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Neoadjuvant targeted therapy in non-small-cell lung cancer and their impact on surgical outcomes

Running head: Neoadjuvant targeted therapy in NSCLC

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.
**IRB:** Research Ethics Approval was obtained from the Research Board of McGill University (#2022-8070).

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KEY TAKEAWAYS:

- There is currently limited evidence for the use of neoadjuvant tyrosine kinase inhibitors in non-small-cell lung cancer.
- We sought to describe our experience with five non-small-cell lung cancer patients treated by neoadjuvant tyrosine kinase inhibitors.
- We highlight the surgical outcomes of these patients, and demonstrate why the reporting of surgical outcomes in future neoadjuvant TKI Phase III trials is essential.
ABSTRACT:

BACKGROUND: The evidence for neoadjuvant targeted therapy in non-small-cell lung cancer is limited with two Phase III trials currently recruiting and no approved indications.

METHODS: We describe our experience with the use of neoadjuvant targeted therapy for patients with operable non-small cell lung cancer.

RESULTS: Our focus is on surgical outcomes, which represent an under-reported aspect of the patient trajectory. We argue that surgical outcomes are an essential feature of this strategy with significant potential benefits and risks.

CONCLUSIONS: Overall, the patient experience can be significantly impacted by the use of neoadjuvant targeted therapy and its impact on surgical planning, strategy and outcomes.
Patients with operable non-small cell lung cancer (NSCLC) are a growing fraction of newly diagnosed patients thanks to early detection and screening programs. Nearly 50% of these patients will have actionable mutations for which there are approved drugs in the metastatic setting [1]. In recent years, neoadjuvant therapy has gained a lot of attention. Neoadjuvant therapy allows for downstaging of unresectable tumors, rendering them resectable and simultaneously eliminating micrometastatic disease [2]. The long-term benefits of investigational agents in the neoadjuvant setting remain unclear for some therapeutic drug classes in NSCLC. Initial results from CM816 show that the addition of immunotherapy to chemotherapy in the neoadjuvant setting led to a 24% rate of pathological complete response (pCR) compared to a 2% rate for neoadjuvant chemotherapy alone without imparting a negative impact on adverse event rates or surgical resection rates [3]. That said, one of the most striking findings from the results available from CM816 relate to the exploratory surgical outcomes. Overall, patients treated with neoadjuvant chemo-Nivolumab had shorter operations, fewer required open surgery, conversion to open surgery or needed a pneumonectomy to resect remaining disease. These are all important endpoints for the patient experience and no peri-operative therapy has ever shown such impact on the conduct of the surgical resection.

For targeted therapy, the results of the ADAURA trial have brought tyrosine kinase inhibitors (TKIs) to the resectable stages of EGFR mutated lung cancer with a dramatic improvement in DFS [4]. The evidence for the use of neoadjuvant EGFR TKIs is limited as was concluded by two independently performed meta-analyses [5-6]. Future Phase III randomized trials such as the NeoADAURA trial, which will evaluate neoadjuvant Osimertinib with or without chemotherapy versus chemotherapy alone prior to surgery, will provide evidence regarding the use of
neoadjuvant TKIs [7]. Given the limited evidence for this approach so far, we sought to describe our experience with neoadjuvant TKI-treated patients, with a focus on surgical outcomes.

**PATIENTS AND METHODS**

*Retrospective Data Collection and Research Ethics Approval*

Patients were selected from a prospectively collected institutional NSCLC database of patients seen as part of the Thoracic Surgery service at the McGill University Health Centre from January 2015 to July 2022. Five patients met our search criteria of having received neoadjuvant TKI treatment and were included as part of this retrospective analysis. Demographic characteristics (sex, age), baseline characteristics (smoking status), pre-operative or diagnostic data (tests and procedures, neoadjuvant therapy, clinical staging), pathological data (pathological staging, lymph node status, margin status, histology) and operative data (approach) were collected. Lymph node station sampled can be found in Table 1. All available computed tomographic (CT) scans at diagnosis and after completion of neoadjuvant therapy but prior to surgery were studied. For each CT slice, the outline of the tumor was drawn using a pencil selection tool, permitting a higher level of precision. Tumor volumes were then automatically calculated for each tumor using the PACS imaging software which sums the area of tumor for each CT slice. Research Ethics Approval was obtained from the Research Board of McGill University (#2022-8070).

