

Review

Stage III Non-Small-Cell Lung Cancer: An Overview of Treatment Options

Francesco Petrella ^{1,2,*} , Stefania Rizzo ^{3,4} , Ilaria Attili ⁵ , Antonio Passaro ⁵ , Thomas Zilli ^{4,6,7},
Francesco Martucci ⁶, Luca Bonomo ³, Filippo Del Grande ^{3,4} , Monica Casiraghi ^{1,2} , Filippo De Marinis ⁵
and Lorenzo Spaggiari ^{1,2}

¹ Department of Thoracic Surgery, European Institute of Oncology IRCCS, 20141 Milan, Italy

² Department of Oncology and Hemato-Oncology, University of Milan, 20141 Milan, Italy

³ Service of Radiology, Imaging Institute of Southern Switzerland (IIMSI), EOC, Via Tesserete 46, 6900 Lugano, Switzerland

⁴ Faculty of Biomedical Sciences, University of Italian Switzerland, Via Buffi 13, 6900 Lugano, Switzerland

⁵ Division of Thoracic Oncology, European Institute of Oncology IRCCS, 20141 Milan, Italy

⁶ Radiation Oncology, Oncological Institute of Southern Switzerland, EOC, 6500 Bellinzona, Switzerland

⁷ Faculty of Medicine, University of Geneva, 1211 Geneva, Switzerland

* Correspondence: francesco.petrella@ieo.it; Tel.: +0039-0257489362

Abstract: Lung cancer is the second-most commonly diagnosed cancer and the leading cause of cancer death worldwide. The most common histological type is non-small-cell lung cancer, accounting for 85% of all lung cancer cases. About one out of three new cases of non-small-cell lung cancer are diagnosed at a locally advanced stage—mainly stage III—consisting of a widely heterogeneous group of patients presenting significant differences in terms of tumor volume, local diffusion, and lymph nodal involvement. Stage III NSCLC therapy is based on the pivotal role of multimodal treatment, including surgery, radiotherapy, and a wide-ranging option of systemic treatments. Radical surgery is indicated in the case of hilar lymphnodal involvement or single station mediastinal ipsilateral involvement, possibly after neoadjuvant chemotherapy; the best appropriate treatment for multistation mediastinal lymph node involvement still represents a matter of debate. Although the main scope of treatments in this setting is potentially curative, the overall survival rates are still poor, ranging from 36% to 26% and 13% in stages IIIA, IIIB, and IIIC, respectively. The aim of this article is to provide an up-to-date, comprehensive overview of the state-of-the-art treatments for stage III non-small-cell lung cancer.

Keywords: lung cancer; stage III; surgery; medical treatment; radiotherapy



Citation: Petrella, F.; Rizzo, S.; Attili, I.; Passaro, A.; Zilli, T.; Martucci, F.; Bonomo, L.; Del Grande, F.; Casiraghi, M.; De Marinis, F.; et al. Stage III Non-Small-Cell Lung Cancer: An Overview of Treatment Options. *Curr. Oncol.* **2023**, *30*, 3160–3175. <https://doi.org/10.3390/curroncol30030239>

Received: 1 February 2023

Revised: 27 February 2023

Accepted: 6 March 2023

Published: 7 March 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Lung cancer is the second most commonly diagnosed malignant tumor and the first cause of neoplastic death worldwide [1]. The most common histological type is non-small-cell lung cancers (NSCLC), accounting for 85% of all lung cancer cases. About 30% of new NSCLC cases are diagnosed at a locally advanced stage, which encompass a wide group of different clinical scenarios with a heterogeneous spectrum of therapeutic options [2]. In particular, stage III NSCLC is a highly heterogeneous group of lung tumors with significant differences in tumor size, local infiltration, and lymph nodal involvement. To be more specific, as shown in Table 1, stage III A NSCLC includes T3N1, T4N0, and T4 N1 diseases; stage IIIB NSCLC includes T3N2 and T4N2 diseases; and stage III C NSCLC includes T3N3 and T4N3 diseases [3].

Stage III NSCLC therapy is based on the pivotal role of multimodal treatments, including surgery, a wide-ranging option of systemic treatments, and radiotherapy; although the main scope of treatments—in this setting—is potentially curative, overall survival rates are still poor, ranging from 36% to 26% and 13% in stages IIIA, IIIB, and IIIC, respectively [3–6].

The ideal management of stage III NSCLC requires proper clinical and pathological staging, in particular of hilar and mediastinal lymph nodes, to correctly candidate patients to surgical approach or combined chemo–radiotherapy [7,8]. Imaging studies including ultrasound, computed tomography (CT) scan and 18FDG positron emission tomography (PET) scan are widely used to stage and follow-up many different tumors. In the specific setting of lung cancer staging, mediastinal staging by endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) has been introduced and has nowadays almost completely replaced mediastinoscopy. All the above mentioned techniques represent the cornerstone of a proper approach to locally advanced NSCLC [8–16].

Table 1. Descriptors of tumors (T) and nodes in TNM eighth edition, to define stage III lung cancer (adapted from [3]).

| T | N0 | N1 | N2 | N3 |
|-----|------|------|------|------|
| T1a | | | IIIA | IIIB |
| T1b | | | IIIA | IIIB |
| T1c | | | IIIA | IIIB |
| T2a | | | IIIA | IIIB |
| T2b | | | IIIA | IIIB |
| T3 | | IIIA | IIIB | IIIC |
| T4 | IIIA | IIIA | IIIB | IIIC |

2. Surgery

Therapeutic options depend on patient performance status, cardiopulmonary function, tumor characteristics and disease extent. The standard approach—for the vast majority of these patients—is chemoradiotherapy (CRT), although for some patients—with low volume stage III disease—surgery may represent an additional therapeutic option, in particular within a multimodality approach [17–20]. Surgical approach can be considered—within a multimodality approach—in stage IIIA and in very selected cases of stage IIIB; on the contrary it is not recommended in stage III C (N3 disease).

2.1. Incidental III A Disease (Intraoperative)

Patients with NSCLC—classified as stage I or II disease at clinical and pathological staging might be found to present an incidental, unforeseen intraoperative N2 involvement. In this case, postoperative chemotherapy is strictly indicated and these patients present a relatively good prognosis [21]. In this setting, adjuvant chemotherapy after radical resection reduces possible relapse due to micro metastases. On the other hand, the role of postoperative radiotherapy is still debated: in fact, it is not clear whether adjuvant radiotherapy may improve the outcome of such patients. In any case, if a case-by-case evaluation of loco-regional risks discloses a higher chance of local relapse, adjuvant radiotherapy can be taken into consideration as a valuable additional therapeutic option [22]. It can be offered either after postoperative chemotherapy or as concurrent adjuvant chemoradiotherapy [23]. In case of incomplete resection—both with microscopic (R1) or macroscopic (R2) residual disease—adjuvant thoracic radiotherapy or concurrent chemoradiotherapy should be carefully discussed individually by the multidisciplinary team, as no clear guideline currently exists since the number of these patients is extremely small [22].

2.2. Potentially Resectable IIIA(N2) Disease (Preoperative)

Several multimodality therapeutic approaches have been proposed in patients with preoperatively diagnosed IIIA(N2) disease including preoperative chemotherapy followed by surgical resection [23–30], preoperative chemoradiotherapy followed by surgical resection or definitive chemoradiotherapy without surgery [20,31–40].

Only definitive concurrent chemoradiotherapy protocol versus preoperative concurrent chemotherapy and radiotherapy followed by surgical resection has been studied in a prospective randomised trial, comparing potentially resectable stage IIIA (N2) patients [41].

No difference in overall survival (OS) by intent to treat analysis was observed between the two groups; on the other hand, a better progression free survival (PFS) for patients receiving with surgical resection was reported [41]. Although both strategies remain possible treatment options in this setting, on the basis of the final results of this clinical trial—it has been observed a 26% mortality rate in the right-sided pneumonectomies, which is much higher than expected for this procedure [22]. On the other hand, recent papers—focusing on perioperative mortality after induction treatments and pneumonectomy—disclosed a much more acceptable overall 30-day mortality of 7% [42–47].

Another trial by the Swiss Group (SAKK) enrolled cytologically or histologically proven IIIA (N2) patients which were then randomized into preoperative chemotherapy followed by surgery versus sequential neo-adjuvant chemotherapy and then radiotherapy followed by surgery; the primary and the secondary endpoints of the study were OS and PFS, respectively; no significant differences were observed between the two arms [48,49].

In the light of these different trials results, it is generally accepted that—in this complex clinical scenario—a pivotal role in the decisional process is played by the multidisciplinary team, including an expert thoracic surgeon—for an upfront decision about the whole therapeutic pathway, thus avoiding any split in the radiotherapy application, when needed [22].

2.3. Potentially Resectable IIIA(N2) Disease and Selected IIIB Disease (at High Risk of Incomplete Resection)

For potentially resectable Pancoast tumor, concurrent preoperative chemo–radiotherapy followed by surgery represents the standard of care [48], although our personal experience suggests that surgical resection after induction chemotherapy offers valuable results [50–52].

A similar approach using concurrent chemo–radiotherapy to reduce the primary tumor and down-stage the disease can be applied to certain T3 N2 or T4 N0-1 tumors [20,33–35], although—even in this setting—our preference is surgical radical resection after induction chemotherapy [53–57]. A German trial (ESPATU) comparing surgery versus definitive chemoradiotherapy boost following complex induction chemotherapy and concurrent chemoradiotherapy did not disclose any benefit in OS or PFS for surgical resection, but both study arms showed excellent long-term survival results [58]. Radical resection in stage III NSCLC preferably includes parenchyma saving procedures such as sleeve resection, lobectomy, or bi-lobectomy avoiding—whenever possible—pneumonectomy [45]. On the other hand, it has recently become clear—and it is well accepted—that in very selected cases, radical resection will require a pneumonectomy or a tracheal sleeve pneumonectomy, which can be safely performed in experienced high-volume centers [42,43,59–61]. Post-operative mortality in stage III NSCLC receiving surgical treatment is reported to range between 2–3% for lobectomy and 3–8% for pneumonectomy [45]; as a clear relation between postoperative outcome and volume of surgical procedures has been reported, these procedures should be restricted to high-volume experienced centers [45].

