Perioperative management of resectable non small cell lung cancer

Kastelik JA MD, Alwadaei SM

Department of Respiratory Medicine, Hull University Teaching Hospitals NHS Trust, University of Hull and Hull York Medical School, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire HU16 5JQ, UK

Corresponding Author:
Professor Jack Kastelik: jack.kastelik@nhs.net

Lung cancer is very common with around 18% cancer related death worldwide. The treatment options of lung cancer depend on its stage, patients' fitness, histological types and molecular profile composition. Early stages of lung cancer including stage I and stage II are potentially resectable i.e. can be surgically removed. Some stage III cases of lung cancer may also be considered for surgery. Medical operability refers to a patient fitness for surgery for resection of lung cancer. There are a number of factors which may affect it. The main issues that determine operability are patients' fitness including performance level, co-morbidities and pulmonary and cardiac physiological status. The pulmonary physiology is assessed by pulmonary function testing and cardiopulmonary exercise testing. Surgical resectability is defined as the ability to undertake a complete resection of the lung cancer and affected lymph nodes [1]. This is assessed by using a combination of radiological imaging such as computed tomography (CT) scan and Position Emission tomography (PET) scanning and other radiological imaging techniques when required. In addition, histological staging for example using endobronchial ultrasound for mediastinal sampling may be required. In the context of stage III lung cancer there are option of non surgical management in the form of chemoradiotherapy followed by durvalumab or osimertinib [2, 3]. Historically neoadjuvant or adjuvant platinum based chemotherapy showed some promising results with improvement

in overall survival for non small cell lung cancer of around 5% [4]. There is also there is evidence that post operative radiotherapy (PORT) can reduce locoregional recurrence [5].

The R0 resection is the main aim of the surgical treatment and is defined as microscopic resection margin free of cancer, systematic nodal dissection, absence of extracapsular lymph node metastasis, and cancer-free in the highest mediastinal lymph node station [6]. However, in the context of non small cell lung cancer in patients who received curative resection there is a 30 to 55% risk of recurrence [7]. There have been significant developments in therapeutic options for non small cell lung cancer with immune checkpoint inhibitors and targeted therapies. The identifications of specific biomarkers such as such as programmed death ligand 1 (PDL1) levels, epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) and Proto-oncogene tyrosine-protein kinase 1 (ROS1) rearrangements, Kirsten rat sarcoma virus oncogene homologue KRAS G12C mutations allows for the use of targeted therapies in order to improve patients' outcomes [8]. These developments have also been of importance in the context of the resectable lung cancer in the form of perioperative management including after surgery adjuvant and before surgery neoadjuvant treatments [9]. Preoperative approaches can be used for borderline operable patients as well as operable patients. However, it is important to note that micro-metastases have long been known to occur in lung cancer malignancies [1]. There are new techniques that can be used to assess for possible micro-metastases. Circulating tumour cell analysis can assist in the detection of micro-metastases. Measurements of circulating DNA (ctDNA) analysis is gaining significance in perioperative management [10].

The of adjuvant treatment of non small cell lung cancer has been implemented for some time now. For non small cell lung cancer The LACE meta-analysis (Lung Adjuvant Cisplatin Evaluation) showed a 5.4% improvement in survival at 5 years in patients treated with cisplatin-based adjuvant chemotherapy [11]. Adjuvant platinum-based chemotherapy is established as the standard of care for completely resected stages IB to IIIA NSCLC. There have also been studies assessing the effectiveness of immunotherapy in adjuvant settings of non small cell lung cancer but the results have not provided the definitive answers so far [12]. More recently a perioperative approach has been assessed. The perioperative approach involves pre surgical systemic anticancer treatment followed by surgery and then a post surgical systemic anticancer treatment.

The CheckMate-816 study was the initial study assessing preoperative immunotherapy nivolumab with chemotherapy in patients with non small cell lung cancer [13]. This study assessed combination of PD-1 inhibitor nivolumab and platinum based chemotherapy in patients with resectable non small cell lung cancer. The results showed that addition of nivolumab to platinum based hemotherapy resulted in a higher objective response rate of 53.6% [13]. This was more apparent in patients who were age less than 65 years and had a PDL-1 expression of 50% or more. Moreover, the percentage of clearance of ctDNA was higher in patients who received nivolumab and platinum based chemotherapy. Based on the findings the guidelines recommend a combination of nivolumab and chemotherapy in

patients with non small cell lung cancer of size of 4 cm or more or those with mediastinal nodal disease [14, 15].

