PULMONOLOGY

REVIEW

Unresectable stage III non-small cell lung cancer: Insights from a Portuguese expert panel

A. Araújo[a], A. Barroso[b], B. Parente[c], C. Travancinha[d], E. Teixeira[e,f,g], F. Martelo[h], G. Fernandes[i], G. Paupério[j], H. Queiroga[i], I. Duarte[d], J.D. da Costa[d], M. Soares[j], P. Borralho[f], P. Costa[k], P. Chinita[l], T. Almodôvar[d], F. Barata[m,*]

[a] *Medical Oncology Department, Centro Hospitalar Universitário do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal*
[b] *Pulmonology Department, Centro Hospitalar Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, 4434-502 Vila Nova de Gaia, Portugal*
[c] *Hospital CUF Porto, Estrada da Circunvalação 14341, 4100-180 Porto, Portugal*
[d] *Instituto Português de Oncologia Lisboa Francisco Gentil, Rua Prof. Lima Basto, 1099-023 Lisboa, Portugal*
[e] *Centro Hospitalar Lisboa Norte - Hospital Pulido Valente, Alameda das Linhas de Torres, 117 1769-001 Lisboa, Portugal*
[f] *Hospital CUF Descobertas, Rua Mário Botas, 1998-018 Lisboa, Portugal*
[g] *Hospital CUF Tejo, Avenida 24 de Julho 171A, 1350-352 Lisboa, Portugal*
[h] *Hospital da Luz Lisboa, Avenida Lusíada 100, 1500-650 Lisboa, Portugal*
[i] *Centro Hospitalar Universitário de São João, Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal*
[j] *Instituto Português de Oncologia Porto Francisco Gentil, Rua Dr. António Bernardino de Almeida 62, 4200-072 Porto, Portugal*
[k] *Instituto CUF Porto, Rua Fonte das Sete Bicas 170, 4460-188 Senhora da Hora, Porto, Portugal*
[l] *Hospital do Espírito Santo de Évora, Largo do Sr. da Pobreza, 7000-811 Évora, Portugal*
[m] *Centro Hospitalar e Universitário de Coimbra, Praceta Professor Mota Pinto, 3004-561 Coimbra, Portugal*

Abbreviations: ^{18}F-FDG, 2-deoxy-2-(18F)fluoro-D-glucose; ALK, anaplastic lymphoma kinase; BRAF, B-raf proto-oncogene serine/threonine kinase; CCRT, concurrent chemoradiotherapy; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, chemoradiotherapy; CT, computed tomography; DNA, deoxyribonucleic acid; EBUS, endobronchial ultrasound; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EMN, electromagnetic navigation; EUS, oesophageal ultrasound; FBS, flexible bronchoscopy; FDA, Food and Drug Administration; FEV1, forced expiratory volume; FFPE, formalin-fixed paraffin-embedded; FNA, fine needle aspiration; GP, general practitioner; HER2, human epidermal growth factor receptor 2; HER4, human epidermal growth factor receptor 4; IgG1, immunoglobulin G1; IHC, immunochemistry; IMRT, intensity-modulated radiotherapy; KRAS, kirsten rat sarcoma viral oncogene homologue; LN, lymph node; MDT, multidisciplinary team; MRI, magnetic resonance imaging; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OS, overall survival; PCC, patient-centred care; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; PET, positron emission tomography; PFS, Progression-free survival; PI3KCA, phosphatidylinositol 3-kinase catalytic subunit; PS, performance status; ROS1, c-ros oncogene 1 receptor tyrosine kinase; SCRT, sequential chemoradiotherapy; SUVmax, maximum standardised uptake values; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration; TNM, T − Primary Tumour, N − Regional Lymph Nodes, M- Distant Metastasis; TPS, tumour proportion score; TTF1, thyroid transcription factor 1; TTNB, transthoracic needle biopsy; VAM, video-assisted mediastinoscopy; VATS, video-assisted thoracoscopic surgery; VMAT, volumetric modulated arc therapy.
* Corresponding author at: Centro Hospitalar e Universitário de Coimbra, Praceta Professor Mota Pinto, 3004-561 Coimbra, Portugal.
E-mail address: fjssbarata@gmail.com (F. Barata).

KEYWORDS
Stage III non-small
cell lung cancer;
Diagnosis;
Staging;
Treatment;
Immunotherapy

Abstract

Introduction: The management of unresectable stage III non-small cell lung cancer (NSCLC) is clinically challenging and there is no current consensus on optimal strategies. Herein, a panel of Portuguese experts aims to present practical recommendations for the global management of unresectable stage III NSCLC patients.

Methods: A group of Portuguese lung cancer experts debated aspects related to the diagnosis, staging and treatment of unresectable stage III NSCLC in light of current evidence. Recent breakthroughs in immunotherapy as part of a standard therapeutic approach were also discussed. This review exposes the major conclusions obtained.

Results: Practical recommendations for the management of unresectable stage III NSCLC were proposed, aiming to improve the pathways of diagnosis and treatment in the Portuguese healthcare system. Clinical heterogeneity of patients with stage III NSCLC hinders the development of single standardised algorithm where all fit.

Conclusions: A timely diagnosis and a proper staging contribute to the best management of each patient, optimizing treatment tolerance and effectiveness. The expert panel considered chemoradiotherapy as the preferable approach when surgery is not possible. Management of adverse events and immunotherapy as a consolidation therapy are also essential steps for a successful strategy.

Introduction

Locally advanced stage III non-small-cell lung cancer (NSCLC) includes tumours exhibiting extension into extrapulmonary structures, involving hilar or mediastinal lymph nodes, but with no evidence of distant metastasis.[1] According to the 8th edition of the TNM Classification of Malignant Tumours (T — Primary Tumour, N — Regional Lymph Nodes, M- Distant Metastasis), stage III includes three subgroups: i) stage IIIA comprises T4 N0 M0 and T3/4 N1 M0 tumours as well as T1/T2 N2 M0 tumours; ii) stage IIIB tumours are either T3/T4 N2 M0 or T1/T2 N3 M0 and iii) stage IIIC involves T3/T4 N3 M0 tumours.[2] The new classification unveils the anatomical extent and the heterogeneity of the disease when diagnosed in this stage, that accounts for approximately 20−25% of NSCLC.[3] Significant advances emerged in imaging, diagnostic and staging techniques including new generation computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS) and video-assisted thoracoscopic surgery (VATS), which are now routinely used in lung cancer management.[4]

The development of combined treatments for unresectable stage III NSCLC has led to a significant improvement of 5−10% in the 5-year overall survival (OS) rate as opposed to with radiotherapy alone. Concurrent chemoradiotherapy (CCRT) provided a 5-year OS of 16% when compared to 9% with sequential chemoradiotherapy (chemotherapy followed by radiotherapy - SCRT).[5] A complex multimodal treatment strategy, including surgery, radiotherapy and systemic therapy should be discussed by an experienced multidisciplinary team (MDT).

