e-ISSN 2083–4640
ISSN 1507–1367

REVIEW ARTICLE

Reports of Practical Oncology and Radiotherapy
2023, Volume 28, Number 2, pages: 286–303
DOI: 10.5603/RPOR.a2023.0019
Submitted: 16.08.2022
Accepted: 29.03.2023

Locally advanced non-small cell lung cancer: current issues and recent trends

Mohammed Alaswad[1, 2]

[1]Comprehensive Cancer Centre, Radiation Oncology, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia
[2]Princess Nourah Bint Abdulrahman University, Riyadh, Kingdom of Saudi Arabia

ABSTRACT

The focus of this paper was to review and summarise the current issues and recent trends within the framework of locally advanced (LA) non-small cell lung cancer (NSCLC). The recently proposed 8th tumour–node–metastases (TNM) staging system exhibited significant amendments in the distribution of the T and M descriptors. Every revision to the TNM classification should contribute to clinical improvement. This is particularly necessary regarding LA NSCLC stratification, therapy and outcomes. While several studies reported the superiority of the 8th TNM edition in comparison to the previous 7th TNM edition, in terms of both the discrimination ability among the various T subgroups and clinical outcomes, others argued against this interpretation. Synergistic cytotoxic chemotherapy with radiotherapy is most prevalent in treating LA NSCLC. Clinical trial experience from multiple references has reported that the risk of locoregional relapse and distant metastasis was less evident for patients treated with concomitant radiochemotherapy than radiotherapy alone. Nevertheless, concern persists as to whether major incidences of toxicity may occur due to the addition of chemotherapy. Cutting-edge technologies such as four-dimensional computed tomography (4D-CT) and volumetric modulated arc therapy (VMAT) should yield therapeutic gains due to their capability to conform radiation doses to tumours. On the basis of the preceding notion, the optimum radiotherapy technique for LA NSCLC has been a controversial and much-disputed subject within the field of radiation oncology. Notably, no single-perspective research has been undertaken to determine the optimum radiotherapy modality for LA NSCLC. The landscape of immunotherapy in lung cancer is rapidly expanding. Currently, the standard of care for patients with inoperable LA NSCLC is concurrent chemoradiotherapy followed by maintenance durvalumab according to clinical outcomes from the PACIFIC trial. An estimated 42.9% of patients randomly assigned to durvalumab remained alive at five years, and free of disease progression, thereby establishing a new benchmark for the standard of care in this setting.

Keywords: locally advanced-non-small cell lung cancer; tumour node metastases; radiotherapy; volumetric modulated arc therapy; sequential radiochemotherapy; concurrent radiochemotherapy; proton therapy; passive scattering proton therapy; immunotherapy; immune checkpoint inhibitors

Rep Pract Oncol Radiother 2023;28(2):286–303

Introduction

Considering that non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality [1], numerous clinical approaches have been implemented to enhance patient outcomes, including the combination of two oncologic procedures such as in the promising intraoperative radiotherapy, alongside the ongoing effort to establish a novel immunotherapeutic agent for NSCLC [2, 3].

Address for correspondence: Mohammed Alaswad, Comprehensive Cancer Centre, Radiation Oncology, King Fahad Medical City, Riyadh, 11525, Kingdom of Saudi Arabia; e-mail: medphy00@gmail.com

Additionally, clinical cancer staging has been recognized as having a major impact on the development and efficacy of radiotherapy. In accordance with the tumour node metastases (TNM) distribution pattern, it is estimated that one-third of patients with NSCLC will be diagnosed with locally advanced (LA) disease, and the majority of these patients are not eligible for surgery in light of the considerable challenge with disease extension [4]. It is worth noting that the therapeutic management of inoperable LA NSCLC requires controls of both local disease and distant micrometastasis.

LA NSCLC is defined as stage III disease with sub-classification into stages IIIA, IIIB and IIIC in accordance with the newly proposed 8th TNM. Broadly, stage III NSCLC encompasses a heterogeneous combination of tumour presentations characterised as involving locoregional spread through primary tumour extension into extrapulmonary structures (e.g., T3 or T4) or mediastinal lymph node involvement (e.g., N1, N2 or N3), but involving no evidence of distant metastases (M0). Although employing radiotherapy as a sole treatment for this group of patients is potentially with curative intent, long-term survival and local tumour control rates are for the most part discouraging. For instance, the standard fractionation protocol of 60 Gy delivered in 30 sessions yields an unsatisfactory five-year local tumour control rate of just 8% [5].

Management with radiotherapy alone for LA NSCLC has shown undesirable clinical outcomes. Interpretations of the patterns of failure following treatment with radiotherapy alone show that the inferior clinical outcomes are correlated not only with the inability to achieve control of the primary tumour extent, but also with the occurrence of distant metastases. Therefore, it has become increasingly important to establish and assess the potential performance of other treatment modalities, including strategies combining chemotherapy and radiotherapy.

Within this context, a combination of systemic chemotherapy and radiation has been correlated with substantially enhanced local tumour curability and long-term survival [6]. The application of sequential radiochemotherapy has yielded an improvement in overall survival rates from nearly 6% to 12% at five years. With the practical experience of concomitant radiochemotherapy, this rate improved to 15% with an overall survival gain of 4.5% at five years – but at the cost of radiation pneumonitis and oesophageal toxicity [7].

Furthermore, technical advancement in dose optimisation and delivery of radiotherapy (e.g., VMAT and proton therapy) have contributed fundamentally to enhanced clinical outcomes while also diminishing the toxicities confronted during the administration of a concurrent radiochemotherapy approach. Nonetheless, several published studies were unable to reproduce that advancement in clinical outcomes and reduce toxicity for LA NSCLC [8, 9]. A possible explanation for these unexpected outcomes may be due to the uncertainty in the delivered radiation dose.

Notably, the treatment paradigm for patients with stage III NSCLC has substantially changed with the progress of immunotherapy. The incorporation of immunotherapy into the current treatment roadmap has led to improved clinical outcomes for LA NSCLC, with comparable side effects compared with classic chemotherapeutic agents. Potential synergistic effects of combining immune checkpoint inhibitors with radiation therapy have encouraged studies aiming to explore how to optimize the addition of immunotherapy to multimodality treatment in an effort to further advance the field of stage III NSCLC.

Therefore, the general theme of this review was threefold; (1) to compare and analyze the clinical outcomes of the 7th and the newly proposed 8th edition of the TNM staging and; (2) to discuss in depth the current therapeutic management options for LA NSCLC including but not limited to the combination of systemic chemotherapy, immunotherapy and radiotherapy; (3) to summarize the various sources of radiotherapy dose uncertainty during LA NSCLC irradiation.

Review search design

The selected items for the review were accumulated from three electronic sources: Google Scholar, PubMed and ScienceDirect. The search strategy for the PubMed electronic database utilized the following text words (TW) and Medical Subject Headings (MeSH): locally advanced non-small cell lung (MeSH), radiotherapy (TW), concurrent chemoradiotherapy (MeSH), concomitant chemo-

radiotherapy (MeSH), sequential chemoradiotherapy (MeSH) and immunotherapy (MeSH). Accordingly, the same aforementioned terms were diversely merged and utilised across the databases of ScienceDirect and Google Scholar. To restrict the identified relevant items within the scope of the research question and confine the review to the relevant articles, the design of the search was profoundly dependent upon the Boolean logic criteria. Additionally, the bibliographies of relevant publications were also explored to locate additional related studies.

Lung cancer staging

The primary edition of the tumour node metastases (TNM) staging scheme for lung cancer was first introduced in 1974 by the Union for International Cancer Control (UICC) [10], and eight editions of this TNM staging system for lung cancer have been published over the past four decades [11]. These editions have emphasised that the T stage category, defined according to tumour size, is a key prognostic factor in determining disease specific survival.

The UICC was established to update the TNM classification scheme as more data become available. Recently, major changes have occurred in the staging, diagnosis and treatment of lung cancer. The 8th edition of the TNM staging system was released in 2017 in an effort to improve the prognostic accuracy of patients with NSCLC and diminish or eliminate heterogeneity within each stage group (see Tab. 1) [12].

The 8th TNM has analysed a total of 77,156 patients, including 70,967 (92%) NSCLC patients [13]. This current advanced staging system has instituted important modifications in the T category, M category and stage grouping. In relation to the T descriptor, the T1 and T2 categories now consist of subcategories differentiated by 10 mm intervals (see Tab. 2) , and the current edition relies more heavily on tumour size for classification compared with the 7th edition [16].

For instance, T1 is now sub-classified based on tumour size into (a) T1a (< 10 mm), (b) T1b (> 10 mm to 20 mm) and (c) T1c (> 20 mm to 30 mm) which correspond to the three new stage subgroups in patients without lymph node involvement (stages IA1, IA2 and IA3). A detailed and more in-depth analysis of the current edition can be found in [13, 17, 18].