KEYNOTE-671 assessed the role of PD-1 inhibitor pembrolizumab in combination with chemotherapy before surgery followed by pembrolizumab after surgery. The results showed neoadjuvant pembrolizumab and chemotherapy followed by surgical resection and adjuvant pembrolizumab significantly improved event-free survival, major pathological response, and pathological complete response as compared with neoadjuvant chemotherapy alone followed by surgery [14]. For example, the Checkmate-77T study compared in patients with resectable stage IIA to IIIB non small cell lung cancer, with no EGFR mutation and no KRAS translocation, neoadjuvant nivolumab plus chemotherapy with neoadjuvant chemotherapy plus placebo, followed by surgery and adjuvant nivolumab or placebo for 1 year [17]. A pathological complete response occurred in 25.3% of the patients in the nivolumab group. Pathological complete response (pCR) can be defined as the lack of detection of malignant cells in the surgical specimen after neoadjuvant treatment. Major pathological response defined as less than 10% of viable cancer on the pathological specimen. There was also a significantly longer event-free survival in nivolumab group compared with chemotherapy group [17]. In another study patients with resectable non small cell lung cancer stages II to IIIB including N2 nodal disease received platinum-based chemotherapy and durvalumab or placebo. The study showed that perioperative durvalumab plus neoadjuvant chemotherapy was associated with significantly greater event-free survival and pathological complete response than neoadjuvant chemotherapy alone [18]. In the NADIM II trial, perioperative

nivolumab was shown to have a significant improvement in pathological complete response and in progression-free and overall survival in comparison to chemotherapy alone, in patients with stage IIIA or IIIB resectable non small cell lung cancer [19]. The Neotorch study revealed that addition of toripalimab to perioperative chemotherapy showed statistically significant improvements in event free survival or patients with stage III NSCLC (20). In the AEGEAN, KEYNOTE-671, and Neotorch trials, the percentage of patients who received perioperative (durvalumab, pembrolizumab, and toripalimab) immunotherapy and chemotherapy had a pathological complete response between 17.2 to 24.8% [14, 18, 20]. In CheckMate 77T, a pathological complete response occurred in approximately 5 times as many patients in the nivolumab group as in the chemotherapy group [17]. A quarter of patients showed a pathological complete response in the nivolumab and chemotherapy group in CheckMate 816 and CheckMate 77T [13, 17].

It is also important to mention a two additional studies ALINA and ADURA that looked at adjuvant treatment with alectinib and osimertinib [21, 22]. The ALINA trial revealed that patients with resected ALK-positive non small cell lung cancer of stage IB, II, or IIIA, adjuvant alectinib significantly improved disease-free survival as compared with platinum-based chemotherapy [21]. The ADURA trial showed that adjuvant osimertinib provided a significant overall survival benefit among patients with completely resected, EGFR-mutated, stage IB to IIIA non small cell lung cancer [22]. Those studies therefore provided evidence for additional therapeutic options in post surgical adjuvant settings of non small cell lung cancer.

Based on this evidence the patients considered for perioperative treatment should undergo systematic investigations. Radiological imaging in the from of a contrast CT scan of the thorax as well as a PET scan allow for a radiological staging. Many patients would also undergo a mediastinal staging with endobronchial ultrasound. This allows to obtain information in relation to the nodal involvement as well as histological diagnosis. In patients with no mediastinal involvement other diagnostic procedure may be required such as percutaneous CT guided lung mass biopsy or navigational bronchoscopy. Once accurate staging is established and histological conformation together with molecular testing is undertaken a multidisciplinary review of the case involving radiologists, pulmonologists, medical and clinical oncologists, histopathologists should be undertaken. Once decision is made to proceed with perioperative treatment the patients should have Magnetic Resonance Imaging (MRI) of the brain to exclude any brain metastatic disease. The patients also have ctDNA testing as this may contribute to the decision making about potential treatments. In addition, a careful pulmonary and cardia assessment is undertaken including full lung function testing, a six-minute walk and cardiopulmonary exercise assessment. This allows to make decision regarding the patients' fitness for surgery. Together with radiological evaluation this also allows for assessment of operability and resectability. The patients are usually jointly reviewed by a thoracic surgeon and oncologist. The patients are commenced on oncological systemic anticancer treatment as per current guidelines. The aim of perioperative approach to eliminate micro-metastases and to prepare the patients for surgery. Once this treatment is finished, a further evaluation with radiological imaging such as CT scan of the thorax and PET scan is undertaken. The usual practice is to review the investigation at the multidisciplinary