**RESULTS**

We retrospectively reviewed five cases of neoadjuvant TKI treated NSCLC patients from January 2015 to July 2022 at a single center. In terms of treatment trajectories (Figure 1), Patient 1 was a 75-year-old female ex-smoker with clinical stage IIIa (cT4N0M0; T4 due to tumor size) EGFR
mutated invasive acinar predominant lung adenocarcinoma. She was treated with neoadjuvant Gefitinib then down staged to pathological stage IB (ypT2aN0) after a left lower VATS lobectomy and mediastinal node dissection with microscopically positive margins. It is interesting to note that despite a microscopically positive parenchymal margin at final pathology, the patient is without thoracic recurrence now over 2 years post-surgery and without adjuvant radiation. Her tumor decreased in size from 10 cm x 5.7 cm (348.48 cm$^3$) to 4.3 cm x 3.5 cm (63.76 cm$^3$) following neoadjuvant TKI treatment, an 82% reduction in tumor volume. She had a two-day length of stay after surgery. The patient went on to receive 4 cycles of adjuvant cisplatin and pemetrexed. Five months later the patient presented with a brain recurrence causing dysphasia and cognitive changes. She underwent brain metastatectomy via craniotomy followed by Osimertinib. She remains alive without disease 26 months after her initial diagnosis. Patient 2 was a 62-year-old female ex-smoker with clinical stage IIIa (cT4N0M0; T4 due to invasion of the mediastinum and superior vena cava) ALK mutated invasive acinar predominant lung adenocarcinoma. The mass was invading the mediastinal fat and may have been impinging on the superior vena cava. After 1 month of Alectinib, her tumor decreased in size from 3.8 cm x 3.0 cm (31.91 cm$^3$) to 2.8 cm x 1.9 cm (11.21 cm$^3$), a 65% reduction in tumor volume. Following a right upper VATS lobectomy and wedge resection and mediastinal node dissection (R0), she was discharged on the second post-operative day. Final pathology demonstrated visceral pleural invasion and structural invasion of the mediastinum with negative margins resulting in stage IIIa [ypT4N0] disease. She went on to receive adjuvant cisplatin and pemetrexed. She remains without evidence of disease now 13 months after surgery. Patient 3, a 68-year-old female never smoker, had EGFR mutated clinical stage IIa (cT2bN0M0) lepidic predominant adenocarcinoma for which she received Gefitinib that was stopped after a month due to skin toxicity. This led to a slight interval decrease in tumor
volume from 3 cm$^3$ to 1.82 cm$^3$, a 39% reduction. She then underwent a right upper VATS bilobectomy and mediastinal node dissection (R0). She was discharged on the first post-operative day. Final pathology demonstrated lymphovascular invasion and lepidic predominant and was stage IB [ypT2aN0]. She is now 15 months after surgery with no evidence of disease. Patient 4 was a 29-year-old female with an ALK mutated stage IIIa (cT2aN2M0) acinar predominant adenocarcinoma. She had multi-station N2 disease (levels 2R, 4R and 7) and had been offered concurrent chemoradiation at an outside institution. She declined chemoradiation in favour of neoadjuvant Alectinib followed by surgery. She received two months of neoadjuvant Alectinib with a decrease in tumor size from 1.8 cm$^3$ to 0.43 cm$^3$, a 76% reduction. She underwent a right VATS lower lobectomy with lymph node dissection and was discharged on the third post-operative day. On final pathology, she was found to have lymphovascular and visceral pleural invasion and was down-staged to stage IB [ypT2aN0] following an R0 resection with a major pathological response [less than 10% remaining viable tumor cells]. She resumed Alectinib on post-operative day 3 and is scheduled to undergo adjuvant chemotherapy. Patient 5 was a 74-year-old never-smoker female with an exon 19 EGFR mutated stage IIIa [cT4N0M0; T4 due to tumor size] adenosquamous carcinoma. She received neoadjuvant Osimertinib for two months which led to a decrease in tumor volume from 378.23 cm$^3$ to 37.63 cm$^3$, a 90% reduction. She underwent a right VATS upper lobectomy with lymph node dissection. She was down-staged to stage IA2 [ypT1bN0] with a major pathological response and is scheduled to receive adjuvant Osimertinib.
COMMENT