3. Systemic Treatments

In the complex and varied scenarios that might occur within the stage III NSCLC definition, the use of systemic therapies virtually always represents a mainstay of treatment for patients with such a diagnosis [62].

Until recently, platinum-based chemotherapy was the only standard systemic treatment considered for stage III NSCLC, either resectable or not, with limited benefit both as neoadjuvant/adjuvant (absolute survival benefit about 5% at 5 years compared with placebo; in stage III: HR for neoadjuvant 0.84, 95% CI, 0.75–0.95 | HR for adjuvant 0.83, 95% CI, 0.72–0.94) [21] and as a definitive treatment in combination with concurrent or sequential radiotherapy (5-year survival rate of 10–20%) [31,63]. However, recent evolving improvements in biomarker evaluation and patients' selection rapidly moved the investigation on the use of immunotherapy and targeted agents from the advanced disease also to early-stage and stage III, as part of integrated treatments, highlighting the importance of adequate staging and a multidisciplinary approach in this setting [64]. Indeed, the final

aim in the treatment of patients with locally advanced NSCLC may vary consistently from curative to palliative intent (e.g., for the control of pain or symptoms from mediastinal involvement) [62,65].

3.1. Potentially Resectable Stage III Disease

As previously discussed, when stage III NSCLC is considered potentially resectable according to TNM 8th, the goal of the multimodal treatment is curative. In particular, after discussion within the multidisciplinary team, patients should become candidates for induction systemic treatment [62,64]. In those minoritarian cases with unforeseen N2 involvement before primary surgery for T1–T3 tumors, adjuvant systemic therapy is indicated [62].

3.2. Immunotherapy in the Perioperative Setting

In the adjuvant setting, treatment with adjuvant atezolizumab for one year after platinum-based chemotherapy (1 to 4 cycles) has been demonstrated to improve disease-free survival (DFS) compared with best supportive care, in patients with resected stage II–IIIA (7th AJCC) whose tumors have positive programmed death ligand-1 expression (PD-L1 $\geq 1\%$) (median DFS not estimated for 35.3 months; hazard ratio [HR], 0.66; 95% CI, 0.50 to 0.88; $p = 0.004$), and in particular with high PD-L1 ($\geq 50\%$) (median DFS not estimated for 35.7 months; HR, 0.43; 95% CI, 0.27 to 0.68) [66]. With an updated median follow-up of 46 months, an interim analysis demonstrated a trend toward improved overall survival among patients with PD-L1 $\geq 1\%$, stage II–IIIA NSCLC, with particular benefit observed in PD-L1 $\geq 50\%$ (HR 0.43, 95% CI: 0.26–0.71), resulting in a 5-year survival rate of 84.8% versus 67.5% in this population [67]. Based on these results, adjuvant atezolizumab received approval by the Food and Drug Administration (FDA) in resected stage II–IIIA PD-L1 positive NSCLC, and by European Medicines Agency (EMA) in PD-L1 high, after standard adjuvant chemotherapy, in patients without EGFR mutation or ALK rearrangement. Other immune checkpoint inhibitors (ICIs) are under evaluation in the adjuvant setting, with less strong and controversial efficacy data to date [64,68]. Moving forward, strong preclinical rational and growing clinical evidence support the greater activity of ICIs when administered in the neoadjuvant rather than adjuvant setting. Indeed, the presence of an onsite tumor accounts for a greater potential for T-cell activation and antitumor activity [69,70]. With this background, early phase trials were conducted to evaluate anti-programmed cell death protein-1/PD-L1 and anti-cytotoxic T-cell lymphocyte-4, either alone or in combination in stage I–III NSCLC. The results of these trials showed that the ICI treatment had no adverse effects on surgical outcomes, with previously unreported response rates ranging from 14–45% and a pathological complete response (pCR) up to 16% with single agent anti-PD-1/PD-L1 [70,71]. The pCR rates were up to 29% when anti-PD-1/PD-L1 were used in combination with anti-CTLA-4, but with relevant safety signals [72]. Subsequently, different combinations of chemotherapy and ICI in a neoadjuvant setting were assessed. Some of the reasoning behind this is that chemotherapy might be able to destroy cancer cells and cause them to rupture, leading to the release of antigens that the immune system can recognize and target.

With particular concern for stage IIIA NSCLC, the phase 2 NADIM study looked at the combination of three cycles of nivolumab with carboplatin and paclitaxel, followed by surgery and then adjuvant nivolumab for 1 year [73]. Patients with stage IIIA non-small-cell lung cancer and without specific mutations were included, where 89% of the participants were successfully operated on, with none having a progression of the disease during treatment. Here, 83% saw a major pathological response (MPR) in the tissue from surgery and 63% had no cancer cells left in the tissue samples. Interestingly, CT scans showed a lower percentage of complete or partial responses compared with the tissue samples. In this study, 77.1% of patients were progression free after 24 months [73]. The randomized trial Check Mate 816 included 358 patients with stage Ib (≥ 4 cm)-IIIA NSCLC with no mutations in EGFR and ALK. The study assigned the patients to have either immunotherapy plus

chemotherapy or chemotherapy alone before surgery. Immunotherapy plus chemotherapy resulted in more people being able to have the surgery (83%) and they also had a higher pCR (24% compared with 2% $p < 0.0001$) [74]. The experimental arm also had better event-free survival and overall survival, although the results were not quite statistically significant yet. Because of the findings of the study, the combination of chemotherapy and nivolumab was approved by the FDA in March 2022 as a neoadjuvant treatment for resectable NSCLC ≥ 4 cm, including stage III [74].

With respect to surgical implications, a meta-analysis of neoadjuvant ICI trials showed a resection rate of 85.8% with an average surgical delay of 3.8–7.4% and a conversion rate (from minimally invasive to open) of 17.4% [75]. In the CheckMate 816 trial, patients who received a combination of chemotherapy and immunotherapy were more likely to have minimally invasive surgery (77%) and less likely to have pneumonectomies (17%) than those who only had chemotherapy (61% and 25%, respectively) [74].

3.3. Targeted Agents in the Perioperative Setting

In non-squamous NSCLC, the identification of targetable driver gene alterations with a significant impact on survival in the advanced stage has led to evaluating the use of targeted treatments with small molecule tyrosine kinase inhibitors (TKIs) in the perioperative setting (neo or adjuvant or combined), with different trials ongoing enrolling patients with EGFR or ALK positive tumors, but also ROS1, NTRK, and BRAF V600E [76–78]. To date, a paradigmatic change in the adjuvant setting resulted from the ADAURA trial, where patients with resected stage IB–IIIA (7th AJCC) NSCLC harboring EGFR common alterations (del19 or p.L858R) were randomized to receive osimertinib, an oral third generation EGFR TKI, or placebo for 3 years, after platinum-based chemotherapy, administered according to the physician's choice [76]. The trial reported a significant DFS improvement with osimertinib in the intention-to-treat population, with HR 0.23 (95% CI 0.18–0.30) in stage II–IIIA, primary endpoint population, and significantly lower incidence of CNS recurrence: CNS-DFS HR 0.24 in stage II–IIIA (95% CI 0.14–0.42) [77]. These data led to marketing authorization for treatment in the adjuvant setting for patients with stage IB–IIIA NSCLC harboring EGFR exon 19del or exon 21 p.L858R mutation. With specific respect to stage IIIA, the four-year DFS rate with osimertinib was 65% versus 14% with placebo (HR 0.20, 95% CI 0.14–0.29) [79]. Such results were obtained in resected stage IIIA patients who did not receive previous neoadjuvant treatment, thus suggesting the possibility to reconsider the indication of neoadjuvant chemotherapy in those patients with technically resectable N2 disease who are known to harbor del19 or L858R EGFR mutation, in order not to preclude such a valid post-surgical treatment option.

3.4. Unresectable Stage III Disease

The management of unresectable stage III NSCLC usually involves a combination of chemotherapy and radiation, with concurrent schedules being the preferred method when available. Recently, it has been approved to use immunotherapy consolidation with durvalumab administered for 12 months as an additional treatment. Indeed, in the phase III PACIFIC trial, 709 patients were randomized to receive durvalumab or placebo, every two weeks, for a period of up to 12 months [80]. The five-year rates for OS (42.9% versus 33.4%) and PFS (3.1% versus 19.0%) were higher with durvalumab than with the placebo. The benefit of the drug was seen, regardless of PD-L1. Furthermore, no extra toxicity (side-effects) was seen when taking durvalumab. However, based on a post hoc analysis, drug approval in Europe was only limited to people with tumors who were positive for PD-L1 ($\geq 1\%$) [81]. Several different approaches are being explored to further improve survival among patients with stage III NSCLC, and a comparison of the different results between trials is challenging because of how varied the delivery time for the ICIs can be, and also because of the different eligibility criteria for each trial. Additionally, the window for enrollment varied for each trial as well. As for resectable disease, targeted treatments with TKIs are being evaluated in unresectable stage III NSCLC with actionable genomic

alterations (e.g., osimertinib after definitive chemo-radiation in the LAURA trial) [82]. Future developments and the results of the different strategies that have been investigated will potentially further change the paradigm approach to stage III NSCLC [83].