Recent research in oncology has led to an expanded reach and impact of immune checkpoint inhibitors as part of a frontline treatment strategy in metastatic NSCLC. Regarding the treatment of locally advanced disease, until the PACIFIC trial, no improvements were attained, with the standard treatment being definitiveCCRT.[3]

A panel comprising Portuguese lung cancer experts discussed aspects related to staging and treatment of unresectable stage III NSCLC considering current evidence. This document aims to present the outcome of the discussion, proposing practical recommendations for the global management of unresectable stage III NSCLC patients.

Methodology

A panel of 17 Portuguese physicians with recognised clinical expertise (8 pulmonologists, 3 radiation oncologists, 2 thoracic surgeons, 2 oncologists, 1 pathologist and 1 radiologist) reviewed the strengths and limitations of available evidence as well as the constraints of clinical daily practice, in order to elaborate practical recommendations for the clinical management of unresectable stage III NSCLC in Portugal. To overcome the limitations of a round table discussion in which members of the expert committee with stronger opinions may dominate over less assertive ones, an informal qualitative method was implemented in order to determine the percentage of consensus. Experts were asked to answer anonymously to a survey, indicating the level of agreement regarding the statements presented. In addition, a PubMed search was conducted to complement the panel discussion with the following terms: "lung cancer", "diagnosis", "staging", "NSCLC stage III", "locally advanced NSCLC", "resectable and unresectable locally advanced NSCLC", "neoadjuvant treatment" "chemotherapy", "radiotherapy", "concurrent chemoradiotherapy", "sequential chemoradiotherapy", "durvalumab", "immunotherapy in stage III". This manuscript included published articles in the last ten years prior to April 2020. Only articles published in English were reviewed. Up-to-date and evolving management guidelines related to NSCLC were selected as well as original research and reviews on the basis of their clinical relevance to each section of this manuscript.

Discussion

Diagnosis and staging of unresectable stage III NSCLC

Initial evaluation

The majority of stage III patients present symptoms at their initial presentation, that can be tumour related (persistent coughing, chest/shoulder pain, breathing changes and haemoptysis) and/or systemic (loss of weight or appetite, fatigue).[6,7] On this basis, the intention of the initial evaluation is to obtain enough information to reach a definitive diagnosis and establish a treatment plan with the fastest, safest and cost-effective strategy, taking into consideration patient's values and preferences. This evaluation comprises contrast-enhanced CT scan, complete laboratory evaluation and cardiorespiratory assessment,[8,9] where patient's comorbidities and functional status must be also assessed.[10]

Adequate sampling for tumour diagnosis

Techniques for sample collection should provide enough material for routine preparations (haematoxylin-eosin staining), immunohistochemistry (IHC) and molecular characterisation. Percutaneous transthoracic needle biopsy (TTNB), endobronchial biopsies and EBUS-transbronchial needle aspiration (EBUS-TBNA) provide adequate material if enough sample is collected.[11] Cytology samples obtained from pleural effusions are sometimes highly cellular and can also be used for diagnosis, programmed cell death ligand-1 (PD-L1) expression determination[12] and molecular characterisation.[13] Samples should be of the highest quality and tumour cell purity as possible to permit adequate deoxyribonucleic acid (DNA) extraction.

Diagnosis and staging strategy

The diagnostic recommendations rely firstly on an imaging evaluation to identify the tumour location (Fig. 1A). Bronchoscopy is highly sensitive for central tumours and for peripheral lesions with the complementary use of imaging guiding systems, as radial EBUS, fluoroscopy, electromagnetic navigation (EMN) or computerised navigation systems.[14] For peripheral lesions, accessed through the chest wall transthoracic biopsy guided by CT scan is considered a sensitive and easily available approach. Also, transthoracic puncture guided by ultrasound may be used for pleural-based lung lesions to obtain an adequate amount of tissue, increasing the diagnosis accuracy (Fig. 1A).[15]

Accurate staging improves patient outcomes. The recommendations state that every patient suspected of having lung cancer should undergo a contrast-enhance thoracic CT scan and PET-CT.[16] Thoracic MRI may be necessary and complementary for the assessment of lung cancer tumour invasion of the chest wall,[17] brachial plexus, superior sulcus, diaphragm and great blood vessels (in cine mode).[18] If PET scans are unavailable, bone scan and abdominal CT are reasonable alternatives. All NSCLC patients planned to be treated with curative intention should undergo a brain MRI or, if MRI is not available, a contrast-enhanced CT scan.[10]

Staging of the mediastinum is recommended for patients with lymph node enlargement (short axis diameter ≥ 1 cm) on CT scan and/or ^{18}F-FDG uptake on PET scan, in the absence of distant metastasis. Also, tumours larger than 3 cm, with central location and with N1 disease should undergo mediastinal staging (Fig. 1B).

For the assessment of mediastinal node involvement, minimally invasive needle techniques (EBUS-TBNA, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or combined EBUS/EUS) are the first choice (Fig. 1B). These recommendations are in line with De Leyn et al.[16] which reflects the most updated guidelines from European Society of Thoracic Surgeons. Negative results from endosonographic methods should be confirmed with surgical staging (mediastinoscopy, VATS) only in highly suspicious cases (PET and/or CT positive), and when surgery is being considered as an option, given that after a negative EBUS-TBNA the prevalence of mediastinal lymph nodes is low (near 5%).[19] On the other hand, bulky mediastinal involvement does not need pathological confirmation.

Practical recommendations from patients first visit to diagnosis, staging, treatment decision and follow-up are summarised in Fig. 2.

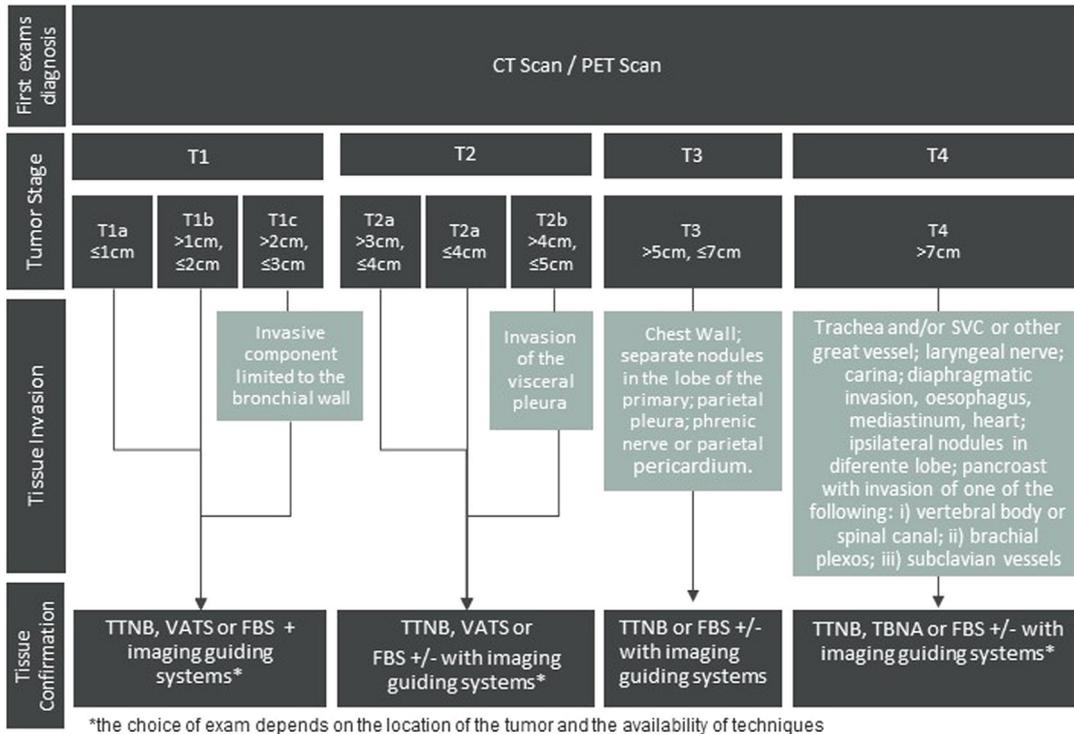### Criteria for operability, resectability and limits for resectability