In our case series, two out of five patients achieved a major pathological response (MPR), no patients achieved complete pathological response (pCR) and no patients experienced surgical complications. All patients were operated by a minimally invasive technique with none requiring conversion to open surgery. Post-operative length of stay ranged from 1 to 3 days. Overall, four out of five patients had downstaging following neoadjuvant TKI treatment with direct impact on the surgical approach (Table 2). The anecdotal nature of these findings are obvious limitations and it is impossible to say if the surgical and clinical outcomes of these patients would had been worse or different had they not received neoadjuvant TKI therapy. However, in our judgement, the use of neoadjuvant TKI simplified the surgical experience for these patients. For example, patient 1 had a very large tumor that would have required a large incision simply to remove the mass. However, with significant response a relatively simple VATS lower lobectomy was performed allowing the patient to be discharged on the second post-operative day. For patient 2, the mass was invading the mediastinal fat and may have been impinging on the superior vena cava. After 1 month of Alectinib, there was significant regression allowing for an uncomplicated VATS resection and again, she was discharged on the second post-operative day. In patient 4, neoadjuvant therapy offered her a radiation sparing approach to her local control, which may be important in a 29-year-old patient. She was also down-staged from multi-station N2 to N0, which is encouraging with respect to local control of her disease. Patient 5 would have undergone a thoracotomy with bronchial sleeve before neoadjuvant treatment but instead underwent a VATS lobectomy following 2 months of Osimertinib. An example of the surgical approach following neoadjuvant TKI therapy can be observed in Video 1. Overall, neoadjuvant therapy has the potential to allow for less morbid local therapy compared to adjuvant therapy. Future Phase III trials investigating
the effects of neoadjuvant TKIs should offer detailed and systematic reporting of the surgical outcomes in addition to survival, response and pathological endpoints.

In particular, it is crucial for such studies to comment on expected surgical approach at presentation and compare this to the operation carried out after treatment in a prospective controlled fashion. As an example, the increased morbidity linked to extended lung resections such as pneumonectomy are well-described in comparison to lobectomy or segmentectomy. Indeed, this is important as pneumonectomy is associated with higher 30-day mortality than lobectomy and worse quality of life after surgery, including worse physical functioning, role functioning, social functioning, and general pain [8-9]. As an example, the CHECKMATE816 study found a 43% reduction in stage IIIa patients who required pneumonectomies in the chemo-Nivolumab patients versus chemotherapy alone (17% vs 30%) and a 45% reduction in conversion from minimally invasive to open surgery (11% vs 20% respectively) with the addition of Nivolumab3 [3]. Conversion from minimally invasive to open surgeries has also been associated with higher 30-day mortality, longer length of stay and increased blood loss when compared to minimally invasive surgery alone [9]. As such, interventions that enable lesser lung resections have the potential to dramatically improve the patient experience of curative therapy.

