, B) In this regard, three prospective [95] [96] [97] studies involving patients with oligometastasis at diagnosis have been published (supplementary 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 (NCCN) 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 radiotherapy with immunotherapy [98].

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 (supplementary Table 6), as well as other predictive variables currently under investigation[99][100]. These patients are candidates for radical RT, with the dose adjusted for the lesion location and size. The most common metastatic sites in patients with stage IV NSCLC are the brain, lungs, liver, bone, and adrenal glands.

4.C.2 Radiotherapy in metastatic patients

In metastatic disease, the main objective of RT is symptom relief and better quality of life (QoL). Prior to radiotherapy, it is important to assess the patient's functional status, social and family situation, and systemic treatment. Thank to the important advances in targeted therapies and immunotherapy in recent years, survival in this subgroup

has substantially improved[101]. The specific symptoms will depend on the tumour location; symptom relief is the main indication for RT in this setting. The recommended doses and fractions for each indication are shown in supplementary Table 7.

Based on currently available data[102], symptom control appears to be similar regardless of the specific palliative RT scheme (I, A). Short course radiotherapy is associated with a higher risk of reirradiation, which is why it is recommended only in patients with poor performance status or short life expectancy[103][104]. (II, A) Higher doses (20-30 Gy in 5-10 fractions) have been shown to improve OS by 5% in selected patients[105], 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[106]. (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[107] . (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 radiotherapy[108]. (III, B)

At present, there are no clear recommendations on how to best combine RT and immunotherapy. However, two phase II studies (one randomised)[109][110] found that combined treatment was safe and provided adequate symptom control without negatively affecting QoL. (III, B)

5. DEFINITION OF VOLUMES AND RISK ORGANS. CONSTRAINTS

5.A. Definition of tumour volumes

Systematic errors (inaccurate contouring of the target volume, OARs, and/or margins) reduce the likelihood of local control 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[111].

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[112]. Respiratory motion should be quantified by four-dimensional CT (4D-CT), particularly in lower lobe tumours or treatments involving SBRT. (IV, A)

Treatment volumes[113]:

- **GTV (gross tumour volume):** The primary tumour 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 tumours invading the mediastinum/chest wall). (III, A)
- **GTV-P:** Areas of atelectasis should be excluded[114], which is why PET-CT imaging is particular valuable. If neoadjuvant ChT is administered, the initial volume based on the current CT scan should be used for contouring. (III, B)
- **-GTV-N**[115][116][117]**:** 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[118][119][120].

- **CTV** (clinical target volume): The CTV **i**ncludes the GTV plus adjacent subclinical disease. It is generally not contoured in SBRT. (III, B)
- **CTV-P**[121]: 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 [122] 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[123]: 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.

***ITV (internal target volume):** The ITV takes into account the internal motion of the tumour. 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[124][125] .

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 (MIP) 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)

***PTV (planning target volume):** This is generated by expanding the ITV to account for geometric uncertainties. The PTV will vary according to the radiotherapy 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)

5.B. 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.[126] 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[127][128].

1. 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).
2. 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.
3. 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.[128]
4. 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.
5. Brachial plexus[129]. Tumours 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:

   Upper limit: the exit point between C4-C5

   Lower limit: subclavian artery and vein.

   Internal limit: the neural foramina extending from the lateral aspect of the spinal canal to the small space between the two scalene muscles

   Outer limit: the space between the two scalene muscles.

For tumours located in the right lung base, the liver should also be contoured (IV, C).

SBRT OARs[130]

1. Chest wall[131] (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 tumours, the ribs closest to the tumour should be contoured separately in a bone window setting (IV, C).

2. 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)

3. 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)

4. Aorta and great vessels[132] (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.

5. **Skin** (mediastinal window). This is a hollow organ. Automatically contour the body and subtract 5 mm (IV, B).

5.C. Constraints in normofractionated RT, hypofractionated RT, and SBRT

Normofractionated radiation therapy

The QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) study was published in 2010[133] . 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:

A. Lung: With conventional fractionation (2 Gy/fx), the recommended V20 limit for both lungs is ≤ 30-35% and MD ≤ 20-23 Gy to minimise the risk of symptomatic pneumonitis to < 20%[134][135]. 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%)[136] 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 tumour was located in the lower lobe.

Limitations in patients with pneumonectomy

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 (MSKCC)[137] compared dosimetric parameters in 285 patients with NSCLC treated with PORT between 2004 and 2017. The incidence of pneumonitis ≥ 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 ≥ G2 to less than 5% in patients receiving PORT, the authors recommended the following limits: lung V5 ≤ 65% in patients < 65 years of age and V5 ≤ 36% in patients ≥ age 65. After pneumonectomy, the recommended limits are lung V5 < 60%, V20 < 4%-10%, and median lung dose (MLD) < 8 Gy[134].

B) Esophagus: In a study published in 2015, Al-Halabi et al.[138] 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 ≥ G3. The proposed dose contraints 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.

C) Heart: A subanalysis of the RTOG 0617 dose escalation trial[139] evaluated the association between heart dosimetric parameters and OS. Heart V_{50} < 25% vs. ≥ 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 V_{50} was significantly higher (20.8% vs. 13.9%, p < 0.0001) in patients with ≥ G1 cardiac toxicity.

D) 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% ≤ 69 Gy) and maximum dose > 75 Gy at 2 cc of the brachial plexus. (43% vs. 13%) [140].