4. Radiotherapy

Radiotherapy represents one of the mainstay treatments for patients with stage III NSCLC, although its role and timing differs depending on the extent and location of the disease [3,7].

For superior sulcus (Pancoast) tumors, Buderer et al., in a systematic review including 550 patients [84], showed that induction chemo-radiotherapy followed by surgery resulted in superior OS compared with radiotherapy followed by surgery or surgery alone (five-year OS ranging between 36.4 and 84%; 11 and 49%; and 20 and 30%, respectively). Two prospective trials confirmed this approach. In the Southwest Oncology Group Trial 9416 (Intergroup Trial 0160) [85], 111 patients were treated with concomitant neo-adjuvant chemotherapy (two cycles of cisplatin and etoposide) and radiotherapy (45 Gy in 25 fractions) followed by surgical resection and two additional cycles of adjuvant chemotherapy. The five-year OS rate was 44% for the whole population, increasing up to 54% after complete resection. The Japanese 9806 phase II prospective trial confirmed these results with a reported five-year DFS and OS rate of 45% and 56%, respectively [86].

For patients with potentially resectable N2-NSCLC disease, the use of neoadjuvant chemoradiotherapy was not associated with an OS or PFS benefit compared with induction chemotherapy alone, despite higher rates of mediastinal downstaging, complete pathologic response of mediastinal lymph nodes, and higher rates of R0 resections observed in patients receiving preoperative radiotherapy [18,87,88]. In the postoperative setting, two contemporary clinical trials failed to demonstrate a better outcome with postoperative radiotherapy (PORT) in patients with a completely resected NSCLC disease with mediastinal N2 involvement and who had received neoadjuvant or adjuvant platinum-based chemotherapy. In the Lung ART trial, 501 patients with completely resected NSCLC with pathologically proven N2 disease were randomly assigned to receive PORT (252 patients, 54 Gy in 27 to 30 fractions) or no PORT (249 patients). In this trial, 3-year DFS (47.1% vs. 43.8%) and OS (66.5% vs. 68.5%) rates were similar between patients treated with or without PORT, despite a lower rate of mediastinal relapse (46.1% vs. 25%). On the other hand, grade 3–4 pneumonitis (5% vs. <1%) and late cardiopulmonary toxicity (11% vs. 5%) were higher in patients treated with PORT compared with the control arm [89]. These findings were confirmed by the phase III PORT-C trial. No DFS or OS benefit was observed with PORT compared to the observation in 394 patients with pIIIA-N2 NSCLC who underwent complete resection and adjuvant platinum-based chemotherapy [90]. On the other hand, PORT may be considered in selected patients with positive surgical margins and extracapsular extension (both excluded in the Lung ART trial), based the potential OS benefit observed with PORT in this specific subpopulation [91].

As far as NSCLC patients with N2 unresectable or with N3 lymph nodes are concerned, definitive concurrent chemo-radiotherapy is the standard-of-care treatment, as demonstrated by the EORTC 08941 [22] and ESPATUE trials [58] and by a meta-analysis of six randomized trials [92]. A platin doublet with radiotherapy up to a total dose of 60 Gy should be offered to these patients [93,94], with consolidation therapy with durvalumab for up to 12 months in patients without disease progression, as per the PACIFIC trial [80,95]. Because of the high rates of local and regional recurrence after concurrent radio-chemotherapy, different strategies have been attempted in order to enhance the efficacy of radiotherapy treatments: increasing the total delivered dose [96–99], hypofractionation [100,101], boosting the dose in more active tumour areas [98,99], different dose levels depending on PET avidity [102,103], and hyperfractionation [104]. Despite these assumptions, the RTOG 0617 randomized phase III trial failed to demonstrate a benefit from dose escalation, showing worse outcome results with 74 Gy in 37 fractions of 2 Gy compared with the standard dose of 60 Gy in 30 fractions [105]. On the other hand, modern

radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) decreased the incidence of severe pneumonitis compared with conformational three-dimensional techniques (3.5% vs. 7.9%) and limited the doses delivered to the heart [89].

In poor-risk patients who are not candidates for standard combined-modality therapy, radiotherapy alone results in a median OS of 10 months only, with an estimated OS rate at 5-year of 5% [106–109]. Nevertheless, in this population, exclusive radiotherapy at doses ranging between 40 and 50 Gy provide a modest, but significant, survival advantage at one year compared with observation (18 vs. 14%) [110].

The number of patients and outcome data with confidence intervals, where available, are summarized in Table 2.

Table 2. Number of patients and outcome data with confidence intervals, for the included articles, where available.

| Article | Number of Patients | Outcome Data | 95% Confidence Intervals |
|------------------|----------------------|--|---------------------------|
| Goldstraw [3] | 8275 | ND | ND |
| Kim [45] | 2126 | 30-day mortality (right vs. left pneumonectomy) = 1.97 OR | 1.11–3.49 |
| Pignon [21] | 4584 (628 stage III) | Absolute effect of chemotherapy on OS (5.4% at 5 years). For stage III HR 0.83 | 0.72–0.94 (for stage III) |
| Felip [66] | 1280 | The stratified HR for DFS was 0.66 | 0.50–0.88 |
| Wakelee [67] | 1005 | When PD-L1 \geq 50% HR 0.43 | 0.26–0.71 |
| Forde [70] | 21 | The rate of recurrence-free survival at 18 months was 73% | 53–100 |
| Cascone [71] | 53 | The primary endpoint of MPR, was observed in 5/23 of patients in the nivolumab arm | 7–44 |
| Forde [74] | 358 | The median event-free survival was 31.6 months with nivolumab plus chemotherapy | Not reached |
| Jiang [75] | 988 | In patients treated by neo-adjuvant immunotherapy, resection rate of 85.8% with an average surgical delay 7.4% | NA |
| Tsuboi [76] | 224 | DFS improvement with osimertinib in the intention-to-treat population, HR 0.23 | 0.18–0.30 |
| Wu [77] | 682 | The 4-year DFS rate with osimertinib was 65% versus 14% with placebo; HR 0.20 | 0.14–0.29 |
| Faivre-Finn [80] | 709 | OS (HR = 0.71) PFS (HR = 0.55) | 0.57–0.88 0.44–0.67 |
| Buderi [84] | 550 | Induction chemo–radiotherapy followed by surgery, RT followed by surgery, and surgery alone resulted in 5-year OS ranging between 36.4–84%; 11–49%; 20–30%, respectively | NA |
| Rusch [85] | 110 | The 5-year OS rate was 44% for the whole population, 54% after complete resection | ND |
| Kunitoh [86] | 76 | The 5-year OS rate was 56% The 5-year PFS rate was 45% | ND |
| Le Pechoux [89] | 501 | The 3-year DFS was 47% with PORT versus 44% without PORT | 40–54 |

ND = not declared; NA = not applicable; OR = odds ratio; OS = overall survival; DFS = disease free survival; PFS = progression free survival; HR = hazard ratio; CI = confidence interval; MPR = major pathological regression.

5. Future Perspectives Offered by Imaging

In recent years, advances in imaging options have been applied to many oncologic imaging settings, including lung cancer [10,14,111–113]. Interesting new evidence and hints have indeed studied the possibility for the early identification of patients who may benefit from target therapies and immunotherapy, as well as to predict what patients will respond to therapies or will develop complications, through the use of artificial intelligence aided techniques. Artificial intelligence (AI) is an umbrella term encompassing any technique that enables computers to mimic human intelligence. Machine learning is part of artificial intelligence, and describes algorithms that self-improve after further exposure to data. Deep learning is a specific subtype of machine learning, mainly relying on convolutional neural network techniques [114]. Radiomics is an emerging translational field of research aiming to extract high-dimensional data from clinical images [115], that can rely on machine learning and deep learning techniques to help with the construction of meaningful predictive models. For example, Sun et al. aimed to develop and validate a radiomics-based biomarker of tumor-infiltrating CD8 cells in four cohorts of patients, including lung cancer patients, enrolled into clinical trials to undergo anti-programmed cell death protein (PD)-1 or anti-programmed cell death ligand 1 (PD-L1) monotherapy [116]. The authors demonstrated that in patients treated with anti-PD-1 and PD-L1, a high baseline radiomic score was associated with a higher proportion of patients who achieved an objective response at 3 months and a higher proportion of patients who had an objective response or stable disease at 6 months. A high baseline radiomic score was also associated with improved overall survival in univariate and multivariate analyses [116]. In another interesting study, Lou et al. aimed to identify radiation sensitivity parameters that can predict treatment failure and thus guide the individualization of radiotherapy dose [117]. To this end, they queried pre-therapy lung CT images into a multitask deep neural network that incorporates radiomics into the training process, and then combined these data with clinical variables. So, they derived an individualized radiation dose resulting in an estimation of failure probability below 5% at 24 months [117]. However, in their study, they included all stages of lung cancer, and it is not possible to derive specific data for lung cancer patients in stage III. Hosny et al. investigated the ability of deep learning networks to quantify radiographic lung cancer characteristics and to predict overall survival likelihood [118]. They designed a rigorous analytical setup with seven large and independent datasets of 1194 non-small-cell lung cancer patients staged I-IIIb, imaged by computed tomography across five institutions, to discover and validate the prognostic power of a convolutional neural network in patients treated with radiotherapy and surgery [118]. The authors demonstrated that in patients who were treated using surgery, deep learning networks significantly outperformed models based on predefined tumor features, as well as tumor volume and maximum diameter [119]. Furthermore, they demonstrated that the study of the areas around the tumor had the largest contributions to the prognostic signature [118]. In a specific group of 126 stage III lung cancer patients treated with radio-chemotherapy, Li et al. demonstrated that dual-omics features from different lung functional regions can improve the prediction of radiation pneumonitis [119]. Yoo et al. assessed a machine learning model that was able to predict pathological complete response after treatment with neoadjuvant chemoradiotherapy by analyzing the texture features from pre- and post-treatment PET-CT studies of patients with stage III non-small-cell lung cancer [120].

