

Surgical Demand Impact of New Immunotherapy Neoadjuvant Approaches in Lung Cancer

C. Gleeson¹, D. Healy¹, T. McCarthy².

1. Department of Cardiothoracic Surgery, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland.
2. Department of Orthopaedic Surgery, Mater Misericordiae University Hospital, Eccles St., Phibsborough, Dublin 7, Ireland.

Abstract

Aims

The standard of care for stage III lung cancer has been combined chemotherapy with radiotherapy without recourse to surgery. The Checkmate 816 trial has established neoadjuvant chemo-immunotherapy followed by surgery as the new standard for management of stage III disease. We explore the service demand implications of this new additional surgical cohort.

Methods

Retrospective study of non-small cell lung cancer (NSCLC) patients amongst those discussed in multi-disciplinary meetings (MDM) from January 1st to December 31st 2023. Patients were included if there was a documented diagnosis of NSCLC with a defined TNM Classification (8th Edition).

Results

In this 12-month period, 1034 unique patients were discussed. A new diagnosis of NSCLC was made in 252 cases. Stage I / II cases accounted for 98 (39%) of cases with 70 (27%) in the stage III group. Among the stage III group, PD-L1 was expressed in 29/70 (41%).

Discussion

Surgery has been limited to stage I & II cases. With new immunotherapy approaches, stage III cases should now be considered for surgery also. This could increase surgical demand, with very specific demands regarding timing. Not all patients will be suitable by performance status, but the service plans need to anticipate an increase in activity.

Introduction

Following on from the Checkmate 816 trial assessing the efficacy of neoadjuvant nivolumab plus chemotherapy in resectable non-small cell lung cancer, the National Cancer Control Programme (NCCP) in May 2024 adjusted the recommended guidelines for treatment of patients with Stage IIIA/IIIB NSCLC.¹ This proposed change indicated that a neoadjuvant strategy using a combination of chemotherapy plus immunotherapy followed by surgical intervention would be the preferred course of management moving forward for this cohort of patients. Prior to this adjustment in the standard of care, concurrent chemoradiotherapy without surgical intervention was offered to those with locally advanced NSCLC having suitable functional fitness.² The increased number of potentially eligible surgical candidates in this population will now place greater demands on surgical services. Ultimately, the performance status of the individual patient must be accounted for to gather a true representation of those who will be suitable candidates for surgery. Potential cases with resectable cancer might not be deemed operable as a result of several potential factors such as poor overall fitness, significant comorbidities or poor lung function amongst other metrics. However, the projected increased strain placed on surgical resources highlights the critical need for effective infrastructure planning and resource allocation to manage the changing landscape of NSCLC treatment.

Methods

This evaluation of the increased surgical burden of the newly proposed guideline changes for Stage IIIA/IIIB was carried out as a retrospective study of newly diagnosed cases of NSCLC patients amongst those discussed in St Vincent's University Hospital (SVUH) lung multi-disciplinary meetings (MDM) over a one-year period from January 1st to December 31st 2023. The collection of data was conducted using a digital recording system and stored solely on SVUH hospital computer systems. Audit and ethical approval were obtained from the Department of Clinical Audit and Research Ethics Committee of St Vincent's Healthcare Group respectively.

Inclusion criteria required patients to have a documented diagnosis of NSCLC. Patients were included in our data set if they had a confirmed diagnosis of NSCLC on the SVUH Lung MDM form or by histopathology result on their personal SVUH clinical database. Confirmation of diagnosis was achieved through tissue sampling using endoscopic procedures or core needle biopsy and subsequent pathological investigations.

A specified TNM Classification (8th edition) of those confirmed cases of NSCLC was needed for involvement in the study. TNM Classification was either displayed on the SVUH Lung MDM form or reported on the histopathology result on the patient's personal SVUH clinical

database. Programmed death ligand 1 (PD-L1) expression was assessed in the Stage III subgroup to evaluate the number of potential candidates for systemic therapy with nivolumab. Patients with EGFR mutations and/or ALK fusions were not accounted for in this sample population. Performance status was another metric that was excluded in our study.