In early-stage NSCLC, surgical resection is the treatment of choice.[20] However, the determination of resectability should be discussed by the MDT[21] which includes certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice. Surgery should always be considered when R0 surgical resection is feasible (resection margins with no microscopic evidence of tumour cells; systematic nodal dissection or lobe-specific systematic nodal dissection; nodule capsule removed separately and of lymph nodes located at the margin of the main lung must be without extracapsular tumour invasion; highest mediastinal lymph node must be tumour free[22] as is usually reserved for N1 or N0 patients. However, patients with preoperative pathological proven N2 disease are candidates for surgical multimodality treatment under two circumstances: Single station N2 disease or patients with multiple N2 disease who present downstaging after induction treatment).[16] Under this situation, induction treatment is considered to decrease the extent of tumour involvement, reducing the complexity of surgical resection and thus increasing resectability but also to improve local control of the disease and eliminate micrometastases.[23] The group of experts also considered that after assessment of resectability, a precise clinical/functional evaluation is required prior to surgery, underlying the need to perform functional evaluation, namely: general health and performance status (PS) assessment, cardiac function, pulmonary mechanics, diffusion capacity, exercise capacity, extent of resection and age.[20,24]

Limits of resectability

The panel propose the following limits for resectability in stage III, that should not be exceeded:

○ Single station N2 disease up to 3 cm in diameter where other nodal stations have been biopsied and proved to be benign,[21]
○ Some multiple N2 disease after induction therapy, when there has been nodal downstaging and a pneumonectomy can be avoided,[21]

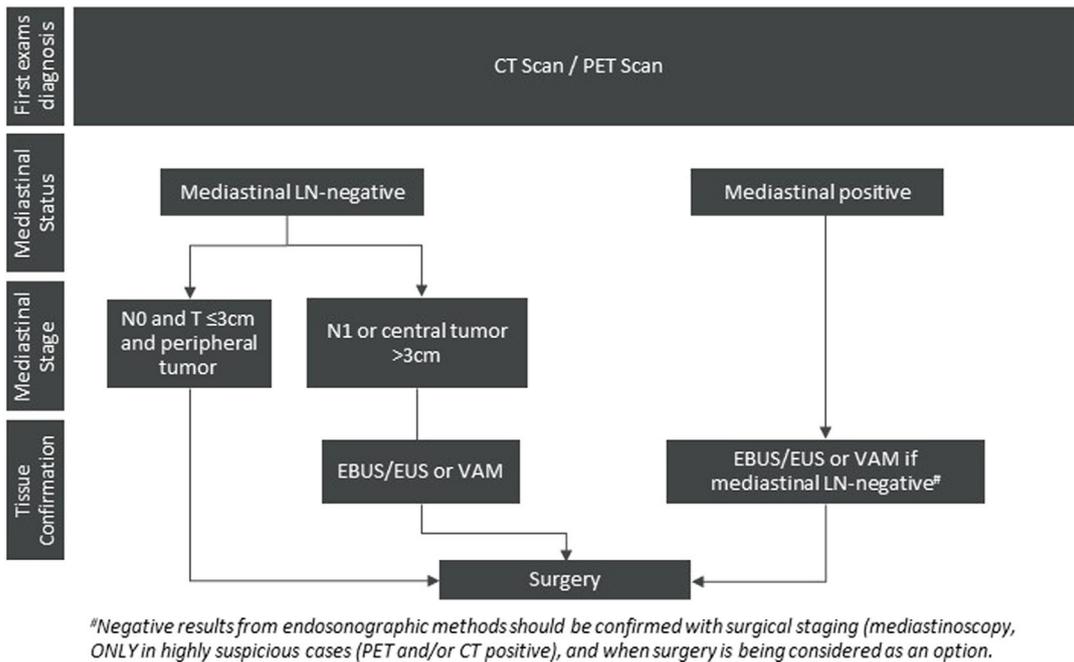## A. Diagnostic recommendations according to tumor status

Fig. 1 Algorithm representing the practical recommendations for diagnosis of locoregional NSCLC according to (A) tumour and (B) lymph-node status. The recommendations present in diagram B were adapted from Leyn et al. Eur J Cardio-Thoracic Surg. 2014.[16] Abbreviations: CT = computed Tomography; EBUS = endobronchial ultrasound; EUS = oesophageal ultrasound; FBS = flexible bronchoscopy; LN = lymph Node; MRI = magnetic resonance imaging; PET = positron emission tomography; TBNA = transbronchial needle aspiration; TTNB = transthoracic needle biopsy; VAM = video-assisted mediastinoscopy; VATS = video-assisted thoracoscopic surgery.

○ T3 with lymph nodes classified as N0 and N1 in addition to the involvement of the main bronchus (less than 2 cm from the carina, but without invasion of the carina),[21]