All of the abovementioned findings encourage further prospective studies validating their utility in lung cancer patient stratification and the development of personalized cancer treatment plans. In fact, while medical imaging has always provided an individual assessment of ailments, AI algorithms based on imaging biomarkers promise accurate patient stratifications and enable new research avenues for personalized healthcare. Although the use of AI to better understand and treat lung cancer patients has shown interesting results, some of which have been mentioned above, the implementation of these algorithms in clinical practice still faces obstacles, including mainly technical difficulties, the need for validation, and regulatory aspects. For instance, patient records exist in multiple forms, such

as free text, recorded speech, or medical images, and are rarely appropriately organized for computational analysis. The possibility to access large amounts of well-organized high-quality data is essential for the application of AI techniques in health care. Furthermore, stakeholders may not be willing to share data due to responsibilities related to personal privacy laws [121,122].

6. Final Considerations

The vast majority of clinical studies have only enrolled patients presenting performance status (PS) scores ranging from 0 to 1, with few patients with PS scores of 2 or higher; usually, patients presenting with a PS score of 3 or higher are excluded. For this reason, supportive care alone is usually recommended for patients with an advanced PS score. On the other hand, in daily clinical practice, approximately 25% of lung cancer patients present with a PS score of 3 or 4 at the beginning of treatment or attain scores between 3 and 4 during the course of therapy. Many patients with higher PS scores can be successfully treated using individualized anti-tumor treatment and additional life-support strategies. For example, patients diagnosed with early-stage NSCLC and suffering from other underlying cardiopulmonary comorbidities can be offered many advanced support technologies that may optimize preoperative assessment, intraoperative protection, and postoperative support.

Moreover, radiotherapy can be tailored in patients with concurrent severe comorbidities to pursue a radical approach in patients who cannot tolerate surgical resection in the early stages diseases, can be effectively combined with systemic treatment in locally advanced stages, and can be offered as a tailored palliative option in advanced stages to improve symptom management [123].

With regard to the risk factor assessment profile, the available findings for stage III NSCLC suggest that, on the whole, the distribution of risk factors at this stage is analogous to that for lung cancer (there is a high percentage of smokers (58%), while the percentage of never smokers is quite low, ranging from 4% to 11.1%) [124].

With respect to residential radon, there are no published studies on its distribution by stage at diagnosis [125].

7. Conclusions

Stage III lung cancer includes a heterogeneous group of patients with significant differences in terms of tumor volume, local diffusion, and lymphnodal involvement. Although the survival rate is still poor (13–36% according to the different subgroups), stage III NSCLC can be treated with a curative intent. For this reason, in these patients, a pivotal role relies on multimodal treatment, including surgery, radiotherapy, and multiple options of systemic treatments. Furthermore, surgeons, oncologists, radiotherapists, and radiologists may be willing to integrate machine learning tools into the clinical care of lung cancer patients, joining a digital revolution that will help to provide a consistent, timely, and personalized treatment strategy to eventually improve patient outcomes.

Author Contributions: Conceptualization, F.P., S.R., M.C. and I.A.; methodology, F.P., S.R., I.A., T.Z. and F.M.; software, F.P. and S.R.; validation, all authors.; formal analysis, not applicable; investigation, F.P., S.R., I.A., T.Z., F.M. and L.B.; resources, S.R.; data curation, F.P., S.R., I.A., A.P., M.C., T.Z. and F.M.; writing—original draft preparation, F.P., S.R., I.A. and T.Z.; writing—review and editing, all authors; visualization, F.P.; supervision, F.D.G., F.D.M. and L.S.; project administration, S.R.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)] [[PubMed](#)]
2. Ferro, A.; Sepulcri, M.; Schiavon, M.; Scagliori, E.; Mancin, E.; Lunardi, F.; Gennaro, G.; Frega, S.; Dal Maso, A.; Bonanno, L.; et al. The Multidisciplinary Approach in Stage III Non-Small Cell Lung Cancer over Ten Years: From Radiation Therapy Optimisation to Innovative Systemic Treatments. *Cancers* **2022**, *14*, 5700. [[CrossRef](#)] [[PubMed](#)]
3. Goldstraw, P.; Chansky, K.; Crowley, J.; Rami-Porta, R.; Asamura, H.; Eberhardt, W.E.; Nicholson, A.G.; Groome, P.; Mitchell, A.; Bolejack, V.; et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J. Thorac. Oncol.* **2016**, *11*, 39–51. [[CrossRef](#)] [[PubMed](#)]
4. Detterbeck, F.C.; Boffa, D.J.; Kim, A.W.; Tanoue, L.T. The Eighth Edition Lung Cancer Stage Classification. *Chest* **2017**, *151*, 193–203. [[CrossRef](#)]
5. Salgia, R.; Boehmer, L.M.; Celestin, C.; Yu, H.; Spigel, D.R. Improving Care for Patients With Stage III or IV NSCLC: Learnings for Multidisciplinary Teams From the ACCC National Quality Survey. *JCO Oncol. Pract.* **2021**, *17*, e1120–e1130. [[CrossRef](#)]
6. Kay, F.U.; Kandathil, A.; Batra, K.; Saboo, S.S.; Abbara, S.; Rajiah, P. Revisions to the Tumor, Node, Metastasis staging of lung cancer (8th edition): Rationale, radiologic findings and clinical implications. *World J. Radiol.* **2017**, *9*, 69–279. [[CrossRef](#)]
7. Ettinger, D.S.; Wood, D.E.; Aisner, D.L.; Akerley, W.; Bauman, J.R.; Bharat, A.; Bruno, D.S.; Chang, J.Y.; Chirieac, L.R.; D'Amico, T.A.; et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. *J. Natl. Compr. Cancer Netw.* **2021**, *19*, 254–266. [[CrossRef](#)]
8. Cassano, E.; Rizzo, S.; Bozzini, A.; Menna, S.; Bellomi, M. Contrast enhanced ultrasound of breast cancer. *Cancer Imaging* **2006**, *6*, 4–6. [[CrossRef](#)]
9. De Jong, E.C.; van Elmpt, W.; Rizzo, S.; Colarieti, A.; Spitaleri, G.; Leijenaar, R.T.; Jochems, A.; Hendriks, L.E.; Troost, E.G.; Reymen, B.; et al. Applicability of a prognostic CT-based radiomic signature model trained on stage I-III non-small cell lung cancer in stage IV non-small cell lung cancer. *Lung Cancer* **2018**, *124*, 6–11. [[CrossRef](#)]
10. Rizzo, S.M.; Kalra, M.K.; Schmidt, B.; Raupach, R.; Maher, M.M.; Blake, M.A.; Saini, S. CT images of abdomen and pelvis: Effect of nonlinear three-dimensional optimized reconstruction algorithm on image quality and lesion characteristics. *Radiology* **2005**, *237*, 309–315. [[CrossRef](#)]
11. Dalal, T.; Kalra, M.K.; Rizzo, S.M.; Schmidt, B.; Suess, C.; Flohr, T.; Blake, M.A.; Saini, S. Metallic prosthesis: Technique to avoid increase in CT radiation dose with automatic tube current modulation in a phantom and patients. *Radiology* **2005**, *236*, 671–675. [[CrossRef](#)]
12. Fanti, S.; Farsad, M.; Battista, G.; Monetti, F.; Montini, G.C.; Chiti, A.; Savelli, G.; Petrella, F.; Bini, A.; Nanni, C.; et al. Somatostatin receptor scintigraphy for bronchial carcinoid follow-up. *Clin. Nucl. Med.* **2003**, *28*, 548–552. [[CrossRef](#)]
13. Guarize, J.; Casiraghi, M.; Donghi, S.; Diotti, C.; Vanoni, N.; Romano, R.; Casadio, C.; Brambilla, D.; Maisonneuve, P.; Petrella, F.; et al. Endobronchial Ultrasound Transbronchial Needle Aspiration in Thoracic Diseases: Much More than Mediastinal Staging. *Can. Respir. J.* **2018**, *2018*, 4269798. [[CrossRef](#)]
14. Botta, F.; Raimondi, S.; Rinaldi, L.; Bellerba, F.; Corso, F.; Bagnardi, V.; Origgi, D.; Minelli, R.; Pitoni, G.; Petrella, F.; et al. Association of a CT-Based Clinical and Radiomics Score of Non-Small Cell Lung Cancer (NSCLC) with Lymph Node Status and Overall Survival. *Cancers* **2020**, *12*, 1432. [[CrossRef](#)]
15. Petrella, F.; Borri, A.; Casiraghi, M.; Cavaliere, S.; Donghi, S.; Galetta, D.; Gasparri, R.; Guarize, J.; Pardolesi, A.; Solli, P.; et al. Operative rigid bronchoscopy: Indications, basic techniques and results. *Multimed Man Cardiothorac. Surg.* **2014**, *2014*, mmu006. [[CrossRef](#)]
16. Shahraki Mojahed, B.; Saravani, K.; Parooie, F. Thoracic staging in patients with non-small cell lung cancer: A systematic review and meta-analysis on diagnostic accuracy of [18F]FDG PET/MRI and [18F]FDG PET/CT. *Nucl. Med. Rev. Cent. East Eur.* **2022**. *ahead of print.* [[CrossRef](#)]
17. Betticher, D.C.; Hsu Schmitz, S.F.; Tötsch, M.; Hansen, E.; Joss, C.; von Briel, C.; Schmid, R.A.; Pless, M.; Habicht, J.; Roth, A.D.; et al. Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. *Br. J. Cancer* **2006**, *94*, 1099–1106. [[CrossRef](#)]
18. Pless, M.; Stupp, R.; Ris, H.B.; Stahel, R.A.; Weder, W.; Thierstein, S.; Gerard, M.A.; Xyrafas, A.; Früh, M.; Cathomas, R.; et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: A phase 3 randomised trial. *Lancet* **2015**, *386*, 1049–1056. [[CrossRef](#)]
19. Schaake-Koning, C.; van den Bogaert, W.; Dalesio, O.; Festen, J.; Hoogenhout, J.; van Houtte, P.; Kirkpatrick, A.; Koolen, M.; Maat, B.; Nijs, A. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N. Engl. J. Med.* **1992**, *326*, 524–530. [[CrossRef](#)]
20. Albain, K.S.; Crowley, J.J.; Turrisi, A.T., 3rd; Gandara, D.R.; Farrar, W.B.; Clark, J.I.; Beasley, K.R.; Livingston, R.B. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group phase II study, SWOG 9019. *J. Clin. Oncol.* **2002**, *20*, 3454–3460. [[CrossRef](#)]