team meeting and if the results are favourable to proceed with surgical resection. Pathological complete response and major pathological response form important measurement in the context of perioperative treatments and have been shown be predictive measures of event-free survival [24]. Circulating DNA are DNA fragments released by tumour cells into the blood stream. In the CheckMate 816 study nivolumab and chemotherapy resulted in 56% clearance rate of ctDNA with pathological clearance and overall survival benefits in the patients showing ctDNA clearance [13]. Currently, the use of ctDNA remains subject of further research. The efficacy of immunotherapy and chemotherapy in neoadjuvant setting is more limited in patient with tumour with PDL-1 less or equal to 1% [25]. The International Association for the Study of Lung Cancer (IASLC) recommends that in absence of disease spread patients who remain operable and resectable should be offered surgery [9]. This may be of particular issue in patients with persistent N2 disease. Another issue that may affect surgery is the presence of immunotherapy resulting perihilar and perivascular fibrosis, which can lead to increased risk of bleeding and more difficult dissection. However, the rates of surgical complication in the neoadjuvant settings remain acceptable [23]. Therefore, for patients with non small cell lung cancer with clinical stages II and III there are a number of therapeutic options. If EGFR or ALK are present upfront surgery followed by a possible adjuvant chemotherapy and possible adjuvant tyrosine kinase inhibitors (TKI) can be considered. If there is no EGFR or ALK present there are potential three treatment options. First upfront surgery and if pathological stage II to III lung cancer completely resected followed by adjuvant chemotherapy and possible immune oncology. Second option is neoadjuvant chemotherapy immune oncology followed by surgery. Third option is

neoadjuvant chemotherapy immune oncology followed by surgery followed by immune oncology. However, there are still unanswered question with regards to which pathway may be the most appropriate. For example, an ADOPT-LUNG trial which is assessing benefits of adding durvalumab after neoadjuvant treatment with platinum based chemotherapy is looking at patients who did not achieve a complete pathological response to evaluate effects of adjuvant immunotherapy on disease free survival [26]. NEOCOAST-2 trail assessed patients with stage IIa to III non small cell cancer. The patients were randomized to receive neoadjuvant durvalumab with platinum based chemotherapy with oleclumab, a CD73 inhibitor, or with monalizumab, a NKG2A inhibitor, or neoadjuvant durvalumab with a single-agent platinum chemotherapy with the TROP-2 antibody - drug conjugate (ADC) datopotamab deruxtecan, followed by surgical resection and adjuvant durvalumab with oleclumab or monalizumab or durvalumab alone. The results showed an ADC plus chemo-immunotherapy in resectable NSCLC, pCR rates were highest in the datopotamab-deruxtecan-containing arm [27]. Therefore, showing some additional promising results that would require further evaluation.

In conclusion perioperative approach to managing non small cell lung cancer is a rapidly evolving field. The developments in oncological therapies and surgical techniques allow for an increasing number of patients to be considered for perioperative approach. Neoadjuvant chemotherapy and immunotherapy working on the PD1 pathway blockades provides clinical benefits with low toxicity compared to chemotherapy. CtDNA and pathologic response are

potential biomarkers of benefits from immunotherapy. Perioperative approach therefore offers additional treatment options for non-small cell lung cancer.

References

1. Updates on the perioperative management of resectable non small cell lung cancer. Frumm SD, Florez N, Lee J, Rotow JK, Chaft J. Natl Compr Canc Netw, doi:10.6004/jnccn.2026.7005
2. The PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. J Clin Oncol 2022;40:1301–1311.
3. Lu S, Kato T, Dong X, et al. Osimertinib after chemoradiotherapy in stage III EGFR-mutated NSCLC. N Engl J Med 2024;391:585–597.
4. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561–1571.
5. Thomas M, Rube C, Hoffknecht P, 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.
6. Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25–33.
7. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res. 2014;3:242–9.
8. Lahiri, A, Maji, A, Potdar, P.D, Singh, N, Parikh, P, Bisht, B, Mukherjee, A, Paul, MK. Lung cancer immunotherapy: Progress, pitfalls, and promises. Mol. Cancer 2023, 22, 40.
9. Spicer, JD, Cascone, T, Wynes, MW, Ahn, MJ, Dacic, S, Felip, E, Forde, PM, Higgins, KA, Kris, MG, Mitsudomi, T, et al. Neoadjuvant and Adjuvant Treatments for Early Stage