Of note, large tumour volumes adversely affect the clinical outcomes of radiation therapy. This phenomenon may well be explained by evidence that the amount of cancer stem cells grows propor-

Table 1. Published definitions for primary tumour of non-small cell lung cancer (NSCLC) according to the T descriptors of the 8th editions [13–15]

Label	8th
T0	No indication of primary tumour extension
TX	Primary tumour cannot be measured or tumour cells confirmed by bronchial washing procedure or through the presence of malignant cell in the sputum, although not perceived by bronchoscopy or imaging
Tis	Carcinoma in situ, this is defined herein as a cluster of abnormal cells that reside in the region where they originally developed (e.g., not spread yet). These irregular cells can evolve to become cancerous and spread into adjacent healthy tissues
T1	Tumour 3 cm in the greatest dimension in the immediate vicinity of the lung or visceral pleura without bronchoscopic indication of invasion (i.e., no evidence of invasion to the main bronchus)
T2	Tumour > 3 cm but ≤ 5 cm that meets either of the following particular conditions: encompasses main bronchus irrespective of distance from the carina but without including the carina invades visceral pleura associated with atelectasis or obstructive pneumonitis that extends to the hilar region, including part or the entire lung
T3	Tumour > 5 cm but ≤ 7 cm in the greatest dimension that meets either of the following particular conditions: invades either of the following particular organs; chest wall, phrenic nerve, and parietal pericardium associated with separate tumour nodule(s) in the same lobe as the primary tumour
T4	Tumour > 7 cm in the greatest dimension that meets either of the following particular conditions: invades either of the following particular organs; diaphragm, mediastinum, great vessels, heart, recurrent laryngeal nerve, esophagus, carina or vertebral body associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumour

Table 2. Comparison of the T-descriptor and patient distribution as recommended by the 7th and 8th Tumor–node-Metastases (TNM) classification systems (n = 354)

7th TNM classifications	Recommended tumour size [mm]	Published tumour size [mm] [24]	# of patients
	Any size	91 ± 27	27
	> 70	72 ± 2.7	80
	> 50 to ≤ 70	59 ± 8.1	54
	> 30 to ≤ 50	39 ± 8.7	113
	n/a	n/a	n/a
	> 20 to ≤ 30	26 ± 3.1	48
	< 20	16 ± 3.8	32

	T1a	T1b	T1c	T2a	T2b	T3	T4
# of patients	6	26	48	69	52	81	72
Published tumour size [mm] [24]	9.1 ± 0.7	17 ± 2.6	26 ± 3.1	33 ± 6.9	46 ± 3.4	56 ± 11	79 ± 26
Recommended tumour size [mm]	≤ 10	> 10 to ≤ 20	> 20 to ≤ 30	> 30 to ≤ 40	> 40 to ≤ 50	> 50 to ≤ 70	> 70
8th TNM classifications							

tionately with the expanding tumour size and that the radiation dose required to attain local tumour curability relies on the logarithm of surviving clonogenic cells to be deactivated.

Zips [19] observed a linear diminution of clonogenic density as radiotherapy doses increase, corroborating the results of Alaswad et al. [20, 21]. It is also evident that tumours become more radioresistant under hypoxic states, and hypoxia is more prevalent in large tumours than in small tumours [22, 23]. Clinically, a large planning target volume (PTV) frequently restricts the use of high curative radiotherapy doses due to the tolerance limit of the adjacent organs at risk [24]. Consequently, attaining the optimum local tumour control could be adversely affected.

Within this framework, there is a large volume of retrospective studies detailing the function of tumour size as a prognostic determinant in NSCLC patients. Bradley et al. [25] determined whether gross tumour volume (GTV) is a prognostic factor in 207 cases of inoperable NSCLC treated with definitive three-dimensional conformal radiation therapy (3D-CRT).

Statistical analysis confirmed that tumour volume is highly prognostic for local tumour control and overall survival. Additionally, they suggested that tumour volume could be a fundamental basis for stratifying patients in clinical trials. Stinchcombe et al. [26] analysed 102 cases with medically inoperable stage III NSCLC treated with concurrent chemoradiotherapy versus radiotherapy alone, and they concluded that GTV is a major critical predictor of local tumour control.

In recent years, there has been an increasing amount of literature emphasising the superiority of the 8th TNM over the 7th TNM [27–29] in terms of clinical outcomes, albeit others disagree with this conclusion [30].

In an external validation study of the 8th TNM classification for lung cancer, Chansky et al. [28] found that the discrimination by the 8th edition of stage combinations and classifications is adequately valid for clinical, pathologic and, most reliably, in stage separations for NSCLC. They further confirm the geographic transportability of this newly proposed stage grouping and its applicability to primarily non-surgically treated cohorts.

This view was supported by Sui et al. [27] who analysed a total of 3,599 NSCLC patients, concluding that the 8th edition yielded marginally higher discrimination compared with the 7th edition, as implied by the R^2 values of the recurrence-free survival (RFS) and the overall survival (OS) (RFS = 0.183 *vs.* 0.178; OS = 0.172 *vs.* 0.162). Similarly, Yang et al. [29] provided an in-depth analysis of 858,909 NSCLC patients whose data were obtained from the National Cancer Database (NCDB). In this major study, Yang and his colleagues [29] deduced that the T distribution schema of the 8th edition is more reliable than that of the 7th edition in discriminating various T subgroups, particularly in the pT1 stage.

In terms of the overall performance of the two editions, the concordance index of the 7th edition in terms of pT subgrouping (0.608 ± 0.001) was slightly lower than that of the 8th edition (0.610 ± 0.001).

Moreover, they compared the cT subgrouping of the 7th edition (0.551 ± 0.001) to the cT subgrouping of the 8th edition (0.551 ± 0.001), and their results further demonstrated the superiority of the 8th edition over the 7th edition.

By contrast, in a retrospective study involving 1,316 NSCLC cases, Jung et al. [30] remarked that the T descriptors of the 8th edition of the TNM did not yield a higher explicit predictor of prognosis than the 7th edition. This study revealed that the survival curves and the five-year survival rates based on the T descriptors of the 8th TNM classification did not significantly differ between sequential stages, more specifically for the T1a and T1b ($p = 0.752$) and T1c, T2a and T2b ($p = 0.832$) subcategories. Nevertheless, the study clarified that the 8th edition might not be inferior to the 7th edition in terms of prognostic stratification based on an analysis involving a single small cohort.

Numerous studies have shown that certain limitations still exist in the N classification of the 8th TNM staging system [31]. Currently, data are being collected to release the 9th edition of the TNM categorization, which is expected to be published in 2024. A potential innovation of this new TNM edition would be the combination of TNM distribution pattern with tumor-related factors, including biomarkers (e.g., protein alterations, copy number alterations and genetic biomarkers). This is to provide an enhanced and individualized prognosis [32].

Within this context, a recent investigation indicated that the number of lymph nodes has a considerable influence on the clinical outcomes of NSCLC cases, signifying that the number of lymph nodes will be perceived as a possible prognostic indicator in the forthcoming 9th TNM edition. For instance, Chen et al. [33] verified that the ratio of lymph nodes might be employed as an independent prognostic factor, which is essential for N1 NSCLC cases [34]. Particular attention has also been placed on exploring the prognostic relevance of pathologic nodal status following induction therapy (ypN) to clarify, for instance, whether pN0 or pN2 have the same prognosis as ypN0 or ypN2. This is crucial since patients who had received induction therapy were omitted from previous analyses of the N component. A more accurate and reliable N categorisation is absolutely essential for a personalised precision therapy.

Synergistic cytotoxic chemotherapy with radiotherapy

LA NSCLC can be perceived hypothetically as having two compartment regions: a loco-regional compartment in the chest and a distant compartment harbouring potential micrometastases. Thus, the paramount objective in managing this disease can be described in two aspects: eradicating the visible intrathoracic disease and diminishing the incidence of subsequent systemic intrathoracic metastases.

Within this context, a combination of systemic chemotherapy and radiation has been correlated with substantially enhanced local tumour curability and long-term survival. Chemotherapy is aimed at eradicating cancer cells that may have metastasised (spread) to other parts of the body from the original primary tumour, shrinking primary tumours, and slowing tumour growth [35]. Currently, more than 100 cytostatic chemotherapy drugs are employed in daily clinical practice [36].

Furthermore, the two fundamental oncologic treatment regimens for delivering the aforementioned combining modalities are: (a) sequential, whereby chemotherapy modality is completed prior to the initiation of the radiotherapy and (b) concurrent, according to which radiation and chemotherapy are administered simultaneously [37]. The former approach diminish the risk of distant metastases, may also reduce the volume of the primary tumour making subsequent irradiation more effective, and may even make the tumour resectable. Nevertheless, prolonged total treatment time, postponed irradiation, and the possibility of accelerated repopulation of tumour cells can adversely affect local tumour control.

A recent phase I study conducted by Higgins et al. [47] of Winship Cancer Institute revealed a significantly positive clinical outcome of radiotherapy concurrent with chemotherapy. In that study, 19 patients with stages IIIA and IIIB NSCLC received 44 Gy of conventionally fractionated thoracic radiation with concurrent chemotherapy, along with a dose-escalated stereotactic ab-

Table 3. Published data that examine two treatment arms, comparing and analysing clinical outcomes of radiotherapy alone with radiochemotherapy in patients with histologically verified, locally advanced, nonresectable non-small cell lung cancer (NSCLC)

Ref	Radiation therapy alone (n = 441)						Combined chemoradiotherapy (n = 400)				
	n	TD [Gy]	d/f [Gy]	Local tumour control rates (%)			n	CCRT regimen	Local tumour control rates (%)		
				1-year LC (%)	2-year LC (%)	3-year LC (%)			1-year LC (%)	2-year LC (%)	3-year LC (%)
[38]	33	56	2.0	15	NA	NA	33	CIS 100 mg/m^2 and ETOP 120 mg/m^2 in addition to 56 Gy/28 fractions.	17	n/a	n/a
[39]	46	60	2.0	20	11	NA	43	DOC 120 mg/m^2 in addition to 60 Gy/30 fractions	32	19	n/a
[40–42]	23	60	2.0	18	10	8.0	23	CARB 600 mg/m^2 in addition to 60 GY/30 fractions	40	20	18
[43]	114	60	3.0	35	21	9	110	CIS 120 mg/m^2 in addition to 60 Gy / 20 fractions	60	33	29
[44]	20	63	2.0	24	15	15	21	PAX 360 mg/m^2 in addition to 63 Gy/ 32 fractions	63	38	38
[45]	82	65	2.0	30	17	10	43	Platinum-taxol regimen in addition to 65 Gy/ 33 fractions	40	35	13
[6]	23	70	2.0	45	30	25	45	PAX/CARB (prescription not specified) in addition to 70 Gy/35 fractions	83	50	38
[46]	70	80	2.0	50	35.4	30	82	Wide range of drugs in addition to 80 Gy/40 fractions	56	43.1	38

No — number of patients enrolled in each arms; TD — total dose, d/f — dose per fraction; LC — local tumour control; CIS — cisplatin; ETOP — etoposide; DCO — docetaxel; CARB — carboplatin; PAX — paclitaxel

lative radiotherapy (SABR) boost to the primary tumour as well as the involved mediastinal lymph nodes. The overall survival rates for the one-, two- and three-year follow-ups were 62%, 56% and 39%, respectively.