21. Pignon, J.P.; Tribodet, H.; Scagliotti, G.V.; Douillard, J.Y.; Shepherd, F.A.; Stephens, R.J.; Dunant, A.; Torri, V.; Rosell, R.; Seymour, L.; et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. *J. Clin. Oncol.* **2008**, *26*, 3552–3559. [[CrossRef](#)]
22. Eberhardt, W.E.; De Ruyscher, D.; Weder, W.; Le Péchoux, C.; De Leyn, P.; Hoffmann, H.; Westeel, V.; Stahel, R.; Felip, E.; Peters, S. 2nd ESMO Consensus Conference in Lung Cancer: Locally advanced stage III non-small-cell lung cancer. *Ann. Oncol.* **2015**, *26*, 1573–1588. [[CrossRef](#)] [[PubMed](#)]
23. Keller, S.M.; Adak, S.; Wagner, H.; Herskovic, A.; Komaki, R.; Brooks, B.J.; Perry, M.C.; Livingston, R.B.; Johnson, D.H. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N. Engl. J. Med.* **2000**, *343*, 1217–1222. [[CrossRef](#)]
24. van Meerbeeck, J.P.; Kramer, G.W.; Van Schil, P.E.; Legrand, C.; Smit, E.F.; Schramel, F.; Tjan-Heijnen, V.C.; Biesma, B.; Debruyne, C.; van Zandwijk, N.; et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J. Natl. Cancer Instig.* **2007**, *99*, 442–450. [[CrossRef](#)] [[PubMed](#)]
25. Roth, J.A.; Fossella, F.; Komaki, R.; Ryan, M.B.; Putnam, J.B.; Lee, J.S., Jr.; Dhingra, H.; De Caro, L.; Chasen, M.; McGavran, M. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J. Natl. Cancer Instig.* **1994**, *86*, 673–680. [[CrossRef](#)] [[PubMed](#)]
26. Rosell, R.; Gómez-Codina, J.; Camps, C.; Maestre, J.; Padille, J.; Cantó, A.; Mate, J.L.; Li, S.; Roig, J.; Olazábal, A. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N. Engl. J. Med.* **1994**, *330*, 153–158. [[CrossRef](#)]
27. Roth, J.A.; Atkinson, E.N.; Fossella, F.; Komaki, R.; Bernadette Ryan, M.; Putnam, J.B.; Lee, J.S., Jr.; Dhingra, H.; De Caro, L.; Chasen, M. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* **1998**, *21*, 673–680. [[CrossRef](#)]
28. Rosell, R.; Gómez-Codina, J.; Camps, C.; Javier Sánchez, J.; Maestre, J.; Padilla, J.; Cantó, A.; Abad, A.; Roig, J. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: A 7-year assessment of a randomized controlled trial. *Lung Cancer* **1999**, *26*, 7–14. [[CrossRef](#)]
29. Scagliotti, G.V.; Pastorino, U.; Vansteenkiste, J.F.; Spaggiari, L.; Facciolo, F.; Orłowski, T.M.; Maiorino, L.; Hetzel, M.; Leschinger, M.; Visseren-Grul, C.; et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. *J. Clin. Oncol.* **2012**, *30*, 172–178. [[CrossRef](#)]
30. Lorent, N.; De Leyn, P.; Lievens, Y.; Verbeken, E.; Nackaerts, K.; Dooms, C.; Van Raemdonck, D.; Anrys, B.; Vansteenkiste, J.; Leuven Lung Cancer Group. Long-term survival of surgically staged IIIA-N2 non-small-cell lung cancer treated with surgical combined modality approach: Analysis of a 7-year prospective experience. *Ann. Oncol.* **2004**, *15*, 1645–1653. [[CrossRef](#)]
31. Curran, W.J.; Paulus, R.; Langer, C.J.; Komaki, R.; Lee, J.S.; Hauser, S.; Movsas, B.; Wasserman, T.; Rosenthal, S.A.; Gore, E.; et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: Randomized phase III trial RTOG 9410. *J. Natl. Cancer Instig.* **2011**, *103*, 1452–1460. [[CrossRef](#)]
32. Eberhardt, W.; Wilke, H.; Stamatis, G.; Stuschke, M.; Harstrick, A.; Menker, H.; Krause, B.; Müller, M.R.; Stahl, M.; Fläschke, M.; et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: Mature results of a phase II trial. *J. Clin. Oncol.* **1998**, *16*, 622–634. [[CrossRef](#)]
33. Eberhardt, W.E.; Gauler, T.C.; Lepechoux, C.; Stamatis, G.; Bildat, S.; Krbek, T.; Welter, S.; Grunewald, D.; Fischer, B.; Rodrigo, H.d.L.; et al. 10-year long-term survival (LTS) of induction chemotherapy with three cycles cisplatin/paclitaxel followed by concurrent chemoradiation cisplatin/etoposide/45 Gy (1.5 Gy bid) plus surgery in locally advanced non-small-cell lung cancer (NSCLC)-a multicenter phase-II trial (CISTAXOL). *Lung Cancer* **2013**, *82*, 83–89.
34. Stamatis, G.; Eberhardt, W.; Stüben, G.; Bildat, S.; Dahler, O.; Hillejan, L. Preoperative chemoradiotherapy and surgery for selected non-small cell lung cancer IIIB subgroups: Long-term results. *Ann. Thorac. Surg.* **1999**, *68*, 1144–1149. [[CrossRef](#)]
35. Stupp, R.; Mayer, M.; Kann, R.; Weder, W.; Zouhair, A.; Betticher, D.C.; Roth, A.D.; Stahel, R.A.; Majno, S.B.; Peters, S.; et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in selected patients with stage IIIB non-small-cell lung cancer: A multicentre phase II trial. *Lancet Oncol.* **2009**, *10*, 785–793. [[CrossRef](#)]
36. Friedel, G.; Budach, W.; Dippon, J.; Spengler, W.; Eschmann, S.M.; Pfannenberger, C.; Al-Kamash, F.; Walles, T.; Aebert, H.; Kyriss, T.; et al. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: A single-center study. *J. Clin. Oncol.* **2010**, *28*, 942–948.
37. Kim, A.W.; Liptay, M.J.; Bonomi, P.; Warren, W.H.; Basu, S.; Farlow, E.C.; Faber, L.P. Neoadjuvant chemoradiation for clinically advanced non-small cell lung cancer: An analysis of 233 patients. *Ann. Thorac. Surg.* **2011**, *92*, 233–241. [[CrossRef](#)]
38. Seder, C.W.; Allen, M.S.; Cassivi, S.D.; Deschamps, C.; Nichols, F.C.; Olivier, K.R.; Shen, K.R.; Wigle, D.A. Stage IIIA non-small cell lung cancer: Morbidity and mortality of three distinct multimodality regimens. *Ann. Thorac. Surg.* **2013**, *95*, 1708–1716. [[CrossRef](#)]