Table 8: Dose constraints in normofractionated radiotherapy

Organ	*Volume*	*Endpoint*	*Dose (Gy), dose/volume*	*Rate %*	*Study*
Spinal cord	Partial	Myelopathy	Dmax 50 Dmax 60 Dmax 69	0.2% 6% 50%	
Lung	Whole organ, both lungs	Pneumonitis	V20 ≤ 30% MD =7 MD =13 MD =20 MD =24 MD =27	< 20% 5% 10% 20% 30% 40%	Palma et al. 2013 [136] Shepherd et al. 2020 [137] Marks LB et al. 2010 [133]
Esophagus	Whole organ	≥ grade 3 acute esophagitis ≥ grade 2 acute esophagitis	MD < 34 V60 ≤17% V35 < 50% V50 < 40% V70 < 20%	5-20% <30% <30% <30%	Al-Halabi et al. [138]
Heart	Pericardium Whole organ	Pericarditis Cardiac mortality long term	MD < 26 V30 < 46% V25 < 10% V50 ≤ 25%	<15% <15% <1%	Speirs et al. 2017 [139]
Brachial plexus	Whole organ	Brachial plexopathy	MD > 69 Gy Dosis maximum 75 Gy to 2 cc of the brachial plexus.		Amini et al. 2012 [140]

Abbreviations: Dmax: maximum dose; MD: median dose.

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[141][142][143][83][144][145][146].

Table 9: Dose constraints for moderate hypofractionation

Organ	**Concurrent RT/ChT (55 Gy/20fx)**	**Sequential RT/ChT (60 Gy/20fx)**	**RT (50 58Gy/15fx)**	**RT (50-60 Gy/15fx)**
Spinal cord	MD 44Gy (0.1cc)	Dmax ≤ 36	MD 42Gy (0.1cc)	MD < 38 Gy
Esophagus*	MD <55 Gy (1cc)	V42 < 32%	MD < 52 Gy (1cc)	MD < 50 Gy (1cc) V45< 10cc
Lungs-GTV	V20<35% MD < 18 Gy	V20<25-30% MD ≤ 15 Gy	V19<35% MD < 16 Gy	V20 <30% V5 <60% MD< 20 Gy
Heart	V30< 36%	V33< 25%	D100%< 33 Gy D67%< 40 Gy D33%< 52 Gy	MD 63 Gy V57<10cc
Great vessels	NA	NA	MD 58Gy	MD 63 Gy V57<10cc
Trachea, Carina and main bronchus	NA	NA	MD 58 Gy	MD 63 Gy V57<10cc
Rib	MD <63 Gy	NA	V30< 30 cc	MD 63 Gy ; V30<30cc

Abbreviations: MD: median dose; Dmax, maximum dose; Fx, fraction; ChT, chemotherapy; NA, not available.

* Esophagus within the PTV ≤ 12 cm

SBRT

Several reviews have described the constraints to OARs in SBRT based on the studies shown in Table 10. [146][147][148][149][150][151][152]

Organ	Single fraction (30-34Gy)		Three fractions (54-60 Gy)		Four fractions (48Gy)		Five fractions (50-60 Gy)		Eight fractions (60 Gy)		Source/Study
	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Brachial Plexus	14Gy<3cc	17.5Gy ≤ 0.035cc	20.4<3cc	24Gy≤0.035cc			27Gy<3cc	30.5Gy≤0.035cc			TG101[146]
	14.4Gy<3cc	17.5Gy Dmax	22.5Gy<3cc	24Gy			30 Gy<3cc	32Gy			RTOG0813 [155]
					23.6Gy<3cc 30 Gy<10cc 35Gy<1cc	27.2Gy Dmax 40 Gy Dmax					RTOG 0915 [154] EC STARS [156]
			24Gy≤0.5cc	26≤0.5cc			27Gy≤0.5cc	29Gy≤0.5cc	27Gy≤0.5cc	38Gy≤0.5cc	Hanna et al [148]
Spinal Cord	10 Gy<0.35cc 7 Gy<1.2 cc	14 Gy≤0.035cc	14Gy<0.35cc. 12.3Gy<1.2cc	18Gy≤0.035cc			23Gy<0.35cc 14.5<1.2cc	30 Gy≤0.035cc			TGT 101[146]
	7Gy<1.2cc	7Gy<1.2cc	18Gy<0.25cc. 11.1Gy<1.2cc	18Gy	20.8Gy<0.35c 13.6Gy<1.2cc	26Gy DMax	22.5Gy<0.25cc 13.5cc<1.2cc 13.5Gy<0.5cc				RTOG0813 [155] RTOG 0915 [154] RTOG 0618 [153]
			18Gy<0.1cc	21.9GyGy<0.1cc			23Gy<0.1cc	30 Gy<0.1cc	25Gy<0.1cc	32Gy<0.1cc	Hanna et al [148]
Esophagus	11.9Gy<5cc 14.5Gy<5cc	15.4Gy Dmax	17.7Gy<5cc	25.2Gy			19.5Gy<5cc	35Gy			RTOG 0915 [154]
			21Gy<5cc	27Gy	18.8Gy<5cc 30 Gy<10cc 35Gy<1cc	30 Gy DMax 50 Gy DMax	27.5Gy<5cc	35Gy 52.5Gy			RTOG 0618 [153] RTOG0813 [155] EC STARS [156]
				25.2Gy <0.5cc			32Gy<0.5cc	34Gy<0.5cc		40 Gy<0.5cc	Hanna et al [148]