Similarly, a phase III clinical trial performed by Sause et al. [48] investigated whether chemotherapy followed by radiotherapy could yield exceptional clinical outcomes in surgically unresectable NSCLC cases wherein patients underwent either hyperfractionated radiation or standard fractionation radiotherapy. The clinical outcomes of that study implied a trend toward an improvement in overall survival, wherein the one-year survival rate of the patients treated with radiotherapy alone was 45% and the survival rate of those treated with concurrent chemo-radiation was 60%.

Several studies have shown that concurrent radiochemotherapy yielded improved local control and median survival rates contrary to the sequential radiochemotherapy; one example is the noteworthy and continual effort by the NSCLC Collaborative Group., who conducted a meta-analysis of six randomised trials that evaluated the superiority of concurrent radiochemotherapy versus sequential radiochemotherapy. They have analysed 1,205 LA-NSCLC cases and indicated a substantial enhancement in the five-year rate of overall survival (11.3% to 16.2%) and a diminution in local recurrence (35% to 29%) with concomitant radiochemotherapy. Nonetheless, a significant increase in oesophageal toxicity was observed, yet no persuasive evidence of radiation pneumonitis was given in this study [49].

A phase III randomized clinical trial conducted in Japan indicated superior response rates (84% *vs.* 66%; p = 0.0002), five- year survival rates (15.8% *vs.* 8.9%) and median overall survival (16.5 *vs.* 13.3 months; p = 0.04), with concomitant radiochemotherapy versus sequential radiochemotherapy [50]. Additionally, chemotherapy for both arms included mitomycin (8 mg/m^2 on days 1 and 29), vindesine (3 mg/m^2 on days 1, 8, 29, and 36) and cisplatin (80 mg/m^2 on days 1 and 29).

Within this framework, analysis by Maguire et al. [51] has indicated that the one- and two-year PFS rates were 55% and 34%, respectively, for the concurrent therapy arm, and 52% and 24% for the sequential therapy arm. Confirmatory trials conducted by various countries demonstrated a similar enhanced clinical outcome for the concomitant scheme [52, 53].

Nevertheless, concern persists as to whether major incidences of toxicity may occur due to the addition of chemotherapy [54]. Additionally, clinical experience of such patients with concurrent radiochemotherapy is constrained by the sensitivity of healthy lung tissues to radiation dose which, clinically, may cause radiation pneumonitis and other oesophageal toxicity. Within this framework, large volumes of retrospective studies detail the clinical experience of the related toxicity following concurrent radiochemotherapy for LA NSCLC. For instance, Tsujino et al. [55] determined whether the percentage of pulmonary volume exposed to radiotherapy doses greater than 20 Gy (V20) was associated with the incidence and grade of radiation pneumonitis in 71 patients with inoperable LA NSCLC treated by concurrent radiochemotherapy.

Statistical analysis confirmed that the cumulative rates of grade ≥ 2 radiation pneumonitis at 6 months were 50.0% and 23.7% in patients with V20 of > 25% and ≤ 25%, respectively. Palma et al. [56] indicated that the rates of symptomatic radiation pneumonitis were 30.3% and 8.6% in patients with V20 of 20–30% and < 20%, respectively, and the rates of fatal pneumonitis were 3.5% and 2.9% in patients with V20 of ≥ 40% and 30–40%, respectively. In this major meta-analysis, Palma and his colleagues demonstrated that mean lung doses were a predictor of radiation pneumonitis in patients ≤ 65 years treated with carboplatin/paclitaxel chemotherapy; the rates of radiation pneumonitis were 41–48% and 0%–9% among patients with mean lung dose ≥ 10 Gy and < 10 Gy, respectively [56]. Other investigators revealed that the rates of grade ≥ 2 radiation pneumonitis were 19% and 2.2% in patients with mean lung doses ≥ 18 Gy and < 18 Gy, respectively [56].

In a similar vein, Graham et al. [57] examined 99 patients with LA NSCLC and determined that the percentage of total lung volume irradiated to 20 Gy corresponds significantly with the incidence of symptomatic radiation pneumonitis. Within this context, the potential advantages of concurrent radiochemotherapy include but not limited to sensitisation of tumour cells to radiation by the administration of chemotherapy drugs and shortening of overall treatment time compared with sequential therapy.

Thus, patient selection is an essential consideration, and sequential radiochemotherapy might be suitable for patients whose performance status and comorbidities limit the tolerability of concurrent radiochemotherapy. It is worth pointing out that concomitant radiochemotherapy is broadly employed in the UK, Ireland and other European countries as the standard treatment procedure for unresectable stage III NSCLC [58–63].

Radiation therapy

External beam radiotherapy

Three dominant factors make LA NSCLC challenging to manage with radiotherapy: (1) dosimetric complications induced by the presence of tissue inhomogeneities (i.e., lung has notably low density in comparison with surrounding at-risk organs such as heart, kidneys, liver and oesophagus), (2) respiratory motion, and (3) proximity of

Table 4. Summary of radiation dose tolerances of the common organs at risk (OARs) within the thorax; note that V20 represents the volume receiving ≥ 20 Gy and V30 represents the volume receiving ≥ 30 Gy

Dose limits for OARs	QUANTEC [64]	3D-CRT (RTOG 0617) [65]	SABR (RTOG 0618, 18 Gy delivered in 3 fractions) [66]
Lung	V_{20} ≤ 30%	Mean lung dose ≤ 20 Gy V_{20} ≤ 37%	V_{20} ≤ 10%
Heart	Mean dose < 26 V_{30} < 46%	≤ 60, ≤ 45, ≤ 40 Gy for 1/3, 2/3, 3/3 of heart	≤ 30 Gy (10 Gy/fraction)
Spinal cord (point dose)	≤ 50.0 Gy	≤ 50.0 Gy	≤18 Gy (6 Gy/fraction)
Oesophagus	Mean dose ≤ 34 Gy	Mean dose ≤34 Gy	≤ 27 Gy (9 Gy/fraction)

various adjacent healthy organs with low radiation tolerances. Notably, the radiation dose tolerances of these organs at risk (OAR) regulate the daily radiotherapy practice and are adopted in multicentre trials in cooperative groups such as the Radiation Therapy Oncology Group (RTOG). Fundamentally, cutting-edge technologies, such as four-dimensional computed tomography (4D-CT) and volumetric modulated arc therapy (VMAT), should yield therapeutic gains due to their capability to conform radiation doses to tumours.

Nevertheless, some questions may be raised concerning the application of VMAT for thoracic cancers due to the respiratory motion involved. Additionally, in contrast to conventional 3D-CRT, VMAT irradiates only a portion of the target volume at a certain time. This creates the possibility of significant dosimetric missing of the target volume, which may, in turn, have an undesirable influence on local tumour control. This phenomenon has been recognised as "interplay effect" [67, 68].

On the basis of the preceding evidence, the optimum radiotherapy technique for LA NSCLC has been a controversial and much-disputed subject within the field of radiation oncology. Notably, no single-perspective research has been undertaken to determine the optimum radiotherapy modality for LA NSCLC, and the published retrospective reports are contradictory. Liao et al. [69] provided an in-depth retrospective analysis of 496 LA NSCLC patients who were treated at the MD Anderson Cancer Center between 1999 and 2006. In this major study, Liao and his colleagues compared toxicity and disease outcomes in patients treated with either 4D-CT/VMAT or 3D-CRT following concurrent radiochemotherapy regimens. The findings of this study concluded that modern technologies such as VMAT and 4D-CT are associated with substantially improved local tumour control and survival rates, as well as a remarkable reduction in toxicity compared to 3D-CRT.

In agreement with the previous findings, a single-institution retrospective investigation suggested that intensity-modulated radiotherapy (IMRT) can improve overall survival and reduce treatment-related pneumonitis [70]. Within this context, Liu et al. [58] compared 3D-CRT plans with VMAT plans for which mean lung dose and V20 were diminished for all patients, with median reductions of 2 Gy and 8%, respectively. Yom et al. [71] revealed that the rate of grade 3 radiation pneumonitis was 32% for 3D-CRT patients, compared with 8% for VMAT patients ($p = 0.002$). Liao et al. [69] detailed that VMAT considerably diminished the incidence of grade 3 radiation pneumonitis (HR = 0.33, $p = 0.017$). Thus, dosimetrically, VMAT appears to be more encouraging compared to 3D-CRT in advanced-stage disease with complicated and large gross tumour volumes, as well as in adherence to critical structures.