Results

Over the course of a 12-month period, a total of 1,034 individual patients were discussed within the lung multi-disciplinary meetings in St Vincent's University Hospital. Amongst this sample population, there was a total of 252 cases of newly diagnosed NSCLC. Basic demographics are represented below in **Table 1**.

Table 1 : SVUH Lung MDM Discussion 2023

Patient Demographics	N = 252 (NSCLC Cases)
Median Age	71 years (42 – 86 years)
Gender	
<i>Male</i>	123 (48.8%)
<i>Female</i>	129 (51.2%)
Histology Subtype	
<i>Adenocarcinoma</i>	144 (57.1%)
<i>Squamous Cell Carcinoma</i>	74 (29.4%)
<i>Other</i>	34 (13.5%)

Among the individuals in this group the median age was 71 years (range 42-86 years) with 123 males (48.8%) and 129 females (51.2%) included in the population. Histological subtypes for the patients involved in the study were adenocarcinoma (144/252 {57.1%}), squamous cell carcinoma (74/252 {29.4%}), large cell neuroendocrine (5/252 {2%}) and pleomorphic carcinoma (1/252 {0.4%}). Histological subtype could not be evaluated in 28 cases (28/252{11.1%}) due to a lack of documentation in the histological analysis report on the SVUH clinical database for these particular patients. Focusing on staging at time of diagnosis, these individuals were further divided with 98 patients (39%) identified with early-stage disease, classified as either stage I or stage II. A further 70 patients (27%) were diagnosed at stage III. The remaining 84 patients (34%) displayed metastatic disease and were classified as having stage IV disease.

Within this stage III cohort, testing for levels of PD-L1 revealed that 29 out of the 70 patients (41%) exhibited positive expression (>1%) of this biomarker. This finding has significant clinical

implications, as PD-L1 expression is a key factor in determining eligibility for certain immunotherapies. Consequently, the identification of PD-L1 positivity in these 29 patients could potentially lead to an increased consideration for surgical intervention. Consequently, the identification of PD-L1 positivity in these patients could potentially lead to a further 29 cases now being considered as potential surgical candidates in line with the newly proposed NCCP guideline changes. This anticipated increase underlines the importance of resource planning and allocation to accommodate the evolving treatment pathways in NSCLC care.

Discussion

The management of stage III non-small cell lung cancer is complex due to its heterogeneous nature encompassing a wide range of tumour sizes, locations and degrees of lymph node station involvement.

Approximately 20-25% of patients who receive a diagnosis of NSCLC have resectable disease³ however 30-55% of patients who undergo curative surgery have recurrence and ultimately die of their disease.^{4,5}

Of those patients with locally advanced NSCLC who undergo surgery there is a high risk of recurrence with 5-year survival rates standing at approximately 36% for stage IIIA. Thus, despite surgical management, the risk of post-operative recurrence remains high and poses a major challenge.⁶

Surgery remains best practice for early-stage NSCLC and confers multiple benefits for the patient including the possibility of achieving complete resection over the course of several hours, tissue availability being made possible and minimising the patient to the cytotoxic effects of alternative systemic therapy.^{7,8} Unfortunately, surgery has been limited to early stage disease with other systemic approaches being historically favoured for locally advanced and metastatic disease.

Advancements in immunotherapy as demonstrated in the Checkmate 816 trial has influenced change to the traditional approach for the treatment of resectable non-small cell lung cancer. Checkmate 816 revealed that a potentially higher percentage of patients with later stage disease could become eligible for surgery with the use of nivolumab and chemotherapy in the neoadjuvant setting as compared with chemotherapy alone.⁹

Checkmate 816 trial was a randomised phase 3 trial conducted on an international basis looking at the potential enhanced efficacy of combined chemo-immunotherapy using nivolumab, an anti-PDL1 antibody, with platinum-based chemotherapy as opposed to those receiving chemotherapy alone as a neoadjuvant strategy.

The primary end points of the study favoured the combined use of nivolumab and chemotherapy as opposed to chemotherapy alone with both extended event free survival (31.6 months vs 20.8 months after 21 months follow up) and increased incidence of pathological complete response (24% vs 2% respectively) being seen in the investigational arm receiving nivolumab in combination with chemotherapy.¹⁰ These results seem to be observed across the entire study population, however particular benefit was observed in those with stage IIIA cancers, a population who would typically exhibit a poorer prognosis with higher rates of recurrence, than in those with stage IB or II disease.