	One (30-34Gy)		Three fractions (54-60 Gy)		Four fractions (48Gy)		Five fractions (50-60 Gy)		Eight fractions (60 Gy)		Source/Study
	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory	
Heart	16Gy<15cc 16Gy<15cc	22Gy Dmax 22Gy Dmax	24Gy<15cc 24Gy<15cc	30 Gy Dmax 30 Gy Dmax	28Gy<15cc 35Gy<10cc 40 Gy<1cc	34GyDmax 50 Gy Dmax	32 Gy<15cc 32Gy<15cc	38GyDmax 38GyDmax 52.5GyDmax			TGT101 [146] , RTOG 0618 [153] , RTOG 0915 [154] RTOG 0813 [155] EC STARS [156]
			24Gy<0.5cc	26Gy<0.5cc			27Gy<0.5cc	29Gy<0.5cc	50 Gy<0.5cc	60 Gy	Hanna et al [148]
Great Vessels	31Gy<10cc	37Gy Dmax	39Gy<10cc	45Gy Dmax			47Gy<10cc	53Gy Dmax			TGT 101[146]
	31Gy<10c	37Gy<0.035cc	39Gy<10cc	45 Gy Dmax	43Gy<10cc 35Gy<10cc 40 Gy<1cc	49GyDmax	47Gy<10cc	52.5GyDmax			RTOG0813 [155] RTOG 0915 [154] EC STARS [156]
				45Gy<0.5cc		53Gy<5cc					Hanna et al [148]
Trachea and Bronchus	10.5Gy<4cc	20.2Gy Dmax	15Gy<4cc	30 Gy Dmax			16.5Gy<4cc	40 Gy Dmax			TGT 101[146]
	8.8Gy<4cc 10.5Gy<4cc	22Gy Dmax 20.2Gy<0.035cc	21Gy<5cc	30 Gy Dmax	30 Gy<10cc 35Gy<1cc 15.6Gy<4cc	50 Gy Dmax 34.8Gy Dmax					RTOG0813[155].RTOG 0915 [154] , RTOG 0618 [153] EC STARS [156] RTOG 0915 [154]
			30 Gy<0.5cc	32Gy<0.5cc			32Gy<0.5cc	35Gy<0.5cc	32Gy<0.5cc	44Gy<0.5cc	Hanna et al. [148]
Skin	23Gy<10cc 14.4Gy<10cc	26Gy Dmax 16Gy Dmax	30 Gy<10cc 22.5Gy<10cc	33Gy Dmax 24Gy Dmax			36.5<10cc 30 Gy<10cc	39.5Gy Dmax 32Gy Dmax			TGT 101 [146] EC STARS [156] RTOG [154]

					35Gy<10cc 40 Gy<1cc 33.2Gy<10cc	36Gy Dmax					
Chest wall	22Gy<1cc	30 Gy Dmax	28.8 Gy<1cc 30 Gy<30cc	36.9Gy Dmax			35Gy<1cc	43Gy Dmax			TGT [146]
	22Gy<1cc	30 Gy Dmax	30 Gy<30cc 50 Gy<2.3cc		35Gy<10cc 32Gy<1cc	40 Gy D max	30 Gy<30cc 50 Gy<2.3cc 60 Gy<1.4cc				RTOG 0915 [154] (145,147) (145), RTOG 0915 [154]
			37Gy<0.5cc 30 Gy<30cc				39Gy<0.5cc 32Gy<30cc		39Gy<0.5cc 35Gy<30cc		Hanna et al. [148]
Normal Lungs	Minimal critical volume under threshold 1500cc 1000cc	Threshold dose 7 Gy 7.4 Gy		Threshold dose 11.6 Gy 12.4 Gy			Threshold dose 12.5 Gy 13.5Gy				TGT [146]

	Minimal critical volume under threshold 1500cc 1000cc 1500cc 1000cc	7 Gy 7.4 Gy	20 Gy<10% 20 Gy<15%	10.5Gy 11.4Gy	11.6Gy 12.4Gy 20 Gy<20%. 30 Gy<10%		12.5 Gy 13.5 Gy 20 Gy<20% 30 Gy<10%				RTOG0813 [155] RTOG 0915 [154] EC STARS [156]
				V20<10% V12.5<15%			V20<10% V12.5<15%		V20<10% V12.5<15%		Hanna et al. [148]
	Treatment on lesion: V20 <10%; Treatment 2-3 lesions: V20<12.5% (optimal); V20< 15% (acceptable); V20< 20% (selected cases) 3-8 fractions on alternating days. If the lesions are not included in the treatment field, alternate the treatment days for the different lesions.										Hanna et al. [148] Milano et al. [151]
	In 3-5 fraction Dmean ≤ 8 Gy and V20 ≤ 10-15%										Kong et al. [152]

6. RADIOTHERAPY TECHNIQUES (3DRT, 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 conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), together with advances in image-guided radiotherapy (IGRT) and the introduction of proton radiotherapy.

Based on data from non-randomised studies, these more sophisticated techniques reduce toxicity to OARs and improve tumour control, thereby leader to better survival outcomes when compared to 3D-CRT[157][158]. 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 (≥ G3) pneumonitis and lower heart doses, which is a predictor of survival[159] [160]. 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[161] .

Intrathoracic motion of lung tumour 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 tumour, thus providing better tumour control and lower doses to OARs. During planning, several techniques can be used to quantify tumour 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 (DIBH), 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” tumour tracking—used mainly in SBRT[162]. 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[163].

The incorporation of cone beam CT (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[164][165][166]. This capacity to adjust the treatment plan, known as adaptive radiotherapy, permits administration of higher radiation doses to the tumour with lower doses to the OARs[165][167][168].