Nevertheless, a number of published studies were unable to reproduce that improvement in clinical outcomes and reduction in toxicity [8, 9]. For instance, in a major retrospective study involving 3,986 LA NSCLC cases accumulated from the Surveillance, Epidemiology, and End Results (SEER) Medicare database, Shirvani et al. [72] highlight the fact that clinical experience strongly encourages the adoption of VMAT in managing LA NSCLC. Nonetheless, the study findings identified no significant differences between 3D-CRT and VMAT in the context of oesophageal, pulmonary or cardiac toxicity rates.

Some questions may be posed in relation to the inconsistency and contradictory conclusions exhibited in the literature. Is the interplay effect the major contributing factor behind such discrepancies among scholars' findings, or do other factors influence those findings, such as the dosimetric challenge in accurately delivering the VMAT plan?

Additionally, in a recent analysis involving multi-radiotherapy UK centres, Bolt et al. [73] showed that uncertainty in machine beam output measurements may result in variation of up to 10% in tumour control probability (TCP) model outcomes, which coincides with the findings published by Alaswad et al. [21]

It is important to note that VMAT delivers the radiotherapy prescription doses by modulating photon beam intensities through the continuous variation of dose rates, gantry speeds and multileaf collimator (MLC) positions at each control point. Such a sophisticated delivery of radiation dose may introduce additional uncertainty in the mechanical operation of the Linac due to profound dependence on the application of high numbers of small irregular field shapes, leading to discrepancies in dose distributions between computed and delivered plans. Within this framework, various quality assurance (QA) practices have been recommended

to assess the dosimetric accuracy of the VMAT delivery technique.

One of the most popular tools for performing patient-specific VMAT QA techniques is the 2D dosimetric comparison between the treatment plan and the measurement. During this procedure, a measurement is obtained before the patient begins treatment. This measurement (i.e., the patient-specific QA) is evaluated using the gamma analysis concept. The accepted gamma analysis criteria of a 3% dose difference and a 3-mm distance to agreement (DTA) are the most commonly used [74]. This step is fundamental in radiotherapy to ensure that VMAT treatment is delivered with high accuracy.

Notwithstanding the foregoing, several investigators have argued that the traditional patient-specific VMAT QA is not sensitive enough to detect dosimetric discrepancy between the treatment plan and the delivered plan. Furthermore, one drawback to the patient-specific VMAT QA technique is a weak-to-moderate correlation between clinically relevant dosimetric errors and 2D gamma analysis passing rates [75]. For instance, Mu et al. [76] deliberately introduced random (± 1 mm and ± 2 mm) and systematic (± 0.5 mm or ± 1 mm) errors in the MLC positions to evaluate the dosimetric effect. They found no significant dosimetric variation for either PTV or OARs that were introduced by random leaf position errors, whereas clinically significant differences (8% variation in D95% and approximately 12% in D0.1 cc to critical organs) were noted by systematic leaf position errors in complex IMRT plans. Alaswad and Coleman [77, 78] concluded that when 2D gamma analysis is performed using a 3% dose difference and a 3-mm DTA, both QA results and the error detectability are heavily dependent on the plane chosen for measurement acquisition, and no relationship was found between the error levels in several verification planes.

Recently, log files have been established on numerous treatment machines to address concerns about traditional QA approaches in identifying both minor random and systematic errors. One of the benefits of utilising this technique is that the log files are acquired and verified whenever the treatment plan is delivered. Hence, it can be verified during patient treatment. Furthermore, log files yield an immediate performance of VMAT plan checks and reduce the ampere-hours utilised in traditional QA techniques to a matter of minutes [79–81]. However, there are still concerns about whether the log file-based QA technique offers confidence equal to that of measurements used by one of the traditional approaches.

Proton therapy

In recent years, proton therapy has gained momentum amongst the procedures of interest due to the absence of any exit radiation dose. This distinctive feature of proton therapy may potentially enable radiotherapy dose escalation without added toxicity to healthy tissues in the vicinity of the target volume. Thus, potentially improving local control and survival while at the same time reducing toxicity and improving quality of life. For instance, proton beam dose deposition initially exhibits a slow increase in dose with depth, followed by a sharp increase near the end of the range. This peak or sharp rise in dose deposition is termed the *Bragg peak*.

Unfortunately, the instalment of proton therapy machinery is associated with prohibitively expensive generating equipment. For instance, the cost of a proton machine can be three to four times greater than that of a typical linac, thus limiting its widespread use [82]. Note that a state-of-the-art linac such as Varian TrueBeam or Elekta Versa HD costs between 750,000–1,500,000 EUR [83].

Despite the high potential of proton therapy, the clinical evidence encouraging the wide application of protons is varied. It is widely recognised that proton therapy is effective, safe, and proposed for various classes of pediatric cancers, chondrosarcomas, ocular melanomas and chordomas.

In consideration of the high cost of establishing and running proton therapy centres, questions have been posed in relation to their cost effectiveness. General consensus is that there is a necessity to conduct randomized trials and/or collect clinical outcomes data in multi-institutional registries to clearly validate the value of protons.

Within this context, numerous single-arm studies have been published with promising clinical outcomes that employ concurrent chemotherapy and proton beam therapy in LA NSCLC [84, 85]. In a retrospective analysis using the National Cancer Database, Higgins et al. [86] concluded that proton therapy yields a substantial improvement in the survival rates compared to photon therapy. However, a notable limitation of this study is

the absence of toxicity data. The interest in proton therapy led to the phase II randomised trial comparing conformal passive scattering proton therapy against VMAT for LA NSCLC. Nonetheless, this ongoing NCT00915005 phase II trial comparing passive scattering proton therapy (PSPT) against IMRT for LA NSCLC revealed no significant difference between the two arms in terms of radiation pneumonitis or oesophageal toxicity [87].

The authors have stated that proton therapy was correlated with larger high-dose lung volumes due to the application of relatively large safety margins during the PSPT treatment plans. Notably, the authors have also observed that the rate of pneumonitis for the proton arm diminished with time during the trial evaluation, and hypothesise that this may be attributable to a learning curve in proton therapy planning, as re-plans of previous patients resulted in improved dosimetry.

It is worth mentioning that the management of LA NSCLC by employing proton therapy is still in the early developmental stages with some specific barriers, such as proton range uncertainty inside the boundaries of moving targets, which may restrict its practical applicability in the foreseeable future.

Immunotherapy for locally advanced NSCLC

The landscape of immunotherapy in lung cancer is rapidly evolving. Currently, the use of immune checkpoint inhibitors has become the standard of care management for patients with resectable, locally advanced, and metastatic NSCLC with notable enhancement in the reported clinical outcomes. The fundamental motive in utilizing immunotherapy is to boost the immune system's response to cancerous cells. The adaptive immune system, particularly T cells, has a curial role in anticancer immune responses [88].

Clinical investigations to date have centered on the following two-immunotherapeutic strategies in the framework of NSCLC treatment: immune checkpoint inhibitors (ICIs) and cancer vaccines. ICIs are antigen non-specific treatments that overcome tumor immunosuppression, whereas cancer vaccines are antigen-specific immunotherapies that augment tumor recognition by the immune system.

Within this context, ICIs are the most encouraging clinical form of NSCLC immunotherapy. ICIs have mostly been examined in clinical trial settings with patients with NSCLC by employing antibodies against programmed cell death protein 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). A principal benefit of these ICIs is their capability to elicit antitumor immune responses irrespective of the specified tumor antigens [89].

It is important to note that the interaction of ICIs with ionizing radiation produces synergistic influence, which has been comprehensively explored by several scholars [90–92]. In the clinical setting, the therapeutic value of combining ICIs with radiotherapy has been shown primarily in metastatic NSCLC patients [93]. Nonetheless, this therapeutic notion has evolved since the publication of the PACIFIC trial, serving to restructure the clinical practice for unresectable stage III NSCLC to a notable degree by demonstrating a substantial advantage obtained from the administration of sequential durvalumab in addition to standard definitive chemoradiotherapy [94].

Fundamentally, ionization radiation has the potential to enhance the activation of the immune system. This is because the damage of cancerous cells by radiotherapy causes the release of tumor-specific antigens, which boosts both T-cell activation and dendritic-cell presentation, and as a consequence, promotes greater immune-dependent cell death.

The use of durvalumab for LA NSCLC arose from the PACIFIC trial and is the most widely recognized combination radio-immunotherapy procedure for NSCLC. In that study, patients with unresectable stage III NSCLC who had not progressed following concomitant radiotherapy and platinum-based chemotherapy were randomized, double-blinded, to be given 12 months of placebo (n = 236) or PD-L1 inhibitor durvalumab at a dose of 10 mg/kg every two weeks (n = 473) [94].

This trial revealed the advantage of progression-free survival in patients treated with the PD-L1 inhibitor durvalumab in comparison with a placebo (16.8 months *vs.* 5.6 months; HR: 0.52; 95% CI: 4.6–7.8). The recently updated clinical outcomes analysis showed the persistent advantage with two-year and five-year overall survival (OS) rates of 66.3% and 42.9% in the cohort treated with

durvalumab in comparison with 55.6% and 33.4% in the placebo group, respectively. Hence, the application of the PD-L1 inhibitor (durvalumab) following chemoradiation has been shown to have a continuous benefit in the durvalumab-based treatment of unresectable LA NSCLC, thereby becoming the standard of care in this setting. These updated clinical outcomes indicate durable PFS and sustained OS benefit with durvalumab following chemoradiotherapy [95]. Additionally, sub-cohort analysis has revealed that OS was superior in patients who commenced durvalumab within 14 days of radiotherapy.