Checkmate 816 trial included PD-L1 expression amongst the measured variables and highlighted its potential value as a significant predictive factor in those with resectable NSCLC. A meta-analysis evaluating the correlation between PD-L1 expression and its prognostic value in patients with NSCLC undergoing pre-operative neoadjuvant chemoimmunotherapy¹¹ showed that only PD-L1 positive tumours conferred significant benefit from an overall survival standpoint and that PD-L1 negative tumours were at a higher risk of relapse.^{12,13} Higher levels of PD-L1 expression were also seen to be associated with lower risk of disease progression which could encourage further progress in maximising surgical eligibility in this patient population. Although further research is warranted to solidify these results, PD-L1 detection in clinical practice can provide a potentially valuable prognostic factor for predicting outcomes of patients with resectable NSCLC receiving neoadjuvant chemo-immunotherapy and should be assessed when selecting the appropriate treatment for the individual.

On the basis of this trial showing statistical and clinically relevant improvements in both event free survival and pathological complete response, the United States in March 2022 approved the use of nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression exceeding 1%.^{14,15} This motivation to pursue new approaches in the treatment of lung cancer was mirrored by the NCCP in May 2024 when they committed to funding this new treatment strategy.¹

Although Checkmate 816 was a landmark trial in influencing the current management of resectable NSCLC, there have been numerous other trials exploring the potential efficacy of neoadjuvant and perioperative immunotherapy in locally advanced NSCLC.

Upon performing a review of current literature, the growing array of therapeutic options is highlighted throughout. Evidence of such can be seen in the KEYNOTE-671 trial and AEGEAN trial which evaluate pembrolizumab and durvalumab respectively in the neoadjuvant setting.^{16,17} These trials display significant benefits in patient outcomes with improved event free survival and pathological complete response for those exposed to immunotherapy, reinforcing the role of immune checkpoint inhibitors in early-stage disease. The NADIM trial further

established the efficacy of nivolumab based regimens in stage IIIA NSCLC, displaying prolonged survival outcomes and increased response rates.¹⁸

Treatment possibilities are continuing to expand and with several immunotherapy agents such as nivolumab, pembrolizumab and durvalumab amongst others, there is scope for clinicians to have a multitude of treatment strategies for personalisation purposes of the individual patient's management. As advancing research continues to emerge, the role of immunotherapy will continue to be refined and expanded ensuring better outcomes for patients with locally advanced NSCLC.

The implication of the inclusion of neoadjuvant chemo-immunotherapy in current guidelines means that there is now an increased number of potential surgical candidates in the cohort of locally advanced NSCLC patients. The number of potentially resectable tumours may see an increase however not all patients will be deemed operable by performance status. Checkmate 816 showed that the inclusion of neoadjuvant immunotherapy did not reduce receipt of surgery as conversion rates to non-operable status was low, meaning those deemed initially eligible to undergo surgical intervention remained operable candidates capable of withstanding the physiological stress of surgery following on from this neoadjuvant systemic therapy.¹⁰ A systematic review and meta-analysis looking at 2473 patients across 6 randomised trials comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy in resectable NSCLC demonstrated that patients exposed to combination therapy underwent surgery marginally more often than in those receiving chemotherapy alone (83% vs 79% respectively).¹⁹

Although the benefits of neoadjuvant immunotherapy are accumulating, the inflammatory consequences of immunotherapy may pose difficulties with dissections which may potentially lengthen operative times and result in higher conversion rates to open from minimally invasive approaches.²⁰ This was not represented in the findings from Checkmate 816 as the median duration of procedures was numerically shorter and the use of minimally invasive approaches more common in the investigational arm undergoing surgery after immunotherapy.¹⁰ Furthermore, the trial also demonstrated that the addition of nivolumab did not lead to an increased delay in surgery for the patient and the incidence of grade 3 or 4 adverse events occurred in 33.5% of patients in the nivolumab plus chemotherapy group whereas 36.9% of the patients in the chemotherapy alone group experienced an adverse event during their treatment.¹⁰ Although results from Checkmate 816 suggest otherwise, it is important to be cognisant that the technical difficulty of surgical resection of NSCLC after immunotherapy may be more demanding and challenging on the operating surgeon due to frequent hilar inflammation and fibrosis.²¹ The paucity of data leaves it unclear how patient outcomes are impacted by surgical experience with such management options and whether the broadcasting of such treatment strategies can be safely deployed to the broader community of thoracic surgeons. Although there is encouragement of minimally invasive approaches and