Data from small studies suggest that adaptive radiotherapy improves local control[169]. This technique is currently being evaluated in the phase II RTOG 1106 trial (NCT01507428) comparing standard concomitant CRT (60 Gy) to adaptive radiotherapy based on PET-CT imaging.

Data from both retrospective and prospective studies suggest that proton radiation therapy (PRT) may be superior to photon radiotherapy in the treatment of NSCLC[170][171][172]. However, only one randomised study has compared SBRT to PRT in stage I disease and that trial was closed early[173]. In patients with stage III disease, prospective and retrospective studies have shown acceptable locoregional control with PRT combined with ChT[174]. PRT has the potential to reduce toxicity to OARs such as the lung, heart, and esophagus, especially in unresectable central tumours[175][176][177]. 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 local control[178]. Consequently, the theoretical advantages of PRT need to be validated in randomised trials, such as RTOG 1308, which is currently recruiting patients[179].

7. REIRRADIATION

Approximately 20%–40% of patients with early stage or locally-advanced NSCLC develop locoregional progression or metachronous disease at 2 years[180]. 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 tumours. However, there is no consensus on the optimal approach to radiotherapy for local recurrences in previously-irradiated patients[181].

7.1. 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 radiotherapy, anatomic location of the recurrence, and whether the lesion is located in or outside of the original radiotherapy field. Several factors—good performance status, lung function, small PTV, and a BED dose > 100 Gy—are predictive of better local control 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[182] because SBRT-related toxicity can be severe when the tumour is located near the bronchial tree and/or esophagus. Vyfhuiss et al. [183] reported a 92% local control rate in patients treated with 50 Gy in four fractions (SBRT) while Killburn et al.[184] reported a 2-year local control 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[185] show that IMRT is the most appropriate technique for reirradiation in central tumours, as high doses are required to achieve better local control. IMRT also reduces the dose to healthy tissues, thus limiting toxicity.

7.2 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. McAvoy et al. reported a significant decrease in OAR toxicity in patients reirradiated with PRT[186][187].

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 (LET) and relative biological effectiveness (RBE), its use is currently very limited[188].

The ROCOCO dosimetric comparison study[189] showed that PRT reduced the integral dose and doses to OARs, even with dose escalation. Chao et al.[190] found that patients treated with PRT had a high rate of toxicity, with 39% of patients developing ≥ 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 (≥ 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[191]; however, large multicentre trials are required to confirm these findings .

To conclude this section, the best candidates for reirradiation have the following characteristics: good performance status, small volume recurrences, non-central locations, and the capacity to tolerate high dose radiation (SBRT, IMRT, or particle therapy) [185][192].

8. 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 minimise these deleterious effects. In normofractionated schemes, extending the OTT will negatively impact locoregional control and OS [193][194][195][196]. One report suggested that OS rates may decrease by up to 1.8% for each day of treatment prolongation[197]. In hyperfractionated regimens, interruptions that increased the OTT by ≥ 5 days in high dose schemes (≥ 69.6 Gy) negatively impact OS, especially in patients with good prognostic factors, such as KPS 90%-100%, weight loss < 5%, and ≤ N2 [195].

Compensation for treatment interruption

In the year 2000, the Royal College of Radiologists in the UK published recommendations for the management of unscheduled treatment interruptions, which were updated in 2019[198]. These recommendations divide the treatment type into three categories: radical (categories 1 and 2) and palliative (category 3) treatment, as follows:

Category 1: Patients whose tumours have a high repopulation rate (e.g., squamous cell tumours) who are being treated with radical curative-intent RT. The UK 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.

Category 2: Patients with slow growing cancers (mainly adenocarcinomas) receiving radical-intent RT. This group includes breast, transitional bladder carcinoma, and prostate cancer.

Category 3: Patients undergoing palliative-intent RT. OTT prolongation is less critical in these cases. However, it is advisable to compensate for prolonged (> 7 days) interruptions.

Compensation Methods

Some authors have suggested that modern radiotherapy techniques such as IMRT reduce the incidence of treatment interruptions[199]. 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:

- Compensation on weekends and holidays
- 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:

- Unplanned:
Option 1: Administer two sessions on the same day, 6 hours 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 tumour according to the following formula [200]:

$$N.d\left[1+\frac{d}{\alpha/\beta}\right]$$

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 tumour α/β ratio of 10, the formula would be as follows:

$$N.d\left[1+\frac{d}{\alpha/\beta}\right]-K\,(T-T\kappa)=$$

$$30.2\left[1+\frac{2}{10}\right]-0.45\,(39-28)=67.05\ \text{Gy}$$

where:

+ K (estimated loss of biological efficacy in Gy per day of delay that would need to be added to compensate)[193]: 1) stages T1-3, N0-1: 0.27 Gy/day; 2) stages T1-3 N2-3 or T4: 0.75 Gy/day; 3) all stages: mean 0.45 Gy/day.

+ T: total treatment time. In the example, the T is 39 days and treatment s assumed to start on a Monday.

+ Tκ (time from the start of RT at which accelerated repopulation begins) reported: 3-4 weeks[197]: 28 days.

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).

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

• In hyperfractionated schemes, compensation strategies are more complex, which is why treatment on holidays is preferred. However, if the treatment delay is ≥ 10 days, full compensation is not recommended due to the risk of excess toxicity[198].
• 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[201].

9. 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)[202]. After SBRT, approximately 12% of patients develop locoregional recurrence at 4 years[203] .

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 tumour ranges from 59 to 62 months[204]. 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[205][206].