Consequently, the United States FDA approved durvalumab (IMFINZI®) in February 2018 as a therapeutic regimen for patients with unresectable stage III NSCLC whose disease has not progressed following the therapeutic schedule of radiotherapy alongside platinum-containing chemotherapy. The advisable treatment course for durvalumab is 10 mg/kg administered intravenously every two weeks [96]. Additionally, this form of therapy opens up the use of various immunotherapy combinations to evaluate its efficacy as displayed in Table 5.

On the basis of the preceding trail, the KEYNOTE-799 study is a phase II trial that examined the use of pembrolizumab (a PD-1 inhibitor) with concurrent chemoradiation. The outcomes indicated an encouraging response rate of nearly 70%, although the overall survival analysis remained immature. A remarkable challenge in combining radiotherapy with ICIs is the development of toxicity, particularly pneumonitis. Regarding this concept, in the PACIFIC trial, the rate of grade ≥ 3 pneumonitis was 3.4% compared to 8% reported by the KEYNOTE-799 study [102].

The PACIFIC-2 trial shifted the administration of durvalumab earlier in the course of the treatment in an effort to examine whether concurrent immunotherapy and chemoradiation is superior to consolidative immunotherapy with chemoradiation [106]. Notably, several patients are ineligible for a concurrent chemoradiation regimen; hence, the phase II PACIFIC-6 trial evaluating the safety of durvalumab following sequential chemoradiation. In 2022, these researchers reported evidence that showed safety comparable to that perceived in the PACIFIC-2 trial, proposing that this might also signify a realistic therapeutic approach in patients unable to undergo concomitant chemoradiation [107].

Additionally, in the phase II COAST study, durvalumab was combined with monalizumab (anti-NKG2A mAb) or oleclumab (anti-CD73 mAb) as a consolidative treatment of unresectable stage III NSCLC following concomitant chemoradiation. This study revealed that the durvalumab plus monalizumab and the durvalumab plus oleclumab arms showed enhanced overall response rates of

Table 5. Clinical trials of immune checkpoint inhibitor and radiotherapy combination in LA non-small cell lung cancer (NSCLC)

Ref	n	RT	ICIs	Design
[97]	24	Conventional RT (60 Gy/30 fx); Hypofractionated RT (60 Gy/15 fx)	Durvalumab	Concomitant with definitive RT
[98]	27	Hypofractionated RT 60 Gy/20 fx; Hypofractionated RT 63 Gy/23 fx	Durvalumab	Concomitant with definitive RT
[99]	20	Conventional RT (60 Gy/30 fx)	Ipilimumab + nivolumab	Concomitant with definitive RT and consolidation (nivolumab)
[100]	50	Conventional RT (60 Gy/30 fx)	Ipilimumab ± nivolumab	Concomitant definitive treatment ± consolidative ICI
[101]	63	Conventional RT (60 Gy/30 fx)	Pembrolizumab	Concomitant with definitive RT
[102]	216	Conventional RT (60 Gy/30 fx)	Pembrolizumab	Concomitant and consolidative
[103]	660	Conventional RT (60 Gy/30 fx)	Durvalumab	Concomitant with definitive treatment versus adjuvant ICI
[104]	328	Conventional RT (60 Gy/30 fx)	Durvalumab	Concomitant ± consolidative
[105]	1400	Conventional RT (60 Gy/30 fx)	Nivolumab, ipilimumab, durvalumab	Concomitant + 2 consolidation regimens versus consolidation after CRT

RT — radiotherapy; ICI — immune checkpoint inhibitors; CRT — conformal radiation therapy

37.1% and 38.3% respectively, in comparison with durvalumab alone (25.5%). Toxicity was comparable across all arms of treatment, signifying that combinatorial strategies to consolidation treatment can enhance clinical outcomes [108].

Nonetheless, few researchers have examined the PACIFIC scheme in real world settings. The few published reports on durvalumab treatment in patients with LA NSCLC outside clinical trials contain quite modest numbers of patients, and the clinical outcomes (up to 12 months) are, to a certain degree, insufficient contributions [109, 110]. Therefore, real-world data are required to further evaluate the PACIFIC regimen's tolerability and efficacy. Accordingly, PACIFIC-R enrolled patients who received durvalumab through the early access programme to provide the first real-world data on the use of the PACIFIC therapeutic approach. PACIFIC-R enrolled a population of over 1,000 LA NSCLC patients from 11 countries [111].

An initial safety statistical analysis using data from several retrospective chart extractions confirmed the PACIFIC regimen's real-world tolerability [111]. Within this framework, PACIFIC-R analysis indicated that the median progression-free survival was 21.7 months, and approximately half of all patients were free of disease progression two years after durvalumab administration. These clinical outcomes verify durvalumab's efficacy following definitive radiochemotherapy in a large, predominantly European population with LA NSCLC [111].

Notably, PACIFIC-R's 2-year overall survival rate was superior to that of PACIFIC (71.2% *vs*. 66.3%). The overall survival rate overestimation might be due to the fact that some study sites — such as Germany and the United Kingdom — could not accumulate data on patients who died prior to the PACIFIC-R enrolment. Furthermore, the clinical outcomes from PACIFIC- R agree with other real-world PACIFIC regimen settings [111]. For instance, Taugner et al. [112] provided an in-depth prospective analysis of twenty-six patients to evaluate the real-world efficacy and clinical application of durvalumab maintenance treatment following radiochemotherapy in unresectable LA NSCLC. Taugner and colleagues reported PFS rates of 82% and 62% at months 6 and 12, respectively [112]. This agrees with the corresponding rate of PACIFIC-R.

Furthermore, the parameters for durvalumab use in the early access programme (from which patients were enrolled in PACIFIC-R) were wider in scope than those proposed in the guidelines. Consequently, the PACIFIC-R dosage regimen might not correspond directly with durvalumab's real-world applications. For instance, the early access programme permitted patients to maintain durvalumab treatment in a curative-intent setting until they encountered disease progression [111], yet current recommendations propose a 12-month treatment cap. Additionally, 19.8% and 4.2% of patients received durvalumab for a total duration of more than 12 and 14 months, respectively.

Remarkably, within clinical trial settings, the patient selection criteria are rigorous due to their complexity, ambiguity, lack of patient-centredness, and overly restrictive nature. This could lead to discrepancies between ideal clinical trial settings and clinical practice outcomes. Sakaguchi et al. [113] analysed 81 patients with medically unresectable stage III NSCLC of whom 32.8% of patients did not meet the criteria of the PACIFIC study for the following reasons: poor performance (9.6%), disease progression after CCRT (4.1%), grade 2 or higher radiation pneumonia within 42 days after chemoradiotherapy (16.4%) and other pneumonia (2.7%).

Additionally, the optimum duration of consolidation immunotherapy in an inoperable LA NSCLC setting remains a disputed topic, and many ongoing clinical trials permit therapeutic durations of more than 12 months. Future attempts might be directed towards amending the schedule and dosing of radiotherapy when employed in close proximity with ICIs, which may enhance the feasibility and minimize the toxicity of this approach.

Conclusions

Accurate prognosis and relevant therapy decisions rely on establishing the accurate staging of NSCLC. The recently proposed 8th edition TNM staging system exhibited significant amendments in the distribution of the T and M descriptors. Several studies have demonstrated the superiority of the 8th edition over the 7th edition. Nonetheless, numerous studies have shown that certain limitations still exist in the N classification of the 8th TNM staging system, which might be overcome in the forth-

coming 9th TNM edition. Although employing radiotherapy as a sole treatment for LA NSCLC is potentially with curative intent, long-term survival and local tumour control rates are for the most part discouraging. Thus, synergistic cytotoxic chemotherapy with radiotherapy is most prevalent in treating LA NSCLC. Evidently, concomitant radiochemotherapy is largely utilized in the UK, Ireland and other European countries as a typical therapeutic procedure for unresectable stage III NSCLC. Nonetheless, sequential radiochemotherapy is associated with lower toxicity (e.g., oesophageal toxicity and less radiation pneumonitis). Furthermore, technical advancement in dose optimisation and delivery of radiotherapy (e.g., VMAT and proton therapy) have contributed fundamentally to enhanced clinical outcomes while also diminishing the toxicities confronted during the administration of a concurrent radiochemotherapy approach. Currently, the standard of care for patients with inoperable LA NSCLC is concurrent chemoradiotherapy followed by maintenance durvalumab according to clinical outcomes from the PACIFIC trial. Combining ICIs with radiotherapy, either sequentially or concomitantly, has been an area of great interest. In the foreseeable future, the outcomes of ongoing clinical trials will continue to evolve clinical practice in LA NSCLC. Future attempts might be also directed towards amending the schedule and dosing of radiotherapy when employed in close proximity with ICIs, which may enhance the feasibility and minimize the toxicity of this approach.

Conflict of interest

None declared.