Our anecdotal experience with neoadjuvant targeted therapy reveals certain aspects of the care trajectory that can be optimized by such an approach. The majority of data on neoadjuvant targeted therapy involve EGFR mutant patients with a growing list of approved agents for various other mutations to be tested in the coming years. Future and ongoing neoadjuvant targeted therapy trials should report detailed surgical outcome data. The patient experience is significantly impacted by the influence of neoadjuvant treatment on surgical decision-making. These effects have pivotal consequences on resulting quality of life, incurred morbidity of treatment and survival.
REFERENCES


Figure 1. Treatment trajectories of neoadjuvant TKI treated NSCLC patients. Timelines include mutation status, clinical and pathological stage, type of neoadjuvant TKI used, type of surgery used, type of adjuvant therapy used and information on recurrence. CT scans at diagnosis and after neoadjuvant TKI treatment are also provided.
Table 1. Lymph node stations for each patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Lymph node station</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 year old female</td>
<td>Level 11, interlobar; level 7, subcarinal; level 10, hilar; level 5 and subaortic</td>
</tr>
<tr>
<td>62 year old female</td>
<td>Level 7; level 11R; mediastinal lymph nodes and level 4R</td>
</tr>
<tr>
<td>68 year old female</td>
<td>Level 9R, pulmonary ligament; level 7, subcarinal; level 10, hilar; level 11, interlobar; level 4, lower paratracheal and level 2, upper paratracheal</td>
</tr>
<tr>
<td>29 year old female</td>
<td>Level 7 subcarinal; level 11R, interlobar; level 12R, lobar; level 10R; level 4R and level 2R</td>
</tr>
<tr>
<td>74 year old female</td>
<td>Level 7; level 11, interlobar; level 10, hilar; level 4R, lower paratracheal; level 2, right paratracheal and prevascular</td>
</tr>
</tbody>
</table>
Table 2. Proposed surgical approach at diagnosis prior to neoadjuvant TKI treatment and surgery performed after neoadjuvant TKI therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Surgical approach before neoadjuvant therapy</th>
<th>Surgical approach after neoadjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 year old female</td>
<td>Thoracotomy LUL lobectomy</td>
<td>VATS LUL lobectomy</td>
</tr>
<tr>
<td>62 year old female</td>
<td>Thoracotomy RUL lobectomy , SVC resection and reconstruction</td>
<td>VATS RUL lobectomy</td>
</tr>
<tr>
<td>68 year old female</td>
<td>VATS upper bilobectomy</td>
<td>VATS upper bilobectomy</td>
</tr>
<tr>
<td>29 year old female</td>
<td>Thoracotomy RLL</td>
<td>VATS RLL lobectomy</td>
</tr>
<tr>
<td>74 year old female</td>
<td>Thoracotomy RUL Sleeve lobectomy</td>
<td>VATS RUL lobectomy, resection of azygous vein</td>
</tr>
</tbody>
</table>
Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Benjamin Shieh reports a relationship with Novartis Pharmaceuticals Corporation that includes: board membership. Benjamin Shieh reports a relationship with Bristol Myers Squibb Co that includes: board membership. Benjamin Shieh reports a relationship with Pfizer Inc that includes: board membership. Benjamin Shieh reports a relationship with Takeda Oncology that includes: board membership. Benjamin Shieh reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with Amgen Inc that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with EMD Serono Inc that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with Merck Canada Inc that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with Pfizer Canada Inc that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with F Hoffmann-La Roche Ltd that includes: consulting or advisory. Pierre Olivier Fiset reports a relationship with Bristol Myers Squibb Co that includes: funding grants. Pierre Olivier Fiset reports a relationship with Cancer Research Society that includes: funding grants. Scott Owen reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Scott Owen reports a relationship with Bayer Corporation that includes: consulting or advisory. Scott Owen reports a relationship with Takeda Pharmaceutical Co Ltd that includes: consulting or advisory. Jonathan Spicer reports a relationship with Merck & Co Inc that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with Bristol Myers Squibb Co that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with Roche that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with Novartis Pharmaceuticals Corporation that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with ChemoCentryx Inc that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with Protalix Biotherapeutics that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with Amgen Inc that includes: board membership and consulting or advisory. Jonathan Spicer reports a relationship with AstraZeneca Pharmaceuticals LP that includes: funding grants. Jonathan Spicer reports a relationship with Merck & Co Inc that includes: funding grants.