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 months after treatment. Based on recommendations from the ESTRO[207], the UK SBRT consensus statement[208], and updates on high-risk CT features [209] , 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 weeks of treatment completion. The first CT scan should be performed at least 3 months after treatment. Clinical evaluation, including contrast-enhanced CT, should be performed every 3 months for at least one year.

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

Third to fifth year after treatment: CT imaging should be performed every 6 months 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[210][211], 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[212], the Italian Association of Medical Oncology[213], and SEPAR[15], we recommend the following:

Unsalvageable patients
Perform clinical evaluations (complete medical history, physical examination, and blood tests) every 6 months for two years. A chest CT should be performed at months 12 and 24, with annual follow-up thereafter (III, B).

Salvageable patients
First three years: CT IV contrast every 3-6 months (III, B).
Years four and five: Follow-up every 6 months; 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[214] (III, A). Behavioral therapy combined with pharmacological intervention (I, A).

- Influenza and pneumococcal vaccination should be offered if not contraindicated.

10. RECOMMENDATIONS

Summary of recommendations is provided in table 11.

Table 11: Summary of recommendations

Diagnosis	Level of evidence, grade of recommendation
If lung cancer is suspected, refer patient to a rapid diagnostic service for evaluation by a multidisciplinary team	**II, C**
PET-CT is recommended for initial staging in patients with stage I-III disease who are candidates for radical treatment	**I, A**
EBUS/EUS is recommended for clinical staging in patients with enlarged lymph nodes without distant metastases, with or without PET uptake	**I, C**
EBUS/EUS is recommended for stating in patients with positive PET-CT scans and normal-sized lymph nodes without distant metastases	**I, A**
Histological confirmation of the mediastinum by EBUS/EUS is recommended in central tumours, tumours > 3 cm, and N1 cases	**I, C**
Histological confirmation is required in cases with a single metastatic lesion and positive PET-CT	**II, A**
Brain MRI is recommended in candidates for curative-intent treatment	**II, A**
VAMS should be performed when EBUS/EUS findings are not evaluable	**I, B**
Differentiation between adenocarcinomas and squamous cell carcinomas is recommended even for small biopsies or cytology	**I, B**
EGFR mutations and ALK rearrangements should be assessed in patients with stage IV, non-squamous cell carcinomas. This determination should be performed in all cases (regardless of smoking status) and in all non-smokers independently of tumour histology	**I, B**

Early stage NSCLC - SBRT	
Inoperable	II, A
Operable	III, C
High surgical risk	III,A

Locally-advanced disease	
Concomitant radiotherapy: This is the treatment of choice for unresectable stage IIIA/IIIB with ECOG 0-1 and weight loss <5% in 3 months	I, A
60-66 Gy in 30-33 daily fractions of 2 Gy/fx and 2-4 ChT cycles	I, A
Platinum-based ChT	I, A
Treatment should be completed in < 7 weeks	III, B
Sequential radiotherapy:	
If concomitant treatment is not possible, the alternative is sequential CRT	I, A
Treatment should be completed in a short period of time	I, A

Neoadjuvant radiotherapy:	
Assessment by a multidisciplinary team is recommended	IV, C
In potentially-resectable upper sulcus tumours, the recommended approach is neoadjuvant CRT followed by surgery	III, A
This approach can be considered in potentially-resectable T3/T4 tumours, but only in well-selected cases at experienced centres	III, B
Surgery must be performed within 4 weeks after completion of RT	III, B
Adjuvant radiotherapy:	
Not recommended in early stage disease with complete resection (R0)	I, A
It should be considered if resection is incomplete or margins are involved (R1)	IV, B
Not recommended as standard in R0 cases with N2 involvement	I, A
In N2 disease, adjuvant RT could be considered based on risk factors for local recurrence	IV, C
If adjuvant ChT and RT are both administered, the recommended sequence is ChT followed by RT	V, C
Altered fractionation schemes	
Accelerated hyperfractionation schemes provide better disease control than conventional RT	I, A

Recommended fractionation schemes for RT administered alone or sequentially after ChT: 55 Gy (20 fx, 2.75 Gy), 60 Gy (20 fx, 3 Gy), 60 Gy (15 fx, 4 Gy), 45-50 Gy (15 fx, 3-3.33 Gy)	II, A
If RT administered concurrently with ChT in patients with good performance status: 55 Gy (20 fx 2.75 Gy).	II, B
General considerations: There is no evidence to support prophylactic WBRT in stage III disease	II, A

Stage IV	
Oligometastatic disease:	
Patients with 1-5 synchronous metastases at diagnosis may benefit from consolidation SBRT and systemic therapy	II, B
Patients with 1-5 metachronous metastases can be treated with SBRT	III, B
Solitary lesions in the contralateral lung are considered synchronous metastasis in most cases. These patients may benefit from ablative SBRT	IV, B
Patients with extra-cranial oligoprogression with driver mutations (ALK and EGFR) who are receiving treatment with targeted molecular therapy can benefit from SBRT	II, B
Patients with "symptomatic" brain oligoprogression with driver mutations (ALK and EGFR) receiving treatment with targeted molecular therapy may benefit from SRS	II, A
SRS can be delayed in patients with "asymptomatic" brain oligoprogression with driver mutations (ALK and EGFR) being treated with targeted molecular therapy	II, A
Patients with "de novo", "recurrent" or "induced" oligometastatic disease treated with immunotherapy may benefit from SBRT (improved local control and symptom relief)	III, B
SRS doses ≧ BED_{10} 100 Gy are recommended in thoracic lesions, if OAR tolerances are met	II, A
Metastatic disease	
In symptomatic patients, palliative RT is recommended for symptom control (hemoptysis, airway obstruction, chest pain, bone metastases, superior vena cava syndrome, spinal cord compression)	II, B
Short course RT is recommended in patients with poor functional status or short life expectancy	II, A
In patients with good functional status or life expectancy > 4 months, higher dose RT (20-30 Gy in 5-10 fx) is recommended based on the proven survival benefit	II, B
External beam RT alone is more effective than endobronchial brachytherapy alone for symptom palliation	II, B
WBRT should not be offered to patients with class III RPA	I, A
For WBRT, comparable results are observed with 20 Gy in 5 fx and 30 Gy in 10 fx	I, A