Funding

None declared.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–E386, doi: 10.1002/ijc.29210, indexed in Pubmed: 25220842.
2. Neuboeck N, Lindenmann J, Matzi V, et al. Intraoperative radiotherapy (IORT) — alternative treatment in functionally nonresectable nonsmall cell lung cancer (NSCLCc). Eur Surgery. 2010; 42: 209–213.
3. Manegold C, Dingemans AMC, Gray JE, et al. The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC. J Thorac Oncol. 2017; 12(2): 194–207, doi: 10.1016/j.jtho.2016.10.003, indexed in Pubmed: 27729297.
4. Puri S, Saltos A, Perez B, et al. Locally Advanced, Unresectable Non-Small Cell Lung Cancer. Curr Oncol Rep. 2020; 22(4): 31, doi: 10.1007/s11912-020-0882-3, indexed in Pubmed: 32140986.
5. Saito Y, Hayakawa K, Nakayama Y, et al. Radiation therapy for stage III non-small cell lung cancer invading chest wall. Lung Cancer. 1997; 18(2): 171–178, doi: 10.1016/s0169-5002(97)00058-5, indexed in Pubmed: 9316008.
6. Wolski MJ, Bhatnagar A, Flickinger JC, et al. Multivariate analysis of survival, local control, and time to distant metastases in patients with unresectable non-small-cell lung carcinoma treated with 3-dimensional conformal radiation therapy with or without concurrent chemotherapy. Clin Lung Cancer. 2005; 7(2): 100–106, doi: 10.3816/CLC.2005.n.024, indexed in Pubmed: 16179096.
7. 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): 2181–2190, doi: 10.1200/JCO.2009.26.2543, indexed in Pubmed: 20351327.
8. Harris JP, Murphy JD, Hanlon AL, et al. A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014; 88(4): 872–884, doi: 10.1016/j.ijrobp.2013.12.010, indexed in Pubmed: 24495591.
9. Mell LK, Roeske JC, Mundt AJ. A survey of intensity-modulated radiation therapy use in the United States. Cancer. 2003; 98(1): 204–211, doi: 10.1002/cncr.11489, indexed in Pubmed: 12833473.
10. Yoh Watanabe M. TNM classification for lung cancer. Ann Thorac Cardiovasc Surg. 2003; 9.
11. Goldstraw P. New TNM classification: achievements and hurdles. Transl Lung Cancer Res. 2013; 2(4): 264–272, doi: 10.3978/j.issn.2218-6751.2013.07.02, indexed in Pubmed: 25806242.
12. Detterbeck FC, Boffa DJ, Kim AW, et al. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017; 151(1): 193–203, doi: 10.1016/j.chest.2016.10.010, indexed in Pubmed: 27780786.
13. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015; 10(7): 990–1003, doi: 10.1097/jto.0000000000000559.
14. Groome PA, Bolejack V, Crowley JJ, et al. IASLC International Staging Committee, Cancer Research and Biostatistics, Observers to the Committee, Participating Institutions. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol. 2007; 2(8): 694–705, doi: 10.1097/JTO.0b013e31812d05d5, indexed in Pubmed: 17762335.
15. Goldstraw P, Crowley J, Chansky K, et al. International Association for the Study of Lung Cancer International Staging Committee, Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours.

J Thorac Oncol. 2007; 2(8): 706–714, doi: 10.1097/JTO.0b013e31812f3c1a, indexed in Pubmed: 17762336.
16. Vallières E, Shepherd FA, Crowley J, et al. International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol. 2009; 4(9): 1049–1059, doi: 10.1097/JTO.0b013e3181b27799, indexed in Pubmed: 19652623.
17. Neppl C, Keller MD, Scherz A, et al. Comparison of the 7th and 8th Edition of the UICC/AJCC TNM Staging System in Primary Resected Squamous Cell Carcinomas of the Lung-A Single Center Analysis of 354 Cases. Front Med (Lausanne). 2019; 6: 196, doi: 10.3389/fmed.2019.00196, indexed in Pubmed: 31552253.
18. Alaswad M, Kleefeld C, Foley M. Comparison of the T descriptor of the 7th and 8th editions of the TNM staging system for non-small cell lung cancer after radiotherapy: An analysis from the TCP modelling perspective. Physica Medica. 2021; 84: 302, doi: 10.1016/j.ejmp.2021.01.053.
19. Zips D. Tumour growth and response to radiation. In: Basic clinical radiobiology. CRC Press, Boca Raton 2018: 81–88.
20. Alaswad M, Kleefeld C, Foley M. Radiation dose intensity and local tumour control of non-small cell lung cancer: A radiobiological modelling perspective. J Phys Conference Series. 2019: 012071.
21. Alaswad M, Kleefeld C, Foley M. Optimal tumour control for early-stage non-small-cell lung cancer: A radiobiological modelling perspective. Phys Med. 2019; 66: 55–65, doi: 10.1016/j.ejmp.2019.09.074, indexed in Pubmed: 31561206.
22. Salem A, Asselin MC, Reymen B, et al. Targeting Hypoxia to Improve Non-Small Cell Lung Cancer Outcome. J Natl Cancer Inst. 2018; 110(1), doi: 10.1093/jnci/djx160, indexed in Pubmed: 28922791.
23. Forster JC, Marcu LG, Bezak E. Approaches to combat hypoxia in cancer therapy and the potential for in silico models in their evaluation. Phys Med. 2019; 64: 145–156, doi: 10.1016/j.ejmp.2019.07.006, indexed in Pubmed: 31515013.
24. Neppl C, Keller MD, Scherz A, et al. Comparison of the 7th and 8th Edition of the UICC/AJCC TNM Staging System in Primary Resected Squamous Cell Carcinomas of the Lung-A Single Center Analysis of 354 Cases. Front Med (Lausanne). 2019; 6: 196, doi: 10.3389/fmed.2019.00196, indexed in Pubmed: 31552253.
25. Bradley JD, Ieumwananonthachai N, Purdy JA, et al. Gross tumor volume, critical prognostic factor in patients treated with three-dimensional conformal radiation therapy for non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys. 2002; 52(1): 49–57, doi: 10.1016/s0360-3016(01)01772-2, indexed in Pubmed: 11777621.
26. Stinchcombe TE, Morris DE, Moore DT, et al. Post-chemotherapy gross tumor volume is predictive of survival in patients with stage III non-small cell lung cancer treated with combined modality therapy. Lung Cancer. 2006; 52(1): 67–74, doi: 10.1016/j.lungcan.2005.11.008, indexed in Pubmed: 16499996.
27. Sui X, Jiang W, Chen H, et al. Validation of the Stage Groupings in the Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2017; 12(11): 1679–1686, doi: 10.1016/j.jtho.2017.07.028, indexed in Pubmed: 28782726.
28. Chansky K, Detterbeck FC, Nicholson AG, et al. IASLC Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. The IASLC Lung Cancer Staging Project: External Validation of the Revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2017; 12(7): 1109–1121, doi: 10.1016/j.jtho.2017.04.011, indexed in Pubmed: 28461257.
29. Yang L, Wang S, Zhou Y, et al. Evaluation of the 7 and 8 editions of the AJCC/UICC TNM staging systems for lung cancer in a large North American cohort. Oncotarget. 2017; 8(40): 66784–66795, doi: 10.18632/oncotarget.18158, indexed in Pubmed: 28977996.
30. Jung HS, Lee JGu, Lee CY, et al. Validation of the T descriptor in the new 8th TNM classification for non-small cell lung cancer. J Thorac Dis. 2018; 10(1): 162–167, doi: 10.21037/jtd.2017.12.20, indexed in Pubmed: 29600045.
31. Katsumata S, Aokage K, Ishii G, et al. Prognostic Impact of the Number of Metastatic Lymph Nodes on the Eighth Edition of the TNM Classification of NSCLC. J Thorac Oncol. 2019; 14(8): 1408–1418, doi: 10.1016/j.jtho.2019.04.016, indexed in Pubmed: 31055075.
32. Rami-Porta R. Future Perspectives on the TNM Staging for Lung Cancer. Cancers (Basel). 2021; 13(8), doi: 10.3390/cancers13081940, indexed in Pubmed: 33920510.
33. Chen W, Zhang C, Wang G, et al. Feasibility of nodal classification for non-small cell lung cancer by merging current N categories with the number of involved lymph node stations. Thorac Cancer. 2019; 10(7): 1533–1543, doi: 10.1111/1759-7714.13094, indexed in Pubmed: 31207184.
34. Qiu C, Dong W, Su B, et al. The prognostic value of ratio-based lymph node staging in resected non-small-cell lung cancer. J Thorac Oncol. 2013; 8(4): 429–435, doi: 10.1097/JTO.0b013e3182829c16, indexed in Pubmed: 23486264.
35. Ko EC, Raben D, Formenti SC. The Integration of Radiotherapy with Immunotherapy for the Treatment of Non-Small Cell Lung Cancer. Clin Cancer Res. 2018; 24(23): 5792–5806, doi: 10.1158/1078-0432.CCR-17-3620, indexed in Pubmed: 29945993.
36. Rompelman FMv, Smit AAj, Franssen EJf, et al. Drug-drug interactions of cytostatics with regular medicines in lung cancer patients. J Oncol Pharm Pract. 2017; 23(7): 483–490, doi: 10.1177/1078155216664200, indexed in Pubmed: 27530243.
37. Rajappa S, Sharma S, Prasad K. Unmet Clinical Need in the Management of Locally Advanced Unresectable Lung Cancer: Treatment Strategies to Improve Patient Outcomes. Adv Ther. 2019; 36(3): 563–578, doi: 10.1007/s12325-019-0876-4, indexed in Pubmed: 30693419.
38. Crinò L, Latini P, Meacci M, et al. Induction chemotherapy plus high-dose radiotherapy versus radiotherapy alone in locally advanced unresectable non-small-cell lung cancer. Ann Oncol. 1993; 4(10): 847–851, doi: 10.1093/oxfordjournals.annonc.a058391, indexed in Pubmed: 8117604.
39. Scagliotti GV, Szczesna A, Ramlau R, et al. Docetaxel-based induction therapy prior to radiotherapy with or without docetaxel for non-small-cell lung cancer. Br J Cancer. 2006; 94(10): 1375–1382, doi: 10.1038/sj.bjc.6603115, indexed in Pubmed: 16641904.