○ T3 with chest wall involvement (including superior sulcus tumour) could receive neoadjuvant chemoradiotherapy (CRT) followed by surgery,
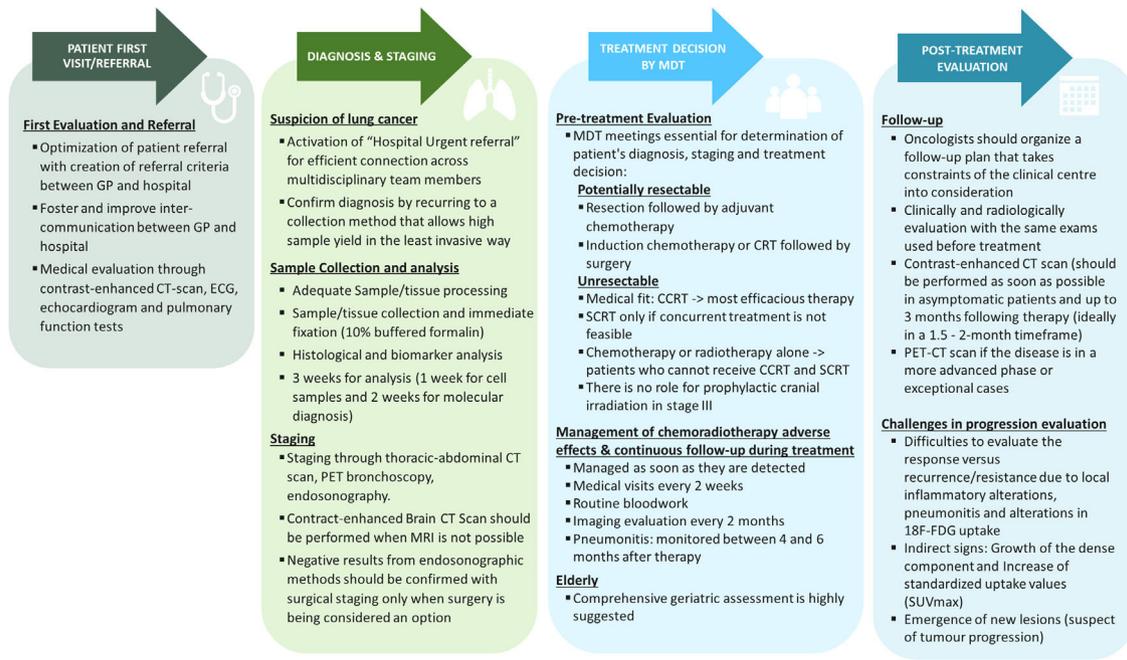
Fig. 2 Highlights the overall management of unresectable Stage III NSCLC. Abbreviations: BRAF = B-Raf proto-oncogene serine/threonine kinase; CCRT = Concurrent chemoradiotherapy; CRT: chemoradiotherapy; CT = computed tomography; ECG = Electrocardiogram; EGFR = Epidermal growth factor receptor; GP = General practitioner; LA-NSCLC: Locally advanced non-small cell lung cancer; MRI = magnetic resonance imaging; NSCLC = Non-small cell lung cancer; PD-L1 = Programmed cell death ligand-1; PET = Positron emission tomography; ROS1 = c-ros oncogene 1 receptor tyrosine kinase; SCRT: Sequential chemoradiotherapy; SUVmax = Maximum standardized uptake values; TTF1 = Thyroid transcription factor 1.

○ T4N0 tumours where nodal disease had been excluded by invasive methods and when a R0 resection is considered to be feasible.[21]

Management of unresectable stage III NSCLC
The standard treatment for unresectable stage III NSCLC is CCRT. However, for unfit patients SCRT remains an option, and for those with a poor PS the option could be single treatment radiation. The treatment decision depends on several factors: i) patient age, ii) PS and comorbidities, iii) tumour location and total tumour volume. Chemoradiotherapy may be offered following proper individual assessment.[25−27] Treatment should start as soon as possible according to the available resources and best clinical practices.[28] After CRT, consolidation with immunotherapy is an option for patients without contraindications, with recent evidence from the phase III PACIFIC trial showing that immunotherapy is a promising therapeutic strategy for consolidation therapy in stage III patients.[29,30]

Concurrent vs sequential chemoradiotherapy
Data from several phase III trials comparing SCRT to CCRT was abridged in a meta-analysis leading to the conclusion that CCRT is considered the preferred treatment for patients who are fit, as it leads to higher 5-year survival rates (with an absolute benefit of 4.5% at 5 years).[1,31,32] In CCRT, depending of the selected protocol, at least two cycles of platin-based chemotherapy should be performed during radiotherapy. Ideally, radiation treatment should start on day 1 of chemotherapy or within the first 2 cycles.[33] CCRT with a platinum-doublet chemotherapy improve progression free survival (PFS) in comparison with a single-agent chemotherapy.[34] The SCRT regimens comprise four cycles of platinum-based chemotherapy that should be performed before radiation therapy, which should start up to 4 weeks after the end of chemotherapy.[21] Most studies of CCRT and SCRT use cisplatin and etoposide or cisplatin and vinca alkaloid (typically: cisplatin / vinorelbine), carboplatin and paclitaxel (weekly) or cisplatin and pemetrexed if non-squamous histology.

Ideally, radiotherapy treatment should not exceed 7 weeks. A total dose of 60−66 Gy administered in 30−33 fractions once daily, 5 times a week, is the standard treatment for both regimens (CCRT and SCRT).[35,36] Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques should be preferred, as they compare favourably with 3D treatment options. The advantages of these techniques lies in safe dose escalation, providing optimal doses for tumour irradiation while sparing the surrounding tissue.[37] In addition, IMRT and VMAT have low toxicity and decrease the incidence of acute and late onset adverse effects and, therefore, decrease the need for treatment cessation.[38,39]

Immunotherapy
Recent advances in the understanding of tumour immunology led to the development of new therapeutic agents, such as immune checkpoint inhibitors.[40] This strategy is already part of the standard treatment in more advanced stages.[41]

Rationale for immunotherapy following chemotherapy is based on the knowledge that chemotherapy is able to upregulate tumour antigens.[42] Moreover, radiation on tumour cells leads to priming and activation of cytotoxic T cells, facilitating the recruitment and infiltration of immune cells in the residual tumour.[43] European Medicines Agency (EMA) approved durvalumab in adult patients locally advanced, unresectable non-

Table 1 Consensus on management of unresectable stage III NSCLC.

STATEMENT		LEVEL OF CONSENSUS	TOTAL VOTERS
1	NSCLC patients planned to be treated with curative intention should undergo a Brain MRI. If not available, CT scan with contrast can be considered as alternative.	Agree: 94% (n = 16) Disagree: 6% (n = 1)	N = 17
2	Mediastinum pathologic staging should be performed for patients with lymph node enlargement (short-axis lymph node diameter ≥ 1 cm) on CT scan and or 18F-FDG uptake on PET scan.	Agree: 94% (n = 16) Disagree: 6% (n = 1)	N = 17
3	Mediastinum pathologic staging should be performed in tumours larger than 3 cm, with central location and with N1 disease.	Agree: 100% (n = 17)	N = 17
4	Negative results from endosonographic methods should be confirmed with surgical staging only:		
	4a in highly suspicious cases (PET and/or CT positive)	Agree: 75% (n = 12) Disagree: 25% (n = 4)	N = 16
	4b when surgery is being considered as an option	Agree: 71% (n = 12) Disagree: 29% (n = 5)	N = 17
5	Bulky mediastinal involvement does not require pathological confirmation.	Agree: 76% (n = 13) Disagree: 24% (n = 4)	N = 17
6	Patients with confirmed N2 disease are candidates for surgery if presenting		
	6a single station N2 disease	Agree: 94% (n = 15) Disagree: 6% (n = 1)	N = 16
	6b multiple N2 disease who present downstaging after induction treatment	Agree: 56% (n = 9) Disagree: 44% (n = 7)	N = 16
7	All patients should be discussed at a MDT that must present at least a medical oncologist/pulmonologist, a radiation oncologist and a thoracic surgeon.	Agree: 100% (n = 17)	N = 17
8	Sequential chemoradiotherapy should be provided instead of CCRT only if concurrent treatment is not feasible due to clinical conditions	Agree: 100% (n = 16)	N = 16
9	After chemoradiotherapy, consolidation with durvalumab is an option for patients who do not present contraindication		
	9a regardless of the CRT regimen (SCRT and CCRT), and who have not progressed following CRT and have PD-L1≥1%	Agree: 87% (n = 13) Disagree: 13% (n = 2)	N = 15
	9b only in patients who performed concurrent CRT, and who have not progressed following CRT and have PD-L1≥1%	Agree: 33% (n = 5) Disagree: 67% (n = 10)	N = 15
10	Patients follow-up should occur		
	10a every 6−8 weeks during active treatment, with imaging exams	Agree: 80% (n = 12) Disagree: 20% (n = 3)	N = 15
	10b occur up to 1.5−2 months after treatment	Agree: 93% (n = 14) Disagree: 7% (n = 1)	N = 15