WBRT can be delayed in patients with multiple "asymptomatic" brain metastases with driver mutations who are receiving (or about to start) targeted molecular therapy	III, B
The use of palliative RT combined with immunotherapy has demonstrated an adequate safety and efficacy profile in terms of symptom control	III, B
Technical aspects	
Planning	
Contrast-enhanced CT facilitates contouring of central tumours and mediastinal lymph nodes	III, A
PET-CT is recommended for volume contouring and image acquisition in the treatment position	III, A
Recommended CT slice thickness is 23 mm to improve contouring accuracy	IV, A
4D-CT recommended to quantify respiratory motion, especially in lower lobe tumours and/or SBRT	IV, A
Treatment	
Minimum required technique: 3DCRT	I, A
IMRT/VMAT preferred to 3D-CRT	I, A
Breathing control recommended, especially in SBRT	II, A
Perform daily imaging control (IGRT) depending on the technique, preferably with CBCT	III, A
Consider adaptive radiotherapy in large volumes and high doses in OARs	IV, A
Volume contouring	
GTV (gross tumour volume)	
Recommended CT parameters for tumour/nodal contouring: parenchyma: W = 1600 and L = 600; and W = 400 and L = 20 for mediastinal nodes	III, A
If neoadjuvant chemotherapy (ChT) administered: contour volumes on the post-ChT CT image (i.e., the initial CT scan)	III, B
Elective irradiation of mediastinal lymph nodes not recommended	III, A
Recommended to include lymph nodes with positive biopsy, pathologic on PET-CT or CT (≥ 1cm). Highly suspicious nodes on	III, A

PET-CT with negative EBUS should be included due to risk of false negatives	
CTV (clinical target volume): Recommended CTV margin = 58 mm. Assess manually and adjust as necessary to account for adjacent healthy tissues (e.g. bone).	III, B
ITV (Internal target volume): Contour the ITV based on the CT scan performed to quantify motion. If 4D-CT is performed, it is recommended to contour the volume in each respiratory phase or directly in the MIP reconstruction. If this is not possible, a slow acquisition CT or inspiration, expiration and free-breathing CT can be obtained to contour volumes in each phase.	III, B
PTV (planning target volume): The PTV should account for geometric uncertainties and should be adapted to the each centre, since multiple factors (immobilization system, respiratory motion compensation, image-guided technique, etc.) can influence the PTV	III, A
Organs at risk (OAR): Consider applying margins around the OAR (PRV) to avoid exceeding dose constraints	IV, C

DATA SUPPLEMENT

Table: 3: Accelerated fractionation- hyperfractionation studies

Study Type	No. of patients	Radiotherapy	Chemotherapy	Results	Toxicity
Phase III RCT [15,16]	n=563: Stage I (29%), II (7%), IIIA (38%), IIIB (23%). Similar in both arms.	cRT: 60 Gy, 2 Gy/d (6 weeks). INP 44 Gy + boost 16 Gy tumour and involved nodes versus CHART: 54 Gy, 1.5 Gy/3 times/day, 6h apart, on 12 consecutive days. INP 37.5 Gy in 25 fx + boost 16.5 Gy in 11 Gy to tumour and involved nodes	No	Absolute 2-year survival improvement of 9%: 20% (cRT) vs. 29% (CHART). 21% relative risk reduction for PL. Major improvement in squamous cell disease: 13% 2-year survival: 20% (cRT) vs. 33% (CHART). 25% relative risk reduction of PL	Clinical pneumonitis 19% cRT and 10% CHART.
Phase III RCT [17]	n=141: Stage III A-B unresectable ECOG 0-1	cRT: 64 Gy, 2 Gy/d (6 ½ weeks) versus HART: 57.6 Gy, 1.5 Gy 2 times/day (2.5 weeks)	Induction: Carboplatin AUC6 + Paclitaxel 225 mg/m2 2 cycles prior to RT.	2-year OS: 44% HART vs 24% cRT; 3 yrs: 34% vs 14%. Non-significant trend towards better survival with HART. Feasible treatment Trial close early due to slow recruitment.	Esophagitis ≥ G3 23% HART vs 15% cRT. Pneumonitis ≥ G3: 0 HART vs 10% cRT.
Phase III RCT [18]	n=406: stage I 10%, II 5%, IIIA 38%, IIIB 46% Similar in both arms	CHARTWEL: 60 Gy, 1.5 Gy 2 times/day in 2.5 weeks Versus cRT: 66 Gy, 2 Gy/d, 6.5 weeks	Neoadjuvant 27%. Similar in both arms	Better LC in CHARTWEL No difference between arms in OS at 2, 3, 5 yrs. Better LC CHARTWEL trend in advanced stages and after neoadjuvant ChT.	Greater acute dysphagia CHARTWEL. Greater radiological pneumonitis CHARTWEL, no differences in clinical pneumonitis.
Retro. [19]	n=849, 9 UK centres Stage I 33%, II 13%, IIIA 24%, IIIB 24%, IV 1%	CHART: 54 Gy, 1.5 Gy/3 times/day, 6h apart, in 12 days	Induction 27% patients, 82% stage III (96% platinum doublets: cisplatin or carboplatin with vinorelbine, gemcitabine or paclitaxel)	OS 2 and 3 yrs: 47% and 32%. OS 3 yrs: 38% stage I and 27% stage III. Tendency to better survival in stage III after ChT.	Esophagitis, pneumonitis ≥ G3 5%