40. Atagi S, Kawahara M, Tamura T, et al. Japan Clinical Oncology Group (JCOG9812). Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced non-small cell lung cancer: a phase III trial of the Japan Clinical Oncology Group (JCOG9812). Jpn J Clin Oncol. 2005; 35(4): 195–201, doi: 10.1093/jjco/hyi060, indexed in Pubmed: 15845568.
41. Atagi S, Mizusawa J, Ishikura S, et al. Japan Clinical Oncology Group Lung Cancer Study Group. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol. 2012; 13(7): 671–678, doi: 10.1016/S1470-2045(12)70139-0, indexed in Pubmed: 22622008.
42. Atagi S, Mizusawa J, Ishikura S, et al. Chemoradiotherapy in Elderly Patients With Non-Small-Cell Lung Cancer: Long-Term Follow-Up of a Randomized Trial (JCOG0301). Clin Lung Cancer. 2018; 19(5): e619–e627, doi: 10.1016/j.cllc.2018.04.018, indexed in Pubmed: 29887243.
43. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med. 1992; 326(8): 524–530, doi: 10.1056/NEJM199202203260805, indexed in Pubmed: 1310160.
44. Sarihan S, Kayisogullari U, Ercan I, et al. Randomized phase 2 study of radiotherapy alone versus radiotherapy with paclitaxel in non-small cell lung cancer. J Int Med Res. 2004; 32(4): 375–383, doi: 10.1177/147323000403200405, indexed in Pubmed: 15303768.
45. Lee JHo, Wu HG, Kim HJ, et al. Influence of Comorbidities on the Efficacy of Radiotherapy with or without Chemotherapy in Elderly Stage III Non-small Cell Lung Cancer Patients. Cancer Res Treat. 2012; 44(4): 242–250, doi: 10.4143/crt.2012.44.4.242, indexed in Pubmed: 23341788.
46. Sim S, Rosenzweig KE, Schindelheim R, et al. Induction chemotherapy plus three-dimensional conformal radiation therapy in the definitive treatment of locally advanced non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2001; 51(3): 660–665, doi: 10.1016/s0360-3016(01)01666-2, indexed in Pubmed: 11597806.
47. Higgins KA, Pillai RN, Chen Z, et al. Concomitant Chemotherapy and Radiotherapy with SBRT Boost for Unresectable Stage III Non-Small Cell Lung Cancer: A Phase I Study. J Thorac Oncol. 2017; 12(11): 1687–1695, doi: 10.1016/j.jtho.2017.07.036, indexed in Pubmed: 28919394.
48. Sause W, Kolesar P, Taylor S IV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest. 2000; 117(2): 358–364, doi: 10.1378/chest.117.2.358, indexed in Pubmed: 10669675.
49. 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): 2181–2190, doi: 10.1200/JCO.2009.26.2543, indexed in Pubmed: 20351327.
50. 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): 2692–2699, doi: 10.1200/JCO.1999.17.9.2692, indexed in Pubmed: 10561343.
51. Maguire J, Khan I, McMenemin R, et al. SOCCAR: A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III Non-Small Cell Lung Cancer and good performance status. Eur J Cancer. 2014; 50(17): 2939–2949, doi: 10.1016/j.ejca.2014.07.009, indexed in Pubmed: 25304298.
52. Fournel P, Robinet G, Thomas P, et al. Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie. 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): 5910–5917, doi: 10.1200/JCO.2005.03.070, indexed in Pubmed: 16087956.
53. 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, doi: 10.1016/j.lungcan.2004.03.004, indexed in Pubmed: 15364136.
54. Chen CY, Chen KY, Shih JY, et al. Clinical factors associated with treatment toxicity of pemetrexed plus platinum in elderly patients with non-small cell lung cancer. J Formos Med Assoc. 2020; 119(10): 1506–1513, doi: 10.1016/j.jfma.2019.12.007, indexed in Pubmed: 31917064.
55. Tsujino K, Hirota S, Endo M, et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys. 2003; 55(1): 110–115, doi: 10.1016/s0360-3016(02)03807-5, indexed in Pubmed: 12504042.
56. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013; 85(2): 444–450, doi: 10.1016/j.ijrobp.2012.04.043, indexed in Pubmed: 22682812.
57. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys. 1999; 45(2): 323–329, doi: 10.1016/s0360-3016(99)00183-2, indexed in Pubmed: 10487552.
58. Lim E, Baldwin D, Beckles M, et al. British Thoracic Society, Society for Cardiothoracic Surgery in Great Britain and Ireland. Guidelines on the radical management of patients with lung cancer. Thorax. 2010; 65 Suppl 3: iii1–ii27, doi: 10.1136/thx.2010.145938, indexed in Pubmed: 20940263.
59. Pallis AG, Gridelli C, van Meerbeeck JP, et al. EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population. Ann Oncol. 2010; 21(4): 692–706, doi: 10.1093/annonc/mdp360, indexed in Pubmed: 19717538.
60. Postmus PE, Kerr KM, Oudkerk M, et al. ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28(suppl_4): iv1–iv21, doi: 10.1093/annonc/mdx222, indexed in Pubmed: 28881918.

61. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013; 143(5 Suppl): e314S–e340S, doi: 10.1378/chest.12-2360, indexed in Pubmed: 23649445.
62. Helbrow J, MacNicoll F, Bayman N, et al. Concurrent chemoradiotherapy for locally advanced, unresectable non-small cell lung cancer: a UK survey of current practice. Clin Oncol (R Coll Radiol). 2012; 24(8): e127, doi: 10.1016/j.clon.2012.04.003, indexed in Pubmed: 22578886.
63. Brunelli A, Charloux A, Bolliger CT, et al. European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009; 34(1): 17–41, doi: 10.1183/09031936.00184308, indexed in Pubmed: 19567600.
64. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010; 76(3 Suppl): S10–S19, doi: 10.1016/j.ijrobp.2009.07.1754, indexed in Pubmed: 20171502.
65. van Diessen JNA, La Fontaine M, van den Heuvel MM, et al. Phase I/IIa study of cetuximab with gemcitabine plus carboplatin in patients with chemotherapy-naive advanced non-small-cell lung cancer. J Clin Oncol. 2005; 23(36): 9089–9096, doi: 10.1200/JCO.2004.00.1438, indexed in Pubmed: 16301597.
66. Timmerman R, Paulus R, Pass H, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. J Clin Oncol. 2013; 31(15_suppl): 7523–7523, doi: 10.1200/jco.2013.31.15_suppl.7523.
67. Ceberg, S, Ceberg, C, Falk M, et al. Evaluation of breathing interplay effects during vmat by using 3d gel measurements, J Phys Conference Series. 2013: p.
68. Palmer AL, Nash D, Kearton JR, et al. A multicentre 'end to end' dosimetry audit of motion management (4DCT-defined motion envelope) in radiotherapy. Radiother Oncol. 2017; 125(3): 453–458, doi: 10.1016/j.radonc.2017.09.033, indexed in Pubmed: 29037776.
69. Liao ZX, Komaki RR, Thames HD, et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2010; 76(3): 775–781, doi: 10.1016/j.ijrobp.2009.02.032, indexed in Pubmed: 19515503.
70. Bezjak A, Rumble RB, Rodrigues G, et al. Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of lung cancer. Clin Oncol (R Coll Radiol). 2012; 24(7): 508–520, doi: 10.1016/j.clon.2012.05.007, indexed in Pubmed: 22726417.
71. Yom SS, Liao Z, Liu HH, et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2007; 68(1): 94–102, doi: 10.1016/j.ijrobp.2006.12.031, indexed in Pubmed: 17321067.
72. Shirvani SM, Jiang J, Gomez DR, et al. Intensity modulated radiotherapy for stage III non-small cell lung cancer in the United States: predictors of use and association with toxicities. Lung Cancer. 2013; 82(2): 252–259, doi: 10.1016/j.lungcan.2013.08.015, indexed in Pubmed: 24018022.
73. Bolt M, Clark C, Chen T, et al. A multi-centre analysis of radiotherapy beam output measurement. Phys Imag Radiat Oncol. 2017; 4: 39–43, doi: 10.1016/j.phro.2017.12.001.
74. Mynampati DK, Yaparpalvi R, Hong L, et al. Application of AAPM TG 119 to volumetric arc therapy (VMAT). J Appl Clin Med Phys. 2012; 13(5): 3382, doi: 10.1120/jacmp.v13i5.3382, indexed in Pubmed: 22955639.
75. Hussein M, Rowshanfarzad P, Ebert MA, et al. A comparison of the gamma index analysis in various commercial IMRT/VMAT QA systems. Radiother Oncol. 2013; 109(3): 370–376, doi: 10.1016/j.radonc.2013.08.048, indexed in Pubmed: 24100148.
76. Mu G, Ludlum E, Xia P. Impact of MLC leaf position errors on simple and complex IMRT plans for head and neck cancer. Phys Med Biol. 2008; 53(1): 77–88, doi: 10.1088/0031-9155/53/1/005, indexed in Pubmed: 18182688.
77. Alaswad M, Coleman L. The sensitivity of patient-specific imrt qa methods in detecting systematic errors: Field-by-field versus single-gantry-angle composite. J Phys Conference Series. 2019: 012063.
78. Alaswad M, Coleman L. Comparison of IMRT QA measurement methodology. Physica Medica. 2017; 42: 363, doi: 10.1016/j.ejmp.2017.05.074.
79. Agnew CE, Irvine DM, McGarry CK. Correlation of phantom-based and log file patient-specific QA with complexity scores for VMAT. J Appl Clin Med Phys. 2014; 15(6): 4994, doi: 10.1120/jacmp.v15i6.4994, indexed in Pubmed: 25493524.
80. McGarry CK, Agnew CE, Hussein M, et al. The use of log file analysis within VMAT audits. Br J Radiol. 2016; 89(1062): 20150489, doi: 10.1259/bjr.20150489, indexed in Pubmed: 27072390.
81. Viola P, Romano C, Craus M, et al. Prediction of VMAT delivery accuracy using plan modulation complexity score and log-files analysis. Biomed Phys Eng Express. 2022; 8(5), doi: 10.1088/2057-1976/ac82c6, indexed in Pubmed: 35858537.
82. Durante M, Flanz J. Charged particle beams to cure cancer: Strengths and challenges. Semin Oncol. 2019; 46(3): 219–225, doi: 10.1053/j.seminoncol.2019.07.007, indexed in Pubmed: 31451308.
83. ROS. Linear accelerator (linac) price guide & costs. https://www.oncologysystems.com/resources/linear-accelerator-guides/used-linac-price#:~:text=Linear%20accelerators%20that%20can%20be%20purchased%20for%20%24750%2C000%20to%20%241.5,Varian%20TrueBeam(18/01/),.
84. Nguyen QN, Ly NB, Komaki R, et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. Radiother Oncol. 2015; 115(3): 367–372, doi: 10.1016/j.radonc.2015.05.014, indexed in Pubmed: 26028228.
85. Hoppe BS, Henderson R, Pham D, et al. A Phase 2 Trial of Concurrent Chemotherapy and Proton Therapy for Stage III Non-Small Cell Lung Cancer: Results and Reflections Following Early Closure of a Single-Institution Study. Int J Radiat Oncol Biol Phys. 2016; 95(1): 517–522, doi: 10.1016/j.ijrobp.2015.11.004, indexed in Pubmed: 26774428.
86. Higgins KA, O'Connell K, Liu Y, et al. National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017; 97(1): 128–137, doi: 10.1016/j.ijrobp.2016.10.001, indexed in Pubmed: 27979443.