39. Thomas, M.; Rube, C.; Hoffknecht, P.; Macha, H.N.; Freitag, L.; Linder, A.; Willich, N.; Hamm, M.; Sybrecht, G.W.; Ukena, D.; et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: A randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol.* **2008**, *9*, 636–648. [[CrossRef](#)]
40. Katakami, N.; Tada, H.; Mitsudomi, T.; Kudoh, S.; Senba, H.; Matsui, K.; Saka, H.; Kurata, T.; Nishimura, Y.; Fukuoka, M. A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903). *Cancer* **2012**, *118*, 6126–6135. [[CrossRef](#)]
41. Albain, K.S.; Swann, R.S.; Rusch, V.W.; Turrisi, A.T.; Shepherd, F.A., 3rd; Smith, C.; Chen, Y.; Livingston, R.B.; Feins, R.H.; Gandara, D.R.; et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. *Lancet* **2009**, *374*, 379–386. [[CrossRef](#)] [[PubMed](#)]
42. Weder, W.; Collaud, S.; Eberhardt, W.E.; Hillinger, S.; Welter, S.; Stahel, R.; Stamatis, G. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J. Thorac. Cardiovasc. Surg.* **2010**, *139*, 1424–1430. [[CrossRef](#)] [[PubMed](#)]
43. Kris, M.G.; Pisters, K.M.; Ginsberg, R.J.; Rigas, J.R.; Miller, V.A.; Grant, S.C.; Gralla, R.J.; Heelan, R.T.; Martini, N. Effectiveness and toxicity of preoperative therapy in stage IIIA non-small cell lung cancer including the Memorial Sloan-Kettering experience with induction MVP in patients with bulky mediastinal lymph node metastases (Clinical N2). *Lung Cancer* **1995**, *12* (Suppl. S1), S47–S57. [[CrossRef](#)] [[PubMed](#)]
44. Eichhorn, F.; Storz, K.; Hoffmann, H.; Muley, T.; Dienemann, H. Sleeve pneumonectomy for central non-small cell lung cancer: Indications, complications, and survival. *Ann. Thorac. Surg.* **2013**, *96*, 253–258. [[CrossRef](#)] [[PubMed](#)]
45. Kim, A.W.; Boffa, D.J.; Wang, Z.; Detterbeck, F.C. An analysis, systematic review, and meta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non-small cell lung cancer. *J. Thorac. Cardiovasc. Surg.* **2012**, *143*, 55–63. [[CrossRef](#)]
46. Maisonneuve, P.; Petrella, F.; Galetta, D.; Gasparri, R.; Spaggiari, L. Bronchopleural Fistula After Pneumonectomy: Risk Factors and Management, Focusing on Open-Window Thoracostomy. *Semin. Thorac. Cardiovasc. Surg.* **2018**, *30*, 104–113.
47. Pelosi, G.; Petrella, F.; Sandri, M.T.; Spaggiari, L.; Galetta, D.; Viale, G. A primary pure yolk sac tumor of the lung exhibiting CDX-2 immunoreactivity and increased serum levels of alkaline phosphatase intestinal isoenzyme. *Int. J. Surg. Pathol.* **2006**, *14*, 247–251. [[CrossRef](#)]
48. Pless, M.; Stupp, R.; Ris, H.-B.; Stahel, R.A.; Weder, W.; Thierstein, S.; Xyrafas, A.; Frueh, M.; Cathomas, R.; Zippelius, A.; et al. Neoadjuvant chemotherapy with or without preoperative irradiation in stage IIIA/N2 non-small cell lung cancer (NSCLC): A randomized phase III trial by the Swiss Group for Clinical Cancer Research (SAKK trial 16/00). *J. Clin. Oncol.* **2013**, *31*, 7503. [[CrossRef](#)]
49. Pless, M.; Stupp, R.; Ris, H.-B.; Stahel, R.A.; Weder, W.; Thierstein, S.; Xyrafas, A.; Früh, M.; Cathomas, R.; Zippelius, A.; et al. Final results of the SAKK 16/00 trial: A randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC). *Ann. Oncol.* **2014**, *25* (Suppl. S4), iv417. [[CrossRef](#)]
50. Spaggiari, L.; D’Aiuto, M.; Veronesi, G.; Leo, F.; Solli, P.; Elena Leon, M.; Gasparri, R.; Galetta, D.; Petrella, F.; Borri, A.; et al. Anterior approach for Pancoast tumor resection. *Multimed Man Cardiothorac. Surg.* **2007**, *2007*, mmcts.2005.001776. [[CrossRef](#)]
51. Spaggiari, L.; Tessitore, A.; Casiraghi, M.; Guarize, J.; Solli, P.; Borri, A.; Gasparri, R.; Petrella, F.; Maisonneuve, P.; Galetta, D. Survival after extended resection for mediastinal advanced lung cancer: Lessons learned on 167 consecutive cases. *Ann. Thorac. Surg.* **2013**, *95*, 1717–1725. [[CrossRef](#)]
52. Scanagatta, P.; Leo, F.; Veronesi, G.; Solli, P.; Gasparri, R.; Galetta, D.; Petrella, F.; Borri, A.; Spaggiari, L. Pneumocephalus after Pancoast’s tumor surgery: To be or not to be conservative? *J. Cardiovasc. Surg.* **2007**, *48*, 385–387.
53. Spaggiari, L.; Petrella, F.; Leo, F.; Veronesi, G.; Solli, P.; Borri, A.; Galetta, D.; Gasparri, R.; Scanagatta, P. Superior vena cava resection for lung and mediastinal malignancies. *Multimed Man Cardiothorac. Surg.* **2006**, *2006*, mmcts.2005.001511. [[CrossRef](#)]
54. Spaggiari, L.; Galetta, D.; Veronesi, G.; Leo, F.; Gasparri, R.; Petrella, F.; Borri, A.; Pelosi, G.; Venturino, M. Superior vena cava replacement for lung cancer using a heterologous (bovine) prosthesis: Preliminary results. *J. Thorac. Cardiovasc. Surg.* **2006**, *131*, 490–491. [[CrossRef](#)]
55. Spaggiari, L.; Leo, F.; Veronesi, G.; Solli, P.; Galetta, D.; Tatani, B.; Petrella, F.; Radice, D. Superior vena cava resection for lung and mediastinal malignancies: A single-center experience with 70 cases. *Ann. Thorac. Surg.* **2007**, *83*, 223–229. [[CrossRef](#)]
56. Borri, A.; Leo, F.; Veronesi, G.; Solli, P.; Galetta, D.; Gasparri, R.; Petrella, F.; Scanagatta, P.; Radice, D.; Spaggiari, L. Extended pneumonectomy for non-small cell lung cancer: Morbidity, mortality, and long-term results. *J. Thorac. Cardiovasc. Surg.* **2007**, *134*, 1266–1272. [[CrossRef](#)]
57. Casiraghi, M.; Maisonneuve, P.; Piperno, G.; Bellini, R.; Brambilla, D.; Petrella, F.; Marinis, F.; Spaggiari, L. Salvage Surgery After Definitive Chemoradiotherapy for Non-small Cell Lung Cancer. *Semin Thorac. Cardiovasc. Surg.* **2017**, *29*, 233–241. [[CrossRef](#)]
58. Eberhardt, W.E.; Pöttgen, C.; Gauler, T.C.; Friedel, G.; Veit, S.; Heinrich, V.; Welter, S.; Budach, W.; Spengler, W.; Kimmich, M.; 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 (ESPA-TUE). *J. Clin. Oncol.* **2015**, *33*, 4194–4201. [[CrossRef](#)]

59. Spaggiari, L.; Petrella, F.; Galetta, D. Carinal resection. *Multimed Man Cardiothorac Surg.* **2012**, *2012*, mms001. [[CrossRef](#)]
60. Spaggiari, L.; Sedda, G.; Petrella, F.; Venturino, M.; Rossi, F.; Guarize, J.; Galetta, D.; Casiraghi, M.; Iacono, G.L.; Bertolaccini, L.; et al. Preliminary Results of Extracorporeal Membrane Oxygenation Assisted Tracheal Sleeve Pneumonectomy for Cancer. *Thorac. Cardiovasc. Surg.* **2021**, *69*, 240–245. [[CrossRef](#)]
61. Mazzella, A.; Bertolaccini, L.; Petrella, F.; Spaggiari, L. Venovenous extra-corporeal membrane oxygenation-assisted right tracheal-sleeve pneumonectomy. *Interact. Cardiovasc. Thorac. Surg.* **2021**, *33*, 49–651. [[CrossRef](#)] [[PubMed](#)]
62. Postmus, P.E.; Kerr, K.M.; Oudkerk, M.; Senan, S.; Waller, D.A.; Vansteenkiste, J.; Escriu, C.; Peters, S.; 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*, iv1–iv21. [[CrossRef](#)] [[PubMed](#)]
63. Steuer, C.E.; Behera, M.; Ernani, V.; Higgins, K.A.; Saba, N.F.; Shin, D.M.; Pakkala, S.; Pillai, R.N.; Owonikoko, T.K.; Curran, W.J.; et al. Comparison of Concurrent Use of Thoracic Radiation With Either Carboplatin-Paclitaxel or Cisplatin-Etoposide for Patients With Stage III Non-Small-Cell Lung Cancer: A Systematic Review. *JAMA Oncol.* **2017**, *3*, 1120–1129. [[CrossRef](#)]
64. Passaro, A.; Attili, I.; de Marinis, F. Neoadjuvant Chemotherapy Plus Immunotherapy in Early-Stage Resectable Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* **2022**, *40*, 2871–2877. [[CrossRef](#)] [[PubMed](#)]
65. Jazieh, A.R.; Zeitouni, M.; Alghamdi, M.; Alrujaib, M.; Lotfi, S.; Abu Daff, S.; Alomair, A.; Alshehri, S.; Alhusaini, H.; Allehebi, A.; et al. Management guidelines for stage III non-small cell lung cancer. *Crit. Rev. Oncol. Hematol.* **2021**, *157*, 103144. [[CrossRef](#)]
66. Felip, E.; Altorki, N.; Zhou, C.; Csőszi, T.; Vynnychenko, I.; Goloborodko, O.; Luft, A.; Akopov, A.; Martinez-Marti, A.; Kenmotsu, H.; et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. *Lancet* **2021**, *398*, 1344–1357. [[CrossRef](#)]
67. Wakelee, H.; Altorki, N.; Felip, E.; Vallieres, E.; Vynnychenko, I.O.; Akopov, A.; Martinez-Marti, A.; Chella, A.; Bondarenko, I.; Sugawara, S.; et al. PL03.09 IMpower010: Overall Survival Interim Analysis of a Phase III Study of Atezolizumab vs Best Supportive Care in Resected NSCLC. *J. Thorac. Oncol.* **2022**, *17*, S2. [[CrossRef](#)]
68. O'Brien, M.; Paz-Ares, L.; Marreaud, S.; Dafni, U.; Oselin, K.; Havel, L.; Esteban, E.; Isla, D.; Martinez-Marti, A.; Faehling, M.; et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): An interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol.* **2022**, *10*, 1274–1286. [[CrossRef](#)]
69. Cascone, T.; Hamdi, H.; Zhang, F.; Poteete, A.; Li, L.; Hudgens, C.W.; Williams, L.J.; Wu, Q.; Gudikote, J.; Peng, W.; et al. Abstract 1719: Superior efficacy of neoadjuvant compared to adjuvant immune checkpoint blockade in non-small cell lung cancer. *Cancer Res.* **2018**, *78*, 1719. [[CrossRef](#)]
70. Forde, P.M.; Chaft, J.E.; Smith, K.N.; Anagnostou, V.; Cottrell, T.R.; Hellmann, M.D.; Zahurak, M.; Yang, S.C.; Jones, D.R.; Broderick, S.; et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *N. Engl. J. Med.* **2018**, *378*, 1976–1986. [[CrossRef](#)]
71. Cascone, T.; William, W.N.; Weissferdt, A., Jr.; Leung, C.H.; Lin, H.Y.; Pataer, A.; Godoy, M.C.B.; Carter, B.W.; Federico, L.; Reuben, A.; et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: The phase 2 randomized NEOSTAR trial. *Nat. Med.* **2021**, *27*, 504–514. [[CrossRef](#)]
72. Reuss, J.E.; Anagnostou, V.; Cottrell, T.R.; Smith, K.N.; Verde, F.; Zahurak, M.; Lanis, M.; Murray, J.C.; Chan, H.Y.; McCarthy, C.; et al. Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer. *J. Immunother Cancer* **2020**, *8*, e001282. [[CrossRef](#)]
73. Provencio, M.; Nadal, E.; Insa, A.; García-Campelo, M.R.; Casal-Rubio, J.; Dómine, M.; Majem, M.; Rodríguez-Abreu, D.; Martínez-Martí, A.; De Castro Carpeño, J.; et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): An open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol.* **2020**, *21*, 1413–1422. [[CrossRef](#)]
74. Forde, P.M.; Spicer, J.; Lu, S.; Provencio, M.; Mitsudomi, T.; Awad, M.M.; Felip, E.; Broderick, S.R.; Brahmer, J.R.; Swanson, S.J.; et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N. Engl. J. Med.* **2022**, *386*, 1973–1985. [[CrossRef](#)]
75. Leal, T.A.; Ramalingam, S.S. Neoadjuvant therapy gains FDA approval in non-small cell lung cancer. *Cell Rep. Med.* **2022**, *3*, 100691. [[CrossRef](#)]
76. Jiang, J.; Wang, Y.; Gao, Y.; Sugimura, H.; Minervini, F.; Uchino, J.; Halmos, B.; Yendamuri, S.; Velotta, J.B.; Li, M. Neoadjuvant immunotherapy or chemoimmunotherapy in non-small cell lung cancer: A systematic review and meta-analysis. *Transl. Lung Cancer Res.* **2022**, *11*, 277–294. [[CrossRef](#)]
77. Tsuboi, M.; Weder, W.; Escriu, C.; Blakely, C.; He, J.; Dacic, S.; Yatabe, Y.; Zeng, L.; Walding, A.; Chaft, J.E. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. *Future Oncol.* **2021**, *31*, 4045–4055. [[CrossRef](#)]
78. Solomon, B.J.; Ahn, J.S.; Barlesi, F.; Dziadziuszko, R.; Nishio, M.; Shaw, A.T. ALINA: A phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* **2019**, *37*, 15. [[CrossRef](#)]
79. Lee, J.; Wistuba, I.; Ngiam, C.; Yu, W.; Katja Schulze, K.; Rocha, M.; Ilze Bara, I.; Carbone, D.P.; Johnson, B.E.; David, J.; et al. P03.04 Phase II Study of TKIs as Neo(adjuvant) Therapy in Stage II–III Resectable NSCLC with ALK, ROS1, NTRK or BRAFV600 Alterations. *J. Thor. Oncol.* **2020**, *16*, S259–S260. [[CrossRef](#)]