Table 4: Studies of moderate hypofractionated radiotherapy

Type of stud	No. patients	Radiotherapy	Chemotherapy	Results	Toxicity
Prospective [78]	30 stage III-IVA ECOG ≥ 2	60 Gy (20 fx 3 Gy) (BED_{10} 79.4 Gy)	Sequential (80% patients)	LR 37% OS 2-yr 38.1% LR 37% Distant relapse 57%	Acute esophagitis G3 7% Acute pneumonitis G3 3% No chronic toxicity
Prospective [79]	83 (32 stage III)	66 Gy (24 fx 2.75Gy) (BED_{10} 84 Gy)	Sequential 90.6% stage III (platinum + vinorelbine)	OS 2 yr 37.5% SCE 2 yr 41.5%	No toxicity ≥ G3
Retrospective[80]	300 stage III, inoperable, MEG	3 arms: 45 Gy (15 fx 3Gy); 60-63 Gy (6 weeks); > 63 Gy (6 weeks)		No significant differences in LC, distant control, or OS. > DFS in 60-63 Gy	Lower in hypofractionated arm
Retrospective [81]	609 (9 centres) Stage IA (18%), IB (30.7%), II (14.8%), IIIA (16.4%), IIIB (19.2%) Unresectable or inoperable	55 Gy (20 fx 2.75Gy)	ChT 28% (83% stage III) Platinum doublets Most neoadjuvant	OS at 2, 3 and 5 years: 50%, 36% and 20%. 2 yr OS: stage IA, 72%, stage Ib 51%, stage IIIA 40%. Adenocarcinoma better median survival (31 m) vs. squamous (20.4 m). No difference in OS between ChT vs. no ChT. Stage III, trend towards better OS with ChT.	No toxicity ≥ G3 Pneumonitis G1-2, 15%

Retrospective [82]	n=31 stage I (15), II (15), IIIA (57), IIIB (43) Medically inoperable or unresectable	3 arms: 66 Gy (24 fx 2.75Gy) + daily cisplatin (6 mg/m2); same sequential RT after 2 cycles cisplatin/gemcitabine ; RT alone 66 Gy (24 fx 2.75Gy) or 60 Gy (20 fx 3 Gy)	C: Cisplatin daily (6 mg/m2) Sequential: (2 cycles cisplatin/gemcitabine) prior to RT	LR 36%, DM 46% Better RT+ChT than RT alone 5 yrs OS: concurrent CRT, 23%. No significant difference between concurrent and sequential CRT. LR 36%, DM 46%	Severe late toxicity greater in CRT (27% C, 23% S) than in RT alone (8%)
Phase III RCT [83] *	60, stage II/III (11.6%/88.3%) ECOG ≥2 Not candidates for ChT/RT	cRT 60- 66Gy/30-33fx vs. accelerated Hypofx 60Gy/15 fx 4 Gy	Non-concurrent ChT. Possible neoadjuvant or adjuvant.	OS and PFS without significant differences between cRT and hypofx.	No G4 toxicity G3 toxicity: 35% cRT and 18.75% hypofx
Phase III RCT [84]	158 stage I (3% S, 1% C), II (4% S, 5% C), IIIA (45% S, 30% C), IIIB (47% S64% C) Inoperable ECOG 0-1	66 Gy (24 fx 2.75Gy)	Concurrent: daily cisplatin (6 mg/m2) + RT 66 Gy (24fx 2.75Gy) vs. sequential: 2 cycles gemcitabine1250 mg/m2 days 1, 8 and cisplatin (75mg/m2 day 2 prior to RT 66 Gy (24 fx 2.75Gy)	No significant differences between the 2 groups in DM, OS, PFS. OS 2 and 3 yr: 39% -34% C and 34% - 22% S. Both schemes well tolerated. Due to early closure, no conclusions drawn.	Acute esophagitis G3/4 more common in concurrent (14% vs. 5%) Late esophagitis G3= 4% in both arms. Pneumonitis G3/4 = 18% C and 14% S
Phase II RCT [85]	n=130 stage III inoperable ECOG 0-1	55 Gy (20 fx 2.75Gy)	Concurrent: cisplatin 20 mg/m2 days 1-4 and 16-19 and vinorelbine 15 mg/m2 days 1,6,15 and 20 RT and 1 or 2 post ChT cycles (CDDP) 80 mg/m2 day 1 and vinorelbine 25 mg/m2 days 1 and 8)	No significant differences. OS 1 yr: 70% C vs. 83% S and 2 yr: 50% C vs. 46% S. PFS 1 yr: 74% C vs 85% S; 2 yr: 47% C vs. 45% S.	Similar esophagitis ≥ G3 in both arms (8.8% concurrent and 8.5% sequential. Pneumonitis ≥ G3: 3.1% C vs.