Resectable NSCLC: Consensus Recommendations From the International Association for the Study of Lung Cancer. J. Thorac. Oncol. 2024, 19, 1373–1414

10. Lin, D, Shen, L, Luo, M, Zhang, K, Li, J, Yang, Q, Zhu, F, Zhou, D, Zheng, S, Chen, Y, et al. Circulating tumor cells: Biology and clinical significance. Signal Transduct. Target. Ther. 2021, 6, 404
11. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T. LACE Collaborative Group.J Clin Oncol. 2008 Jul 20;26(21):3552-9.
12. Wakelee, H, Liberman, M, Kato, T, Tsuboi, M, Lee, SH, Gao, S, Chen, KN, Dooms, C, Majem, M, Eigendorff, E, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N. Engl. J. Med. 2023, 389, 491–503
13. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022;386: 1973–85.
14. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer. [Internet]. National Comprehensive Cancer Network, Inc.; ©2024 [cited 2024 Mar 25]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
15. Hsu R, Arter ZL, Poei D, Benjamin DJ A narrative review on perioperative systemic therapy in non-small cell lung cancer. Explor Target Antitumor Ther. 2024;5(4):931-954

16. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee S, Gao S, et al.. KEYNOTE-671 Investigators. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med. 2023;389: 491–503.
17. Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, et al.; CheckMate 77T Investigators. Perioperative Nivolumab in Resectable Lung Cancer. N Engl J Med. 2024;390:1756–69.
18. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non-cell lung cancer. N Engl J Med 2023; 389: 1672-84.
19. Provencio M, Nadal E, González-Larriba JL, et al. Perioperative nivolumab and chemotherapy in stage III non–small-cell lung cancer. N Engl J Med 2023; 389: 504-13.
20. Lu S, Zhang W, Wu L, et al. Perioperative toripalimab plus chemotherapy for patients with resectable non–small cell lung cancer: the Neotorch randomized clinical trial. JAMA 2024; 331: 201-11
21. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, Lee JS, Zhong W, Horinouchi H, Mao W, Hochmair M, de Marinis F, Migliorino MR, Bondarenko I, Lu S, Wang Q, Ochi Lohmann T, Xu T, Cardona A, Ruf T, Noe J, Solomon BJ. ALINA Investigators Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024 Apr 11;390(14):1265-1276.
22. Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, Wang J, Goldman JW, Lu S, Su WC, de Marinis F, Shepherd FA, Lee KH, Le NT, Dechaphunkul A, Kowalski D, Poole L, Bolanos A, Rukazenkov Y, Wu YL. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. ADAURA Investigators. N Engl J Med. 2023 Jul 13;389(2):137-147.

23. Kumbasar U, Dikmen E, Dikmen ZG, Tenekeci A, Mender I, Gryaznov S, Bilgin B, Kilickap S. Perioperative Management of Non-Small Cell Lung Cancer in the Era of Immunotherapy. Cells. 2025 Jun 25;14(13):971.

24. Marinelli, D, Nuccio, A, Di Federico, A, Ambrosi, F, Bertoglio, P, Faccioli, E, Ferrara, R, Ferro, A, Giusti, R, Guerrera, F, et al. Improved Event-Free Survival After Complete or Major Pathologic Response in PatientsWith Resectable NSCLC Treated With Neoadjuvant Chemoimmunotherapy Regardless of Adjuvant Treatment: A Systematic Review and Individual Patient DataMeta-Analysis. J. Thorac. Oncol. 2025, 20, 285–295.

25. Banna, GL, Hassan, MA, Signori, A, Giunta, EF, Maniam, A, Anpalakhan, S, Acharige, S, Ghose, A, Addeo, A. Neoadjuvant Chemo-Immunotherapy for Early-Stage Non–Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. JAMA Netw. Open 2024, 7, e246837

26. ADOPT-LUNG Trail https://www.etop.ibcsg.org/projects/clinical-trials/open-trials/25-23-adopt-lung

27. Cascone T, Bonanno L, Guisier F, Insa A, Liberman M, Bylicki O, Livi L, Egenod T, Corre R, Kim DW, Garcia Campelo MR, Provencio Pulla M, Shim BY, Metro G, Bennouna J, Bielska AA, Yohannes AR, He Y, Dowson A, Kar G, McGrath L, Kumar R, Grenga I, Spicer J, Forde PM. Perioperative durvalumab plus chemotherapy plus new agents for resectable non-small-cell lung cancer: the platform phase 2 NeoCOAST-2 trial. Nat Med. 2025 Aug;31(8):2788-2796.