87. Liao Z, Lee JJ, Komaki R, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018; 36(18): 1813–1822, doi: 10.1200/JCO.2017.74.0720, indexed in Pubmed: 29293386.
88. Doroshow DB, Sanmamed MF, Hastings K, et al. Immunotherapy in Non-Small Cell Lung Cancer: Facts and Hopes. Clin Cancer Res. 2019; 25(15): 4592–4602, doi: 10.1158/1078-0432.CCR-18-1538, indexed in Pubmed: 30824587.
89. Collins JM, Redman JM, Gulley JL. Combining vaccines and immune checkpoint inhibitors to prime, expand, and facilitate effective tumor immunotherapy. Expert Rev Vaccines. 2018; 17(8): 697–705, doi: 10.1080/14760584.2018.1506332, indexed in Pubmed: 30058393.
90. Mohamad O, Diaz de Leon A, Schroeder S, et al. Safety and efficacy of concurrent immune checkpoint inhibitors and hypofractionated body radiotherapy. Oncoimmunology. 2018; 7(7): e1440168, doi: 10.1080/2162402X.2018.1440168, indexed in Pubmed: 29900043.
91. Sheng H, Huang Y, Xiao Y, et al. ATR inhibitor AZD6738 enhances the antitumor activity of radiotherapy and immune checkpoint inhibitors by potentiating the tumor immune microenvironment in hepatocellular carcinoma. J Immunother Cancer. 2020; 8(1), doi: 10.1136/jitc-2019-000340, indexed in Pubmed: 32461345.
92. Käsmann L, Eze C, Dantes M, et al. State of clinical research of radiotherapy/chemoradiotherapy and immune checkpoint inhibitor therapy combinations in solid tumours-a German radiation oncology survey. Eur J Cancer. 2019; 108: 50–54, doi: 10.1016/j.ejca.2018.11.026, indexed in Pubmed: 30648629.
93. Chen D, Menon H, Verma V, et al. Response and outcomes after anti-CTLA4 versus anti-PD1 combined with stereotactic body radiation therapy for metastatic non-small cell lung cancer: retrospective analysis of two single-institution prospective trials. J Immunother Cancer. 2020; 8(1), doi: 10.1136/jitc-2019-000492, indexed in Pubmed: 31996395.
94. Antonia SJ, Villegas A, Daniel D, et al. PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018; 379(24): 2342–2350, doi: 10.1056/NEJMoa1809697, indexed in Pubmed: 30280658.
95. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022; 40(12): 1301–1311, doi: 10.1200/JCO.21.01308, indexed in Pubmed: 35108059.
96. Socinski MA, Özgüroğlu M, Villegas A, et al. Durvalumab After Concurrent Chemoradiotherapy in Elderly Patients With Unresectable Stage III Non-Small-Cell Lung Cancer (PACIFIC). Clin Lung Cancer. 2021; 22(6): 549–561, doi: 10.1016/j.cllc.2021.05.009, indexed in Pubmed: 34294595.
97. Lin S. Accelerated hypofractionated or conventionally fractionated radiotherapy and durvalumab in treating patients with stage ii-iii non-small cell lung cancer. ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine.ClinicalTrials. gov Identifier: NCT03801902. https://clinicaltrials. gov/ct2/show/NCT03801902.
98. Biswas T. Proton based cardiac sparing accelerated fractionated radiotherapy in unresectable nsclc. ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT03818776. https://clinicaltrials. gov/ct2/show/NCT03818776.
99. As T. Ipilimumab and nivolumab in combination with radiation therapy in treating patients with stage 2-3 non-small lung cancer. ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT04013542. https://clinicaltrials. gov/ct2/show/NCT04013542.
100. Perez B. Radiation and chemotherapy with ipilimumab followed by nivolumab for patients with stage iii unresectable non-small cell lung cancer (nsclc). ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT03663166. https://clinicaltrials. gov/ct2/show/NCT03663166.
101. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials. J Thorac Oncol. 2021; 16(1): 140–150, doi: 10.1016/j.jtho.2020.09.022, indexed in Pubmed: 33166718.
102. Sharp M. Dohme corp. A trial of pembrolizumab in combination with chemotherapy and radiotherapy in stage iii nsclc (keynote-799, mk-3475-799).(keynote-799). Nct03631784. ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT03631784. https://www. clinicaltrials. gov/ct2/show/NCT03631784.
103. Pennell N. Testing the addition of an antibody to standard chemoradiation followed by the antibody for one year to standard chemoradiation followed by one year of the antibody in patients with unresectable stage iii non-small cell lung cancer. ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT04092283. https://clinicaltrials. gov/ct2/show/NCT04092283.
104. Bradley J. Study of durvalumab given with chemoradiation therapy in patients with unresectable non-small cell lung cancer. ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT03519971. https://www. clinicaltrials. gov/ct2/show/NCT03519971.
105. Squibb B.M. A study of nivolumab and ipilimumab in untreated patients with stage 3 non-small cell lung cancer (nsclc) that is unable or not planned to be removed by surgery (checkmate73l). ClinicalTrial. gov [Internet]. Bethesda (MD): US National Library of Medicine. ClinicalTrials. gov Identifier: NCT04026412. https://clinicaltrials. gov/ct2/show/NCT04026412.
106. Bradley J, Nishio M, Okamoto I, et al. PACIFIC-2: Phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC. J Clin Oncol. 2019; 37(15_suppl): TPS8573–TPS8573, doi: 10.1200/jco.2019.37.15_suppl.tps8573.
107. Garassino MC, Mazieres J, Reck M, et al. 108MO Safety and efficacy outcomes with durvalumab after sequential chemoradiotherapy (sCRT) in stage III, unresectable NSCLC (PACIFIC-6). Ann Oncol. 2022; 33: S81–S82, doi: 10.1016/j.annonc.2022.02.135.
108. Martinez-Marti A, Majem M, Barlesi F, et al. LBA42 COAST: An open-label, randomised, phase II platform study of

durvalumab alone or in combination with novel agents in patients with locally advanced, unresectable, stage III NSCLC. Ann Oncol. 2021; 32: S1320, doi: 10.1016/j.annonc.2021.08.2121.
109. Shaverdian N, Thor M, Shepherd AF, et al. Radiation pneumonitis in lung cancer patients treated with chemoradiation plus durvalumab. Cancer Med. 2020; 9(13): 4622–4631, doi: 10.1002/cam4.3113, indexed in Pubmed: 32372571.
110. Jung HAe, Noh JM, Sun JM, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. Lung Cancer. 2020; 146: 23–29, doi: 10.1016/j.lungcan.2020.05.035, indexed in Pubmed: 32505077.
111. McDonald F, Mornex F, Garassino MC, et al. 79MO PACIFIC-R: Real-world characteristics of unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. J Thorac Oncol. 2021; 16(4): S738–S739, doi: 10.1016/s1556-0864(21)01921-3.
112. Taugner J, Käsmann L, Eze C, et al. Real-world prospective analysis of treatment patterns in durvalumab maintenance after chemoradiotherapy in unresectable, locally advanced NSCLC patients. Invest New Drugs. 2021; 39(4): 1189–1196, doi: 10.1007/s10637-021-01091-9, indexed in Pubmed: 33704621.
113. Sakaguchi T, Ito K, Furuhashi K, et al. Patients with unresectable stage III non-small cell lung cancer eligible to receive consolidation therapy with durvalumab in clinical practice based on PACIFIC study criteria. Respir Investig. 2019; 57(5): 466–471, doi: 10.1016/j.resinv.2019.03.011, indexed in Pubmed: 31104989.