			Sequential: Cisplatin 80 mg/m2 day 1 and Vinorelbine 25 mg/m2 days 1 and 8, x 3-4 cycles before RT	Both safe and effective treatments. Non-significant trend towards better survival with concurrent RT/ChT.	5.2% S. No grade 4/5 esophagitis G3 neutropenia lower in C. (37%) vs. S (55%).
Retrospective [86]	n=100 stages IIIA-B 95%, II 5% ECOG 0/1	55 Gy (20 fx 2.75Gy)	Concurrent: cisplatin 20 mg/m2 days 1-4 and 16-19 RT and vinorelbine 15 mg/m2 days 1,6,15,20 and 2 cycles post RT/ChT	OS 2 yr 58% PFS 2 yr 49%	Esophagitis G3/4 14% Pneumonitis G3/4 4%

*Interim analysis of NCT01459497 with 226 patients: Arm A (experimental), 60 Gy in 15 fractions (3 weeks) with IGRT versus arm B, cRT 60-66 Gy in 30-33 fractions (6 weeks) with optional concurrent carboplatin/taxol. Final data expected in December 2021 and December 2022.

Abbreviations: RT, radiotherapy; cRT, conventional RT; LR, local recurrence; DM, distant metastases; LC, local control; G, grade; S, sequential; C, concurrent; ChT, chemotherapy; PFS, progression-free survival; MFS, metastasis-free survival; OS, overall survival; months, m; CDDP, concurrent cisplatin.

Table 5: Radiation therapy in patients with oligometastatic NSCLC

Study	Type	Design	Pts	Histology	Presentation	No. of metastases/ location	RT type	Follow-up	PFS, m	MFS , m	OS, m
OliGomez *Gómez D,JCO, 2019*	Phase II RCT Multicentre	Induct. ChT: RT+MT vs. MT	49	NSCLC (No EGFR,ALK)	Synchronous Metachronous	≤ 3 (1:65%)/ Lung, CNS, bone, liver SSRR, nodes	SABR/SBRT (MTX) Hypofrac. RT (primary)	38.8 m	14.2 (SABR/ SBRT+ MT) vs. 4.4 (MT)	11.9 (SABR/SBRT+MT) vs. 5.7	41 (SABR/SBRT +MT) vs. 17
UTSW *Iyengar P, JAMA, 2018*	Phase II RCT Multicentre	Induct. ChT: SBRT+ mChT vs. mChT	29	NSCLC (No GFR,ALK)	Synchronous	≤ 5 (1: 21%, 2-3: 76%) / Lung, Lymph, Bone, SSRR	SABR/SBRT (MTX) Hypofrac. RT (Primary)	9.6 m*	9.7 (SABR/ SBRT+ MT) vs. 3.5 (MT)	NR	NR (SABR/SBRT +MT vs. 17
SABR-COMET Palma D, JCO, 2020	Phase II RCT Multicentre	ChT+PT vs. ChT+SABR/SBRT	99	Lung (18/99)	Synchronous Metachronous	≤ 5 (1-3:93%)/ Lung, Bone, CNS, Liver, SSRR	SABR/SBRT	51 m	11.6 (SABR/ SBRT+ MT) vs. 5.4 (TP-MT)	NR	50 (SABR/ SBRT+MT) vs. 22

Abbreviations: RT, radiotherapy; MT, maintenance treatment; mChT, maintenance chemotherapy; PT, palliative treatment; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; EGFR, epidermal growth factor receptor ; ALK, anaplastic lymphoma kinase; MTX, metastasis NR, not reported; PFS, progression-free survival; MFS, metastasis-free survival; OS, overall survival; months, m.

* Study stopped early due to significant difference in PFS between the two arms

Table 6: Prognostic factors associated with better survival in oligometastatic patients with NSCLC

FACTOR	COMMENTS
Gender	Female > male
Histology	Adenocarcinoma > Squamous cell carcinoma
Presentation	Metachronous > synchronous
Karnofsky index - ECOG	>80% - ≤ 1
Number of lesions	1 > 2-3 > 4-10
Size	< 3 cm
Location	Lung, bone> adrenal glands, lymph nodes> liver, brain

Table 7: Most common radiotherapy schemes according to metastatic site

Location	Fractions/Total dose	REFERENCES
Brain	1 fx: 18-24 Gy 3 fx: 24-27 Gy 5 fx: 25-35 Gy	*Shaw E, Int J Radiat Oncol Biol Phys,2000* *Ahmed KA, Am J Clin Oncol, 2016* *Arvold ND, Neuro Oncol, 2016* *Pessina F, Br J Radiol, 2017*
Lung	***SEE EARLY STAGE LUNG CANCER***	
Adrenal gland	3 fx: 36-45 Gy 5 fx: 40-50 Gy	*Chawla S, Int J Radiat Oncol Biol Phys, 2009* *Casamassima F, Int J Radiat Oncol Biol Phys 2012* *Plichta K, Adv Radiat Oncol, 2017*
Liver	1 fx: 24-26 Gy 3 fx: 45-60 Gy 5 fx:40-50 Gy 8 fx: 60 Gy	*Rusthoven KE, J Clin Oncol, 2009* *Mahadevan A, Radiat Oncol, 2018* *Stintzing S, Acta oncol, 2013*
Bone (vertebra included)	1 fx: 16-24 Gy 3 fx: 27-30 Gy 5 fx: 30-40 Gy	*Bedard G, Ann Palliat Med, 2016* *Huo M, Surg Neurol Int, 2017* *Zeng KL, Front Oncol, 2019* *Moraes FY, Neurosurg Clin N Am, 2020*

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