80. Wu, Y.L.; Tsuboi, M.; He, J. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2020**, *29*, 1711–1723. [[CrossRef](#)]
81. Faivre-Finn, C.; Vicente, D.; Kurata, T.; Planchard, D.; Paz-Ares, L.; Vansteenkiste, J.F.; Spigel, D.R.; Garassino, M.C.; Reck, M.; Senan, S.; et al. Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial. *J. Thorac. Oncol.* **2021**, *16*, 860–867. [[CrossRef](#)] [[PubMed](#)]
82. Antonia, S.J.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Yokoi, T.; Chiappori, A.; Lee, K.H.; de Wit, M.; et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2017**, *377*, 1919–1929. [[CrossRef](#)] [[PubMed](#)]
83. Lu, S.; Casarini, I.; Kato, T.; Cobo, M.; Özgüroğlu, M.; Hodge, R.; van der Gronde, T.; Saggese, M.; Ramalingam, S.S. Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non-small-cell Lung Cancer: LAURA Trial in Progress. *Clin. Lung Cancer* **2021**, *22*, 371–375. [[CrossRef](#)] [[PubMed](#)]
84. Petrella, F.; Coccè, V.; Masia, C.; Milani, M.; Salè, E.O.; Alessandri, G.; Parati, E.; Sisto, F.; Pentimalli, F.; Brini, A.T.; et al. Paclitaxel-releasing mesenchymal stromal cells inhibit in vitro proliferation of human mesothelioma cells. *Biomed. Pharm.* **2017**, *87*, 755–758. [[CrossRef](#)] [[PubMed](#)]
85. Buderer, S.I.; Shackcloth, M.; Woolley, S. Does induction chemoradiotherapy increase survival in patients with Pancoast tumour? *Interact. Cardiovasc. Thorac. Surg.* **2016**, *23*, 821. [[CrossRef](#)]
86. Rusch, V.W.; Giroux, D.J.; Kraut, M.J.; Crowley, J.; Hazuka, M.; Winton, T.; Johnson, D.H.; Shulman, L.; Shepherd, F.; Deschamps, C.; et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: Long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J. Clin. Oncol.* **2007**, *25*, 313–318. [[CrossRef](#)]
87. Kunitoh, H.; Kato, H.; Tsuboi, M.; Shibata, T.; Asamura, H.; Ichinose, Y.; Katakami, N.; Nagai, K.; Mitsudomi, T.; Matsumura, A.; et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: Report of Japan Clinical Oncology Group trial 9806. *J. Clin. Oncol.* **2008**, *26*, 644. [[CrossRef](#)]
88. Pourel, N.; Santelmo, N.; Naafa, N.; Serre, A.; Hilgers, W.; Mineur, L.; Molinari, N.; Reboul, F. Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate of pathological complete response. *Eur. J. Cardiothorac. Surg.* **2008**, *33*, 829. [[CrossRef](#)]
89. Chen, Y.; Peng, X.; Zhou, Y.; Xia, K.; Zhuang, W. Comparing the benefits of chemoradiotherapy and chemotherapy for resectable stage III A/N2 non-small cell lung cancer: A meta-analysis. *World J. Surg. Oncol.* **2018**, *16*, 8. [[CrossRef](#)]
90. Le Pechoux, C.; Pourel, N.; Barlesi, F.; Lerouge, D.; Antoni, D.; Lamezec, B.; Nestle, U.; Boisselier, P.; Dansin, E.; Paumier, A.; et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): An open-label, randomised, phase 3 trial. *Lancet Oncol.* **2022**, *23*, 104–114. [[CrossRef](#)]
91. Hui, Z.; Men, Y.; Hu, C.; Kang, J.; Sun, X.; Bi, N.; Zhou, Z.; Liang, J.; Lv, J.; Feng, Q.; et al. Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non-Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy: The Phase 3 PORT-C Randomized Clinical Trial. *JAMA Oncol.* **2021**, *7*, 1178. [[CrossRef](#)]
92. Wang, E.H.; Corso, C.D.; Rutter, C.E.; Park, H.S.; Chen, A.B.; Kim, A.W.; Wilson, L.D.; Decker, R.H.; Yu, J.B. Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* **2015**, *33*, 2727. [[CrossRef](#)]
93. Aupérin, A.; Le Péchoux, C.; Rolland, E.; Curran, W.J.; Furuse, K.; Fournel, P.; Belderbos, J.; Clamon, G.; Ulutin, H.C.; Paulus, R.; et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J. Clin. Oncol.* **2010**, *28*, 2181. [[CrossRef](#)]
94. Perez, C.A.; Pajak, T.F.; Rubin, P.; Simpson, J.R.; Mohiuddin, M.; Brady, L.W.; Perez-Tamayo, R.; Rotman, M. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* **1987**, *59*, 1874–1881. [[CrossRef](#)]
95. Perez, C.A.; Stanley, K.; Rubin, P.; Kramer, S.; Brady, L.; Perez-Tamayo, R.; Brown, G.S.; Concannon, J.; Rotman, M.; Seydel, H.G. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable nonoat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer* **1980**, *45*, 2744–2753. [[CrossRef](#)]
96. Schild, S.E.; Stella, P.J.; Geyer, S.M.; Bonner, J.A.; Marks, R.S.; McGinnis, W.L.; Goetz, S.P.; Kuross, S.A.; Mailliard, J.A.; Kugler, J.W.; et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2002**, *54*, 370–378. [[CrossRef](#)]
97. Bradley, J.D.; Paulus, R.; Komaki, R.; Masters, G.; Blumenschein, G.; Schild, S.; Bogart, J.; Hu, C.; Forster, K.; Magliocco, A.; et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* **2015**, *16*, 187–199.
98. Bradley, J.; Graham, M.V.; Winter, K.; Purdy, J.A.; Komaki, R.; Roa, W.H.; Ryu, J.K.; Bosch, W.; Emami, B. Toxicity and outcome results of RTOG 9311: A phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* **2005**, *61*, 318–328. [[CrossRef](#)]