Abbreviations: ^{18}F-FDG = 2-deoxy-2-(18F)fluoro-D-glucose; CCRT = concurrent chemoradiotherapy; CT = computed tomography; MDT = multidisciplinary team; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand-1; PET = positron emission tomography; SCRT = sequential chemoradiotherapy.

small cell lung cancer whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.[44]

This approval was based on the results of the phase III PACIFIC trial, which included patients with unresectable stage III NSCLC whose disease did not progressed after two or more cycles of platinum-based CCRT, and received their last radiation dose within 1−42 days before randomisation.[29] Durvalumab was compared to placebo for up to 12 months after CCRT. The results at a median follow-up of 33.3 months showed that the median OS had still not been reached in the durvalumab arm compared with 29.1 months in the placebo arm (stratified HR, 0.69; 95% CI 0.55 to 0.86). The immunotherapy should start as soon as possible (within 1 to 2 weeks) as benefits seem to be greater.

Concerning adverse events, pneumonitis was reported to be higher in patients who received durvalumab, however grade 3 or 4 pneumonitis was similar in both groups: 1.9% in the durvalumab arm and 1.7% in the control group.

Moreover, pneumonitis resulting from radiation contributed to durvalumab discontinuation in 1.3% of patients, as in the placebo arm.[30] Hui et al.[45] reported that toxicity was manageable and quality of life was not compromised by adding 12 months of durvalumab after standard CCRT.

Although durvalumab is approved for use in Europe, the label is limited to patients whose tumours express PD-L1 on ≥ 1% of tumour cells and this restriction was based on a post hoc analysis consisting of a small sample size that prevent robust conclusions regarding OS in patients with PD-L1 expression <1%. This analysis has been focus of attention of a panel of international lung cancer experts[46] but will not be further discussed in this document given that local reimbursement of durvalumab also excluded patients with PD-L1 expression <1% .[47,48]

The Portuguese experts agreed that durvalumab should be recommended as consolidation treatment after CRT for unresectable stage III. The majority of experts (87%) approves this recommendation for patients who do not present

Table 2 Recommendations for improvement of patient care − from early diagnosis to access to innovations.

Detection of lung cancer
  ○ Increase population awareness about lung cancer symptoms
  ○ Lung cancer symptoms are often insidious and difficult to identify the disease
  ○ Eliminate budgetary constraints for screening of high-risk groups and access to diagnostic testing for lung cancer
Foster early diagnosis
  ○ Creation of a " pathway for diagnosis and treatment
  ○ Creation of a patient manager
  ○ Definition of a maximum period from referral to treatment
  ○ Implementation of new communication technologies for MDT meetings
  ○ Establishment and implementation of timeframes
    •Referral from primary health care
    •Diagnosis and staging
    •From MDT meeting to the start of treatment
Measures for curative outcomes
  ○ Avoid long waiting lists for treatment
  ○ Improve communication between patients and referral centers
  ○ Facilitate transport for patients who live far from the reference centers for diagnosis and treatment
  ○ Create a communication network across referral centers to provide better quality treatment
Access to innovative treatments
  • Periodic funding
  • Evaluation of health outcomes to ensure equity
  • Promotion of a national cancer registry
Patient-centred care
  • Improvement of quality of care and satisfaction
  • Treatment decision taken by both patient and physician
  • Local patient support: involvement of the social services, nutrition, psychiatry/psychology and pain consultation teams
  • General patient support: encourage on the creation of non-governmental associations
  • National patient support: Creation of an electronic National Cancer Registry

Abbreviations: MDT = Multidisciplinary team.

contraindications, regardless of the regimen (SCRT or CCRT) and who have not progressed following CRT and have PD-L1≥1% (Table 1).

Follow-up and post-treatment evaluation experience
During the transition from active treatment to post-treatment follow-up, a defined strategy with follow-up schedules should be implemented, aiming at maximization of the benefit. Thus, while during treatment tumour re-evaluation should be performed every 6−8 weeks (timed to coincide with the end of a cycle),[49] post-CRT evaluation is usually performed within 1.5−2 months, when the maximal therapeutic effect is expected.[50] CRT response should be routinely evaluated by plain X-ray[51] or preferably by contrast-enhanced CT scan.[52] These results should be compared to those obtained before treatment. Also, a PET-CT scan to evaluate tumour metabolic activity is recommended when abnormalities, particularly if suggesting progression of the disease, are detected on CT scans.[35] However, changes in ^{18}F-FDG uptake that normally occur between 8 and 12 weeks after radiation therapy should be taken into account, as they are potential confounding factors in this setting.[53] Moreover, many benign conditions (such as atelectasis, consolidation, and radiation fibrosis) are difficult to differentiate from neoplasm because areas previously treated with radiation therapy can remain ^{18}F-FDG avid for up to 2 years.

Adverse events (e.g., pneumonitis) should be immediately managed. Clinically, induced pneumonitis may hinder evaluation of response.[54] The panel indicated that in the presence of indirect progression signs namely growth of the dense component, increase of maximum standardized uptake values (SUVmax) or the emergence of new lesions, histological confirmation of progression must be assessed.

Furthermore, a summary of the management of unresectable Stage III NSCLC is presented in Table 2 and agreement level between experts is presented in Table 1.

Recommendations for early diagnosis in daily clinical practice

Regardless of the disease stage, all patients with lung cancer should have access to treatment and supportive care options and be fully informed of their treatment options. A care plan must be developed for every patient to facilitate timely and effective information exchange. Services should collect data and measure patient experience to improve lung cancer care.