investment into robotic-assisted surgery at present, this change in management might motivate our training and fellowships to focus and accommodate for open approach skills to provide sufficient experience in complex surgeries to ensure that surgeons and those in training have appropriate skills and exposure in procedures which may require conversion to an open approach if deemed necessary by the clinician.

The success of immunotherapy in the neoadjuvant setting in other subspecialties including breast surgery²² and urology²³ combined with the remarkable success of immune checkpoint inhibitors as an adjuvant to chemoradiation in stage III NSCLC contribute to a strong rationale for further exploration in neoadjuvant study in lung cancer. For example, the landscape of oncology care in lung cancer could mirror that of the evolution of surgical management of breast cancer with further pursuits in systemic therapy. A parallel could be drawn in how pre-operative therapy could allow for greater lung parenchyma preservation and function similar to the progression seen in breast conserving surgery as a result of effective systemic therapy.²⁴

The shift in current treatment of NSCLC with new immunotherapy approaches and scope for further developments should allow for optimism however the current increase of the surgical population and potential for expansion means urgent prioritisation of surgical resource allocation is necessary to match the unprecedented strain on surgical services. The health care system must now anticipate increased presentations of patients requiring complex thoracic surgeries, often with a narrow window of opportunity following on from neoadjuvant treatment. Delays in surgery can compromise treatment efficacy, underscoring the importance of streamlined surgical pathways, increased theatre room capacity, and efficient co-ordination between surgical and oncology departments in the hospital. A potentially cost-effective measure could be to prioritise the growing investment into robotic-assisted surgery and the encouragement of minimally invasive techniques to optimise resource application and improve patient recovery times²⁵, ultimately reducing hospital stays and increasing surgical throughput. Addressing disparities in access to specialist care for these patients is crucial as many will face logistical challenges in obtaining appropriate care which underlines the importance of the collaborative work of multidisciplinary teams to enhance surgical planning and ensure timely intervention for these patients which do manage to undergo treatment to ultimately improve overall survival for those receiving treatment²⁶. To meet this growing demand, pertinent initiatives including workforce expansion, funding for high volume centres and increasing theatre availability and capacity alongside those discussed above within this text should be prioritised to ensure an appropriate response from health services to this growing surgical cohort. The true benefits of neoadjuvant chemo-immunotherapy can be realised by prioritising these measures ensuring that all eligible patients receive timely and effective surgical intervention.

Declarations of Conflicts of Interest:

None declared.

Corresponding author:

Conor Gleeson,
Department of Cardiothoracic Surgery,
St Vincent's University Hospital,
Elm Park,
Dublin 4,
Ireland.

E-Mail: conorgleeson5@gmail.com

References:

1. National Cancer Control Programme. Nivolumab 360mg and Chemotherapy [Internet]. NCCP National SACT Regimen, Version 1. 2024 [cited 2024 Feb 5]. Available from: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/lung/849->
2. National Cancer Control Programme. Diagnosis, staging and treatment of patients with lung cancer. National Clinical Guideline No. 16 [Internet]. 2024 [cited 2024 Feb 5]. Available from: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/lung-cancer/nccp-lung-guideline-summary.pdf>
3. Liang Y, Wakelee HA. Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC). *Transl Lung Cancer Res*. 2013 Oct;2(5):403.
4. Al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. *Eur J Cardiothorac Surg*. 1997 Sep 1;12(3):380-4.
5. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. *Lancet*. 2000;355:479-85.
6. Rosner S, Reuss JE, Zahurak M, Zhang J, Zeng Z, Taube J, et al. Five-year clinical outcomes after neoadjuvant nivolumab in resectable non-small cell lung cancer. *Clin Cancer Res*. 2023 Feb 16;29(4):705-10.
7. Al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. *Eur J Cardiothorac Surg*. 1997 Sep 1;12(3):380-4.
8. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al. Non-small-cell lung cancer. *Nat Rev Dis Primers*. 2015 May 21;1(1):1-6.
9. Liu Z, Gao Z, Zhang M, Wang X, Gong J, Jiang S, et al. Real-world effectiveness and prognostic factors analysis of stages I–III non-small cell lung cancer following neoadjuvant chemo-immunotherapy or neoadjuvant chemotherapy. *Ann Thorac Cardiovasc Surg*. 2022;28(2):111-20.

10. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022 May 26;386(21):1973-85.
11. Mo DC, Huang JF, Lin P, Huang SX, Wang HL, Luo PH, et al. The role of PD-L1 in patients with non-small cell lung cancer receiving neoadjuvant immune checkpoint inhibitor plus chemotherapy: a meta-analysis. *Sci Rep*. 2024 Oct 31;14(1):26200.
12. Deng H, Zhao Y, Cai X, Chen H, Cheng B, Zhong R, et al. PD-L1 expression and tumor mutation burden as pathological response biomarkers of neoadjuvant immunotherapy for early-stage non-small cell lung cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2022 Feb 1;170:103582.
13. Banna GL, Hassan MA, Signori A, Giunta EF, Maniam A, Anpalakhan S, et al. Neoadjuvant chemo-immunotherapy for early-stage non–small cell lung cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2024 Apr 1;7(4):e246837.
14. Bristol-Myers Squibb. Opdivo (nivolumab) prescribing information. Princeton (NJ): Bristol-Myers Squibb; 2020 Dec.
15. Forde PM, Spicer J, Girard N, Provencio M, Lu S, Wang C, et al. 84O Neoadjuvant nivolumab (N)+ platinum-doublet chemotherapy (C) for resectable NSCLC: 3-y update from CheckMate 816. *J Thorac Oncol*. 2023 Apr 1;18(4):S89-90.
16. Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024 Sep 28;404(10459):1240-52.
17. Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024 Sep 28;404(10459):1240-52.
18. Provencio M, Nadal E, Insa A, Campelo RG, Casal J, Dómine M, et al. Perioperative chemotherapy and nivolumab in non-small-cell lung cancer (NADIM): 5-year clinical outcomes from a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2024 Nov 1;25(11):1453-63.
19. Marinelli D, Gallina FT, Pannunzio S, Di Civita MA, Torchia A, Giusti R, et al. Surgical and survival outcomes with perioperative or neoadjuvant immune-checkpoint inhibitors combined with platinum-based chemotherapy in resectable NSCLC: A systematic review and meta-analysis of randomised clinical trials. *Crit Rev Oncol Hematol*. 2023 Dec 1;192:104190.
20. Broderick SR, Bott MJ. Neoadjuvant immunotherapy in patients with resectable non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019 Nov 1;158(5):1471-4.

21. Marinelli D, Gallina FT, Pannunzio S, Di Civita MA, Torchia A, Giusti R, et al. Surgical and survival outcomes with perioperative or neoadjuvant immune-checkpoint inhibitors combined with platinum-based chemotherapy in resectable NSCLC: A systematic review and meta-analysis of randomised clinical trials. *Crit Rev Oncol Hematol*. 2023 Dec 1;192:104190.
22. Schmid P, Park YH, Muñoz-Couselo E, Kim SB, Sohn J, Im SA, et al. Pembrolizumab (pembro)+ chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173. *Abstract; publication details not complete*.
23. Necchi A, Raggi D, Gallina A, Madison R, Colecchia M, Luciano R, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. *Eur Urol*. 2020 Apr 1;77(4):439-46.
24. Sun Y, Liao M, He L, Zhu C. Comparison of breast-conserving surgery with mastectomy in locally advanced breast cancer after good response to neoadjuvant chemotherapy: a PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)*. 2017 Oct 1;96(43):e8367.
25. Novellis P, Alloisio M, Vanni E, Bottoni E, Cariboni U, Veronesi G. Robotic lung cancer surgery: review of experience and costs. *J Vis Surg*. 2017;3.
26. Denton E, Conron M. Improving outcomes in lung cancer: the value of the multidisciplinary health care team. *J Multidiscip Healthc*. 2016 Mar 30:137-44.