99. Sun, L.M.; Leung, S.W.; Wang, C.J.; Chen, H.C.; Fang, F.M.; Huang, E.Y.; Hsu, H.C.; Yeh, S.A.; Hsiung, C.Y.; Huang, D.T. Concomitant boost radiation therapy for inoperable non-small-cell lung cancer: Preliminary report of a prospective randomized study. *Int. J. Radiat. Oncol. Biol. Phys.* **2000**, *47*, 413–418. [[CrossRef](#)]
100. Socinski, M.A.; Morris, D.E.; Halle, J.S.; Moore, D.T.; Hensing, T.A.; Limentani, S.A.; Fraser, R.; Tynan, M.; Mears, A.; Rivera, M.P.; et al. Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: A dose-escalation phase I trial. *J. Clin. Oncol.* **2004**, *22*, 4341–4350. [[CrossRef](#)]
101. Iyengar, P.; Zhang-Velten, E.; Court, L.; Westover, K.; Yan, Y.; Lin, M.H.; Xiong, Z.; Patel, M.; Rivera, D.; Chang, J.; et al. Accelerated hypofractionated image-guided vs conventional radiotherapy for patients with stage II/III non-small cell lung cancer and poor performance status: A randomized clinical trial. *JAMA Oncol.* **2021**, *7*, 1497–1505. [[CrossRef](#)] [[PubMed](#)]
102. Hoppe, B.S.; Nichols, R.C.; Flampouri, S.; Li, Z.; Morris, C.G.; Pham, D.C.; Mohindra, P.; Hartsell, W.; Mohammed, N.; Chon, B.H.; et al. Hypofractionated proton therapy with concurrent chemotherapy for locally advanced non-small cell lung cancer: A phase 1 trial from the University of Florida and Proton collaborative Group. *Int. J. Radiat. Oncol. Biol. Phys.* **2020**, *107*, 455–461. [[CrossRef](#)] [[PubMed](#)]
103. Van Diessen, J.; De Ruyscher, D.; Sonke, J.J.; Damen, E.; Sikorska, K.; Reymen, B.; van Elmpt, W.; Westman, G.; Fredberg Persson, G.; Dieleman, E.; et al. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial). *Radiother. Oncol.* **2019**, *131*, 166–173. [[CrossRef](#)] [[PubMed](#)]
104. Van Elmpt, W.; De Ruyscher, D.; van der Salm, A.; Lakeman, A.; van der Stoep, J.; Emans, D.; Damen, E.; Öllers, M.; Sonke, J.J.; Belderbos, J. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother. Oncol.* **2012**, *104*, 67–71. [[CrossRef](#)]
105. Cox, J.D.; Azarnia, N.; Byhardt, R.W.; Shin, K.H.; Emami, B.; Perez, C.A. N2 (clinical) non-small cell carcinoma of the lung: Prospective trials of radiation therapy with total doses 60 Gy by the Radiation Therapy Oncology Group. *Int. J. Radiat. Oncol. Biol. Phys.* **1991**, *20*, 7–12. [[CrossRef](#)]
106. Bradley, J.D.; Hu, C.; Komaki, R.R.; Masters, G.A.; Blumenschein, G.R.; Schild, S.E.; Bogart, J.A.; Forster, K.M.; Magliocco, A.M.; Kavadi, V.S.; et al. Long-term results of NRG Oncology RTOG 0617: Standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J. Clin. Oncol.* **2020**, *38*, 706–714. [[CrossRef](#)]
107. Dillman, R.O.; Herndon, J.; Seagren, S.L.; Eaton, W.L.; Green, M.R., Jr. Improved survival in stage III non-small-cell lung cancer: Seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J. Natl. Cancer Instig.* **1996**, *88*, 1210. [[CrossRef](#)]
108. Sause, W.T.; Scott, C.; Taylor, S.; Johnson, D.; Livingston, R.; Komaki, R.; Emami, B.; Curran, W.J.; Byhardt, R.W.; Turrisi, A.T. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J. Natl. Cancer Instig.* **1995**, *87*, 198. [[CrossRef](#)]
109. Johnson, D.H.; Einhorn, L.H.; Bartolucci, A.; Birch, R.; Omura, G.; Perez, C.A.; Greco, F.A. Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. *Ann. Intern. Med.* **1990**, *113*, 33. [[CrossRef](#)]
110. Basaki, K.; Abe, Y.; Aoki, M.; Kondo, H.; Hatayama, Y.; Nakaji, S. Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: Impact of tumor volume. *Int. J. Radiat. Oncol. Biol. Phys.* **2006**, *64*, 449. [[CrossRef](#)]
111. Roswit, B.; Patno, M.E.; Rapp, R.; Veinbergs, A.; Feder, B.; Stuhlbarg, J.; Reid, C.B. The survival of patients with inoperable lung cancer: A large-scale randomized study of radiation therapy versus placebo. *Radiology* **1968**, *90*, 688. [[CrossRef](#)]
112. Rizzo, S.; Manganaro, L.; Dolciami, M.; Gasparri, M.L.; Papadia, A.; Del Grande, F. Computed Tomography Based Radiomics as a Predictor of Survival in Ovarian Cancer Patients: A Systematic Review. *Cancers* **2021**, *13*, 573. [[CrossRef](#)]
113. Rietjens, M.; Villa, G.; Toesca, A.; Rizzo, S.; Raimondi, S.; Rossetto, F.; Sangalli, C.; De Lorenzi, F.; Manconi, A.; Matthes, A.G.Z.; et al. Appropriate use of magnetic resonance imaging and ultrasound to detect early silicone gel breast implant rupture in postmastectomy reconstruction. *Plast. Reconstr. Surg.* **2014**, *134*, 13e–20e. [[CrossRef](#)]
114. Aletti, G.D.; Garbi, A.; Messori, P.; Achillarre, M.T.; Zanagnolo, V.; Rizzo, S.; Alessi, S.; Bociolone, L.; Landoni, F.; Biffi, R.; et al. Multidisciplinary approach in the management of advanced ovarian cancer patients: A personalized approach. Results from a specialized ovarian cancer unit. *Gynecol. Oncol.* **2017**, *144*, 468–473. [[CrossRef](#)]
115. Weikert, T.; Cyriac, J.; Yang, S.; Nesic, I.; Parmar, V.; Stieltjes, B. A Practical Guide to Artificial Intelligence-Based Image Analysis in Radiology. *Investig. Radiol.* **2020**, *55*, 1–7. [[CrossRef](#)]
116. Rizzo, S.; Botta, F.; Raimondi, S.; Origi, D.; Fanciullo, C.; Morganti, A.G.; Bellomi, M. Radiomics: The facts and the challenges of image analysis. *Eur. Radiol. Exp.* **2018**, *14*, 36. [[CrossRef](#)]
117. Sun, R.; Limkin, E.J.; Vakalopoulou, M.; Dercle, L.; Champiat, S.; Han, S.R.; Verlingue, L.; Brandao, D.; Lancia, A.; Ammari, S.; et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: An imaging biomarker, retrospective multicohort study. *Lancet Oncol.* **2018**, *19*, 1180–1191. [[CrossRef](#)]
118. Lou, B.; Doken, S.; Zhuang, T.; Wingerter, D.; Gidwani, M.; Mistry, N.; Ladic, L.; Kamen, A.; Abazeed, M.E. An image-based deep learning framework for individualizing radiotherapy dose. *Lancet Digit Health* **2019**, *1*, e136–e147. [[CrossRef](#)]
119. Hosny, A.; Parmar, C.; Coroller, T.P.; Grossmann, P.; Zeleznik, R.; Kumar, A.; Bussink, J.; Gillies, R.J.; Mak, R.H.; Aerts, H.J. Deep learning for lung cancer prognostication: A retrospective multi-cohort radiomics study. *PLoS Med.* **2018**, *15*, e1002711. [[CrossRef](#)]
120. Li, B.; Ren, G.; Guo, W.; Zhang, J.; Lam, S.K.; Zheng, X.; Teng, X.; Wang, Y.; Yang, Y.; Dan, Q.; et al. Function-Wise Dual-Omics analysis for radiation pneumonitis prediction in lung cancer patients. *Front. Pharmacol.* **2022**, *13*, 971849. [[CrossRef](#)]

121. Yoo, J.; Lee, J.; Cheon, M.; Woo, S.K.; Ahn, M.J.; Pyo, H.R.; Choi, Y.S.; Han, J.H.; Choi, J.Y. Predictive Value of 18F-FDG PET/CT Using Machine Learning for Pathological Response to Neoadjuvant Concurrent Chemoradiotherapy in Patients with Stage III Non-Small Cell Lung Cancer. *Cancers* **2022**, *14*, 1987. [[CrossRef](#)] [[PubMed](#)]
122. Rabbani, M.; Kanevsky, J.; Kafi, K.; Chandelier, F.; Giles, F.J. Role of artificial intelligence in the care of patients with nonsmall cell lung cancer. *Eur. J. Clin. Investig.* **2018**, *48*, e12901. [[CrossRef](#)] [[PubMed](#)]
123. Auffray, C.; Balling, R.; Barroso, I.; Bencze, L.; Benson, M.; Bergeron, J.; Bernal-Delgado, E.; Blomberg, N.; Bock, C.; Conesa, A.; et al. Making sense of big data in health research: Towards an EU action plan. *Genome Med.* **2016**, *8*, 71. [[CrossRef](#)] [[PubMed](#)]
124. Zhou, C.; Li, S.; Liu, J.; Chu, Q.; Miao, L.; Cai, L.; Cai, X.; Chen, Y.; Cui, F.; Dong, Y.; et al. International consensus on severe lung cancer-the first edition. *Transl. Lung Cancer Res.* **2021**, *10*, 2633–2666. [[CrossRef](#)]
125. Khuder, S.A. Effect of cigarette smoking on major histological types of lung cancer: A meta-analysis. *Lung Cancer* **2001**, *31*, 139–148. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.