Considering the rapid evolution of lung carcinogenesis, the diagnosis of this disease shall be straightforward. The panel recommends that increased and high-quality information should be available to the public, targeted accordingly
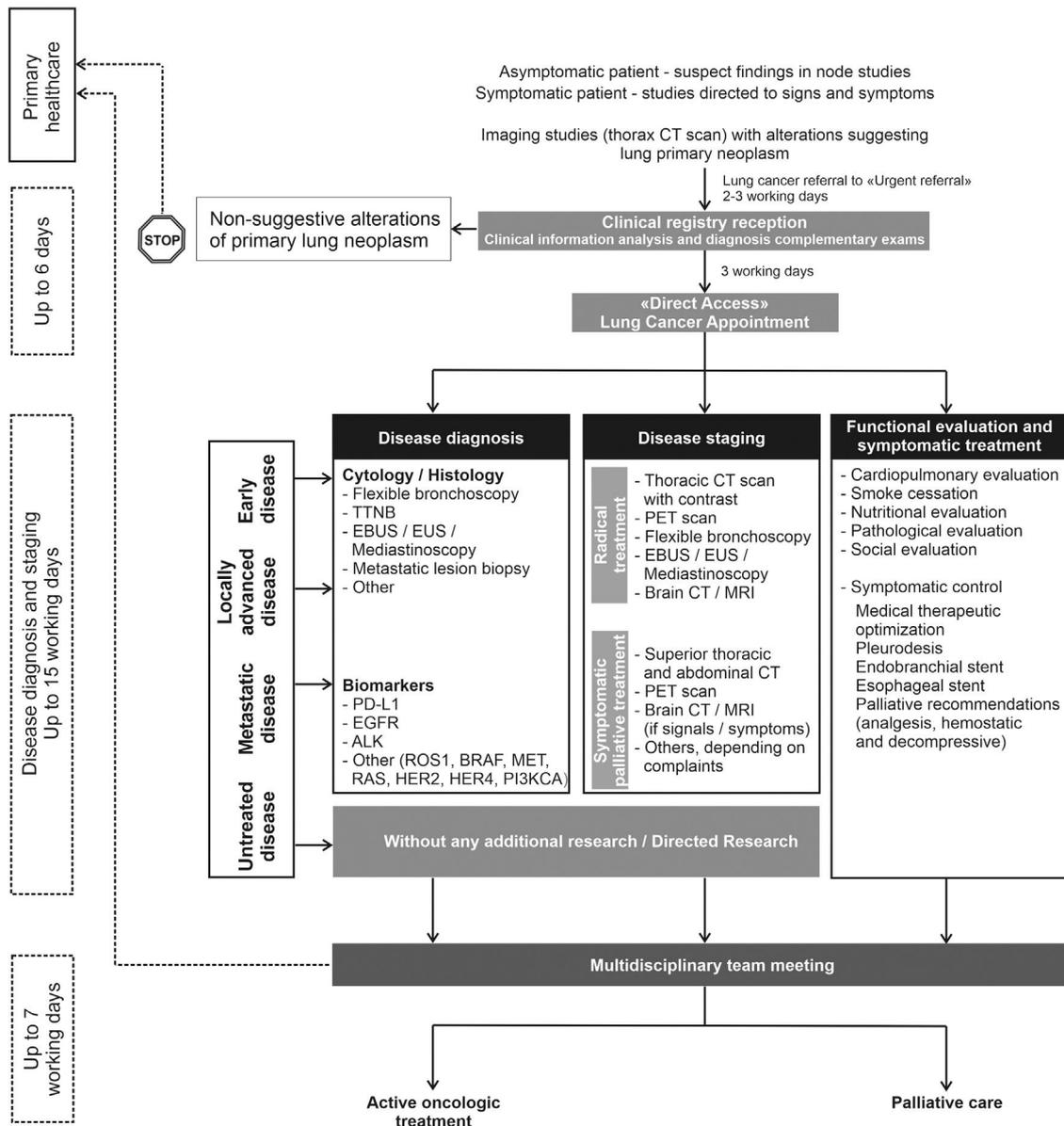
Fig. 3 Flowchart representing the fast-track referral pathway for NSCLC. Abbreviations: ALK = anaplastic lymphoma kinase; BRAF = b-raf proto-oncogene serine/threonine kinase; CT = computed Tomography; EBUS = endobronchial ultrasound; EGFR = epidermal growth factor receptor; EUS = oesophageal ultrasound; HER2 = human epidermal growth factor receptor 2; HER4 = human epidermal growth factor receptor 4; KRAS = kirsten rat sarcoma viral oncogene homologue; MRI = magnetic resonance imaging; PD-L1 = programmed death ligand 1; PET = positron emission tomography; PI3KCA = phosphatidylinositol 3-kinase catalytic subunit; ROS1 = c-ros oncogene 1 receptor tyrosine kinase; TTNB = transthoracic needle biopsy.

to age and literacy of the audience, focusing not only on the suspicious signs and symptoms but also on the link between this disease and tobacco use, as well as measures to encourage tobacco cessation (Table 2).

Multiple clinical practice guidelines recommend rapid evaluation of patients with suspected lung cancer.[8,55] The panel recommendations are: 1) patients with an abnormal chest radiograph or a high suspicion of lung cancer based on clinical judgement must undergo chest CT scan within 2 weeks; 2) patients referred to a specialist or a diagnostic assessment program should expect a consultation within 2 weeks and, having confirmed the diagnosis, pathology results should be available within 2 weeks of the relevant

procedure; 3) molecular evaluation and PD-L1 expression should be available within 2 weeks of specimen arrival at the laboratory and on time for treatment decision.[56] To accomplish these goals, intra-institutional communication and organisation seems to be one of the most determining factors. The panel recommends the implementation of a preferential pathway for lung cancer patients that could facilitate and accelerate the diagnosis and staging, overcoming the constraints of the hospitals. This preferential pathway should embrace an ideal time from general practitioner (GP) referral to conducting complementary exams and initiation of treatment (fast-track for lung cancer) (Fig. 3).

The panel also considers the implementation of an MDT essential to ensuring the best management approach for each patient and that all lung cancer patients should have their treatment discussed by a MDT. The MDT should comprise at least the three main specialists, a medical oncologist/pulmonologist, a radiation oncologist and a thoracic surgeon, with input from other experts, such as a pathologist and a radiologist, whenever possible. The MDT reports vary considerably but should ideally include the following: 1) demographics; 2) results of investigations, such as diagnosis and staging; 3) stage-dependant guideline recommended treatment; 4) treatment plan and reasons for nonadherence to guideline recommendations; 5) whether the MDT came to a unanimous or a majority decision; 6) common treatment adverse events and recommended management; and 7) a clear indication of the expected prognosis and follow-up strategy. The panel considers that access to innovation should be increased and harmonized across Portugal and similar to analogous European countries.

Patient-centred care (PCC) should be adapted to individual patient preferences, and values.[57] PCC has a number of outlined dimensions: access to medical care, emotional support, involvement of relatives and friends, information and education.[58] PCC can improve quality of care and patient satisfaction, as well as reduce healthcare costs (Table 2).[59]

Conclusions

Patients with stage III NSCLC are clinically heterogeneous and it is often difficult to fit them into a standardised algorithm. The expert panel believes that the route from diagnosis to therapy in unresectable stage III NSCLC involves several steps: i) timely diagnosis with priority access to diagnostic techniques and multicentre cooperation; ii) pretreatment evaluation and staging by a MDT; iii) if surgery is not possible, the preferred treatment approach is a CCRT regimen, with SCRT and chemotherapy or radiotherapy alone being considered for unfit patients; iv) post-treatment evaluation for early identification of progression and management of adverse effects (e.g., pneumonitis); v) immunotherapy as a consolidation therapy should be considered if there is no progression and no signs of treatment-induced toxicity.

The continuation or maintenance of treatment in patients with unresectable stage III cancer is always urgent. Moreover, coordination with other specialised units in patient healthcare, such as nutrition, psychology, rehabilitation or geriatrics, can be of great importance to patients. Guidance from other units in terms of nutrition, psychology, rehabilitation or geriatrics would be beneficial to patients. This would facilitate treatment tolerance and also improve its outcomes.

Conflicts of interest

The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2022.11.008.

References

1. Cheema PK, Rothenstein J, Melosky B, Brade A, Hirsh V. Perspectives on treatment advances for stage III locally advanced unresectable non-small-cell lung cancer. Curr Oncol. 2019;26(1):37−42. https://doi.org/10.3747/CO.25.4096.
2. Brierley J, Gospodarowicz MK, Wiitekind C. TNM Classification of Malignant Tumours. 8th Ed. John Wiley & Sons, Ltd; 2017.
3. Makimoto G, Hotta K, Kiura K. Recent trends in the treatment of unresectable stage III non-small-cell lung cancer. Respir Investig. 2019;57(4):330−6. https://doi.org/10.1016/j.resinv.2019.03.004.
4. Currie GP, Kennedy AM, Denison AR. Tools used in the diagnosis and staging of lung cancer: what's old and what's new? QJM An Int J Med. 2009;102(7):443−8. https://doi.org/10.1093/qjmed/hcp038.
5. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol. 1999;17(9):2692−9. https://doi.org/10.1200/JCO.1999.17.9.2692.
6. Corner J, Hopkinson J, Fitzsimmons D, Barclay S, Muers M. Is late diagnosis of lung cancer inevitable? Interview study of patients' recollections of symptoms before diagnosis. Thorax. 2005;60(4):314−9. https://doi.org/10.1136/thx.2004.029264. LP - 319.
7. Hamilton W, Peters TJ, Round A, Sharp D. What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. Thorax. 2005;60(12):1059−65. https://doi.org/10.1136/thx.2005.045880.
8. Ost DE, Jim Yeung SC, Tanoue LT, Gould MK. Clinical and organizational factors in the initial evaluation of patients with lung cancer: diagnosis and management of lung cancer. p e121S, 3rd Ed American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 143. Chest; 2013. p. e121S−41S. https://doi.org/10.1378/chest.12-2352.
9. Latimer KM, Mott TF. Lung cancer: diagnosis, treatment principles, and screening. Am Fam Physician. 2015;91(4):250−6.
10. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 143; 2013. p. 2013e142S−65S. https://doi.org/10.1378/chest.12-2353.
11. Thunnissen E, Kerr KM, Herth FJF, et al. The challenge of NSCLC diagnosis and predictive analysis on small samples. Practical approach of a working group. Lung Cancer. 2012;76(1):1−18. https://doi.org/10.1016/j.lungcan.2011.10.017.
12. Xu J, Han X, Liu C, et al. PD-L1 expression in pleural effusions of pulmonary adenocarcinoma and survival prediction: a controlled study by pleural biopsy. Sci Rep. 2018;8(1):11206. https://doi.org/10.1038/s41598-018-29156-5.

13. Akamatsu H, Koh Y, Kenmotsu H, et al. Multiplexed molecular profiling of lung cancer using pleural effusion. J Thorac Oncol. 2014;9 (7):1048−52. https://doi.org/10.1097/JTO.0000000000000203.

14. Hammerschmidt S, Wirtz H. Lung cancer: current diagnosis and treatment. Dtsch Arztebl Int. 2009;106(49):809−20. https://doi.org/10.3238/arztebl.2009.0809.

15. Khosla R, McLean AW, Smith JA. Ultrasound-guided versus computed tomography-scan guided biopsy of pleural-based lung lesions. Lung India. 2016;33(5):487−92. https://doi.org/10.4103/0970-2113.188961.

16. De leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardio-Thoracic Surg. 2014;45(5):787−98. https://doi.org/10.1093/EJCTS/EZU028.

17. Khalil A, Majlath M, Gounant V, Hess A, Laissy JP, Debray MP. Contribution of magnetic resonance imaging in lung cancer imaging. Diagn Interv Imaging. 2016;97(10):991−1002. https://doi.org/10.1016/j.diii.2016.08.015.

18. Hayes SA, Plodkowski AJ, Ginsberg MS. Imaging of thoracic cavity tumors. Surg Oncol Clin N Am. 2014;23(4):709−33. https://doi.org/10.1016/j.soc.2014.06.005.

19. Taverner J, Cheang MY, Antippa P, See K, Irving LB, Steinfort DP. Negative EBUS-TBNA predicts very low prevalence of mediastinal disease in staging of non-small cell lung cancer. J Bronchol Interv Pulmonol. 2016;23(2):177−80. https://doi.org/10.1097/LBR.0000000000000234.

20. Lang-Lazdunski L. Surgery for nonsmall cell lung cancer. Eur Respir Rev. 2013;22(129):382. https://doi.org/10.1183/09059180.00003913. LP - 404.

21. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(suppl_4). https://doi.org/10.1093/annonc/mdx222. iv1-iv21.

22. Edwards JG, Chansky K, Van Schil P, et al. The IASLC lung cancer staging project: analysis of resection margin status and proposals for residual tumor descriptors for non−small cell lung cancer. J Thorac Oncol. 2020;15(3):344−59. https://doi.org/10.1016/J.JTHO.2019.10.019/ATTACHMENT/318C1AD0-1B49-4DA5-A474-5BB8BA450C5C/MMC1.DOCX.

23. Roller JF, Veeramachaneni NK, Zhang J. Exploring the evolving scope of neoadjuvant immunotherapy in NSCLC. Cancers. 2022;14(3):741. https://doi.org/10.3390/CANCERS14030741. Vol 14, Page 741. 2022.

24. von Groote-Bidlingmaier F, Koegelenberg CFN, Bolliger CT. Functional evaluation before lung resection. Clin Chest Med. 2011;32(4):773−82. https://doi.org/10.1016/j.ccm.2011.08.001.

25. Kelly K. Challenges in defining and identifying patients with non-small cell lung cancer and poor performance status. Semin Oncol. 2004;31:3−7. https://doi.org/10.1053/j.seminoncol.2004.10.003.

26. Jalal SI, Riggs HD, Melnyk A, et al. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier O. Ann Oncol Off J Eur Soc Med Oncol. 2012;23(7):1730−8. https://doi.org/10.1093/annonc/mdr565.

27. 2nd Vokes EE, Herndon JE, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: cancer and Leukemia Group B. J Clin Oncol. 2007;25(13):1698−704. https://doi.org/10.1200/JCO.2006.07.3569.

28. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. Radiother Oncol. 2008;87(1):3−16. https://doi.org/10.1016/j.radonc.2007.11.016.

29. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non−small-cell lung cancer. N Engl J Med. 2017;377(20):1919−29. https://doi.org/10.1056/NEJMoa1709937.

30. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379(24):2342−50. https://doi.org/10.1056/NEJMoa1809697.

31. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small cell lung cancer. J Clin Oncol. 2010;28(13):2181−90. https://doi.org/10.1200/JCO.2009.26.2543.

32. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer. 2004;46(1):87−98. https://doi.org/10.1016/j.lungcan.2004.03.004.

33. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: groupe lyon-saint-etienne d'oncologie thoracique-groupe français de pneumo-cancérologie NPC 95-01 study. J Clin Oncol. 2005;23(25):5910−7. https://doi.org/10.1200/JCO.2005.03.070.

34. G.J. Costa, C.G. Ferreira and L.C.S. Thuler, Concurrent chemoradiotherapy for stage III non-small cell lung cancer: correct clinical management as the basis to move beyond, Ann Transl Med, 6 (Suppl 1), 2018, S65. doi:10.21037/atm.2018.10.38, S65-S65.

35. Eberhardt WEE, Pöttgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). J Clin Oncol. 2015;33(35):4194−201. https://doi.org/10.1200/JCO.2015.62.6812.

36. The royal College of Radiologists. Radiotherapy Dose Fractionation. 3rd Ed. 2019 https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco193_radiotherapy_dose_-fractionation_third-edition-lung-cancer_0.pdf.

37. Chan C, Lang S, Rowbottom C, Guckenberger M, Faivre-Finn C. Intensity-modulated radiotherapy for lung cancer: current status and future developments. J Thorac Oncol. 2014;9(11):1598−608. https://doi.org/10.1097/JTO.0000000000000346.

38. Govaert SLA, Troost EGC, Schuurbiers OCJ, et al. Treatment outcome and toxicity of intensity-modulated (chemo) radiotherapy in stage III non-small cell lung cancer patients. Radiat Oncol. 2012;7(1):150. https://doi.org/10.1186/1748-717X-7-150.

39. Wu K, Xu X, Li X, et al. Radiation pneumonitis in lung cancer treated with volumetric modulated arc therapy. J Thorac Dis. 2018;10(12):6531−9. https://doi.org/10.21037/jtd.2018.11.132.

40. Jain P, Jain C, Velcheti V. Role of immune-checkpoint inhibitors in lung cancer. Ther Adv Respir Dis. 2018;12:1753465817750075. https://doi.org/10.1177/1753465817750075.

41. Pistamaltzian NF, Georgoulias V, Kotsakis A. The role of immune checkpoint inhibitors in advanced non-small cell lung cancer. Expert Rev Respir Med. 2019;13(5):435−47. https://doi.org/10.1080/17476348.2019.1593828.

42. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res. 2015;3(5):436−43. https://doi.org/10.1158/2326-6066.CIR-15-0064.

43. Wang Y, Deng W, Li N, et al. Combining immunotherapy and radiotherapy for cancer treatment: current challenges and future directions. Front Pharmacol. 2018;9:185. https://doi.org/10.3389/fphar.2018.00185.

44. European Medicines Agency. An overview of imfinzi and why it is authorised in the EU.; 2018. https://www.ema.europa.eu/en/documents/overview/imfizi-epar-medicine-overview_en.pdf

45. Hui R, Özgüroğlu M, Daniel D, et al. Patient-reported outcomes with durvalumab after chemoradiation in locally advanced, unresectable NSCLC: data from PACIFIC. J Thorac Oncol. 2017;12(11): S1604. https://doi.org/10.1016/j.jtho.2017.09.096.

46. Peters S, Dafni U, Boyer M, et al. Position of a panel of international lung cancer experts on the approval decision for use of durvalumab in stage III non-small-cell lung cancer (NSCLC) by the committee for medicinal products for human use (CHMP). Ann Oncol. 2019;30(2):161−5. https://doi.org/10.1093/ANNONC/MDY553.

47. Paz-Ares L, Spira A, Raben D, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Ann Oncol Off J Eur Soc Med Oncol. 2020;31(6):798. https://doi.org/10.1016/J.ANNONC.2020.03.287.

48. European Medicines Agency. Assessment Report Imfinzi, International Non-Proprietary Name: Durvalumab, 2018. https://www.ema.europa.eu/en/documents/assessment-report/imfizi-epar-public-assessment-report_en.pdf.

49. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228−47. https://doi.org/10.1016/J.EJCA.2008.10.026.

50. Salvador-Coloma C, Lorente D, Palanca S, et al. Early radiological response as predictor of overall survival in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor mutations. J Thorac Dis. 2018;10(3):1386−93. https://doi.org/10.21037/jtd.2018.02.30.

51. Dyer BA, Daly ME. Surveillance imaging following definitive radiotherapy for non-small cell lung cancer: what is the clinical impact? Semin Oncol. 2017;44(5):303−9. https://doi.org/10.1053/j.seminoncol.2018.01.007.

52. Strauch LS, Eriksen RØ, Sandgaard M, Kristensen TS, Nielsen MB, Lauridsen CA. Assessing tumor response to treatment in patients with lung cancer using dynamic contrast-enhanced CT.

Diagnostics (Basel, Switzerland). 2016;6(3):28. https://doi.org/10.3390/diagnostics6030028.

53. Kong FMS, Frey KA, Quint LE, et al. A pilot study of [18F]fluoro-deoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. J Clin Oncol. 2007;25(21):3116−23. https://doi.org/10.1200/JCO.2006.10.3747.

54. de Castro J, Cobo M, Isla D, et al. Recommendations for radiological diagnosis and assessment of treatment response in lung cancer: a national consensus statement by the Spanish society of medical radiology and the Spanish society of medical oncology. Clin Transl Oncol. 2015;17(1):11−23. https://doi.org/10.1007/s12094-014-1231-5.

55. The Lung Cancer Working Party of the British Thoracic Society Standards of Care Committee. BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. Thorax. 1998;53(Suppl 1):S1−8. https://doi.org/10.1136/thx.53.suppl_1.s1.

56. Direção Geral de Saúde. Diagnóstico e Tratamento Do Carcinoma de Não Pequenas Células Do Pulmão.; 2013. https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0322013-de-31122013-em-discussao-publica-pdf1.aspx.

57. Wilkerson L, Fung CC, May W, Elliott D. Assessing patient-centered care: one approach to health disparities education. J Gen Intern Med. 2010;25(Suppl 2):S86−90. https://doi.org/10.1007/s11606-010-1273-5.

58. Maguire R, Papadopoulou C, Kotronoulas G, Simpson MF, McPhelim J, Irvine L. A systematic review of supportive care needs of people living with lung cancer. Eur J Oncol Nurs. 2013;17(4):449−64. https://doi.org/10.1016/j.ejon.2012.10.013.

59. Nejati M, Razavi M, Harirchi I, Zendehdel K, Nejati P. The impact of provider payment reforms and associated care delivery models on cost and quality in cancer care: a systematic literature review. PLoS One. 2019;14(4):e0214382. https://doi.org/10.1371/journal.pone.0214382.